

# MEDICINAL CHEMISTRY IN THE NEW MILLENNIUM. A GLANCE INTO THE FUTURE

(Special Topic Article)

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Who of us would not be glad to lift the veil behind which the future lies hidden; to cast a glance at the next advances of our science and at the secrets of its development during future centuries?

—David Hilbert in 1900, as quoted recently by R. Breslow [1]

Paul W. Erhardt received his Ph.D. degree in medicinal chemistry from the University of Minnesota in 1974, and spent many years in the pharmaceutical industry before assuming his present position as professor in the College of Pharmacy, University of Toledo, and Director of the Center for Drug Design and Development. He is currently Vice President of IUPAC's Chemistry and Human Health Division, and has played an active role in chairing and coordinating numerous Divisional projects. His background and experience in both the industrial and academic sectors and his familiarity with the intricate interdisciplinary fabric of medicinal chemistry qualify him admirably to offer this authoritative overview, in which the recent history and current status of the field furnish a backdrop for discussing future challenges and opportunities. The article forms part of the special topic coverage offered by *Pure and Applied Chemistry*, to highlight topical themes and to offer critical insight into new and emerging concepts in the chemical sciences.

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# Medicinal chemistry in the new millennium. A glance into the future

## (Special Topic Article)

*Abstract:* The future of medicinal chemistry as both a pure and an applied science has been considered relative to trends that are already having a significant impact upon drug discovery and development. After quickly reviewing how medicinal chemistry has been practiced to date, topics considered into the future include: pursuing therapeutic efficacy, addressing 3D structure within database settings, assuring absorption, directing distribution, controlling metabolism, optimizing elimination, and avoiding toxicity. It is suggested that as the exploration of these topics proceeds into the new millennium by deploying combinatorial chemistry coupled to high-throughput screening, medicinal chemistry will play a key role as a central interpreter of the underlying structure–activity relationships such that the overall process of drug discovery and development will be knowledge-generating. As fundamental knowledge accumulates across all of these areas, virtual approaches will eventually become firmly anchored to experimental and theoretical databases having validated clinical predictability. The potential impact of some of the recent trends in process chemistry, and in analytical chemistry using X-ray diffraction as an exemplary method, are additionally highlighted before reiterating the article's major points in a summary section. From this purview, the summary also considers the education of future medicinal chemists, notes potential issues related to the future of pharmaceutical-related intellectual property, and concludes by alluding to a brewing paradox between enhanced knowledge and enhanced molecular diversity relative to the future discovery of new drugs.

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## 1. INTRODUCTION

Given the highly interdisciplinary nature of medicinal chemistry and the potential for its deployment across a myriad of future, life science research activities, this review has sought to highlight only those possibilities that stand out upon taking a broad purview of the field's most prominent trends. From this vantage point, however, at least "a glance" will have then been "cast" toward some of the more noticeable of the exciting opportunities seemingly in store as medicinal chemistry moves "forward into the new millennium" [1,2]. An overview of the document's several sections is provided below. It lists what topics will and will not be covered and indicates the reasoning behind these choices. The overview also describes the consistent tone that was sought while attempting to elucidate the numerous technologies that necessarily become encompassed by the variously highlighted activities.

While initially contemplating how medicinal chemistry might continue to evolve as both a basic and applied science, it became apparent that it would be useful to first consider where medicinal chemistry has been and how it has come to be what it is today. Thus, toward quickly establishing a context from which the future might be better appreciated, and perhaps even seen to already be repeating itself amongst a new set of players and technologies, Section 2 provides a short discourse about medicinal chemistry's emergence as a formalized discipline, its early developments, and its present status by considering how medicinal chemistry has been practiced across jumps of about 25-year increments. This section does not include a chronological list of medicinal chemistry's many contributions, nor does it highlight the many accomplishments of its noted investigators. Both of the latter can be found elsewhere as part of more traditional, historical treatments [3].

From the backdrop provided in Section 2, medicinal chemistry's near and longer-term futures are considered in Section 3 relative to several of today's trends that are already having a major impact upon the drug discovery process. A working definition for medicinal chemistry is recited at the opening of this section so that medicinal chemistry's immediate and future roles can be more clearly ascertained. Section 3 also sets the stage to later consider where several drug development topics may be headed in the near and longer term.

Discussions about gene therapy, vaccines, and biotech-derived therapeutic agents have not been included in Section 4, which addresses medicinal chemistry's continued pursuit of efficacy. The aforementioned topics primarily reside within the domains of other disciplines. Readers are encouraged, however, to consult other reviews offered for these areas in order to appreciate how their advances are sure to have a dramatic impact upon future life science research and its interface with medicinal chemistry [e.g., 4–6, respectively]. Alternatively, because assessing molecular conformation is such an integral part of practicing medicinal chemistry along any venue, several aspects of this key topic are considered within Section 5. In particular, the handling of chemical structures within database settings (e.g., chemoinformatics) is discussed in detail.

Several drug development topics are regarded as critical factors that will have a pivotal influence upon medicinal chemistry's continuing evolution in the new millennium. Each of these topics is briefly addressed within Section 6. These key topics include: assuring absorption; directing distribution; controlling metabolism; assisting elimination; and, avoiding toxicity [i.e., the traditional absorption, distribution, metabolism, elimination, and toxicity (ADMET) studies that previously have been undertaken by pharmaceutical companies during the secondary stages of preclinical drug development]. As an important extension of the ADMET discussions, nutraceuticals considered in parallel with pharmacological synergy are also addressed within Section 6.

Issues pertaining to medicinal chemistry's future roles in pharmaceutical intellectual property (IP) and to trends associated with process chemistry, are raised within Section 7. With today's highly publicized emphasis upon genomics and proteomics, at least an abbreviated discourse about process chemistry is included at this juncture so that this fundamental aspect of medicinal chemistry's link with synthetic chemistry remains appreciated. Thus, toward providing just some of such coverage, the unmet need for large-scale, stereoselective synthetic methodologies is briefly discussed in Section 7. As part of this discussion, an example is cited that concludes by conveying the medicinal chemistry logic that was encompassed as a critical component of the example's investigations.

While it is beyond the scope of this review to discuss the impact that progress in each of several analytical methods is likely to have upon medicinal chemistry [7], X-ray diffraction has been selected to provide a representative discussion within Section 8. As is often acknowledged by researchers from various disciplines, "science moves forward according to what it can measure", and presently, there appear to be numerous promising advances among various analytical techniques that can be used to study drug-receptor interactions. For example, readers are encouraged to seek other reviews in order to appreciate the potential impact that anticipated developments in nuclear magnetic resonance (NMR inclusive of LC-NMR and high-flowthrough techniques), mass spectrometry (MS inclusive of LC-MS and LC-MS/MS), microcalorimetry and surface plasmon resonance may have upon medicinal chemistry's future [e.g., 7–10, 11–13, 14–15, and 16–17, respectively].

In Section 9, practical implications that stem from some of the earlier discussions are revisited in what also serves as an overall summary for this document. After restating medicinal chemistry's anticipated roles in future life science research, concerns pertaining to the training of medicinal chemists, inventorship, and the interplay of patent trends and future research within the context of the IP arena have all been reserved for comment within the concluding summary.

The document's running dialogue has been developed from future possibilities suggested by the current medicinal chemistry and drug discovery literature, as well as from general observations afforded while consulting with both the private and public sectors. Descriptions of specific research projects have been interspersed throughout so that real case examples, along with their chemical structures, could be

explicitly conveyed. A concerted effort has been made to keep hype to a minimum. Alternatively, jargon has been used whenever it was thought that such terms portray the mind-sets that were important for a given period, or because a particular term or phrase appears to be taking on an enduring significance. Some of the more technical of these terms are listed in Table 1 along with a short definition in each case. Since several acronyms have been used for repeating phrases, an alphabetical listing of all acronyms and their definitions is provided in Table 2 to assist readers as they move deeper into the document. Numerous references to secondary scientific/primary news journals have been cited because these journals are doing an excellent job of both reporting the most recent trends and forecasting the potential future. In several cases, a single citation has been used to list many of the informational Web sites that can often be found for a given topic.

Topics are considered into the future only to about one-half the distance that has been summarized for medicinal chemistry's past, namely for about 75 years with the first 25 being regarded as near term, and the next 50 being regarded as long term. The speculation that has necessarily been interjected throughout the review has been done with the thought that one of the goals for this type of article is to prompt the broadest contemplation possible about the future directions that medicinal chemistry might take. Finally, as medicinal chemistry is shown to move forward in time, it has been considered as both a distinct, pure science discipline and, equally important, as a key interdisciplinary, applied science collaborator seeking to mingle with what should certainly prove to be an extremely dynamic and exciting environment within the life sciences arena of the new millennium.

*(text continues on page 711)*

**Table 1** Selected terms and abbreviated definitions.

Term	Definition
Ab initio calculations	Quantum chemical calculations that use exact equations to account for the complete electronic structure of each atom within a molecule. <sup>a</sup>
AMBER	A molecular mechanics program commonly used for calculations on proteins and nucleic acids. <sup>a</sup>
Basis set	A set of mathematical functions used in molecular orbital calculations, e.g., 3-21G,* 6-31G*, or B3LYP when used in ab initio calculations refer to the type of mathematical function that was deployed. <sup>a</sup>
Bioinformatics	Application of computer science and technology to address problems in biology and medicine. <sup>b</sup>
Bioisostere	Broadly similar atoms or groups of atoms in terms of physiochemical or topological properties that can be used as replacements within a biologically active compound to create a new structure that retains all selected features of the parent compound's biological properties. <sup>c</sup>
Cheminformatics	Handling of chemical structure and chemical properties within database settings; when related to biological properties this field becomes a subdivision of bioinformatics.
Combinatorial chemistry	Synthesis, purification, and analysis of large sets of compounds wherein sets of building blocks are combined at one or more steps during their preparation. <sup>c</sup>
Combinatorial library	A set of compounds prepared by using combinatorial chemistry. <sup>c</sup>
Comparative molecular field analysis (CoMFA)	A 3D-QSAR method that uses statistical correlation techniques for the analysis of the qualitative relationships between the biological activity of a set of compounds with a specified alignment of their 3D electronic and steric properties. Additional parameters such as hydrophobicity and hydrogen-bonding can also be incorporated into the analysis. <sup>c</sup>
Drug-like	Structural motifs and/or physicochemical profiles that can be associated with providing an overall ADME behavior that is conducive to effective use in humans via the oral route.
Electrostatic potential	A physical property equal to the electrostatic energy between the static charge distribution of an atomic or molecular system and a positive unit point charge. Used in 3D-QSAR, molecular similarity assessment, and docking studies. <sup>a</sup>
e-Research	Research asset management via in-house computer networks and across the World Wide Web
Extended Huckel calculations	Low-level, semi-empirical molecular orbital calculations. <sup>a</sup>
Gaussian programs	Type of mathematical function used during ab initio calculations to describe molecular orbitals. Numbers refer to year of program updates.
Genomics	Used herein as the study of the chromosomal and extrachromosomal genes within humans, in particular their complete sequential characterization.
High-throughput screening (HTS)	The level of this activity is rapidly moving from 96- to 384-well microplates [436].
In silico	Tasks undertaken via computer, e.g., virtual screening.
Isosteres	Molecules or ions of similar size containing the same number of atoms and valence electrons. <sup>c</sup>
Ligand-based drug design	The design of new structural arrangements based upon their resemblance to at least a portion of another compound that displays a desired property or biological activity.
Metabophores	Structural features residing within substrates that prompt their specific metabolic conversions [22].

(continues on next page)

**Table 1** (Continued)

Term	Definition
MNDO calculations	Semi-empirical molecular orbital calculations that use a modified neglect of diatomic (differential) overlap approximation. <sup>a</sup>
Molecular mechanics	Calculation of molecular conformational geometries and energies using a combination of empirical force fields. <sup>a</sup>
Molecular orbital calculations	Quantum chemical calculations based on the Schrödinger equation, which can be subdivided into semi-empirical (approximated) and ab initio (nonapproximated) methods. <sup>a</sup>
Multivalent ligands	Molecular displays that provide more than one set of binding motifs for interaction with more than one area on one or more biological surfaces.
Nutraceuticals	Dietary supplements purported to have beneficial therapeutic or disease preventative properties, e.g., herbal medicines. <sup>d</sup>
Pharmacogenetics	The study of genetic-based differences in drug response [106].
Pharmacophores	Structural features needed to activate or inhibit specific receptors or enzyme active sites.
Privileged structures	Molecular frameworks able to provide ligands for diverse receptors [264,265]
Prodrug	A compound that must undergo biotransformation (e.g., metabolism) before exhibiting its pharmacological effects. <sup>c</sup>
Proteomics	The study of protein structure and function [438].
Quantum mechanics	Molecular property calculations based on the Schrödinger equation that take into account the interactions between electrons in the molecule. <sup>a</sup>
Semi-empirical calculations	Molecular orbital calculations using various degrees of approximation and using only valence electrons. <sup>a</sup>
Single nucleotide polymorphisms (SNPs)	Used herein as single-base alterations within the human genome that occur in specified percentages of distinct portions of the population.
Soft drug	A compound that has been programmed to be biodegraded (e.g., metabolized) to predictable, nontoxic and inactive metabolites after having achieved its therapeutic role. <sup>c</sup>
Structure-based drug design	The design of new structural arrangements for use as drugs based upon protein structural information obtained from X-ray crystallography or NMR spectroscopy [65,474].
Toxicophores	Structural features that elicit specific toxicities [481].
Transportophore	Structural features that prompt a specific compound's transport.
Ultra-high-throughput screening (UHTS)	The level of this activity has rapidly moved from 384- to 1536-well microplates with peak throughput rates of over 100 000 compounds per day. It is estimated that this field will soon be closing in on producing 1200 data-points per minute [478].
Xenobiotic	A compound that is foreign to a given organism. <sup>c</sup>

<sup>a</sup>Adapted from definitions provided by the IUPAC [432].<sup>b</sup>Various definitions can be found [433]; this particular definition has been cited because it appears to be used most commonly by the U.S. National Institutes of Health (NIH) [434].<sup>c</sup>Adapted from definitions provided by IUPAC [435].<sup>d</sup>Adapted from definitions provided by the U.S. Office of Dietary Supplements (ODS) [437].

**Table 2** Acronyms and designations.

Acronym	Designation
ADME	Absorption, distribution, metabolism, and elimination
ADMET	ADME and toxicity
CADD	Computer-assisted drug design
CAS	American Chemical Society's Chemical Abstract Services
CCD	Charge-coupled device (as in X-ray area detectors)
CoMFA	Comparative molecular field analysis
CPT	Camptothecin
CYP	Cytochrome P-450 metabolizing enzyme [439]
FDA	U.S. Food and Drug Administration
GI	Gastrointestinal tract
HPLC	High-performance liquid chromatography
HTS	High-throughput screening
IND	Investigational new drug <sup>a</sup>
IP	Intellectual property, e.g., trade secrets and patents
IT	Information technology
KDD	Knowledge discovery in databases [440]
LC	Liquid chromatography
Log P	Log value of a compound's n-octanol/H <sub>2</sub> O partition coefficient
MDR	Multidrug resistance
MS	Mass spectrometry
NBE	New biological entity [441], taken to mean that such a compound has potential diagnostic, therapeutic, or prophylactic value
NCE	New chemical entity, taken to mean that such a compound has potential diagnostic, therapeutic, or prophylactic value
NDA	New drug application <sup>a</sup>
NMR	Nuclear magnetic resonance spectroscopy
PAC	Paclitaxel
Pgp	P-glycoprotein pump associated with the ABC class of membrane transporter systems
PK	Pharmacokinetic
QSAR	Quantitative structure–activity relationships; note that the <i>Q</i> designation also becomes applicable to all of the other SXR possibilities
SAR	Structure–activity relationships wherein <i>activity</i> is equated herein with therapeutic efficacy-related elements from either an agonist or antagonist type of interaction
SAbR	Structure–absorption relationships
SDM	Site-directed mutagenesis
SDR	Structure–distribution relationships
SER	Structure–elimination relationships
SMR	Structure–metabolism relationships
SNP	Single nucleotide polymorphism—within a genome
SPR	Surface plasmon resonance spectroscopy
STR	Structure–toxicity relationships
STrR	Structure–transporter relationships
SXR	Generic representation for simultaneous SAR, SAbR, SDR, SER, SMR, STR, and STrR
UHTS	Ultrahigh-throughput screening
2D	Two-dimensional structure representation
3D	Three-dimensional structure representation

<sup>a</sup>Phrases and acronyms commonly used within the U.S. drug regulatory process.



## 2. PRACTICE OF MEDICINAL CHEMISTRY

### 2.1 Emergence as a formalized discipline

Medicinal chemistry's roots can be found in the fertile mix of ancient folk *medicine* and early natural product *chemistry*, and hence its name. As appreciation for the links between chemical structure and observed biological activity grew, medicinal chemistry began to emerge about 150 years ago as a distinct discipline intending to explore these relationships via chemical modification and structural mimicry of nature's materials, particularly with an eye toward enhancing the efficacy of substances thought to be of therapeutic value [19]. In the United States, medicinal chemistry became formalized as a graduate level discipline about 75 years ago within the academic framework of pharmacy education. From this setting, overviews of medicinal chemistry's subject matter have been offered to undergraduate pharmacy students for many years [20,21]. Understanding structure–activity relationships (SARs) at the level of inherent physical organic properties (i.e., lipophilic, electronic, and steric parameters) coupled with consideration of molecular conformation soon became the hallmark of medicinal chemistry research. Furthermore, it follows that because these fundamental principles could be useful during the design of new drugs, applications toward drug design became the principal domain for a still young, basic science discipline. Perhaps somewhat prematurely, medicinal chemistry's drug design role became especially important within the private sector where its practice quickly took root and grew rampantly across the rich fields being staked out within the acres of patents and intellectual property that were of particular interest to the industry.

### 2.2 Early developments

As a more comprehensive appreciation for the links between observed activity and pharmacological mechanisms began to develop about 50 years ago and then also proceeded to grow rapidly in biochemical sophistication, medicinal chemistry, in turn, entered into what can now be considered to be an adolescent phase. Confidently instilled with a new understanding about what was happening at the biomolecular level, the ensuing period was characterized by the high hope of being able to independently design new drugs in a rational (i.e., *ab initio*) manner rather than by relying solely upon Mother Nature's templates and guidance for such. While this adolescent "heyday of rational drug design" [22] should certainly be credited with having spurred significant advances in the methods that can be deployed for considering molecular conformation, the rate of actually delivering clinically useful therapeutic entities having new chemical structures within the private sector was not significantly improved for most pharmacological targets unless the latter's relevant biomolecules also happened to lend themselves to rigorous analysis (e.g., obtainment of an X-ray diffraction pattern for a crystallized enzyme's active site with or without a bound ligand). One of the major reasons rational drug design fell short of its promise was because without experimental data like that afforded by X-ray views of a drug's target site, medicinal chemistry's hypothetical SAR models often reflected speculative notions that were typically far easier to conceive than were the actual syntheses of the molecular probes needed to assess a given model's associated hypotheses. Thus, with only a small number of clinical success stories to relay, medicinal chemistry's "preconceived notions about what a new drug ought to look like" began to take on negative rather than positive connotations, particularly when being "hand-waved" within the context of a private sector drug discovery program [e.g., 23]. Furthermore, from a practical point of view, the pharmaceutical industry, by and large, soon concluded that it was more advantageous to employ synthetic organic chemists and have them learn some pharmacology, than to employ formally trained medicinal chemists and have them rectify any shortcomings in synthetic chemistry that they might have due to their exposure to a broader range of nonchemical subject matter during graduate school. Indeed, given the propensity for like-to-hire-like, the vast majority of today's investigators who practice medicinal chemistry within big pharma, and probably most within the smaller company segment of the pharmaceutical industry as well, have academic backgrounds from organic chemistry rather than from formalized pro-

grams of medicinal chemistry. While this particular glimpse is important to appreciate as a historical note in that it provides useful insights for the review's later discourse about the formalized training of future medicinal chemists, further references to medicinal chemistry throughout the remainder of this article intend to infer medicinal chemistry's practice as a discipline regardless of how a given investigator may have become trained to do so. Importantly, no matter how its practitioners were being derived, and even though it was still very much under-the-gun within the pharmaceutical industry, medicinal chemistry did continue to thrive quite nicely during this period and certainly moved forward significantly as a recognized discipline within all sectors.

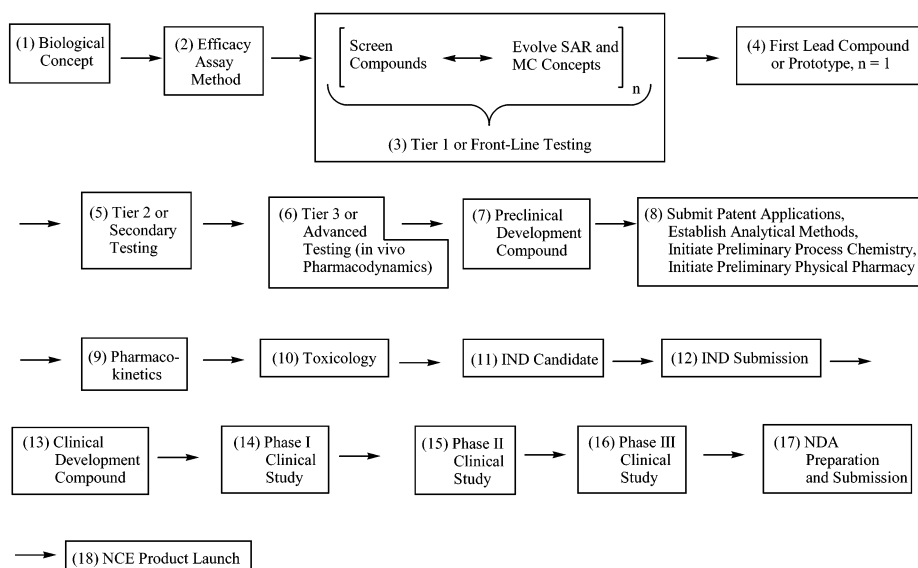
Arriving at the next historical segment, however, one finds that medicinal chemistry's inability to accelerate the discovery of new chemical entities (NCEs) by using rational drug design became greatly exacerbated when the biotechnology rainfall began to hover over the field of drug discovery just somewhat less than about 25 years ago [24]. With this development, not only did the number of interesting biological targets begin to rise rapidly, but also the ability to assay many of these targets in a high-throughput manner suddenly prompted the screening of huge numbers of compounds in very quick timeframes. Ultimately, the need to satisfy high-throughput screening's (HTS's) [25,26] immense appetite for compounds was addressed not by either of natural product or synthetic medicinal chemistry but by further developments within what had quickly become a flood-level, [27] continuing downpour of biotechnology-related breakthroughs. Starting as gene cassette-directed peptide libraries and quickly moving into solid-phase, randomly generated peptide and nucleotide libraries [28–32], this novel technology soon spread across other disciplines to eventually spawn the new field of small-molecule, combinatorial chemistry. Today, using equipment and platforms available from a variety of suppliers (e.g., Table 3), huge libraries of compounds can be readily produced in either a random or directed manner [33–40]. Once coupled with HTS, these paired technologies have prompted what has now come to be regarded as a new paradigm for the discovery of NCEs across the entire big pharma segment of the pharmaceutical enterprise [41–43]. Schemes 1 and 2 provide a side-by-side comparison of the old (classical) and new drug discovery paradigms, respectively.

**Table 3** Suppliers of combinatorial chemistry systems<sup>a</sup> and compound library trends<sup>b</sup>.

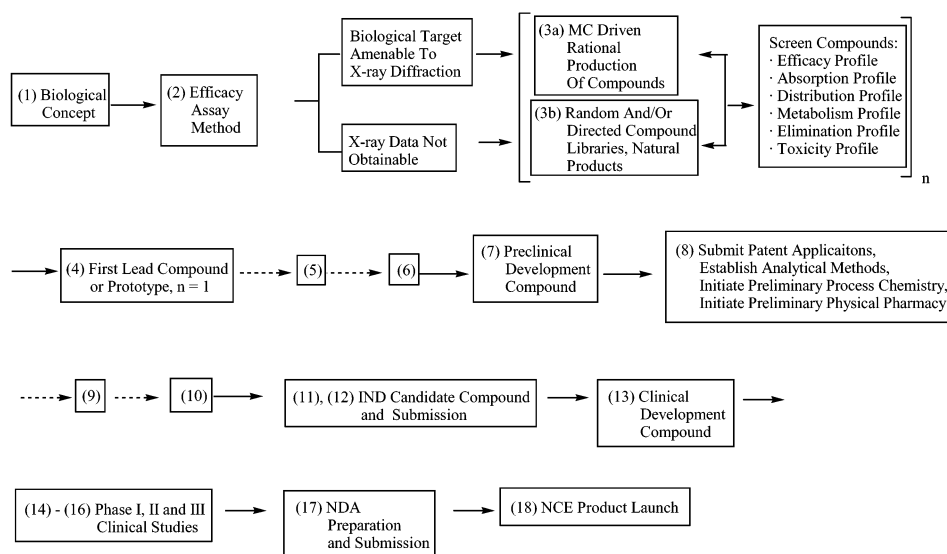
Vendor	Web address
Advanced Chem Tech	Peptide.com
Argonaut Technologies	Argotech.com
Bohdan Automation	Bohdan.com
Charybdis Technologies	Charybtech.com
Chiron Technologies	Chirontechnologies.com
Gilson	Gilson.com
PE Biosystems	Pebiosystems.com
Robbics Scientific	Robsci.com
Tecan	Tecan-us.com
Zymark	Zymark.com

<sup>a</sup> As largely reported in 1999 within an article by R. K. Brown [36].

<sup>b</sup> The number of reported libraries with or without disclosure of their biological activities has grown from only a few that were produced primarily by the private sector in the early 1990s to nearly 1000 in 1999 with nearly half of the latest total now being contributed by the academic sector [40]. Over this same period, the percentage of libraries directed toward unbiased discovery has gone from about 60 to 20 % while that for targeted/optimization of biased structural systems has risen from about 40 to 80 % [40].



**Scheme 1** Classical drug discovery and development paradigm [41,477–482]. This model portrays interactions with U.S. regulatory agencies and uses terms related to those interactions for steps 11 to 17. All of the other terms typify generic phrases that have been commonly used by the international pharmaceutical community. While some of the noted activities can be conducted in parallel or in an overlapping manner, the step-wise, sequential nature of this paradigm's overall process is striking. Furthermore, whenever a progressing compound fails to meet criteria set at an advanced step, the process returns or draws again from step 3 for another reiteration. Numerous reiterations eventually identify a compound that is able to traverse the entire process. A successful passage through the entire process to produce just one product compound has been estimated to require about 15 years at a total cost of about \$500 M. While the largest share of these time and cost requirements occur during the later steps, the identification of a promising preclinical development compound, step 7, can be estimated to take about 4 years from the time of initiating a therapeutic concept. Step 1 is typically associated with some type of physiological or pharmacological notion that intends to amplify or attenuate a specific biological mechanism so as to return some pathophysiology to an overall state of homeostasis. Step 2 typically involves one or two biochemical level assay(s) for the interaction of compounds intending to amplify or attenuate the concept-related mechanism. As discussed in the text, steps 3 and 4 reflect key contributions from MC and typically use all sources of available information to provide for compound efficacy hits, e.g., everything from natural product surveys to rational approaches based upon X-ray diffractions of the biological target. Step 5 generally involves larger *in vitro* models (e.g., tissue level rather than biochemical level) for efficacy and efficacy-related selectivity. Step 6 generally involves *in vivo* testing and utilizes a pharmacodynamic (observable pharmacologic effect) approach toward compound availability and duration of action. Step 7 typically derives from a formal review conducted by an interdisciplinary team upon examination of a formalized compilation of all data obtained to that point. Step 8 specifies parallel activities that are typically initiated at this juncture by distinct disciplines within a given organization. Step 9 begins more refined pharmacokinetic evaluations by utilizing analytical methods for the drug itself to address *in vivo* availability and duration of action. Step 10 represents short-term (e.g., two-week) dose-ranging studies to initially identify toxic markers within one or more small animal populations. Expanded toxicology studies typically progress while overlapping with steps 11 through 14. Steps 11 to 13 represent formalized reviews undertaken by both the sponsoring organization and the U.S. Food and Drug Administration (FDA). Step 14 is typically a dose-ranging study conducted in healthy humans. Steps 15 and 16 reflect efficacy testing in sick patients, possible drug interactions, etc. Step 17 again reflects formalized reviews undertaken by both the sponsoring organization and the FDA. The FDA's "fast-track" review of this information is now being said to have been reduced to an average of about 18 months. It is estimated that it costs a company about \$150 K for each day that a compound spends in development. Finally, step 18 represents the delivery of an NCE to the marketplace.



**Scheme 2** New drug discovery and development paradigm [41,477–482]. This model portrays interactions with U.S. regulatory agencies and uses terms related to those interactions for steps 11 to 17. All of the other terms typify generic phrases that are commonly used by the international pharmaceutical community. The battery of profiling included in step 3 represents a striking contrast to the classical drug discovery paradigm (Scheme 1). Furthermore, all of these screens are/will be of a high-throughput nature such that huge numbers of compounds can be simultaneously tested in extremely short time periods. As the predictive value of the resulting profiles improve, selected compounds will have higher and higher propensities to successfully proceed through steps 5, 6, 9, and 10 (Scheme 1) to the point that these assays may become more of a confirmatory nature or may even be able to be completely omitted (hence their dotted lines in Scheme 2) [483]. The efficiency of successfully traversing the various clinical testing steps 14 to 16 will also be improved, but their complete removal from the overall process is highly unlikely. After the initial investments to upgrade step 3 and enough time has passed to allow for the generation of knowledge from step 3's raw data results (see text for discussion), the overall time frame and cost for a single NCE to traverse the new paradigm should be considerably improved from the estimates provided in Scheme 1. Step 1 is likely to be associated with some type of genomic and/or proteomic derived notion that intends to amplify or attenuate a specific biological mechanism so as to return some pathophysiology to an overall state of homeostasis. Step 2 will be a high-throughput assay derived from using molecular biology and bioengineering techniques. In step 3a, MC = medicinal chemistry. Because step 3a exploits actual pictures of what type of structural arrangements are needed to interact with the biological targets, this approach toward identifying new compound hits will continue to operate with high efficiency. However, because of this same efficiency, the biological targets that lend themselves to such experimental depiction (by affording crystals suitable for X-ray diffraction) are likely to be quickly depleted very early into the new millennium. Step 3b represents various combinatorial chemistry-derived libraries, natural product collections, and elicited natural product libraries (see text for discussion of this topic). Steps 4 to 18 are similar to the descriptions noted in Scheme 1.

### 2.3 Present status

Interestingly, the marriage of HTS with combinatorial chemistry has led to a situation where identifying initial lead compounds is no longer considered to be a bottleneck for the overall process of drug discovery and development. Indeed, many of the programs within pharmaceutical companies are presently considered to be suffering from “compound overload” [44] with far too many initial leads to effectively follow up. ADMET assessments are now regarded as the new bottleneck, along with the traditionally sluggish clinical and regulatory steps. This situation, in turn, has prompted an emphasis to move ADMET-related parameters into more of an HTS format undertaken at earlier decision points. Thus,

even though efficacy-related HTS and combinatorial chemistry reflect very significant incorporations of new methodologies, *from a strategic point of view the most striking feature of the new drug discovery and development paradigm shown in Scheme 2, compared to the classical approach depicted in Scheme 1, actually becomes the trend to place ADMET-related assays closer to the beginning of the overall process* by also deploying HTS methods. Clearly, with the plethora of biologically based therapeutic concepts continuing to rise even further and the identification of lead compounds now being much quicker because of the HTS-combinatorial chemistry approach, a more efficient handling of ADMET-related concerns represents one of the most significant challenges now facing drug discovery and development. Because of its importance, this challenge is likely to be resolved within just the near term of the new millennium. Medicinal chemistry's critical role during this further evolution of the present drug discovery paradigm is highlighted in subsequent sections.

#### 2.4 Examples involving site-directed mutagenesis

While the drug discovery process has been influenced by biotechnology in numerous ways (e.g., Tables 4 and 5), one development deserves to be especially noted as this brief account of medicinal chemistry's history and present status is brought to a close. This development is already having a major impact directly upon the process of uncovering SARs relevant to small-molecule drug design [45]. The method involves site-directed mutagenesis (SDM). SDM applies to systematic point mutations directed toward specific sites on genes that translate to proteins associated with enzyme-active sites or drug receptor systems such that the targeted changes can be used to study SARs while holding one or more active site/receptor ligands constant during the assessment (Fig. 1). Numerous investigators are now utilizing this reverse SAR approach to explore both enzyme and receptor ligand interactions. Three examples are provided below wherein the site-directed mutagenesis studies have been further coupled with one or more of the latest analytical chemistry techniques such as microcalorimetry, as well as with sophisticated computational approaches. The first pair of examples involve the active sites of some isolable enzymes while the third example involves a nonisolable, membrane-bound receptor complex.

**Table 4** The impact of biotechnology on small-molecule drug discovery and development<sup>a</sup>.

Activity	Impact
Genomics and proteomics	Plethora of new and better defined mechanisms to pursue as therapeutic targets
High-throughput efficacy assays	Screen huge numbers of therapeutic candidates in short timeframes using low compound quantities
High-throughput ADMET assays	An evolving development: once validated and coupled with efficacy assays, should eventually allow for selection or drug design/synthesis of clinical candidate compounds rather than lead compounds that still require considerable preclinical testing and additional chemical tailoring
Peptide and oligonucleotide compound libraries	Provide huge numbers of compounds for screening (spawned the field of <i>combinatorial chemistry</i> as now applied to small organic compounds); can be used as SAR probes and, pending further developments in formulation and delivery, may also become useful as drug candidates
Site-directed mutagenesis	Allows "reverse" structure-activity relationship explorations

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**Table 4** (Continued)

Activity	Impact
Transgenic species	Novel in vivo models of pathophysiology that allow “pharmacological proof of principle” in animal models that mimic the human situation; and animal models modified to have human metabolism genes so as to provide more accurate PK data and risk assessment [442]
Peptide version of pharmacological prototype	Developed to the IND Phase as an i.v. agent can allow for “clinical proof of principle” or concept
Pharmacogenetics	An evolving development: should soon refine clinical studies, market indications/contraindications, and allow for subgrouping of populations to optimize therapeutic regimens; eventually should allow for classification of prophylactic treatment subgroups

<sup>a</sup>This listing is not intended to highlight the numerous activities associated with the development of specific “biotech” or large-molecule therapeutics, e.g., see Table 5. The arrangement of activities follows the order conveyed in Schemes 1 and 2, rather than being alphabetical.

**Table 5** Examples of approved<sup>a</sup> biotechnology-based drugs<sup>b</sup>.

Name <sup>®</sup>	Company	Clinical use
<b>Tissue plasminogen activators (tPAs)</b>		
Activase	Genentech	Dissolution of clots associated with myocardial infarction, pulmonary embolism, and stroke
Retevase	Boehringer-Mannheim; Centocor	
<b>Clotting factors</b>		
BeneFIX	Genetics Inst.	Treatment of various hemophilias
KoGENate	Bayer	
Recombinant	Baxter/Genetics Inst.	
<b>Ceredase-glucocerebrosidase</b>		
Cerezyme	Genzyme	Gaucher’s disease
<b>DNase</b>		
Pulmozyme	Genentech	Cystic fibrosis
<b>Insulins</b>		
Humalog	Eli Lilly	Insulin-sensitive diabetes
Humulin <sup>c</sup>	Eli Lilly	
Novolin	Novo Nordisk	
Novolin L	Novo Nordisk	
Novolin R	Novo Nordisk	
<b>Erythropoietin-related growth factors</b>		
Epogen	Amgen	Anemia associated with renal failure, chemotherapy, surgery, or loss of blood
Procrit	Ortho Biotech	

(continues on next page)

Table 5 (Continued)

Name <sup>®</sup>	Company	Clinical use
<b>Growth hormone</b>		
Biotropin	Bio-Tech. Gen.	Growth hormone deficiency in children* and for use in adults and in Turner's syndrome**; AIDS-related wasting and for pediatric HIV patients
Genotropin	Pharmacia & Upjohn	
Humatrope	Eli Lilly	
Neutropin*	Genentech	
Norditropin	Novo Nordisk	
Protropin	Genentech	
Saizen	Serono Labs	
Serostim**	Serono Labs	
<b>Growth hormone-releasing factor</b>		
Sermorelin	Serono Labs	Evaluation and use in pediatric growth hormone deficiency
<b>Platelet-derived growth hormone</b>		
Regranex	Ortho-McNeil	Lower extremity ulcers in diabetic neuropathy
<b>Fertility hormones</b>		
Gonal-F Serono	Female infertility	
<b>Interferon-alpha</b>		
Alferon N	Interferon Sci.	Genital warts*; Chronic hepatitis C infections**; Several antiviral and anticancer indications
Infergen*	Amgen	
Intron**	Schering-Plough	
Roferon-A**	Hoffman LaRoche	
<b>Interferon-beta</b>		
Avonex	Biogen	Multiple sclerosis
Betaseron	Berlex	
<b>Interferon-gama</b>		
Actimmune	Genentech	Chronic granulomatous disease
<b>Granulocyte-colony and macrophage-stimulating factor</b>		
Leukine	Immunex	Treatment of blood disorders during chemotherapy and blood cell/marrow transplants
Neupogen	Amgen	
<b>Interleukins</b>		
Neumega	Genetics Inst.	Thrombocytopenia subsequent to chemotherapy*; certain cancers
Proleukin*	Chiron	
<b>Monoclonal antibodies</b>		
CEA-scan	Immunomedics	Cancer diagnostic
Herceptin	Genetech	Breast cancer
MyoScint	Centacor	Cardia imaging agent
Neumega	Genetics Inst.	Prevention of chemotherapy-induced thrombocytopenia
OncoScint	Cytogen	Cancer diagnostic
Orthoclone	Ortho Biotech	Transplant rejection

(continues on next page)

**Table 5** (Continued)

Name <sup>®</sup>	Company	Clinical use
Prostascint	Cytogen	Cancer diagnostic
ReoPro	Lilly	Prevention of blood clots during angioplasty
Rituxan	Genetech; IDEC	Non-Hodgkin's lymphoma
Simulect	Novartis	Transplant rejection
Synagis	Med Immune	Respiratory syncytial virus disease
Vepluma	Boehringer-Ingelheim/NesRx	Cancer diagnostic
Zenapax	Hoffman-LaRoche; Protein Design Labs	Transplant rejection

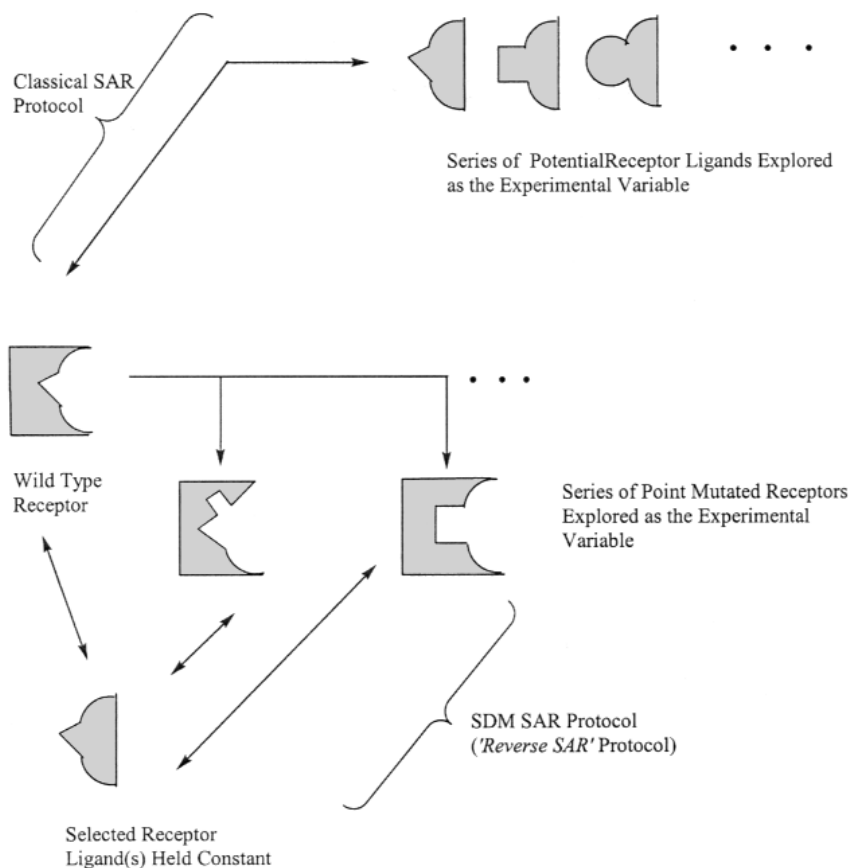
**Antisense nucleotides**

Vitravene	ISIS/Ciba	Retinitis
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<sup>a</sup>Prior to mid-year 1999 and as largely reported in the three-part series published in 1999 by R. Hudson and C. Black [6]. In comparison, a more recent survey reveals that about 375 additional agents were already in, or were nearing entry into, the clinical testing pipeline [443].

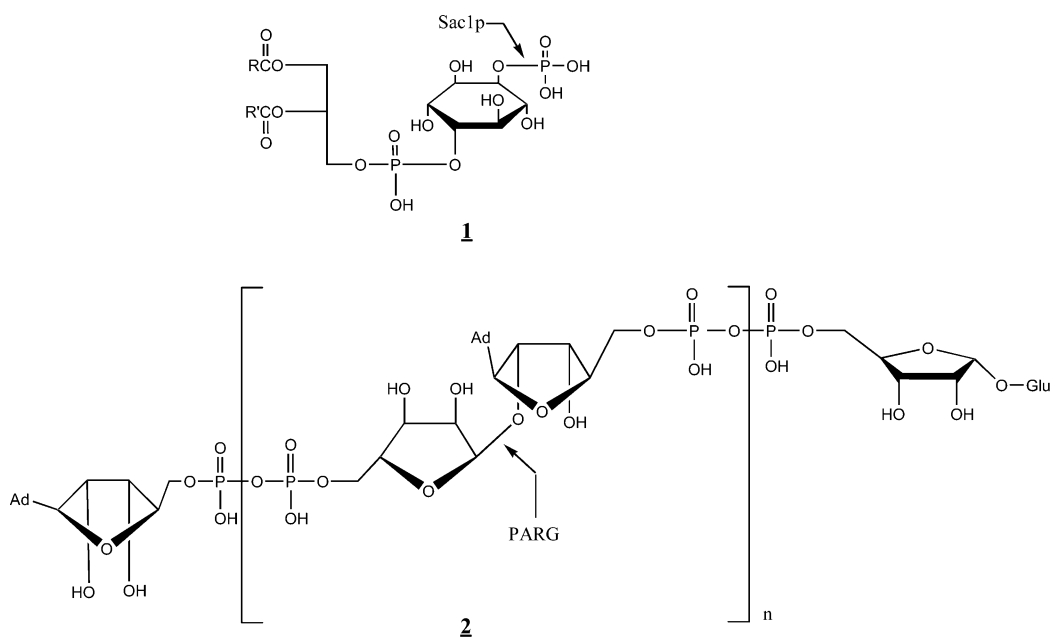
<sup>b</sup>These compounds have also been referred to as *new biological entities* or NBEs by analogy to *new chemical entities* or NCEs [441]. In general, NBEs use, recreate, or improve upon proteins and other biomolecular polymers produced in the body to counter disease [443].

<sup>c</sup>First recombinant-DNA-produced therapeutic protein to enter the market [6].

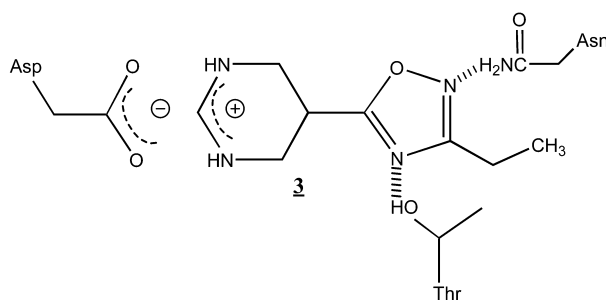
**Fig. 1** Classical vs. site-directed mutagenesis (SDM) exploration of structure–activity relationships (SARs).



Slama et al. have conducted studies involving a phosphatidylinositol-4-phosphate phosphatase (Fig. 2) designated as Sac1p [46]. With this enzyme's peptide sequence in hand, transformation of a bacterial host with an appropriate gene copy plasmid has allowed at least one point-mutated protein to be examined per month in a functional biochemical assay. While this particular example happens to represent a system that lends itself to over expression coupled with a functional protein product that lends itself to ready isolation, it clearly demonstrates that site-directed mutagenesis should no longer be considered to be lengthy and tedious compared to classical SAR studies undertaken by rational synthetic modifications of an enzyme's substrates. Slama et al. [47] are now studying poly(ADP-ribose)glycohydrolase or PARG (Fig. 2) to more definitively assign a tyrosine (i.e., Tyr<sup>796</sup>) to a key role within this enzyme's active site. Previously, this particular residue has only been able to be implicated as being important by using classical inhibitor and photoaffinity labeling studies [48,49]. In this case, one of the PARG assays deploys microcalorimetry measurement of the binding energies for a designated series of ligands that is then held constant as it is surveyed across the various mutant enzymes [50]. Similarly, Messer and Peseckis et al. have collaborated in several site-directed mutagenesis studies involving m1 muscarinic receptors [51–53]. These topographical mapping studies began as a follow-up to better define the receptor interactions exhibited by CDD-0102 (Fig. 3), a selective m1 agonist that is undergoing preclinical development for the potential treatment of Alzheimer's disease [54–56]. Interestingly, these investigator's more recent efforts have additionally turned toward addressing questions about the multivalent nature of m1 muscarinic receptors [57–60]. Thus, in this case the site-directed mutagenesis studies are helping to resolve fundamental issues about the nature of these receptors, as well as helping to implicate amino acid residues involved in the binding of agonists for the purpose of identifying drug structural themes having enhanced selectivity for certain of the receptor subtypes. In all of the m1-related studies, the site-directed mutagenesis results are being coupled to computational studies directed toward mapping the receptor's key topological features [61].



**Fig. 2** Cleavages effected by Sac1p and PARG [46–49]. **1** = Phosphatidylinositol-4-phosphate, wherein R and R' are fatty acid side chains. **2** = Poly (ADP-ribose), wherein Ad is adenine and Glu is glucose. In both cases, arrows indicate bonds undergoing enzymatic hydrolyses.



**Fig. 3** Suspected interactions of CDD-0102 with muscarinic M-1 receptors [51–53]. **3** = 5-(3-Ethyl-1,2,4-oxadiazol-5-yl)-1,4,5,6-tetrahydropyrimidine (CDD-0102) shown as its protonated species. Asn = Asparagine 382, Asp = Aspartic Acid 105, and Thr = Threonine 192. Dashed lines signify suspected hydrogen bonds.

## 2.5 Latest trends

As has been noted by others, the deployment of these new approaches toward studying SARs represents an “exciting” [62] development that has clearly had an invigorating effect upon the practice of medicinal chemistry in many areas. Alternatively, that the SAR hallmark and drug design intellectual domains of medicinal chemistry, along with chemically servicing the experimental approaches toward identifying novel, lead structures, have all been overrun by technologies initially derived from other disciplines, has also had somewhat of an unnerving impact upon medicinal chemistry. This is because it has previously been the nearly exclusive deliverance of these roles from a chemical orientation that has served to distinguish medicinal chemistry as a distinct discipline. Thus, as a field, medicinal chemistry has had to quickly mature from its troubled adolescence only to find itself in the middle of an identity crisis. This crisis has been occurring among both its private sector practitioners and its academicians. Indeed, today’s trend within the public sector funding arena, with a major emphasis upon genomics and proteomics, is causing some academic medicinal chemistry and chemistry investigators to turn their intellectual pursuits further and further toward molecular biology [63]. Likewise, the undergraduate instruction of pharmacy students, that has for so long represented medicinal chemistry’s academic bread and butter, has shifted its emphasis away from the basic sciences toward more of a clinically oriented curriculum. A final development that has contributed to medicinal chemistry’s identity crisis is the fact that the new drug discovery paradigm supplants medicinal chemistry’s long-standing position wherein its practitioners have typically been regarded as the primary inventors of the composition of matter specifications associated with NCE patent applications. This last development along with the overall IP arena of the future, is addressed in the summary section.

Although classical medicinal chemistry rationale, as alluded to earlier and as now practiced in tandem with SDM studies, is still being heavily relied upon to effectively identify and fine-tune lead compounds for systems whose biomolecules have lent themselves to X-ray diffraction and/or NMR analyses, i.e., structure-based drug design [64,65], medicinal chemists of the new millennium must be prepared to face the possibility that the present compliment of these more amenable pharmacological targets is likely to become quickly exploited, perhaps even eventually exhausted. Such a scenario, in turn, suggests that this last stronghold for today’s practice of rational medicinal chemistry could also be lost as a bastion against what could then potentially become an even more serious identity crisis in the future.

Present trends thus leave us with the following paradigm for the immediate future of small-molecule drug discovery (Scheme 2):

- (i) genomics and proteomics will continue to uncover numerous new pharmacological targets, i.e., to the extent that choosing the most appropriate and validating such targets among the many ther-

- apeutic possibilities will also continue to rise as a growing challenge in itself;
- (ii) biotechnology will, in turn, continue to respond by generating quick ligand-identification assays for all new targets chosen to be pursued, namely by deploying HTS protocols [66];
  - (iii) targets that lend themselves to X-ray diffraction and structure-based drug design are likely to be quickly exploited;
  - (iv) ligands for HTS will be supplied by existing and new combinatorial-derived compound libraries, as well as from wild [67] and biotechnology-elicited natural sources; and finally,
  - (v) assessment of ADMET parameters, presently considered to be the bottleneck for the overall drug discovery process (Table 6), will continue to move toward HTS modes that can be placed at earlier and earlier positions within the decision trees utilized to select lead compounds for further development as drugs.

It is important to emphasize at this juncture, that *in order to place confidence in the predictive value of ADMET HTS surveys, these particular screens must become validated relative to actual clinical-related outcomes*. For the moment, however, this situation is best likened to a deep, dark chasm that the rapidly evolving ADMET HTS surveys still need to traverse if they are to ultimately become successful. Nevertheless, because of its importance, it is proposed that not only will this type of validation be forthcoming within the near term, but as the new millennium then continues into the more distant future, ADMET-related parameters derived from HTS will become even further manipulated for their potential to allow for synergistic relationships within the overall course of a given therapeutic or prophylactic treatment. These intriguing future possibilities for exploiting ADMET-related parameters in a proactive and synergistic manner rather than in just a negative filtering mode, along with the likely move toward prophylactic medicines, are further discussed in subsequent sections.

*(text continues on page 723)*

**Table 6** Assessment of drug discovery and development bottlenecks [444–449].

Activity	Estimated time frame	Percentage successfully traversing associated criteria
Biological conception	A plethora of genomic/proteomic characterizations presently lies waiting to be exploited; this situation is expected to prevail well into the new millennium.	The challenge lies in prioritizing which of the numerous mechanisms might be best to pursue (see next entry).
Proof of therapeutic principle	Ultimately requires reaching Phase II clinical testing; BIOTECH derived humanized and/or transgenic disease state models may be able to be substituted at an earlier point depending upon the confidence associated with their validation.	Generally high, although there are some distinct therapeutic categories that continue to have low success rates or lack definitive validation such as the attempted treatments of septic shock or the pursuit of endothelin modulators.
Identification of lead compound based upon efficacy screen	Using HTS, thousands of compounds can be tested in a matter of days or less (10–100x more with UHTS); companies are beginning to have more lead compounds than they can move forward in any given program.	One compound out of 5000 from random libraries/one out of 10 from directed libraries; despite the low efficiency, this is not regarded as a bottleneck because HTS can be done so quickly; much higher percentages can be obtained during ligand-based and structure-based drug design but synthesis is then correspondingly slower.
Progression to preclinical development compound <sup>a</sup>	Approximately 2 years	About one out of 50 wherein all can be examined during the indicated time frame
Progression to clinical development compound <sup>d</sup>	Approximately 2 years	About one out of 10 wherein all can be examined during the indicated time frame
Phase I clinical study <sup>b</sup>	Approximately 1 year <sup>c</sup>	About one out of 2
Phase II clinical study <sup>b</sup>	Approximately 2 years <sup>c</sup>	About one out of 2
Phase III clinical study	Approximately 3 years <sup>c</sup>	About one out of 1.5 and often with modified labeling details
Product launch	Approximately 2 years (NDA submission/approval)	About one out of 1.5 <sup>d</sup>

<sup>a</sup>Presently regarded as the bottleneck for the overall process. These are the points where ADMET properties have been historically assessed. Approximately 40 % are rejected owing to poor pharmacokinetics and about another 20 % because they show toxicity in animals. In the new drug discovery paradigm (Scheme 2), the ADMET assessments are being moved to an earlier point in the overall process and are being conducted in an HTS mode. However, in most cases, validation of the new methods relative to clinical success still needs to be accomplished.

<sup>b</sup>While these studies may not be able to be accomplished any quicker, they may be able to be done more efficiently (e.g., smaller numbers and focused phenotypes within selected patient populations) and with a greater success rate based upon making the same improvements in the ADMET assessment area noted in footnote a.

<sup>c</sup>Timing includes generation and submission of formal reports.

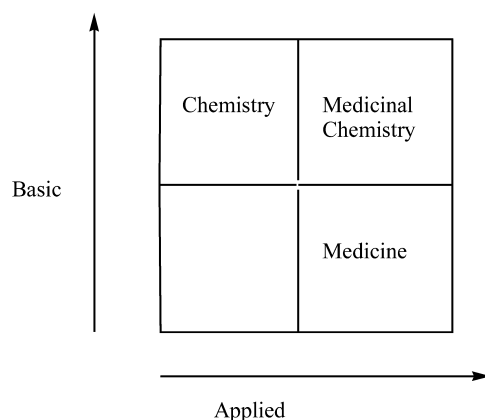
<sup>d</sup>About 1 out of 5 compounds entering into clinical trials becomes approved. The overall process to obtain one marketed drug takes about 12 to 15 years at a cost of about \$500 M.

### 3. EVOLVING DRUG DISCOVERY AND DEVELOPMENT PROCESS

#### 3.1 Working definition for medicinal chemistry

If the targets that are readily amenable to X-ray diffraction and structure-based drug design do become exhausted with time, the only title role presently highlighted for medicinal chemistry within the new paradigm of drug discovery will also disappear. To determine if medicinal chemistry will still be operative under such a circumstance, let us first review medicinal chemistry's present definition. Perhaps further attesting to medicinal chemistry's present identity crisis, however, is the fact that a purview of several of today's major medicinal chemistry texts reveals that although one can find topic-related versions of such within the context of various other discussions, even the textbooks seem reluctant to provide an explicitly stated, general definition for medicinal chemistry [e.g., 68–73]. Turning, instead, to this document's earlier consideration of medicinal chemistry's history, and for the moment disengaging ourselves from any biases that might be interjected by over-reacting to the continuing flood of biotechnology-related trends, it does become possible to devise a general, working definition for medicinal chemistry that can be used to address its present-day identity crisis while also serving in a search for any key roles that medicinal chemistry ought to be playing now and into the future of life science research.

As a working definition for this review, let us simply state that *medicinal chemistry uses physical organic principles to understand the interaction of small molecular displays with the biological realm*. Physical organic principles encompass overall conformational considerations, chemical properties, and molecular electrostatic potentials, as well as distinctly localized stereochemical, hydrophilic, electronic, and steric parameters. Understanding such interactions can provide fundamental, basic knowledge that is general, as well as compound-specific in its applications directed toward either enhancing the overall profile of a certain molecular display or designing an NCE, e.g., by effecting small molecule-driven perturbations of discrete biological processes or of overall biological pathways for the purpose of eliciting a specified therapeutic endpoint. Small molecular displays should be thought of in terms of low-molecular-weight compounds (e.g., usually less than 1 kg) that are typically of a xenobiotic origin and thus not in terms of biotechnology-derived polymers. While the latter are being aggressively addressed by other fields, it should be additionally noted that the consideration of specific details associated with the interaction of small molecular portions of more complex biomolecular systems still falls within the purview of medicinal chemistry's stated focus. Alternatively, the biological realm should be thought of very broadly, i.e., so as to encompass the complete span of new ADMET-related systems as well as the traditional span of biological surfaces that might be exploited for some type of efficacious interaction. The technologies that can be deployed as tools to study these interactions at medicinal chemistry's fundamental level of understanding are, by intent, dissociated from medicinal chemistry's definition. Presently, such tools include biotechnology-related methods such as site-directed mutagenesis, combinatorial chemistry methods provided that the latter are coupled with knowledge-generating structural databases (later discussion), and long-standing synthetic chemistry manipulations that can be conducted in a systematic manner on either one of the interacting species in order to explore SARs. In the future, medicinal chemistry should be equally prepared to exploit whatever new tools and techniques that become available to allow it to proceed more efficiently along the lines of its technology-independent definition. Finally, it should be appreciated that this definition merges both the basic and applied natures of medicinal chemistry's scientific activities into a key mix of endeavors for which a new research paradigm (Fig. 4) has also been recently proposed as being a significant trend [74], even if potentially "dangerous" in that it could compromise the longer-term pursuit of fundamental knowledge by bringing applied science decision criteria into the funding programs that have previously supported pure, basic science [75].



**Fig. 4** Nonlinear relationship of medicinal chemistry to basic and applied research. Adapted from a figure provided by F. A. Cotton [75] as part of his summary and commentary about a book entitled *Pasteur's Quadrant* [74]. Surveys suggest that chemical pharmaceutical companies spend about 9 %, 37 %, and 54 % of their research dollars on basic, applied, and developmental aspects of research, respectively [484].

### 3.2 Immediate and long-term roles for medicinal chemistry

Importantly, no matter what pace targets amenable to X-ray may continue to allow structure-based drug design to be pursued in the new millennium, applying the aforementioned definition across the present drug discovery paradigm reveals that there is an even more vital activity that medicinal chemistry needs to become more involved with. Indeed, as HTS results are amassed into mountains not just for efficacy data, but for each of the ADMET parameters as well, it should ultimately become medicinal chemistry's role, by definition, to attempt to understand and codify these awesome, crisscrossing ranges if such data is to be effectively merged and used to either select or design the most promising preclinical development compounds. For example, while medicinal chemistry's principles and logic may not be needed to identify hits or leads from a single HTS efficacy parameter survey across a library of potential ligands, or perhaps not even needed for two or three of such consecutive surveys involving a few additional ADMET-related parameters, it is extremely doubtful that the same series of compounds identified from within an initial library as a hit subset or as further generated within a directed library based upon the initial hit subset, will be able to sustain themselves as the most preferred leads upon continued HTS parameter surveys when the latter become ramped up to their full potential in the future. Furthermore, this should still be the case even if the downstream selection criteria become more and more relaxed through any of such progressions that ultimately strive to merge even a preliminary HTS-derived ADMET portfolio in conjunction with one or more selective efficacy HTS parameter surveys. In other words, the identification of the optimal end-product, namely the best preclinical candidate compound, is unlikely to be derivable from an experimental process that does not represent a "knowledge" [76,77] generating system that also allows for rational-based assessments and adjustments, or even complete revamping, to be interspersed at several points along the way. In the end, today's move toward "focused libraries" [78,79] and "smarter", presorted relational databases may thus represent a lot more than just the often-touted desire to "be more efficient" [80]. Indeed, this may be the only way for the new drug discovery paradigm, now in its own adolescent phase, to eventually work as it continues to mature and take on more of the ADMET-related considerations in an HTS format. In this regard it can now be emphasized that *the common denominator required to correlate the HTS data from one pharmacological setting to that of another ultimately resides in the precise chemical structure language that medicinal chemistry has been evolving since its emergence as a distinct field* (i.e., SAR defined in terms of physical organic properties displayed in 3D space). This,

in turn, suggests that within the immediate future of the new millennium *it should be medicinal chemistry that rises to become the central interpreter and distinct facilitator that will eventually allow the entire new drug discovery paradigm to become successful.*

This central role for medicinal chemistry may become even more critical longer term, i.e., for the next 50 to 75 years of the new millennium. Speculating that the new drug discovery paradigm will indeed mature within the next 25 years into a synergistic merger of efficacy and thorough ADMET HTS systems that allows for an effective multiparameter survey to be conducted at the onset of the discovery process, the accompanying, validated predictive data that will have been generated over this initial period should be statistically adequate to actually realize today's dream of "virtual" or "in silico screening" [81–86] through virtual compound and virtual informational libraries (not just for identifying potential efficacy leads to synthesize as is already being attempted, but across the entire pre-clinical portion of the new paradigm wherein the best overall preclinical candidate compound is selected with high precession for synthesis at the outset of a new therapeutic program) (Scheme 3). However, this futuristic prediction again depends upon the entire maturation process being able to proceed in a knowledge-generating manner. Central to the latter is again medicinal chemistry as the common denominator. For example, with time it can be expected that just as various pharmacophores and toxicophores have already been identified for various portions of the biological realm associated with efficacious or toxic endpoints, respectively, specific molecular properties and structural features will, likewise, become associated with each of the ADME behaviors. Indeed, work toward such characterizations is already progressing in all of these areas (Table 7). Understanding the pharmacophores, metabophores [22], toxicophores, etc. in terms of subtle differences in molecular electrostatic potentials (from which medicinal chemistry's physical organic properties of interest are derived) as well as in terms of simple chemical structural patterns, will eventually allow for identifying optimal composites of all of these parameters across virtual compound libraries as long as the latter databases have also been constructed in terms of both accurate 3D molecular electrostatic potentials and gross structural properties.

It should be clear that in order to effectively play this key, central role, the medicinal chemist of the new millennium (Fig. 5) will have to remain well versed in physical organic principles and conformational considerations while also becoming even more adept at applying them within the contexts of each of the ADMET areas as has previously been done during medicinal chemistry's pursuit of distinct efficacy-related biochemical scenarios. Because they will continue to represent part of the basic thrust of medicinal chemistry, the pursuit of efficacy into the new millennium and the assessment of molecular conformation are each further considered in the next two sections relative to medicinal chemistry's working definition. Likewise, because the nature of the ADMET area's maturation is regarded as being pivotal toward shaping medicinal chemistry's evolution in the new millennium, each of the ADMET areas are covered within a separate, fifth section. While space limitations dictate that these topics can be highlighted in only an abbreviated manner, a somewhat longer and more technically oriented discourse is provided for the molecular conformation section because it is envisioned that this area will constitute the alphabet for the universal language that medicinal chemistry will help to elaborate in order to bridge and ultimately unite all of the other areas.

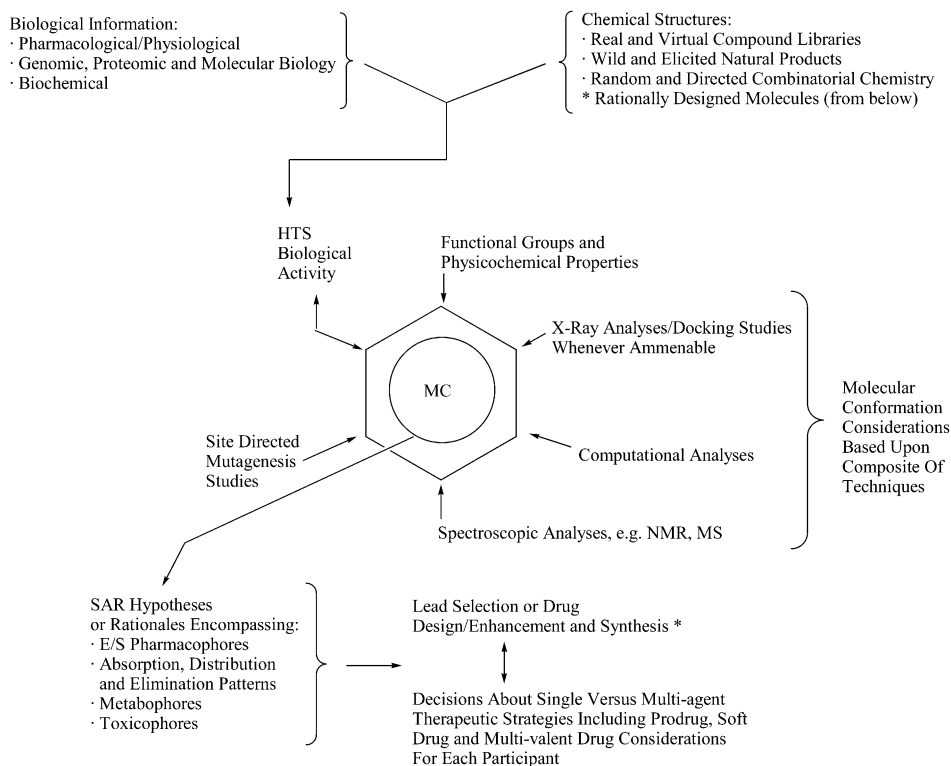




**Table 7** Examples of efforts to establish ADME-related structural patterns<sup>a</sup>.

ADME area	Parameters
Absorption	Physicochemical, e.g., log P, etc. [312,450] Functional groups, e.g., “rule of five” [311]
Distribution	Two-directional flows across Caco-2 cell monolayers [451]
Metabolism	2D structure-metabolism databases [452], e.g., <i>Metabol Expert</i> [453], <i>META</i> [454], <i>Metabolite</i> [455], and <i>Synopsis Metabolism Database</i> [456] 3D models, e.g., CYP1A [457], CYP2A [458], CYP2B [459], CYP2C [560], CYP2D [461,462], and CYP3A [463]
Elimination (half-lives, etc.)	Structural patterns across species [464] Physicochemical, e.g., log P, etc. [465,466]

<sup>a</sup>It is anticipated that the ADME informational area will soon become heavily inundated as pharmaceutical companies begin to share their rapidly accumulating data through publications in the public domain (analogous to what has happened historically for receptor/enzyme active site efficacy information but with the latter having had to previously transpire in a much slower fashion without the arrival of today’s HTS methodologies).



**Fig. 5** Practice of medicinal chemistry (MC) in the new millennium. The most striking differences from the long-standing practice of MC are: (i) data reduction of huge amounts of rapidly derived HTS biological results; (ii) greater emphasis upon multitechnique chemical structure considerations; and most importantly, (iii) the simultaneous attention given to all of the ADMET-related parameters along with efficacy and efficacy-related selectivity (E/S) during lead compound selection and further design or enhancement coupled with an expanding knowledge base that offers the possibility for achieving synergistic benefits by taking advantage of various combinations of multi-agent, prodrug, soft drug, and/or multivalent drug strategies.

#### 4. PURSUING EFFICACY

From an experimental point of view, medicinal chemistry's pursuit of the efficacy displayed by small molecules in a direct manner, probably won't change much in the near term beyond what has already been proposed in terms of logical extensions from some of the latest trends. For example, even the intriguing directions that are encompassed by "chemical genomic" [87] strategies where, in some cases, a small molecule may provide efficacy in an indirect manner though its interactions with biochemically modified genomics and proteomics signaling systems [88–90], still reduce down to being able to exploit the same fundamental principles already cited within medicinal chemistry's definition so as to achieve the specific interaction with the modified biological surface that then serves as a mediator toward efficacy.

In terms of targets, bioinformatics will certainly associate pathophysiology and individual variation with useful genomics and proteomics information so as to maintain the plethora of traditional and novel pharmacological targets well into the millennium [91–98]. Web-based public efforts [99] and commercial databases [100] coupled with desktop programs [101] are already being positioned to make such information readily available to everyone. The ability of infectious microorganisms and viruses to evolve into resistant forms at a pace at least equal to our ability to produce NCE chemotherapeutic agents can also be counted on to continually provide new targets [102,103]. Alternatively, longer term into the new millennium, gene therapy will hopefully have eradicated many of today's targets that derive strictly from hereditary, gene-based abnormalities [4]. Somewhat along these same lines, the ongoing characterization of single nucleotide polymorphisms (SNPs) and the further pursuit of individually tailored therapies, as presently being promoted by the new field of pharmacogenetics, may also contribute toward some new targets [104–111]. Web-based public and commercial databases in the pharmacogenetic [112] and specific SNP areas [113], along with commercial sources for the latter's experimental technologies [114], are also making this type of information generally available. In the near term, the field of pharmacogenetics is likely to have its first major impacts upon refining clinical studies for late-stage preclinical candidates and upon developing improved indications, contraindications, and dosage regimens for marketed drugs and for compounds undergoing clinical study. Longer term, however, pharmacogenetics should become instrumental in shaping the overall nature and subtleties of the efficacy targets that are pursued rather than the numbers of new targets that relate to novel mechanisms that might be deployed. For example, while one can speculate that the present trend to pursue curative rather than palliative treatments will continue for at least the short term, it is likely that in the longer term a growing emphasis will be placed upon preventative rather than either palliative or curative treatments [115,116]. Toward this end, pharmacogenetics should become of central importance owing to its potential to divide recipient populations into distinct treatment subgroups based upon their predisposition profiles coupled with their general ADMET-related drug handling profiles, wherein both sets of criteria may eventually become accessible before or shortly after birth using gene-based assays and to a lesser extent, administration of diagnostic probe molecules [117,118]. Depending upon the variability of an individual's environmental exposures, it can be imagined that in the future, pharmacogenetic profiling will be done at routinely scheduled intervals through the entire course of one's life. Regardless of the number and nature of future pharmacological targets, advances in biotechnology can be expected to continue to flood the overall life sciences arena and to get even better at deriving the required HTS assays. Alternatively, HTS micro-engineering [119], it would seem, may have to level off at about 9600-well (or well-less) tests per plate or, perhaps, move to other platforms involving chip or bead technologies [120].

##### 4.1 Gathering positive, neutral, and negative SARs during HTS

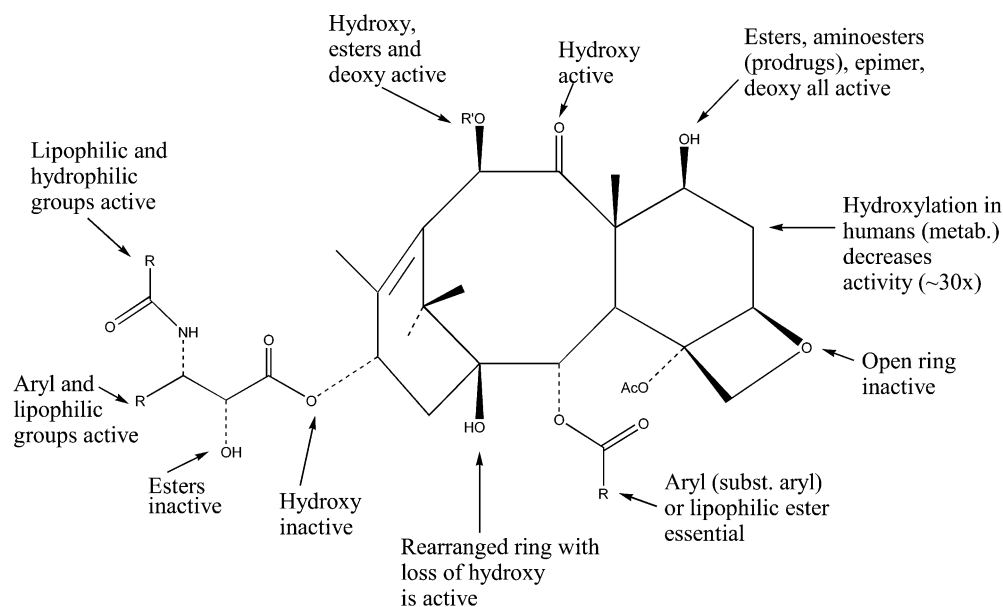
As mentioned, HTS efficacy hits, per se, can certainly be pursued without the aid of medicinal chemistry. Indeed, one can imagine that with one or more compound libraries already in hand from an auto-

mated synthesis [121], and the areas of robotics [122–124] and laboratory information management or LIMS [125] also continuing to rapidly evolve, HTS in the brute force mode may be able to essentially proceed without any significant human intervention, let alone without the need for an interdisciplinary group of investigators from a variety of disciplines. However, as has been emphasized, if the new drug discovery paradigm is to ultimately become successful, this type of screening will need to be accompanied by structure-associated knowledge generation and assessment, with the latter being conducted using the rationale and logic that can only be interjected by human intervention. Furthermore, even though it could run the risk of placing medicinal chemistry into a fall-guy position somewhat analogous to its earlier adolescent phase, it should also be noted that according to the working definition cited herein, as soon as any knowledge assessments become at all sophisticated in terms of molecular structure and biological properties, they quickly fall right into the middle of the domain of medicinal chemistry and its distinct area of expertise.

In this regard, it becomes important to briefly review some aspects about SARs that would be worthwhile to include within the database assemblies that are currently being drawn up to handle the mountains of data already arriving from today's HTS programs. One can predict that once ADMET profiling by HTS is validated in the future, it will become extremely valuable for a knowledge-generating paradigm to be able to discern not just the most active compounds within an efficacy database and to be able to compare their structural patterns to those in another database, but to also be able to flag the regions on compounds that can be altered with little effect upon the desired biological activity as well as those areas that are intolerant toward structural modification. The neutral areas, in particular, represent ideal points for seamless merging of one set of a database's hits with that of another regardless of the degree of pattern overlap, or for further chemical manipulation of a hit so as to adjust it to the structural requirements defined by another data set that may be so distant in structural similarity space that attempted overlap or pattern recognition routines are otherwise futile. The regions that are intolerant of modification represent areas to be avoided during knowledge-based tailoring of an efficacy lead. Alternatively, the intolerant regions represent areas that can be exploited when attempting to negate a particular action, e.g., metabolism or toxicity. An actual example of utilizing both neutral and negative SARs to advantage is provided below to further illustrate how these types of data sets might also be simultaneously deployed by future medicinal chemists (albeit with significantly stepped-up complexity) as more and more parameters become added to the process of early lead identification/optimization.

#### 4.2 Example involving multidrug resistance of anticancer agents

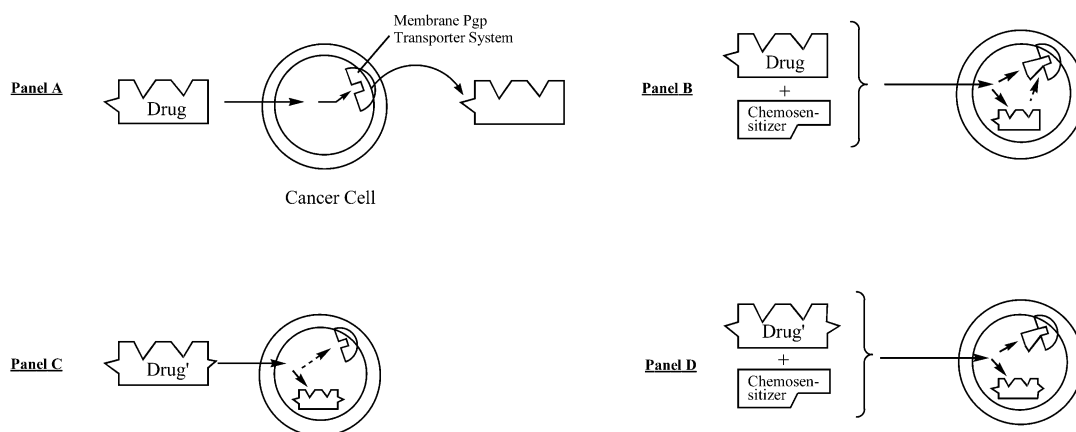
The investigations to be exemplified in this case have been directed toward studying the SAR associated with biological transporter systems with the hope of establishing a database of transportophore relationships that might be generally applicable toward enhancing the selection and/or development of efficacy leads from any type of other data set. To provide immediate relevance to this long-term project, it has initially focused upon the P-glycoprotein pump (Pgp) [126,127] that is associated, in part [128,129], with the development of multidrug resistance (MDR) [130,131] during cancer chemotherapy. Pgp is a 170 kD transmembrane glycoprotein that serves as an energy-dependent, uni-directional efflux pump having broad substrate specificity. In humans it is encoded by the MDR gene, MDR1, whose classical phenotype is characterized by a reduced ability to accumulate drugs intracellularly, and thus the deleterious impact of Pgp activity upon cancer chemotherapy [132–136]. By way of practical example, the cytotoxicity of paclitaxel (PAC) is decreased by nearly three orders of magnitude when breast cancer cell lines become subject to MDR, largely via a Pgp mechanism [137]. In order to explore a series of probes that will systematically span a specified range of physicochemical properties when coupled to the PAC framework, one needs to first identify a region on PAC that is tolerant toward such modification in terms of PAC's inherent efficacy, i.e., where changes are known to not significantly alter PAC's cytotoxicity toward nonresistant breast cancer cells. Figure 6 provides a summary of the accumulated SAR data obtained from the PAC-related review literature [138–142], wherein it becomes clear



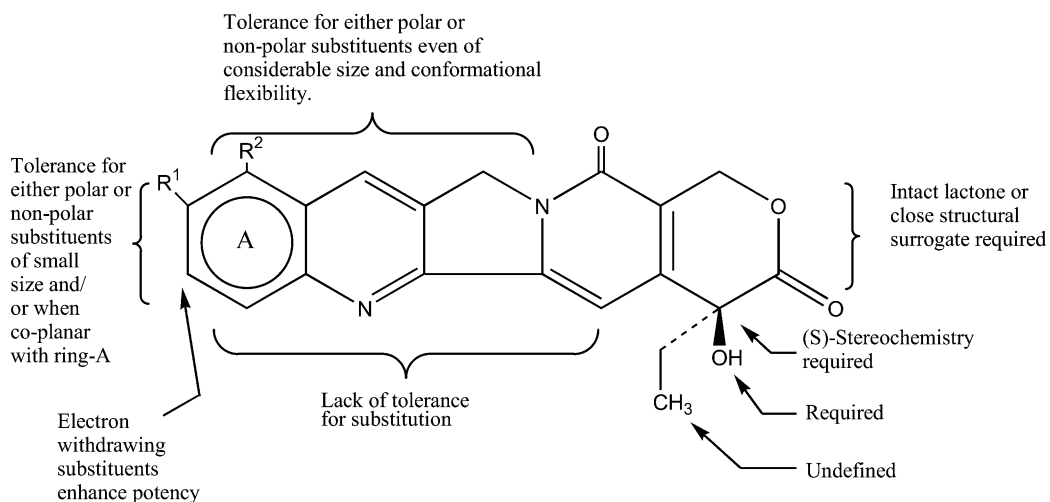
**Fig. 6** Overall SAR profile for paclitaxel-related compounds. This summary represents a consolidation of SAR information contained in several review articles [138–142]. Note the tolerance for structural modification along the northern hemisphere of the taxane ring system. Paclitaxel has  $R = \emptyset$  and  $R' = \text{CH}_3\text{CO}$ .

that several positions along the northern edge represent neutral areas that can lend themselves toward such an exploration.

Inhibitors of Pgp have already been identified by several different investigators, and these types of compounds belong to a class of agents referred to as chemosensitizer drugs for which there are a variety of mechanisms [143,144]. While Pgp inhibitors can be coadministered with a cytotoxic agent in order to negate MDR toward the latter when studied in cell culture, to date these types of chemosensitizers have not fared well clinically [145]. One of the reasons that the inhibitors have not fared well is that they must compete with the accompanying cytotoxic agent for access to the Pgp MDR receptors. Thus, it can be imagined that if an SAR can be identified that is unfavorable for binding with Pgp MDR receptors and, furthermore, that if such a negative transportophore could be incorporated onto the original cytotoxic agent in a neutral position, then the cytotoxic agent might itself avoid MDR or at the very least become better equipped to do so in the presence of a coadministered Pgp MDR inhibitor (Fig. 7) [146]. Toward this end, initial studies are being directed toward exploring the possibility that it may be feasible to identify negative SAR that is undesirable to the Pgp system within the specific chemical context of PAC by manipulating the latter at neutral positions that do not significantly affect PAC's inherent efficacy. To ascertain the generality toward potentially being able to place such a negative transportophore onto other established chemotherapeutic agents and onto lead compounds being contemplated for preclinical development, an identical series of negative SAR probes is being examined within the context of a completely different molecular scaffold, namely that of the camptothecin (CPT) family of natural products for which topotecan represents a clinically useful anticancer drug [147]. CPT, accompanied by a summary account of its SAR-related literature [138,147–170], is depicted in Fig. 8, wherein it becomes clear that the 7- and 9-positions represent the key neutral areas in CPT that might be manipulated analogously to those in PAC. Since these two compounds have very different molecular templates and owe their cytotoxicities to two distinctly different mechanisms (i.e., PAC largely, but not exclusively [171–173] to overstabilization of microtubules [174,175] and CPT largely, but not exclusively [176], to “poisoning” of Topoisomerase I [177]), and because topotecan, a



**Fig. 7** Diminishing the Pgp transporter's role in multidrug resistance (MDR). Panel A: Extrusion of chemotherapeutic agents (drug) by cancer cells upon overexpression of the Pgp transporter system is one mechanism associated with MDR. Panel B: Coadministration of a chemotherapeutic agent and a chemosensitizing agent wherein the latter preferentially interacts with Pgp, thus diminishing the extrusion of the desired drug. The chemosensitizer may block the pump competitively (wherein it becomes extruded) or noncompetitively. Panel C: Administration of a modified chemotherapeutic agent (drug') that retains its desired efficacy-related properties but has a diminished affinity for the Pgp system. Panel D: Coadministration of a modified chemotherapeutic agent and a chemosensitizing agent such that the latter has a better chance of interacting with the Pgp system relative to the desired chemotherapeutic agent.



**Fig. 8** Overall SAR profile for camptothecin-related compounds. This summary represents a consolidation of SAR information contained in several primary references [138,147–170]. Note the tolerance for structural modification along the northern hemisphere of the overall molecule, especially when approaching the western edge. Camptothecin, the parent natural product, has  $R^1 = R^2 = H$ . Topotecan, used clinically, has  $R^1 = OH$  and  $R^2 = CH_2N(CH_3)_2$ .

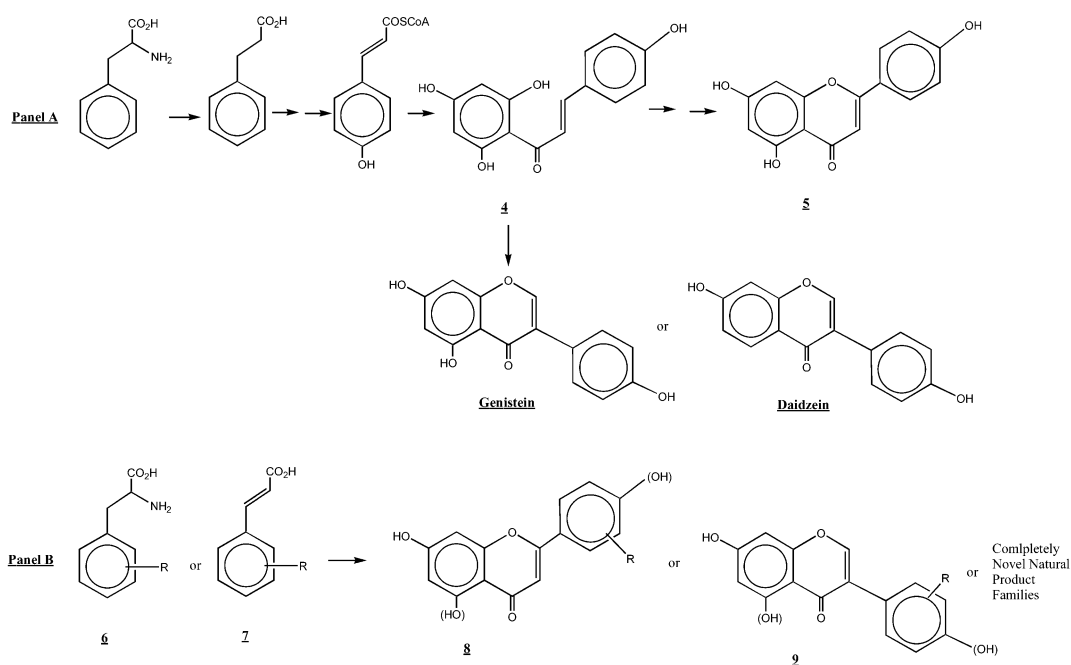
clinically deployed CPT analog (Fig. 8), is at the lower end of the spectrum in terms of being subject to Pgp-related MDR (it loses about one order of magnitude from its initial potency [137]), taken

together these two molecules represent an excellent pair to examine the generality of the transportophore-related SAR findings. Other molecular scaffold systems and biological testing models can also be imagined so as to extend such Pgp investigations into the areas of drug absorption, uptake into hepatic tissue (drug metabolism), and passage across the blood–brain barrier (e.g., for either enhancing or attenuating drug penetration into the CNS). Likewise, additional transporters within the ABC class can be systematically explored by using a similar approach.

Although this particular example reflects a rational SAR strategy, the same types of informational endpoints can certainly be achieved via a coupled HTS/combinatorial chemistry approach providing that the chemical structure components within the resulting databases are initially constructed with architectures flexible enough to allow for such queries. Likewise, while this example reflects a simple query between two different biological behaviors, the same types of queries can be conducted across multiple databases for multiple parameters. That the next 25 years of medicinal chemistry will involve a considerable amount of making sense out of such multiple parameter correlations based upon experimentally derived data is quite clear. That the next 50 to 75 years might then be able to be fruitfully spent in more of a virtual correlations mode is certainly more speculative but is, at least, probably reasonable providing that we can build our knowledge base and fundamental understanding of how the various parameters, as assessed in isolation according to the above HTS scenarios, interact simultaneously within the whole system.

### **4.3 Compound libraries: Example of working with nature to enhance molecular diversity**

Before closing this section, two additional trends need to be mentioned. The first involves the likelihood that industry will even more heavily embrace site-directed mutagenesis as an additional component of its efforts to identify lead compounds. Such modification can be contemplated during the initial development of an HTS assay and then used to contribute to the definition of an overall pharmacophore as the latter is probed via various compound testing paradigms. The importance of gaining a thorough appreciation for the overall pharmacophore rather than for just identifying distinct lead structures is discussed in later sections. The second trend in the efficacy arena that is also likely to become very important in the future can be illustrated by an example from a different research program. Instead of focusing on ADMET-related parameters during rational drug design, this program involves the chemical or library side of the new drug discovery paradigm. In particular, this example seeks to enhance molecular diversity [178,179] along phytochemical structural themes that have shown activity of either a toxic [180] or promising nature during initial efficacy screening such that having related compound libraries would be highly desirable. As described below, this particular example has a certain appeal in its ultimate practicality since it initially seeks to produce directed molecular diversity within common plants indigenous to the midwestern United States. This possibility is being explored by simultaneously exposing plants to both an elicitor (botany's designation for an inducing agent) and selected biochemical feedstocks. For example, the biochemical pathways leading to the anticancer phytoalexins from soybeans shown in Fig. 9, may be able to be elicited by soybean cyst nematode infections to produce a more diverse family of active principles when grown in environments containing biochemically biased nutrients [181,182]. Toward this end, it has been established that the statistical reproducibility of HPLC-derived phytochemical constituent fingerprints from soybean controls is adequate to discern real fluctuations in these types of natural products [183]. Work is now progressing toward ascertaining the differences that result upon exposures of soybeans to various stimuli and feedstocks. Interesting results will be followed up by studying the genetic control of the involved pathways. In this regard it should be additionally noted that an opposite approach that leads to similar, "combinatorial biosynthesis" [184] endpoints, is also being undertaken by various other groups, particularly with an interest toward the production of proteins and peptide families from plant systems [185]. In those studies, directed modification of the genetic regions controlling one or more established phytochemical pathways is first effected,



**Fig. 9** Elicitation of directed and novel natural product families from soybean. Panel A: Normal biochemical pathways leading to the flavones (5) and to the key anticancer isoflavones genistein and daidzein wherein phenylalanine is first converted to cinnamic acid, p-coumaroyl CoA, and finally to key intermediate 4, naringenin chalcone. Panel B: Feeding unnatural starting materials such as the aryl-substituted phenylalanine and cinnamic acid derivatives shown as 6 and 7, respectively, under circumstances where this pathway is also being elicited by external stimuli (e.g., soybean cyst nematode infections), could be expected to produce new flavone derivatives (8), isoflavone derivatives (9), or completely novel natural product families. This diagram of the phytochemical pathway leading to flavones and isoflavones represents a composite of several references [485–487]. An array of inexpensive analogs related to 6 and 7 is available from commercial sources.

and then these types of biotechnology interventions are followed up by characterization of the altered, biocombinatorial expression products.

## 5. ASSESSING AND HANDLING MOLECULAR CONFORMATION

### 5.1 Chemoinformatics

Given the exponential proliferation of technical data and our increasing ability to rapidly disseminate it through a vast maze of electronic networks, it is no wonder that new systems capable of “managing and integrating information” [186] are regarded among “the most important of the emerging technologies for future growth and economic development across the globe” [186,187]. That “information technology” (IT), in turn, is now receiving high priority in all sectors is quite clear [188–195], particularly with regard to systems directed toward integrating bioinformatic-related information as promoted via the World Wide Web [196]. Medicinal chemistry’s contributions toward this sweeping assessment of the future importance of IT primarily reside in the area of handling chemical structures and chemical information, a specialized exercise complicated enough to merit its own designation as a new field, namely that of chemoinformatics [197–200]. In this regard, the increasing use of databases to link chemical structures with biological properties has already been alluded to in terms of both real experimental data sets and virtual compilations. While serious strides are being taken in this area, however, there is a sig-

nificant need for improvement in the handling of chemical structures beyond what is suggested for the immediate future by what now appears to be occurring within today's database assemblies. For example, that "better correlations are sometimes obtained by using two-dimensional displays of a database's chemical structures than by using three-dimensional displays" only testifies to the fact that we are still not doing a very good job at developing the latter [201]. How medicinal chemistry must step up and rise to the challenges already posed by this situation in order to fulfill the key roles described for its near- and longer-term future, are addressed within the next several paragraphs of this section.

Assessment of molecular conformation, particularly with regard to database-housed structures, represents a critical aspect of chemoinformatics. While new proteins of interest can be addressed reasonably well by examining long-standing databases such as the Protein Data Bank [202], and other Web-based resources [203] for either explicit or similar structural motifs and then deploying X-ray (pending a suitable crystal), NMR, and molecular dynamic/simulation computational studies [204–209] as appropriate, the handling of small molecules and of highly flexible molecular systems in general, remains controversial [210]. As alluded to above, the only clear consensus is that treatments of small molecules for use within database collections "have, to date, been extremely inadequate" [211]. Certainly, a variety of automated, 3D chemical structure drawing programs are available that can start from simple 2D representations by using Dreiding molecular mechanics or other, user-friendly automated molecular mechanics-based algorithms, as well as when data is expressed by a connection table or linear string [212]. Some programs are able to derive 3D structure "from more than 20 different types of import formats" [213]. Furthermore, several of these programs can be directly integrated with the latest versions of more sophisticated quantum mechanics packages such as Gaussian 98, MOPAC (with MNDO/d), and extended Huckel [200,212]. Thus, electronic handling of chemical structures, and to a certain extent comparing them, in 3D formats has already become reasonably well worked out [197–200,212–215]. Table 8 provides a listing of some of the 3D molecular modeling products that have become available during the 1990s [214].

Nevertheless, the fundamental problem still remains as to how the 3D structure is initially derived in terms of its chemical correctness based upon what assumptions might have been made during the process. Further, there are still challenges associated with how readily 3D structure information can be linked with other, nonchemical types of informational fields. As has been pointed out by others, the reason that such mingling of data fields often does not afford good fits is because "each was initially designed to optimize some aspect of its own process and the data relationships and structures are not consistent" [197]. At this point, inexpensive Web-based tools that can integrate chemical structure data with other types of information from a variety of sources, including genomic data, have already begun to emerge [216]. This trend will continue to pick up into the new millennium, and because of its overall importance for bioinformatics, user-friendly solutions are likely to arrive early on.

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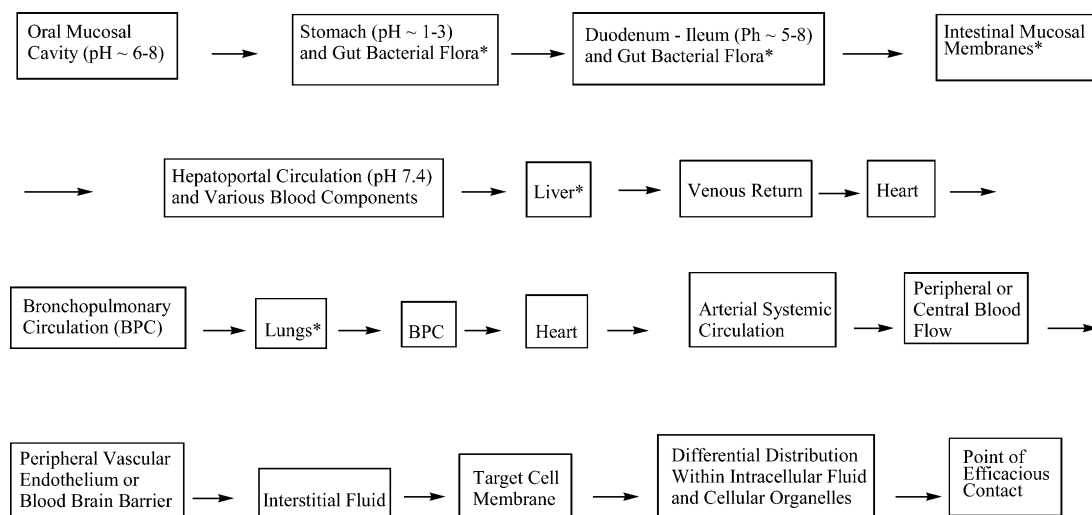
**Table 8** 3D molecular modeling packages that became available during the 1990s [214].

Package	Company	Platform	Description
<b>Low-end sophistication</b>			
Nano Vision	ACS Software	Mac	Simple, effective tool for viewing and rotating structures, especially large molecules and proteins
Ball & Stick	Cherwell Scientific	Mac	Model building and visualization; analysis of bond distances, angles
MOBY	Springer Verlag	IBM (DOS)	Model building and visualization; classical and quantum mechanical computations; large molecules and proteins; PDB files
Nemesis	Oxford Molecular	IMB (Windows), Mac	Quick model building and high-quality visualization; geometry optimization (energy minimization)
CSC Chem. 3D/ Chem 3D Plus	Cambridge Scientific	Mac	Easy-to-use building and visualization; geometry optimization; integrated 2D program and word processing
Alchemy III	Tripos Assoc.	IBM (DOS, Windows), Mac	Quick model building; energy minimization; basic calc.; easy integration to high-end systems
PC Model	Serena Software	IBM (DOS), Mac	Low cost with sophisticated calc.; platform flexibility
<b>Mid-range sophistication</b>			
CAChe	Tektronic	Mac	Sophisticated computation tools; distributed processing
HyperChem	Auto Desk	IBM (Windows), Silicon Graphics	Easy-to-use array of computation tools (classical and semi-empirical quantum mechanics)
Lab Vision	Tripos Assoc.	IBM (RISC-6000), Silicon Graphics, DEC, VAX	Sophisticated but practical modeling for research
<b>High-end sophistication</b>			
SYBL	Tripos Assoc.	IBM (RISC-6000), Silicon Graphics, DEC VAX, Sun 4, Convex	Integrated computation tools for sophisticated structure determination and analysis; database management
CERIUS	Molecular Simulations	Silicon Graphics, IBM (RISC-6000), Stardent Titan	Suite of high-performance tools for building and simulating properties

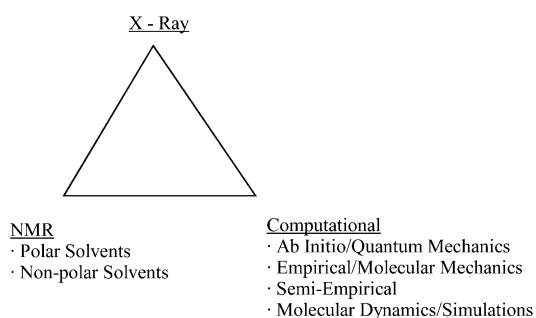
## 5.2 Obtaining chemically correct 3D structures

Unfortunately, the quick assignment of chemically correct 3D structures may not be readily solvable. Recalling from the first sections of this document, medicinal chemistry has been concerning itself with this task for quite some time. Medicinal chemistry's interest in chemical structure is further complicated, however, by the additional need to also understand how a given drug molecule's conformational family behaves during its interactions with each of the biological environments of interest. For example, as a drug embarks on its "random walk" [217] through the biological realm (Scheme 4), the ensuing series of interactions have unique effects upon each other's conformations [218,219] at each step of the journey and not with just the step that finally consummates the drug's encounter and meaningful relationship that is struck with its desired receptor/active site.

In order to track such behavior in a comprehensive manner, it becomes necessary to consider a drug's multiple conformational behaviors by engaging as many different types of conformational assessment technologies as possible, while initially taking an approach that is unbiased by any knowledge that may be available from a specific interacting environment. For example, the three common approaches depicted in Fig. 10 include: (i) X-ray (itself prone to bias from solid-state interactions within the crystal lattice); (ii) solution spectroscopic methods, namely NMR, which can often be done in both polar and nonpolar media (this technique, however, being more limited by the amount of descriptive data that it can generate); and (iii) computational approaches that can be done with various levels of solvation and heightened energy content (limited, however, by the assumptions and approximations that need to be taken in order to simplify the mathematical rigor so as to allow solutions to be derived in practical computational time periods). Analogous to the simple, drawing program starting points, programs are also available for converting X-ray and NMR data into 3D structures [e.g., 220]. While such a three-pronged approach is not new [221], it is emphasized herein because today's medicinal chemistry literature suggests that some investigators still fall into the single technique trap from which fur-



**Scheme 4** Random walk [217] taken by an oral drug on route to its point of efficacious contact within a human target cell. This continuum of interactions between a drug and various biological surfaces within the human biological realm is typically divided into categories associated with ADMET and efficacy. Biological milieu marked with an asterisk represent compartments having particularly high metabolic capabilities. Blood is notably high in esterase capability. In the future, medicinal chemists will utilize knowledge about ADMET-related SARs to more effectively identify the best drug leads and to further enhance the therapeutic profiles of selected compounds.



**Fig. 10** Techniques employed to assess conformational detail. X-ray diffraction requires a suitable crystal, and its results are subject to solid-state interactions. Computational paradigms are most accurate when done at the highest levels of calculation but these types of calculations become computer-time intensive. NMR requires that the molecule be soluble in the chosen solvent and that adequate compound supplies be available. Mass spectrometry is also becoming an important tool for larger molecules although it provides smaller amounts of descriptive data. A composite of all approaches provides for the best possible assessment of molecular conformation.

ther extrapolations of data are then sometimes made with great conviction. This may be because it is often difficult to obtain an acceptable crystal for X-ray analysis, have adequate solubility for highfield conformational analysis by NMR, or perhaps, to become aligned with appropriate computational expertise and computing power. At any rate, practical advances in all three of these areas as the new millennium progresses can be expected to alleviate such implementation-related shortcomings so that the medicinal chemist of the near-term future will be more readily able to consider structures from at least a three-pronged starting point either independently or, more appropriately, through collaboration with other specialists and experts dedicated to each of these areas. A real example that serves to further illustrate how entry structures might be handled and matured using a computational approach is provided below. This problem pertains to the consideration of structures to be placed within a human drug metabolism database [221].

### 5.3 Influence of biological environments: Example involving drug metabolism

Structures are initially considered as closed-shell molecules in their electronic and vibrational ground states with protonated and unprotonated forms, as appropriate, also being entered. If a structure possesses tautomeric options or if there is evidence for the involvement of internal hydrogen bonding, then the tautomeric forms and the hydrogen-bonded forms are additionally considered from the onset. Determination of 3D structure is carried out in two steps. Preliminary geometry optimization is affected by using a molecular mechanics method. For example, in this case the gas-phase structure is determined by applying the MacroModel 6.5 modeling package running on a Silicon Graphics Indigo 2 workstation with modified (and extended) AMBER parameters also being applied from this package. Multiconformational assessment using systematic rotations about several predefined chemical bonds with selected rotational angles is then conducted to define the low-energy conformers and conformationally flexible regions for each starting structure. In the second step, the initial family of entry structures are subjected to ab initio geometry optimizations, which in this case use a Gaussian 98 package running on a T90 machine housed in a state-level supercomputer center resource. Depending upon the size of the molecule, 3-21G\* or 6-31G\* basis sets [223] are used for conformational and tautomeric assessments. Density functional theory using the B3LYP functional [224] is applied for the consideration of exchange correlation energy while keeping the required computer time at reasonable levels. The highest-level structure determination is performed at the B3LYP/6-31G\* level. To ascertain the local

energy minimum character of an optimized structure, vibrational frequency analysis is carried out using the harmonic oscillator approximation. Determination of vibrational frequencies also allows for obtaining thermal corrections to the energy calculated at 0 °K. Free energies are then calculated at 310 °K (human body temperature). The latter values become particularly important for cases where structural (conformational or tautomeric) equilibria occur.

From the calculated relative free energies, the gas-phase equilibrium constant and the composition of the equilibrium mixture can be directly determined. Although these values may not be relevant in an aqueous environment or in the blood compartment, the calculated conformational distribution is relevant for nonpolar environments such as may be encountered when a drug passively traverses membranes or enters the cavity of a nonhydrated receptor/enzyme active site just prior to binding. Repetition of this computational scheme from biased starting structures based upon actual knowledge about the interacting biological systems or from X-ray or NMR studies (particularly when the latter have been conducted in polar media), followed by studies of how the various sets of information become interchanged and how they additionally behave when further raised in energy, complete the chemical conformational analysis for each structure being adopted into the human drug metabolism database.

As mentioned earlier, after taking an unbiased structural starting point, medicinal chemistry needs to especially consider structures (and the energies thereof) by ascertaining what their relevant conformations might be during interactions within various biological milieus. It can be imagined that at least within the immediate future, a useful range of such media to be considered will include: aqueous solutions at acidic and neutral pH, namely at ca. 2 (stomach) and 7.4 (physiological), respectively; one or more lipophilic settings, such as might be encountered during passive transport through membranes; and finally, specific biological receptors and/or enzyme active site settings that are of particular interest. Importantly, with time this list can then be expected to further grow so as to also include: several distinct environmental models deemed to be representative for interaction with various transportophore relationships; several distinct environmental models deemed to be relevant for interaction with specific metabophore relationships such as within the active site of a specific cytochrome P450 metabolizing enzyme; and finally, several distinct environmental models deemed to be relevant for interaction with specific toxicophore relationships. It should also be appreciated that the interaction of even just one ligand within just one of the various biological settings could still involve a wide range of conformational relationships wherein the biological surface may also exist as an equilibrium mixture of various conformational family members. If X-ray, NMR, etc. can be further deployed to assess any one or combination of these types of interactions, then a composite approach that deploys as many as possible of these techniques will again represent the most ideal way to approach future conformational considerations within the variously biased settings. Advances toward experimentally studying the nature of complexes where compounds are docked into real and model biological environments are proceeding rapidly in all of these areas, with MS [11–13] and microcalorimetry [14–15] also now adding themselves alongside X-ray (later discussion) and NMR [225,226] as extremely useful experimental techniques for the study of such SARs. Besides the experimental approaches, computational schemes will likely always be deployed because they can provide the relative energies associated with all of the different species. Furthermore, computational methods can be used to derive energy paths to get from the first set of unbiased structures to a second set of environmentally accommodated conformations in both aqueous media and at biological surfaces. Importantly, these paths and their energy differences can then be compared along with the direct comparison of the structures themselves, while attempting to uncover and define correlations between chemical structure and some other informational field within or between various databases.

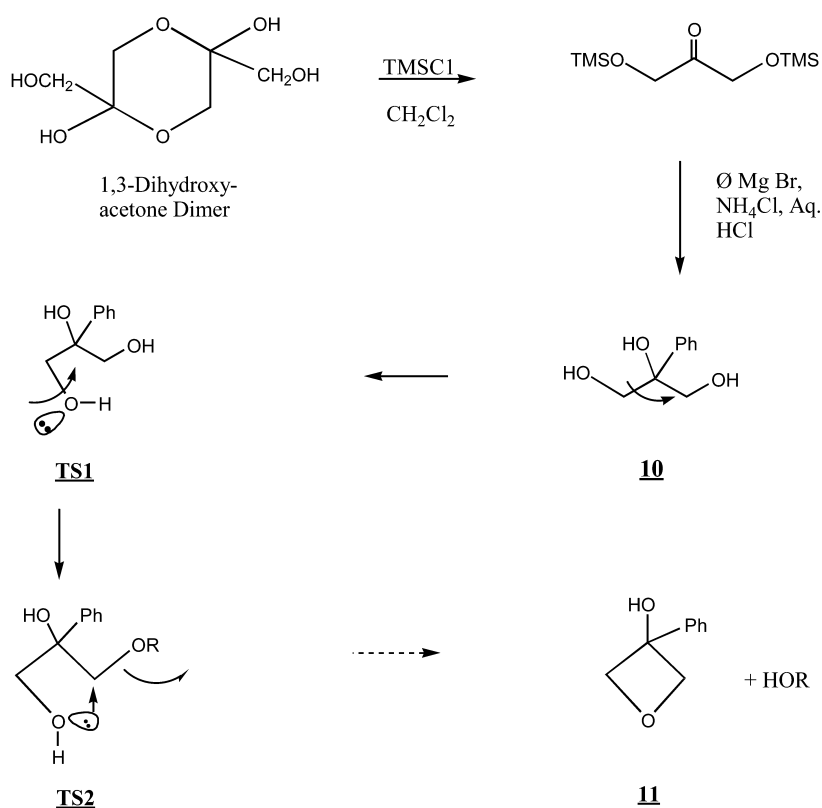
Finally, it should be additionally noted that by using computational paradigms, these same types of comparisons (i.e., among and between distinct families of conformationally related members) can also be done for additional sets of conformational family members that become accessible at appropriately increased energy levels (i.e., at one or more 5 kcal/mol increments of energy) to thus address the beneficial losses of energy that might be obtained during favorable binding with receptors or active

sites [227]. These types of altered conformations can also become candidates for structural comparisons between databases. The latter represents another important refinement that could become utilized as part of SAR queries that will need to be undertaken across the new efficacy and ADMET-related parameters of the future. With time, each structural family might be ultimately addressed by treating the 3D displays in terms of coordinate point schemes or graph theory matrices [228]. This is because these types of methods lend themselves to the latest thoughts pertaining to utilizing intentionally “fuzzy coordinates” [229,230], e.g.,  $x \pm x'$ ,  $y \pm y'$ , and  $z \pm z'$  (rather than just  $x$ ,  $y$ , and  $z$  plots), for each atomic point within a molecular matrix wherein the specified variations might be intelligently derived from the composite of aforementioned computational and experimental approaches. Alternatively, the fuzzy strategy might become better deployed during the searching routines, or perhaps both knowledgeably fuzzy data entry and knowledgeably fuzzy data searching engines handled, in turn, by fuzzy hardware [231], will ultimately best identify the correlations which are being sought in any given search paradigm of the future. It should be noted, however, that for the fuzzy types of structural treatments, queries will be most effective when the database has become large enough to statistically rid itself of the additional noise that such fuzziness will initially create. An ongoing example that serves to demonstrate the value of considering the dynamic energy relationships associated with molecular trajectories as well as the more static conformational displays for a particular molecular interaction of interest, is provided below.

#### 5.4 Dynamic energy relationships: Example involving a small ring system

As a different aspect of the aforementioned MDR-related, anticancer chemotherapeutic program, an effort has been directed toward replacing the complex scaffold of PAC (Fig. 6) with a very simple molecular format that still displays PAC's key pharmacophoric groups in the appropriate 3D orientations purported to be preferable for activity [232–234]. Toward this end, initial interest involved defining the role of the  $\beta$ -acetoxyoxetane system, particularly when the latter is adjacent to planar structural motifs. Since such systems are rather unique among natural products [235] as well as across the synthetic literature [236–238], it became necessary to first study their formation within model systems relevant for this project. 2-Phenylglycerol was synthesized [239] and deployed as a model to study the molecule's conformation by X-ray, NMR, and computational techniques as a prelude to affecting its cyclization [240]. The energy differences that result as the molecule is reoriented so as to be lined up for the cyclization were also calculated. Finally, once properly oriented in 3D space, the energy required to actually traverse the  $S_N2$  reaction trajectory between the 1- and 3-positions was calculated (one of which positions utilizes its oxygen substituent for the attack while the other relinquishes its oxygen as part of a leaving group). The synthesis of 2-phenylglycerol and the pathway and energies associated with the intermediate species and cyclization process to form the oxetane are summarized in Fig. 11 [239,240].

Not surprisingly, given the strained-ring nature of this system, the energy needed to effect the ring closure from the lowest of three closely related local minima conformations belonging to a family common to the independent X-ray and computationally derived starting points was about 28 kcal/mol. What becomes interesting, however, is that within this particular system, nearly half of this energy requirement results from the need to disrupt hydrogen bonds in order to initially reorient the molecule into a conformation appropriate for the reaction. The actual movement of the relevant atoms along the reaction trajectory (Fig. 11, dotted line), despite the resulting strain that becomes placed upon the overall system's bond angles, then accounts for only slightly more than one-half of the total reaction energy. Therefore, from a synthetic point of view the results suggest that it should be beneficial to employ a hydrogen bond acceptor solvent that has a high boiling point, the first property assisting in disruption of the hydrogen bonds that need to be broken for conformational reorientation and the second property for allowing enough thermal energy to be conveniently added so as to prompt progression across the reaction trajectory. That such favorable conformational perturbations could indeed be achieved by simply deploying these types of solvents was then confirmed by reexamination of the independent results



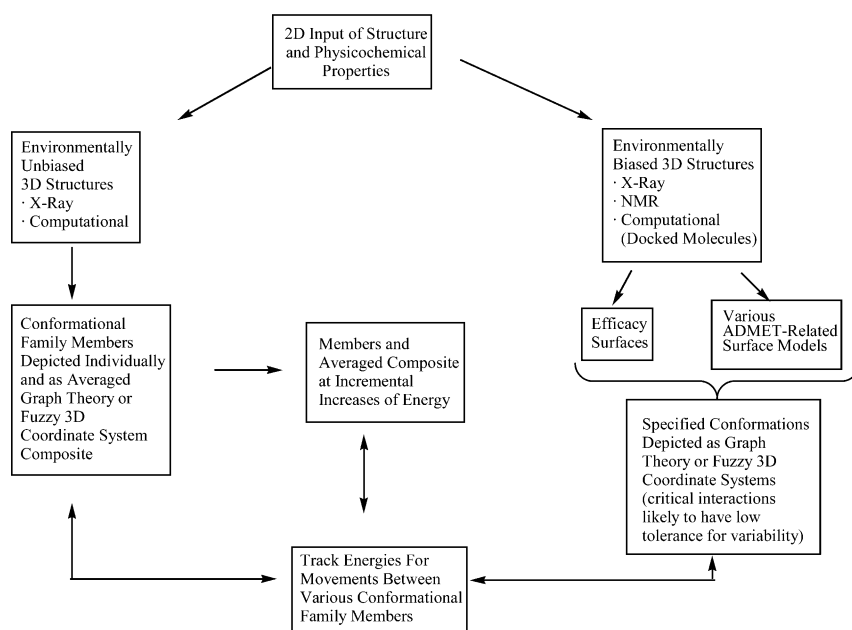
**Fig. 11** Synthesis of 2-phenylglycerol and investigation of its conversion to 3-hydroxy-3-phenyloxetane [239,240,488]. 2-Phenylglycerol, **10**, is depicted so as to convey the lowest energy structure of the three close local minima observed during ab initio calculations performed at the HF/6-31G\* level. TS1 and TS2 represent transition conformers obtained after the indicated bond rotations, while **11** represents the desired 3,3-disubstituted oxetane system. The respective relative energies in kcal/mole for **10**, TS1 and TS2 along with the product oxetane, **11**, are as follows: 0.00; 13.6; 12.4; and 28.2.

obtained from our initial NMR studies conducted in polar, protic media. Alternatively, from a medicinal chemistry point of view, these results serve as a reminder about the long-standing arguments pertaining to the importance and energetics of drug desolvation prior to receptor/active site interaction and, alternatively, the roles that stoichiometric water molecules can play within such sites. That such concerns will be addressed in a much more deliberate manner in the future by using multidisciplinary approaches similar to the example cited herein seems clear. Indeed, a quick survey of the present medicinal chemistry literature suggests that consideration of the dynamic nature of conformational perturbations associated with efficacious events is already beginning to take hold [241–246]. It is predicted, however, that it will be even more critical in the future to correlate SARs from one database to another according to the dynamic energy differences between the various molecule's conformational family members when several ADMET-related interactions are additionally factored into the overall behavior of a molecule being contemplated for further development. In other words, simple comparisons of static structures, even when rigorously assigned in 3D, will probably not be adequate to address a molecule's behavior across all of the efficacy and ADMET-related biological surfaces that become of interest as part of the molecule's optimization during future, new drug design and development paradigms.

What this section points to is that, ultimately, structural databases of the future will probably have several “tiers” [247] of organized chemical and conformational information available which can be distinctly mined according to the specified needs of a directed (biased) searching scheme while still being able to be completely mixed within an overall relational architecture such that undirected (unbiased), “knowledge-generating mining paradigms” can also be undertaken [248–253]. Certainly, simple physicochemical data will need to be included among the parameters for chemical structure storage. Likewise, searching engines will need to allow for discrete substructure queries as well as for assessing overall patterns of “similarity” and “dissimilarity” [254–261] across entire electronic surfaces.

### 5.5 Drug-like properties and privileged structures

It can be noted that it is probably already feasible to place most of the clinically used drugs into a structural database that could at least begin to approach the low to mid-tier levels of sophistication because considerable portions of such data and detail are likely already available within the literature for each drug even if it is presently spread across a variety of technical journals. On the other hand, it should also be clear that an alternate strategy will be needed to handle the mountains of research compounds associated with just a single HTS parameter survey. Unfortunately, it appears that some of the large compound surveys being conducted today do not even have systematically treated 2D structural representations. Indeed, while the present status of handling chemical structure and data associated with HTS is wisely being directed toward *controlling the size of the haystack* [262], the dire status of handling conformational detail is reflected by attempts that try to grossly *distinguish between drug-like and nondrug-like molecules* [263] in a 2D manner or, at best, to identify certain “privileged structures” [264,265] while using 3D constructs derived from less than completely rigorous experimental and computational assessments. Furthermore, in certain companies, notions about drug-like patterns (or actually the lack thereof) are already being set up as the first screen or in silico filter to be deployed against a given compound library’s members while the latter are still on route to an HTS efficacy screen. Unfortunately, this scenario can detract from the definition of an initial efficacy pharmacophore along structural motifs that might, alternatively, be able to readily take advantage of neutral areas by making straightforward chemical modifications that then serve to avoid the nondrug-like features. At present, and for probably much of the near term as well, strategies that use nondrug-like parameters to limit the number of compounds that can otherwise contribute toward the definition of a given efficacy-related structural space would appear to be premature. In the very least, such strategies are counter to the need to continue to accumulate greater knowledge in the overall ADMET arena, let alone in the specific handling of 3D chemical structure at this particular time. Finally, when it is additionally appreciated that in most cases the connection of HTS ADMET data with actual clinical outcomes still remains to be much more securely validated, the strategy to deploy notions about nondrug-like structural hurdles as decision steps prior to efficacy screening becomes reminiscent of medicinal chemistry’s own adolescent phase wherein medicinal chemistry’s efforts to rationally design drugs without the benefit of the additional knowledge afforded by an X-ray of the actual target site ultimately did not enhance either the production of NCEs or the image of medicinal chemistry. A more appropriate strategy toward addressing this area that is knowledge building and, instead, can eventually expect to deploy the evolving ADMET drug-like patterns in a proactive manner, is further discussed in the next section. With regard to chemical structure, the present situation thus indicates that we have a long way to go toward achieving the aforementioned tiers of conformational treatments when dealing with large databases and applying them toward the process of drug discovery. Nevertheless, because of the importance of chemoinformatics toward understanding, fully appreciating and, ultimately, actually implementing bioinformatics along the practical avenues of new drug discovery, it can be imagined that future structural fields within databases, including those associated with HTS, may be handled according to the following scenario, as summarized from the ongoing discussion within this section and as also conveyed within Scheme 5.



**Scheme 5** Handling chemical structures within databases of the future. This figure depicts the quick entry and gradual maturation of structures. Search engines, in turn, would also provide for a variety of flexible paradigms involving physical properties with both full and partial (sub)structure searching capabilities using pattern overlap/recognition, similarity/dissimilarity, CoMFA, etc. Structure entry would be initiated by a simple 2D depiction that is gradually matured in conformational sophistication via experimental and computational studies. Note that structures would be evolved in both an unbiased and in several environmentally biased formats. The highest structural tier would represent tracking/searching the energies required for various conformational movements that members would take when going from one family to another.

### 5.6 Tiered structural information and searching paradigms

For optimal use in the future, it is suggested that several levels of sophistication will be built into database architectures so that a simple 2D format can be input immediately. Accompanying the simple 2D structure field would be a field for experimentally obtained or calculated physicochemical properties (the latter data also to be upgraded as structures are matured). While this simple starting point would lend itself to some types of rudimentary structure-related searching paradigms, the same compound would then gradually progress by further conformational study through a series of more sophisticated chemical structure displays. As mentioned earlier, X-ray, NMR, and computational approaches toward considering molecular conformation will be deployed for real compounds given that it is also likely that advances in all of these areas will allow them to be more readily applied in each case. Obviously, virtual compound libraries and databases will have to rely solely upon computational approaches and upon knowledgeable extrapolation from experimental data derivable by analogy to structures within overlapping similarity space. Eventually, structures would be manipulated to a top tier of chemical conformational information. This tier might portray the population ratios within a conformational family for a given structure entry expressed as both distinct member and averaged electrostatic surface potentials wherein the latter can be further expanded so as to display their atomic orientations by fuzzy graph theory or fuzzy 3D coordinate systems. Thus, at this point one might speculate that an intelligently fuzzy coordinate system could eventually represent the highest level of development for the 3D “quantitative SAR” (3D-QSAR) [266,267] based searching paradigms seemingly rising to the forefront of today’s



trends in the form of comparative molecular field analyses (CoMFA) [268,269]. Furthermore, one can imagine that this tier might actually be developed in triplicate for each compound, that is: one informational field for the environmentally unbiased structural entries; another involving several subsets associated with known or suspected interactions with the biological realm; and, a third for tracking conformational families when raised by about 5 and 10 kcal/mol in energy. Finally, as the new millennium continues to churn its computational technologies forward, conformational and energetic considerations pertaining to a compound's movement between its various displays, similar to that conveyed by the very simple case example provided from the oxetane-related study, can also be expected to be further refined so as to ultimately allow future characterization and searching of the dynamic chemical events that occur at the drug-biological interface, e.g., modes and energies of docking trajectories and their associated molecular motions relative to both ligand and receptor/active site. That this top tier is extremely valuable for understanding the interactions of interest to medicinal chemistry, is apparent from the large amount of effort already going on today in this area [241–246], particularly when such studies are able to take advantage of an X-ray derived starting point.

By the same token, chemical structure search engines of the future will probably be set up so that they can also be undertaken at several tiers of sophistication, the more sophisticated requiring more expert-based enquiries and longer search times for the attempted correlations to be assessed. A reasonable hierarchy for search capability relative to the structural portion of any query might become: (i) simple 2D structure with and without physicochemical properties; (ii) 3D structure at incremented levels of refinement; (iii) 2D and 3D substructures; (iv) molecular similarity/dissimilarity indices; (v) fuzzy coordinate matrices; (vi) docked systems from either the drug's or the receptor/active site's view at various levels of specifiable precision; and finally, in the more distant future (vii) energy paths for a drug's movement across various biological milieu including the trajectories and molecular motions associated with drug-receptor/active site docking scenarios. Emphasizing informatics flexibility, this type of approach where data entry can occur rapidly for starting structure displays and then be gradually matured to more sophisticated displays as conformational details are accurately accrued, coupled with the ability to query at different levels of chemical complexity and visual displays [270] at any point during database maturation, should allow for chemically creative database mining strategies to be effected in the new millennium's near term, as well as into its more distant future.

## 6. ADMET CONSIDERATIONS

### 6.1 Assuring absorption

In addition to conducting *in vivo* bioavailability studies on selected compounds at a later stage of development, early *in vitro* assessments of structural information that might be useful toward *assuring absorption* after a drug's oral administration have now been going on for several years [271–273]. Somewhat more recently, similar studies also began to be directed toward assessing penetration across the blood–brain barrier (BBB) [274,275]. Thus, determination of the pK<sub>a</sub> values for ionizable groups, determination of partition coefficients (e.g., using various types of Log P calculations and measurements), and measurement of passage across models of biological membranes (e.g., Caco cell lines) represent data that has now been shifted toward HTS experimental and purely computational modes [276–287]. These types of studies can be designated as “AHTS” for absorption high-throughput screening (Table 2). Since recent results suggest that the biological transporter systems are extremely important factors in this area [288–290], their study is also becoming part of AHTS (e.g., passage of drugs across Caco cell layers from both directions [291,292]). This trend toward increasing sophistication within AHTS can be expected to continue. That genomics and proteomics will help to identify and initially define absorption-related systems biochemically should be clear. Alternatively, that biotechnology, beyond establishing the complementary AHTS systems, might also be directed toward instilling passageways or specific pores for drugs across the human GI endothelial system [293] is certainly spec-

ulative even for the more distant future, as are chemical [294–296] and nanotechnology [116,297–300] approaches toward prompting or constructing passageways, respectively. Likewise, that advances in formulation and alternate delivery technologies [301–310] could eventually obviate the need for oral administration is also speculative. Nevertheless, all of these possibilities need to be mentioned because, taken together, they make the point that significant advances in any of the ADMET areas, regardless of their technological source, have the potential to eliminate the need for assaying certain of their presently related parameters, perhaps even reversing the initial portions of the present drug discovery paradigm (Scheme 2) back to where it originated, i.e., to being concerned primarily with just efficacy and selectivity during front-line testing (Scheme 1).

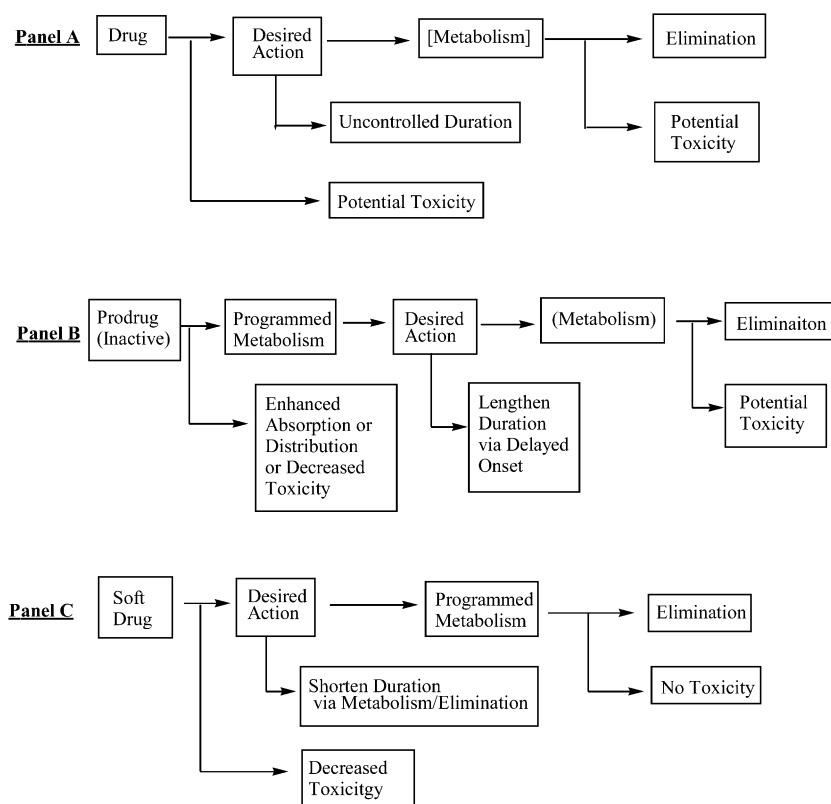
As for deciphering selective efficacy-related SARs, medicinal chemistry's role within the more discernable future is likely to be directed toward making sense out of the AHTS data mountains looming ahead using molecular structure information as the common code, in this instance by relating the latter to structure–absorption relationships or *SABRs*. Such efforts might eventually culminate in affording molecular blueprints for affecting absorption-related structural modifications that are correlated with certain structural themes and absorption characteristics for which efficacy hits may be able to be categorized using structural similarity/dissimilarity indices. Notable advances have already been made toward defining useful *SABRs* in terms of database and virtual compound profiling, e.g., the so-called “rule of five” [311]. The latter should be recognized as an important first step in this direction that can be expected to continue in a more sophisticated manner in the future, e.g., along the lines of 3D structural considerations relevant to the transporter systems, as well as more refined parameterization of physicochemical properties [312].

## 6.2 Directing distribution

The same types of studies mentioned above, along with a panel of assays specific for certain depot tissues such as red blood cells, plasma protein binding factors, adipose tissue, etc. [313–316], will be additionally mobilized toward *directing distribution* of a xenobiotic. Thus, as the handling of chemical structure improves and more sophisticated correlations begin to unfold in the future, AHTS can be thought of as *A/DHTS* that provides both *SABR* and *SDR*. Simultaneous collection of such data will allow investigators to reflect upon drug absorption and distribution as a continuum of drug events that can be effectively incorporated together at an earlier point of the overall lead decision process. Furthermore, in the case of directing distribution it can be anticipated that genomics and proteomics will become instrumental toward identifying numerous key factors that are over-expressed in various pathophysiological states. For example, cancer cells are already known to overexpress a variety of specified factors [317–321]. Ligands designed to interact with such factors residing on cell surfaces can then be coupled with diagnostic and therapeutic agents so as to be delivered at higher concentrations to these locales. For therapeutics, such strategies can be thought of as placing both an “address” and a “message” within a molecular construct [322, 323] that may involve an overlap of two small molecule-related SAR patterns, or perhaps a small molecule conjugated to a bioengineered biomolecule wherein the latter typically serves as the address system. Indeed, the bioconjugate or immunoconjugate strategy has been around for a while [324] and it appears to be benefiting from a renewed interest [325] in that chemotherapeutic “smart bombs” [326] are now being added to our older arsenals of single “arrows” and “combinations” of small molecule “magic bullets” [327]. The earlier example involving PAC and CPT (Figs. 6 and 8) can also be used to further emphasize this theme wherein the chemical knowledge in the area of PAC and CPT protection, and coupling reactions can be additionally used to construct compounds that would be directed toward some of the factors that are overexpressed on certain human cancer cells so as to enhance “selective toxicity” [328], particularly since there is some precedent in this case that this might be feasible by combining two small molecules. One can imagine that as data is amassed in the future for these types of factors, the most promising ones will be quickly pursued according to both of the aforementioned scenarios, paired small molecule SARs and small molecule-

bioconjugate pairs. Whether undertaken in a rational manner or via the merger of two HTS generated databases (i.e., one for an efficacious message and one for determining a selective address) these types of pursuits fall into the general category of tailoring a lead. Therefore, it can be expected that the expertise afforded by medicinal chemistry will again be an integral component of such activities. Likewise, as suggested by the earlier PAC/CPT MDR-related example, medicinal chemistry's expertise will also be vital toward exploiting the opposite cases where it becomes desirable to avoid certain systems (addresses) that become overexpressed as part of a given pathophysiology's resistance mechanisms or because messages delivered to such locales lead to toxicity within a healthy compartment.

Before turning to those parameters that might be considered to be associated with ending a drug's random walk through the biological realm (e.g., metabolism and elimination), it is necessary to discuss a practical limitation to where this overall discourse is leading. Clearly, there will be ceilings for how many molecular adjustments can be stacked into a single compound no matter how knowledgeable we become about the various ADMET-related structural parameters and how they might be merged so as to best take advantage of molecular overlaps. This will be the case even when "prodrug" strategies are adopted [329] (Scheme 6), wherein certain addresses or messages that have been added to deal with one or more aspects of ADMET, become programmatically jettisoned along the way while simultaneously activating the efficacy payload that is to be delivered to only the desired locale as the final statement.



**Scheme 6** Soft drug actions compared to standard drug and prodrug actions [329,352,353]. Panel A depicts a generalized version of a standard drug's pattern of observed activities. Panel B depicts how a prodrug approach can be used to modify the entry-side portion of a given drug's overall profile of actions. Panel C depicts how a soft drug approach can be used to modify the elimination-side portion of a given drug's overall profile of action. Both prodrugs and soft drugs can be used to decrease toxicity.

Thus, this situation prompts the prediction that in order to interact optimally with the entire gamut of efficacy and ADMET-related parameters during a given course of drug therapy, the latter may need to be delivered not as a single agent but as a distinct set of multiple agents wherein each individual component or player makes a specified contribution toward optimizing one or more of the efficacy and ADMET parameters relative to the overall drug team's therapeutic game plan.

### **6.3 Herbal remedies: Example of working with nature to discover ADMET-related synergies**

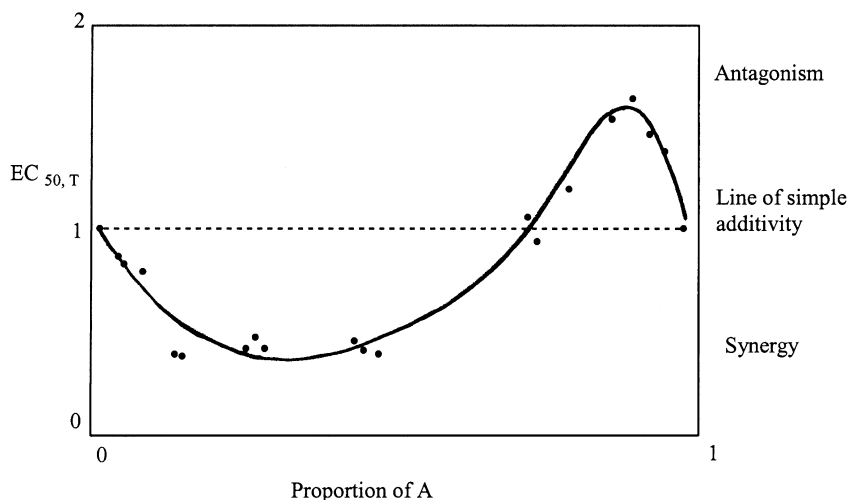
Today's trend to self-administer herbal remedies and preventatives, admittedly driven by rampant consumerism in the United States, rather than by solid science [330,331], thus becomes an important topic to be considered at this point in the review. In this regard, the reconnection to medicinal chemistry's historical roots also becomes interesting to note. One of the major, basic science questions about herbals (that do indeed possess validated pharmacological properties), is why their natural forms are sometimes superior to the more purified versions of their active constituents, even when the latter are adjusted to reflect varying concentration ratios thought to coincide with their natural relative abundances. Given the notoriously incomplete analytical characterizations of most herbal products, it should be apparent relative to the present discourse that numerous unidentified, nonefficacious, and otherwise silent constituents within any given herb could have an interaction with one or more of the efficaciously active constituents at any one or more levels of the latter's ADMET steps. When these interactions are favorable, the resulting overall pharmacological profile becomes altered in a seemingly synergistic manner that is obtainable from the more natural forms of the mixture but lost upon purification to matrices containing only the actives [332]. Indeed, there is already some experimental precedent for this scenario relative to efficaciously silent components improving the absorption [333], enhancing the distribution [334,335], and favorably altering the metabolism [336] of their active herbal counterparts, as well as more classical synergies involving direct interactions that occur at the sites involved with efficacy [337]. Therapeutic enhancements derived directly from multiple interactions at efficacy sites have been pursued for many years, with multivalent, single drug entities reflecting the latest trend in this direction [338]. What will be remarkable is that the new millennium will continue to add the sophistication of the entire ADMET profile into such multi-action-directed considerations [339–343].

Optimization of the overall pharmacological profile is precisely what is being striven for when selecting and/or chemically tailoring an NCE lead according to either the old or new paradigm of drug discovery. Restating, however, that it may be expecting too much even upon extending the new paradigm into the future as a knowledge-generating process, to obtain complete optimization within a single, multi-parameterized molecule, perhaps it will be Mother Nature that will again lend her hand within the next millennium by revealing some of the modes of ADMET synergy that she, long ago, has already instilled into some of her herbal productions. At the very least, medicinal chemistry should take care to not forget its roots in natural product chemistry as it marches forward with biotechnology just behind genomics and proteomics into the new millennium. For example, efforts can be directed toward uncovering efficacy and ADMET-related synergies that may be present among the constituents of herbs purported to have anticancer or cancer-preventative properties by taking advantage of the common cell culture panels already in place to assess anticancer activity along with various transporter system interactions via HTS format. However, because anticancer/cancer-preventative synergy could derive from favorable interactions across a wide variety of ADMET processes relative to any combination of one or more efficacy-related endpoints, several mechanism-based assays associated with several key possibilities for efficacy will also need to be deployed as part of such a program. One can only imagine how sophisticated this type of pursuit will become in the future when such highly interdisciplinary, efficacy networks are further coupled to an even wider network of ADMET parameter experimental protocols.

A more classical approach toward the interactions of multicomponent systems would be to utilize clinical investigations to study the interactions, either positive or negative, that herbals may have with

drugs when both are administered to humans. For example, Bachmann and Reese et al. [344,345] have begun to study the interaction of selected herbals with specific markers for several drug metabolism pathways while V. Mauro and L. Mauro et al. [346,347], among others, are studying the clinical pharmacokinetic consequences of selected herb–drug administrations such as ginkgo biloba with digoxin. Importantly, for all of these herb-related studies, it becomes imperative that extensive chemical constituent fingerprinting is also undertaken so that the observed effects, particularly those suggestive of synergy, can be correlated with overall chemical composition patterns and not with just the distinct concentrations of preselected components already known to possess established activity [183].

In contrast to both of the aforementioned types of studies that can be considered to represent systematic examinations of “herbal-directed, small libraries” and specified herb–drug clinical combinations, it becomes interesting to speculate how a truly random, brute force approach toward identifying synergy might proceed not too far down the road into the new millennium, e.g., as an HTS survey of a huge random compound library in pursuit of optimal pair or even triple compound teams rather than as the pursuit of a single, blue-chip drug that can do it all. In this regard, however, it must first be recognized that the present trend to test mixtures of several compounds within a given well does not even begin to address synergy. This is because based upon considerable experience with various chemotherapeutic agents [348], synergy is most likely to be observed at very select ratios within very distinct concentrations of the involved players. In other words, looking at the most simple case of assessing the potential synergy between just two molecules A and B, requires testing A in the presence of B across a range of molar ratios presented across a range of absolute concentrations. This situation is depicted in Fig. 12 [349,350].



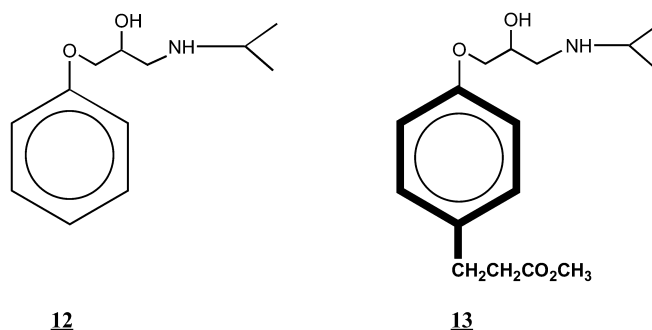
**Fig. 12** Drug interaction plot for two drugs A and B [348].  $EC_{50,T}$  is the total concentration of the combined drugs which gives 50 % of the maximum possible effect. The  $EC_{50,T}$  is shown as a function of the fraction of drug A (drug B’s fraction is one minus the fraction shown). Rescaling of drug concentrations to units of their  $EC_{50}$ ’s allows simple additivity to be set at unity such that deviations below or above this line indicate synergism or antagonism, respectively. The dots are actual experimental results obtained for two anticancer agents, wherein the observed  $EC_{50,T}$  values reflect 20 rays of fixed drug fractions as estimated from the data along that ray alone. The fitted curve was generated by the global model for the entire data set and indicates the complicated nature of interaction relationships within even a well-controlled cell culture environment. That synergism can be accompanied not only by simple additivity but also by ratio-dependent antagonistic relationships is apparent.

### 6.4 Brute force HTS to uncover multicomponent synergies

Pursuing the brute force approach from a purely mathematical viewpoint and in a minimally elaborated pharmacological format, suppose the possibility for A plus B synergy relating to just a single, efficacy or ADMET-related HTS parameter is examined across a compound library having only 100 members wherein paired combinations are tested at just three relative molar ratios (e.g., A/B at 0.5/1, 1/1, and 1/0.5) at only three total concentrations of both members (e.g., 0.1, 1.0, and 10  $\mu\text{M}$ ), then a total of 44 850 drug tests plus numerous control runs would be required for an  $N = 1$  pass through the library [351]. Perhaps because of these rather impressive numbers, brute force HTS in the new millennium will undoubtedly relish such pursuits. Indeed, it strikes this author very surprisingly that nothing along these lines seems to have as yet appeared within the literature. At any rate, once the HTS forces do become mobilized in this area, such testing could set up an interesting “John Henry” competition with more directed investigations, such as those that have been elaborated above that seek to systematically identify the specific synergies seemingly present within certain herbals. Ultimately, no matter how the identification of such favorable drug–drug partnering possibilities are uncovered and are able to better deal with the various ADMET parameters of tomorrow, as well as for the classical efficacy relationships of today, they will certainly prove to be invaluable toward alleviating the situation of trying to establish all of the most desired behaviors for a given therapeutic target within the context of a single molecular framework. Furthermore, it can be anticipated that this type of information will become extremely useful when it becomes further elaborated by medicinal chemistry into general structural motifs that have potential synergistic utilities and applications beyond what was initially uncovered by the specific mixtures of defined compounds.

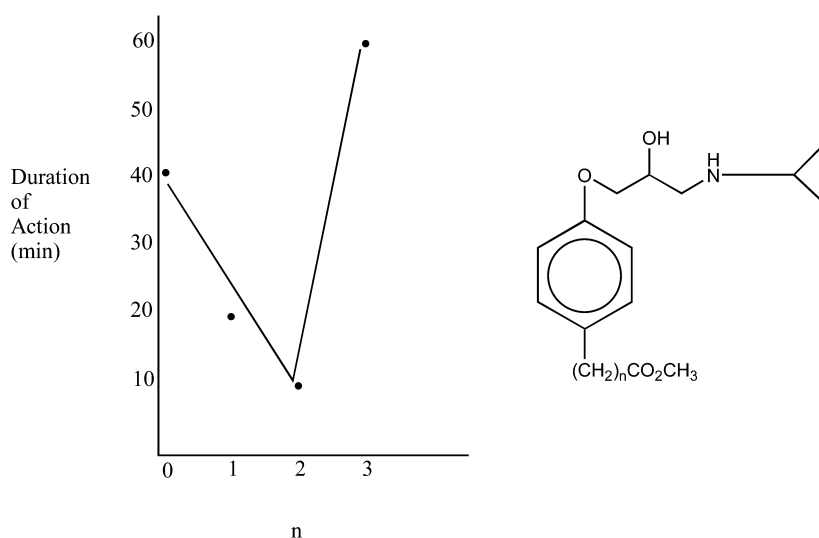
### 6.5 Controlling metabolism: Example involving a soft drug strategy

Although the field of drug metabolism will be more seriously covered within a future submission, there is one general area pertaining to *controlling metabolism* that falls so specifically into medicinal chemistry’s domain of lead tailoring that it merits at least a brief discussion herein. This topic involves exploiting what has come to be called [352,353] “soft drug technology” (Scheme 6) where a metabophore is placed within an established drug or lead compound in order to program a specified course of metabolism for the resulting combination. Although nature has provided numerous examples of soft drugs, esmolol (Fig. 13) has come to be regarded as the prototypical soft drug that was obtained via rational design [354]. In this case, a methyl propionate was appended to the classical ary-



**Fig. 13** Esmolol as the prototypical soft drug [354]. Compound **12** represents the classical aryloxypropanolamine pharmacophore associated with blockade of  $\beta$ -adrenergic receptors. Compound **13** is esmolol, a soft drug version of **12** that has been programmed to have an ultra-short duration of action due to hydrolysis of the methyl ester by the ubiquitous esterases. The methyl 3-arylpropionate (bolded within **13**) thus represents a useful metabophore [22] for the associated human esterases [489].

loxypropanolamine template associated with  $\beta$ -adrenergic receptor blockade (Fig. 13) in order to program the latter's metabolism along the ubiquitous esterase pathways such that the resulting  $\beta$ -blocker would possess an ultra-short duration of action [355–357]. Thus, a methyl 3-arylpropionate system (bolded atoms within Fig. 13) represents a useful metabophore already having clinical proof of principle within the molecular context of an aryloxypropanolamine template. This metabophore can be used to program human drug metabolism by esterases. It can be noted that the rational design of esmolol simultaneously drew upon several of medicinal chemistry's basic science principles mentioned thus far: (i) *negative SAR*, wherein it was determined that only lipophilic or, at most, moderately polar groups could be deployed in the aryl-portion of the aryloxypropanolamine pharmacophore if activity was to be retained; (ii) *electronic physicochemical properties* operative within a biological matrix, wherein it was imagined that while an ester would be permissible in the aryl-portion (*neutral SAR*), a carboxylic acid moiety placed within the same aryl-portion would become too foreign to be recognized by  $\beta$ -adrenergic receptors upon ionization of the carboxylic acid at physiological pH; (iii) general *structure–metabolism relationships* (SMR), wherein it was appreciated that an ester linkage might be relied upon to program a quick metabolism; (iv) *steric physicochemical properties*, wherein it was imagined that the metabolic hydrolysis rate could be quickened by extending the initial ester linkages away from the bulky aryl-group such that the methyl 3-arylpropionate metabophore was identified; and (v) appreciation for the physiologic *drug elimination structural relationship* (SER), where there is a general propensity to excrete low-molecular-weight acids. These are all fundamental physical organic principles applied in a straightforward manner within very specific contexts of the biological realm. Thus, this example serves four purposes. The first is to again emphasize that beyond activity hits per se, neutral and negative SARs should also be tracked so as to be readily retrievable from the databases associated with a given parameter survey of the future. The second is to again emphasize that medicinal chemistry will need to become an active participant in the merging of various HTS parameter surveys by using chemical structure as a common denominator, especially when such activities become considerably more complicated than the esmolol case. Third, the esmolol case demonstrates that even when problems can be reduced to what appears to be a rather simple set of factors, it will still be medicinal chemistry's unique desire to systematically characterize the complete pattern of chemical structural relationships that is likely to be called upon to finalize what other disciplines might consider at that point to be rather subtle, mundane details. In other words, who, besides a medicinal chemist, can be expected to enthusiastically pursue methyl-, ethyl-, propyl-, etc. relationships either synthetically or by tediously purveying huge databases of the future, just to look for those SXR “Goldilocks” situations [354] that could become relevant toward addressing a problem within another structural setting while attempting to merge the two data sets within a common chemical context? The latter was precisely the case for the esmolol-related metabophore upon comparison of methyl benzoate, methyl  $\alpha$ -phenylacetate, methyl 3-phenylpropionate and methyl 4-phenylbutyrate, wherein the observed half-lives for these systems when incorporated into the molecular context of a  $\beta$ -blocker pharmacophore became about 40, 20, 10, and 60 min, respectively (Fig. 14). More current uses of the soft drug technology are likewise underway. For example, the esterase capability in newborns was recently compared to that of adults, and it was found that esmolol's half-life in cord blood (baby side) is about twice as long as that in adult blood. Furthermore, individual variation is significantly more pronounced within the newborns [358,359]. These findings, in turn, have prompted an exploration of the generality of deploying the esmolol metabophore within the chemical contexts of several other types of therapeutic agents, namely those that are commonly used to treat the neonatal population in critical care settings. Thus, this fourth and last aspect of the esmolol example clearly demonstrates the potential impact that such classical medicinal chemistry studies can have upon the new field of pharmacogenetics as the latter is surely to become further evolved within the new millennium. Analogous to the importance of merging SABRs and SDRs with efficacy and selectivity-related SARs, SMRs and numerous metabophore patterns can be expected to be gradually discerned and put to extensive use by medicinal chemistry in the future to either enhance or detract from a candidate drug's metabolism.



**Fig. 14** Relationship between methylene-extended esters and duration of action within a series of esmolol analogs [354–357]. The “Goldilocks” nature of the ethylene extension relative to the desired 10 min duration of action is apparent.

## 6.6 Optimizing elimination

Clearly, SAbRs, SDRs, and SMRs can all be additionally applied toward manipulating and optimizing the elimination pattern of administered drugs, the esmolol example applying here as well. Analogous to the distribution area, genomics and proteomics can be expected to soon delineate important systems, such as specialized transporters within tissues like the kidney and liver, that are especially responsible for the elimination of xenobiotic drugs and their metabolites. Medicinal chemistry’s involvement toward uncovering SERs and deriving generally useful structural patterns that might be used to rationally tailor lead compounds or for merging of different types of databases while attempting to select lead compounds, again falls into the central theme for medicinal chemistry’s future as being elaborated within this review. As for the other areas, more speculative notions in this area can provide some interesting alternatives for this aspect of ADMET. Although SERs are likely to also encompass various endogenous materials and their catabolic fragments, one might still imagine that just like the futuristic examples sited for absorption, in the more distant future, biotechnology, chemical, and nanotechnology approaches might all be successfully applied toward engineering specific drug elimination passages through selected tissues.

## 6.7 Avoiding toxicity

It may very well be that the most profound effect that genomics and proteomics are going to have within the ADMET arena will ultimately pertain to *avoiding toxicity*. Indeed, that toxicology has now become a protagonist through its participation in the design or early selection of drug leads already represents a remarkable turn-around from its historical, antagonist role as a gate keeper or policeman standing at an advanced stage of drug development with an eye toward halting the progression of potentially toxic compounds on route to the clinic [360]. Like the field of drug metabolism (Table 7), toxicology has been collecting its data within databases for quite some time (Table 9). In fact, some of the structural patterns that have come to be associated with distinct toxicities (toxicophores) are probably on much



**Table 9** Toxicology databases and related organizations.

Database or organization	Description
Centers for Health Research (formerly Chemical Industry Institute of Toxicology or CIIT)	Industry consortium-sponsored collection/dissemination of toxicology data; also conducts research and training in toxicology [467]
American Chemistry Council Long-Range Research Initiative	Industry consortium-sponsored initiative to advance knowledge about the health, safety, and environmental effects of products and processes [468]
LHASA, Ltd. (UK-based, nonprofit segment)	Facilitates collaborations in which companies share information to establish rules for knowledge bases associated with toxicology [469]
International Toxicology Information Center (ITIC) <sup>a</sup>	Pilot program to share data in order to eventually be able to predict the toxicology of small molecules, thus lessening the expense of in vitro and in vivo testing [469]
U.S. Environmental Protection Agency (EPA) High-Volume Chemical (HPV) Screening Information Data Set (SIDS)	User-friendly version that will also be submitted to the Organization for Economic Cooperation and Development (OECD) and its tie-in with IUCLID <sup>a</sup> [469]
SNP Consortium: nonprofit; makes its information available to public	Addresses phenotypic aspects relative to individual responses to xenobiotics, e.g., metabolic phenotype and toxicity
Tox Express/Gene Express database offered by Gene Logic (commercial <sup>b</sup> )	Offers a gene-expression approach toward toxicity assessment [469]
National Institute for Environmental Health Science (NIEHS) <sup>c</sup>	Compiling a database of results from toxicogenomic studies in order to divide chemicals into various classes of toxicity based on which genes they stimulate or repress [470]
International Program on Chemical Safety/ Organization for Economic Cooperation IPCS/OECD	Risk assessment terminology standardization and harmonization [471,472]
MULTICASE (commercial)	Prediction of carcinogenicity and other potential toxicities [473]
MDL Toxicity Database (commercial)	Allows structure-based searches of more than 145 000 (Jan. 2001) toxic chemical substances, drugs, and drug-development compounds [96]
DEREK and STAR (LHASA-commercial segments)	Prediction of toxicity [474]
SciVision's TOXSYS (commercial)	General toxicity database to be developed in collaboration with the U.S. FDA [475]
Phase-1's Molecular Toxicology Platform gene expression microarrays (commercial <sup>b</sup> )	Allows detection of gene expression changes in many toxicologic pathways [476]

<sup>a</sup>Includes cooperative efforts with the European Union and the European Chemicals Bureau (ECB) in using the International Uniform Chemical Database (IUCLID) and its relationship to high-volume chemicals (HVPs).

<sup>b</sup>This company's product is representative of several of such technologies that are also being made available by a variety of other vendors.

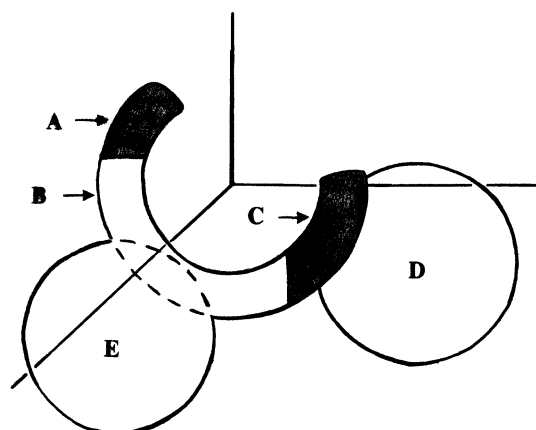
<sup>c</sup>Includes cooperative efforts with the U.S. Environmental Protection Agency (EPA) and the Information Division at the National Institute for Occupational Safety and Health (NIOSH).

firmer ground than are the metabophore relationships. On the other hand, drug metabolism derives from a finite number of genetic constructs that translate into metabolic activity (albeit notorious for their seeming molecular promiscuities) such that with enough time the entire set of metabolic options should eventually become well characterized. Toxic endpoints, alternatively, have no such limitation associated with their possible origins. In other words, to show that a drug and its known or anticipated metabolites are completely nontoxic is comparable to trying to prove the null hypothesis, even when a limited concentration range is specified so as to circumvent the situation that everything becomes toxic someplace at high enough concentration. Nevertheless, genomics, proteomics, and biotechnology do, indeed, appear to be producing some promising technologies that can be directed toward this area. For example, array technologies are already becoming available to assess the influence of a drug on enormous numbers of genes and proteins in HTS fashion [361–368]. Once enough standard data of this type is produced by taking known agents up in dose until their toxicity becomes fingerprinted via distinctive patterns of hot spots, array patterns may be used to cross-check against the profiles obtained in the same HTS mode for new lead compounds. Given the quick rate that these important trends are likely to be further developed and eventually validated within the new millennium, medicinal chemistry could certainly become overwhelmed trying to keep up with its complementary role to identify the corresponding STR for each array hot spot.

In the case of toxicity then, medicinal chemistry will probably need to approach STRs in a different manner, e.g., initially from just the exogenous compound side of the equation for a given toxicity relative to the observed hot spot patterns (unless genomics, proteomics, and biotechnology also quickly step in to additionally define the biochemical nature of the actual endogenous partners that are involved in a given toxic event). Taking a chemically oriented starting point, however, should serve reasonably well for at least a while into the new millennium in that there will likely become a finite number of chemical reactivity patterns that can be associated with toxicity. Medicinal chemistry can be expected to elaborate these reactivities into general STRs and to then use them toward defining the liabilities in new compounds. The notion that there should be a finite number of structurally identifiable toxic-like patterns is analogous to the notion that there should be a restricted number of amenable drug-like patterns that reside within structural databases having high degrees of molecular diversity. Indeed, the case for toxicity is certainly on firmer ground at this particular point in time since there will likely be little added to the area of fundamental chemical reactivity in the new millennium as opposed to proteomic's anticipated revelation of numerous new biochemistries that will, in turn, provide numerous new pharmacologic targets wherein many can be expected to have their own distinct pharmacophore (and potentially new drug-like patterns). Finally, since the precise locales where the toxicity hot spots may ultimately occur are endless, the latter will perhaps be better addressed by directing a second set of database queries toward the ADME profile and intracellular localization patterns that a given drug may exhibit. In the end, after array technologies are producing useful toxicology-related knowledge, the interplay of all of the ADME parameters with STR should become just as important as they are for efficacy in terms of what type of toxicity may ultimately be observed within the clinic.

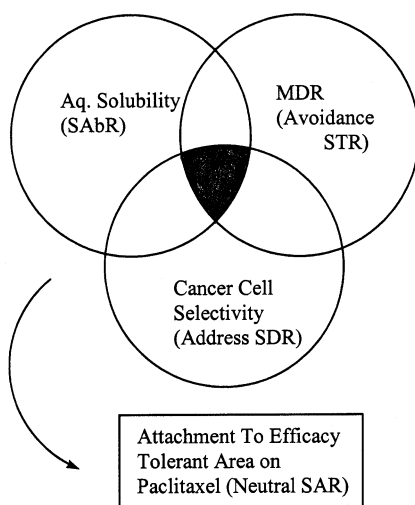
### 6.8 Weighting decision criteria from efficacy and ADMET SAR

Figures 15 and 16 and Schemes 7 and 8 convey how all of the efficacy and ADMET HTS profiling data may eventually be simultaneously deployed toward the design of an optimal preclinical candidate compound. Based upon the magnitudes of the various molecular similarities and dissimilarities across each HTS parameter survey of the compound data set relative to the locations of the generalized pharmacophores associated with various parameters, a balance will be sought between options involving any combination of single or coadministered multiple entities wherein each member has been further tailored according to an unchanging, multivalent, prodrug and/or soft drug strategy once interactions within the biological realm have been initiated. Figure 15 attempts to convey some of these possibilities using a hypothetical set of structural space. Alternatively, serving as a real example that couples

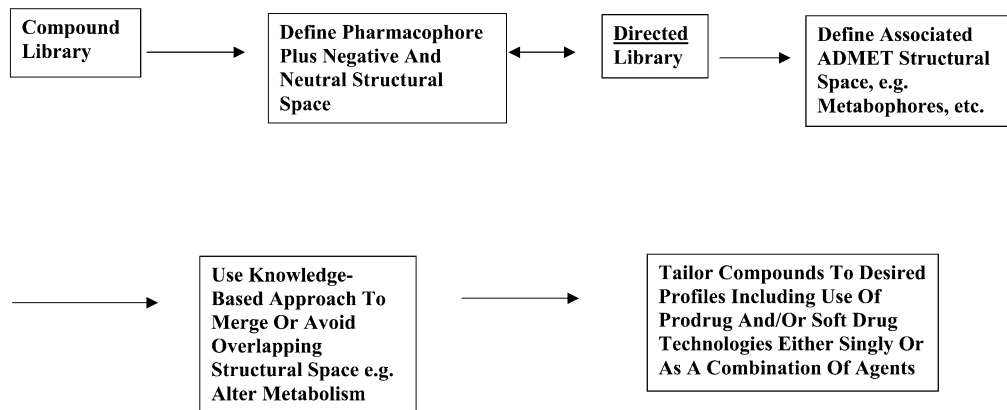


**Fig. 15** 3D pattern recognition example pertaining to the simultaneous consideration of efficacy and ADMET-related pharmacophoric parameters during lead selection and drug design. In this example, SXR space has been mapped according to experimental HTS results from a moderately sized, directed compound library wherein an efficacious template was identified. A and C represent requisite pharmacophoric features oriented in space by structural elements B. Lacking distinctive functionality, B, in turn, tends to prolong the elimination half-life and eventually causes toxic concentrations to be produced in compartments not associated with efficacy. D represents the structural space that provides for a desirable absorption and initial distribution profile. E represents a structural space that is subject to rapid metabolism. Thus, in this case a range of suitable functionality defined by A can be utilized in the northwest region of the efficacious pharmacophore while selected functionalities or bioisosteres that reside within the structural space defined by the overlap of C and D should be utilized in the southeastern region. The latter strategy optimizes absorption and initial distribution features while retaining efficacy such that more complicated prodrug scenarios are not necessary. A soft drug version, however, should be contemplated so that the eventual toxicity problems derived from the connecting chain can be circumvented, especially since the SMR portion of the overall map indicates that there is an intrusion of B by structural features E that prompt rapid metabolism and elimination. The latter can thus be readily exploited by incorporating them into the overall molecular construct and then making adjustments or fine-tuning them to a desired metabolic rate by the incremental insertion of steric impediments near the point of metabolic contact.

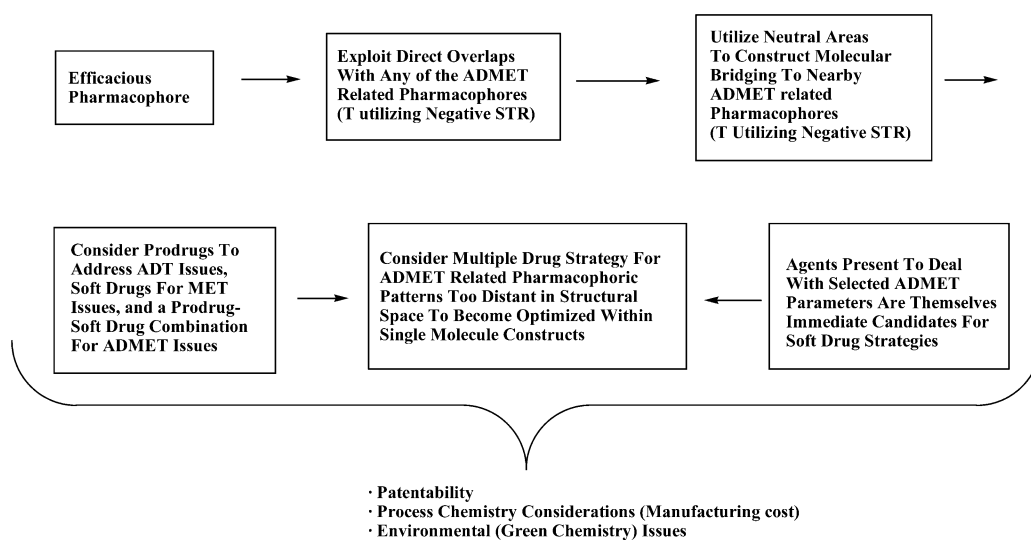
several of the aforementioned anticancer studies, Fig. 16 captures some of the results already obtained from the pursuit of transportophore SARs relative to the paclitaxel template by placing the results within the formalism of the present discussion. Scheme 7 provides an overall, step-by-step strategy for deploying the consideration of ADMET parameters proactively to enhance the process of drug discovery, rather than to just play a negative role as a series of filters toward either the entry or the continued progression of a given compound through such a process. Concerns about today's trend toward filtering the entry of compounds have been alluded to in the drug-like discussion within this review's preceding section on Assessing and Handling Molecular Conformation. In particular, it should be noted from Scheme 7 that it is a completely defined, efficacy-related pharmacophore that serves as the central structural theme to drive the proactive ADMET strategy in that all other structural modifications/biological enhancements are then conducted according to knowledge-based scenarios generated via previous ADMET profiling experiences with analogous structural space or by immediate HTS ADMET profiling of appropriately directed libraries. Clearly, while nondrug-like structural space may thus be effectively used to contribute toward defining the efficacy pharmacophore's electronic surface potentials, such structural components within a library should still be tagged with red flags, indicating that they are also destined to be altered or completely removed by tailoring of the spatial overlaps



**Fig. 16** Design of optimized drug candidate based upon simultaneous consideration of several fields of paclitaxel-related SARs. Studies conducted within the CD3 indicate that there is a distinct region of structural space that is simultaneously overlapped by SARs pertaining to enhanced aqueous solubility, avoidance of multidrug resistance (MDR), and the propensity to selectively associate with cancer cells compared to healthy cells. Coupling of this distinct structural space (depicted as the shaded region) onto an area of paclitaxel that can accommodate structural modification without losing efficacy provides an optimized drug candidate. The specific details of the distinct structural space and the synthetic methods that can be used to couple its useful molecular displays onto paclitaxel are the subject of pending patent applications [490,491].



**Scheme 7** Drug design and development strategy. Note that this strategy emphasizes a complete definition of the efficacy-related pharmacophore as the central theme such that it can be effectively merged with simultaneously generated ADMET-related pharmacophores via a knowledge-driven, proactive process that will ultimately produce the optimized clinical candidate or combination of agents to be deployed for therapy or prophylaxis. It should be noted that this “knowledge-based” decision tree contrasts some of the futuristic schemes that have been suggested by others wherein the various ADMET issues are simply used as consecutive or simultaneous filters to eliminate compounds being selected from huge compound databases. As elaborated within the text, it is this author’s opinion that by medicinal chemistry input, HTS data of the future will be able to take drug discovery investigations to significantly greater heights of knowledge such that the latter can then be used for proactively assembling the positive-type of enhanced property molecular constructs mentioned above. Indeed, if this scenario does not unfold, then the overall new and future processes will be forever locked into a negative mode that simply keeps eliminating compounds failing to meet certain criteria placed at each parameter.



**Scheme 8** Lead selection and drug design decision flow chart based upon efficacy and ADMET-related pharmacophoric parameters. This flow chart has been set up to represent the case where a single-molecule construct having the lowest level of complexity/sophistication is initially sought. However, in the future it is also likely that well-established templates that optimize a certain parameter will be able to be effectively paired with the efficacy-related agent at an early point in the overall design process. For example, a compound that inhibits a transporter system responsible for a given lead's poor passage through the GI endothelium might be ideally coadministered as a soft drug version. In this way, the partner compound would solve the oral absorption problem and then be quickly metabolized and eliminated without doing much of anything else. Structural manipulation of the efficacy construct could then be directed toward enhancing other DMET-related profiles.

according to the type of knowledge base that can be afforded by medicinal chemistry. That the various ADMET-related pharmacophores will eventually be evolved so as to be able to be deployed more independently from a given efficacy-related pharmacophore and in a completely *in silico* manner at any point along the drug design and development flowchart, will indeed occur as well. However, the latter will probably be effectively realized only after we are well into the future and probably only after we have accumulated considerable knowledge about how to additionally manipulate their structural patterns for optimal overlap and/or avoidance with a variety of model efficacy platforms wherein all structural space has been accounted for by 3D electrostatic potential maps derived from rigorous experimental and computational considerations of molecular conformation. Finally, drawing from the overall strategy listed in Scheme 7, Scheme 8 illustrates the specific interplay of all of the aforementioned efficacy and selectivity and ADMET considerations, along with some other practical, drug discovery considerations.

## 7. PROCESS CHEMISTRY CONSIDERATIONS

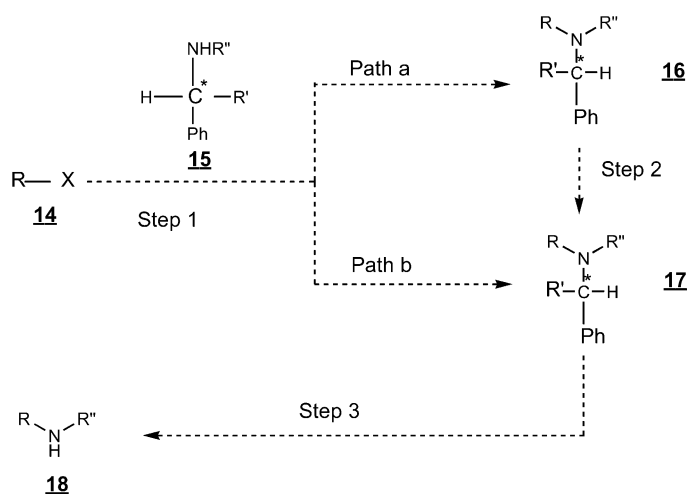
As shown in Scheme 8, practical issues pertaining to intellectual property (IP) such as the structural novelty of biologically interesting compositions of matter, as well as to the latter's synthetic accessibility (relative to process chemistry and manufacturing costs) will also continue to be factored into earlier decision points intending to select the optimal preclinical candidate compounds of the future [369–371]. The changing landscape of IP-related structural novelty is addressed in the final, summary section of this review. Three key issues pertaining to the interplay of medicinal chemistry with process chemistry's responses to current trends are mentioned below.

### 7.1 Cost and green chemistry

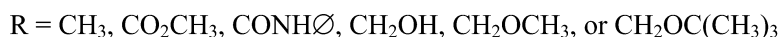
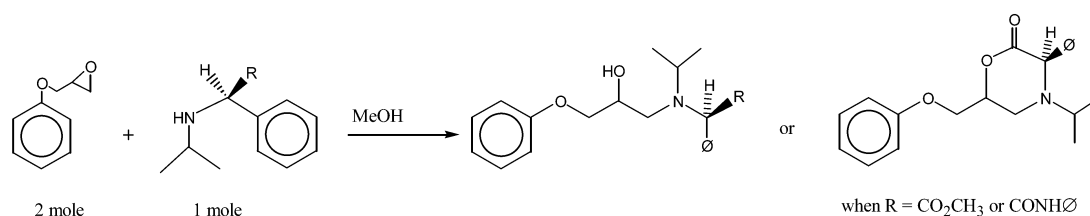
First, the eventual production cost for a new therapeutic agent is much more important today than it has been in the past. This is because pharmaceutical companies must now garner their profits from a marketplace that has become sensitized about the cost of ethical pharmaceutical agents. The days of simply raising the price of such products in parallel to increasing costs associated with discovering and developing them have been over for quite some time [372]. In this regard, the cost-effectiveness of small molecule drugs will probably maintain an edge over biotechnology derived therapeutic agents for at least the near term portion of the new millennium. The second point to be mentioned pertains to the impact of the green chemistry movement [373–376]. This movement has prompted pharmaceutical companies to insure that their productions of drugs are friendly toward the environment in terms of all materials and methods that may be deployed in the process. Finally, the U.S. FDA's initiative to have all stereoisomers present within a drug defined both chemically and biologically has prompted industry's pursuit of drugs that either do not contain asymmetric centers or are enantiomerically pure [377]. This, in turn, has prompted the need for better stereochemically controlled processes during production. Stereocontrol has always represented an extremely interesting area for synthetic chemistry exploration and now for biotechnology-derived chemistry and reagent research as well, e.g., exploitation of enzymes at the chemical manufacturing scale. Considerable progress is being made toward developing such methods on many fronts including enzymatic [378–380] and microarray technologies [381]. Oftentimes, however, the new laboratory techniques do not readily lend themselves toward inexpensive, scale-up/manufacturing type of green chemistry. Alternate approaches that seek to address this situation in a very practical manner can be exemplified by the following study that intends to exploit simple  $\alpha$ -substituted benzylamine systems. The latter are being explored as chiral auxiliary synthetic reagents for the delivery of a nitrogen atom in a stereochemically biased fashion during the synthesis of end-product amines that contain neighboring asymmetry (Fig. 17).

### 7.2 Defining stereochemistry: Example involving benzylamine chiral auxiliary synthetic reagents

Nitrogen systems having  $\alpha$ ,  $\beta$ , or  $\gamma$  asymmetry represent an extremely common structural motif within drug molecules such that the proposed methods immediately become of interest to medicinal chemistry. Given the ease of selectively debenzylating tertiary-amines, the methodology should be particularly well suited for the production of asymmetric secondary amines. While a benzyl- moiety has been previously deployed as either a common *N*- or *O*- protecting group [382,383], the utilization of benzylamine to deliver a nitrogen while simultaneously controlling the degree of substitution is less common, even though such systems can sometimes be quite effective in this regard due to the phenyl- group's inherent steric properties [384]. The use of chiral,  $\alpha$ -substituted benzylamine systems has been even more limited, with such systems most typically being deployed as resolving agent counter-ions for carboxylic acid partners [385]. The rarer deployment of such systems in covalent relationships probably results from the prevailing notion that as the steric environment about the *N*- atom is increased, it eventually becomes more difficult to effect debenzylation via catalytic hydrogenolysis [386]. Thus, in order to first scope the overall applicability of this type of chemistry, recent studies have systematically examined the relationship between a nitrogen's immediate steric environment and the propensity toward debenzylation within relevant model systems. Surprisingly, these results indicate that steric attenuation of debenzylation is not likely to be problematic [387,388]. Explorations are now proceeding toward assessing the diastereomer bias that may be achievable upon reaction of racemic electrophiles with various members of a readily obtainable family of chiral auxiliary benzylamine synthetic reagents [389]. Figure 18 depicts the initial approach toward an area that targets enantiomerically pure aryloxypropanolamines as an appropriately challenging chemical model that is very relevant to the production of pharmaceuticals [390,391]. In addition to its relation to practical, asymmetric pharmaceutical process chemistry appli-



**Fig. 17** Potential stereoselective synthesis of secondary amines using asymmetric benzylamine-related systems as chiral auxiliary reagents [389]. **14** is a racemic precursor where R has an asymmetric center  $\alpha$ ,  $\beta$ , or  $\gamma$  to X; **15** is an optically pure chiral (\*) auxiliary reagent wherein R' is a substituent having selected physical properties such as specified elements of steric bulk; **16** and **17** are diastereomeric tertiary amine intermediates which are mixtures or separated single diastereomers, respectively; and **18** is the desired optically pure secondary amine product. Step 1 represents a variety of *N*-alkylation or reductive alkylation methods, e.g., X = halide, carbonyl, etc.; Step 2 represents a fractional recrystallization or chromatographic separation if necessary; and Step 3 represents a catalytic hydrogenolysis reaction. It is reasonable to anticipate that during Step 1, racemic **14** could combine with optically pure reagent **15** to preferentially provide one or the other of the two possible diastereomers directly (Path b). Even when no asymmetric bias is observed during Step 1 (Path a), the two diastereomers present as intermediate **16** will differ in physical properties such as solubility, chromatographic behavior, boiling point, or melting point. Thus, the desired diastereomer **17** may be able to be conveniently separated under selected conditions involving recrystallization or chromatography during the workup (Step 2) of the first reaction. Alternatively, it may also be possible to effect an asymmetric cleavage during Step 3 if the chiral auxiliary in one or the other of the diastereomeric tertiary amines can be preferentially removed by hydrogenolysis. Also note that Step 3 can be delayed so as to first affect other chemical modifications associated with an overall synthesis while the amino-functionality is still 3°.



**Fig. 18** Attempted diastereoselective opening of a model epoxide using benzylamine-related chiral auxiliary synthetic reagents [391].

cations of the future, the benzylamine example has been cited herein because it further illustrates the important role that physical organic chemistry considerations play within the medicinal chemistry thought process and vice versa. By analogy to medicinal chemistry terms, the preliminary benzylamine studies have determined that there is an allowable region of potential “structure stereochemical relationship” or SSR space to explore because of the neutral effects that were observed relative to a co-event that is required for the overall chemical process (i.e., subsequent debenzoylation). The neutral space was mapped out by using precisely defined “structure–debenzoylation relationship” or SDebR steric probes. The present benzylamine studies, in turn, are now taking advantage of the neutral space to identify useful synthetic “stereophores” that can elicit selected asymmetries analogous to the situation of pharmacophores that can elicit selected efficacies. Finally, upon turning all of these analogies around, the exact same “library” of steric probes can also be used to actually explore the steric tolerance associated with metabolic *N*-dealkylation, i.e., wherein a cytochrome P450 biological surface and its requisite cofactors then substitute for the inorganic catalytic surface and its hydrogenated atmosphere that were present during the aforementioned hydrogenolysis studies. Importantly, such metabolism data will have the potential to be knowledge-generating in that it can then be used to assist in the prediction of the susceptibility toward metabolic *N*-dealkylation not just by specific structural pattern recognition, but also by a parameterized and well-defined physicochemical property that is inherently localized in the space immediately residing about the *N*- atom within any metabolic candidate. The value of this example’s end-point merits reemphasis. In the future, efficacy and ADMET parameters will be maximally defined in terms of their associated pharmacophore’s electrostatic potential space and not just in terms of distinct compound hits or leads. While compound hits and leads can certainly reflect desirable structural prototypes for a given parameter, they can also become restrictive toward a broader conceptualization of the more diverse structural space that can be invoked to better purview the full spectrum of efficacy and ADMET overlaps as the latter parameters are all being addressed simultaneously. Thus, from a broader, knowledge-derived vantage point, the ideal candidate drugs (candidate drug teams) of the future will ultimately be designed by simultaneously considering all of the efficacy and ADMET parameter pharmacophores while not being restricted to any type of predetermined structural template associated with a hit or lead structure that may have been obtained from any one of them.

## 8. ANALYTICAL CHEMISTRY/X-RAY DIFFRACTION

As mentioned in the introduction, new developments in any of several key analytical techniques can be expected to have a profound impact upon medicinal chemistry’s future. X-ray diffraction is taken herein as just one example for these types of possibilities.

### 8.1 Latest trends

At the forefront of current progress and trends in the field of X-ray technology are efforts to properly derive and readily portray electrostatic potentials [392]. As alluded to earlier, the initial recognition and driving forces associated with the interactions between a xenobiotic and the biological surfaces that it will encounter *in vivo* are due to a complementary match between the topography of the electrostatic potential of the xenobiotic ligand and that of the biological site (less anything energetically favorable that is given up when the xenobiotic leaves its solvated environment). As discussed in Section 5, considerable effort has been expended toward calculating accurate depictions of the electrostatic potentials of molecules theoretically. This has been most beneficial, however, for only very small molecules because extended basis sets are required in order to obtain accurate results. Calculations with smaller basis sets have been carried out for larger molecules but, as already pointed out, the results are typically unreliable owing to the nature of the mathematical approximations that will have necessarily been taken. Using larger basis sets for small fragments and then using the fragments as building blocks for



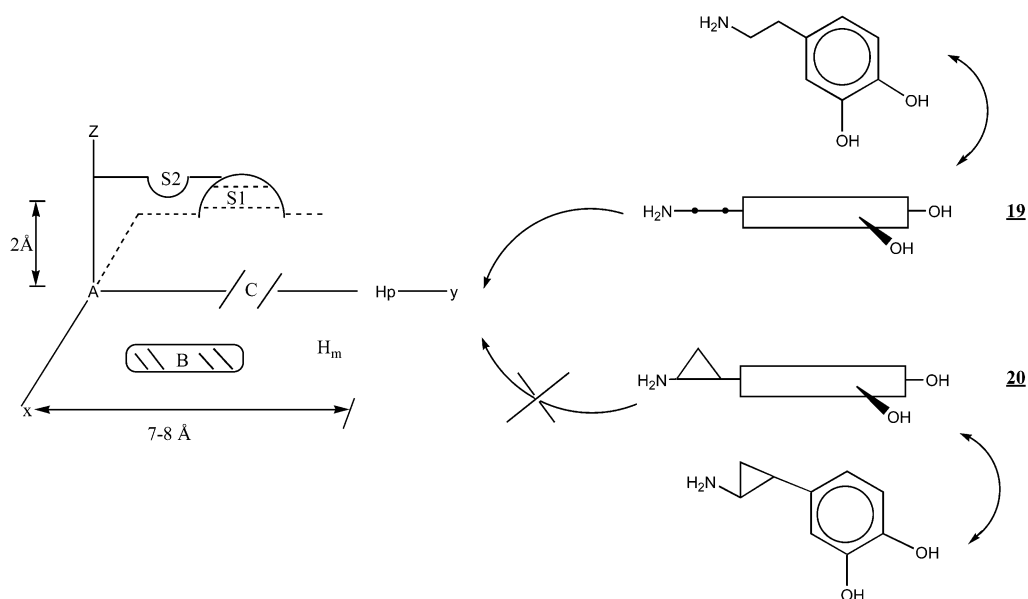
larger molecules is also being done. The latter approach will probably become much more prevalent in the new millennium.

Alternatively, it has been possible for several years to obtain experimental electrostatic potential maps from the molecular charge distribution derived from X-ray diffraction data. This approach has had limited appeal, however, because the experiments needed to provide the large amount of quality data that is used as the starting point, have themselves been extremely time-consuming, typically taking many weeks even for quite small molecules. Nevertheless, from the studies undertaken to date [392], there is growing evidence that results for small molecules can indeed be extrapolated to similar fragments in larger molecules [393] just like what is being suggested by the theoretical approaches that were reiterated above. *The practical implications of potentially using this approach to simultaneously address huge numbers of compounds when they reside along distinct structural themes within compound libraries or databases (e.g., wherein a given scaffold then becomes the common fragment) is worth noting for both the X-ray and computational types of approaches.*

Today, the experimental approach afforded by X-ray diffraction has become much more tractable. With the new generation of X-ray diffractometers using charge-coupled device (CCD) area detectors, the necessary experimental data can be obtained in just a few days, a duration comparable to that currently required for a routine X-ray structure determination [394,395]. Furthermore, with access to X-ray synchrotron beam lines, the time of the experiment may be reduced to a few hours [396]. Shorter experiments, in turn, have allowed development of cooling devices using liquid helium, thus giving access to lower temperatures and improved data [397]. In addition, whereas with a serial diffractometer the length of the experiment scales with the number of atoms in the molecule under study, the size of the molecule is less important when collecting the data using a CCD detector. How large a molecule is tractable in terms of converting this data into electrostatic potentials is still unknown but is likely to be forthcoming within just the near-term future. In this regard, one might speculate that this approach may even be able to handle larger molecules more reliably than will the theoretical approaches elaborated in Section 5. From the present situation it is already clear that it is now possible to map the topology of the electrostatic potential for a typical small-molecule therapeutic agent within very reasonable time periods. This means that the electrostatic potentials may be able to be readily compared for series of molecules, having established biological activities so as to produce refined SAR and to provide the most meaningful data possible relative to the X-ray contributed structures within future databases. Not too much further into the new millennium, one might imagine that it will also be feasible to use this approach toward mapping the complementary electrostatic potential of receptor/enzyme active sites at highly improved resolutions [397–401], especially as promising results have already been obtained for some small proteins [393]. Indeed, certain of the techniques described above for small molecules are already being applied toward the analysis of macromolecules [401].

## **8.2 Examples involving dopamine receptors, c-AMP phosphodiesterase enzymes, and the dynamics of protein folding**

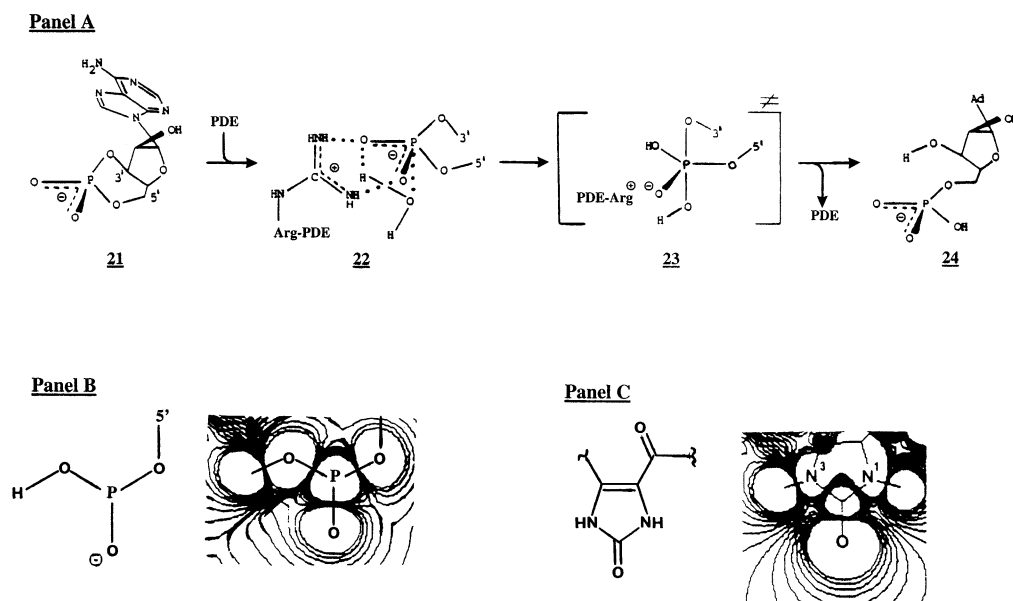
Since applications of these latest trends in X-ray technology are themselves under investigation, studies like the ones being undertaken by Pinkerton et al. [402], that intend to validate the utility of deploying the CCD type of cutting-edge diffractometer approaches toward the study of drug design, represent a critical step at this juncture. For these studies, classical SAR that is available within some established systems of therapeutic interest, such as that for renal dopamine receptors [403] and for c-AMP phosphodiesterase active sites [404], are being reexamined. Long-standing topographical models for these systems (Figs. 19 and 20, respectively) will certainly be interesting to reevaluate based upon refined analyses of the most relevant structural probes that lend themselves to crystallization and refined, extremely accurate X-ray analysis. In this regard, the example depicted by Fig. 20 is especially noteworthy because it clearly demonstrates the “broadest conceptualization of a pharmacophore” theme that was emphasized as being extremely important at the close of the preceding section, i.e., note that it is



**Fig. 19** Topographical model of the renal vascular dopamine receptor [403]. A, C, Hp, and Hm reside in a single plane and represent regions that interact with dopamine's (**19**) amine, catechol ring, para-hydroxy and meta-hydroxy, respectively. Region B represents an auxiliary binding site suggested by apomorphine's SAR, whereas S1 and S2 represent steric limitations toward the binding of receptor ligands. Note that while dopamine, **19**, is nicely accommodated by the model, neither enantiomer of the cyclopropyl analog, **20**, can be accommodated because they will collide with either the receptor's planar floor or S2 ceiling. The cyclopropyl analogs were found to be devoid of activity at either peripheral (renal) or central dopamine receptors [492].

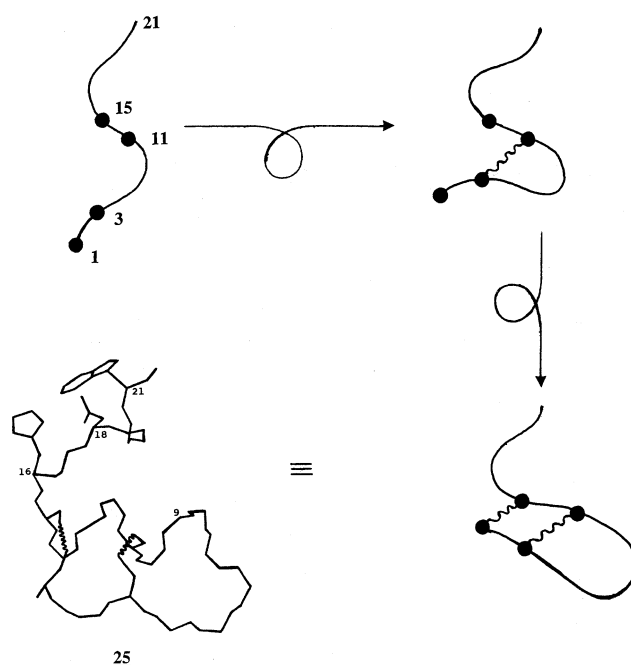
the electrostatic surface potential of a lead compound's imidazolone system that is further likened to the electronic topography of the cyclic phosphate's trigonal bipyramid transition-state species traversed when cAMP is hydrolyzed by phosphodiesterase.

Assuming that refined X-ray techniques will become commonplace within the first 25 years of the new millennium and that they will be coupled with HTS approaches toward crystallization and actual obtainment of diffraction data [122,405,406], it becomes interesting to further ponder what might be on the more distant horizon of X-ray-related technologies. Certainly, the ability to derive X-ray diffraction patterns from noncrystalline, small and large molecules, would allow medicinal chemistry to embark upon a rational approach toward drug design immediately upon the obtainment of such "pictures" for every new pharmacological target of the future. In silico screening of real and virtual libraries, having matured considerably at that point as well, would likewise benefit enormously from such a development and would be expected to be equally interactive with such data in terms of docking virtual compounds into X-ray pictures of enzyme active sites and/or receptors followed by ranking them as potential drug candidates [407]. Further out, but perhaps not too far past the next 75 years of imaginable future, it might be expected that X-ray-type data (even if no longer strictly derived from X-ray's present physics-related principles [408,409]) will be able to be collected at fast enough, real-time intervals such that it may become possible to observe molecular interactions and motions within user-friendly videos after the data is appropriately processed. One can imagine that videos of events such as the actual docking (binding or "affinity" [410]) of a drug, the motions that transpire upon an agonist's triggering of a receptor ("intrinsic activity" [410]), or a substrate's alterations upon action by an enzyme, could all become commonplace in the somewhat more distant future. These displays would be similar to the cartoon (i.e., in Section 1, "hand-waved") versions that we presently generate using com-



**Fig. 20** Conformational and electrostatic potential topographies of c-AMP phosphodiesterase III (PDE III) active site ligands [404]. In Panel A compound **21** represents a c-AMP substrate with its adenine (Ad) and ribose moieties in an 'anti'-relationship. Interaction **22** depicts binding of the phosphate portion using an arginine residue and a water molecule that was initially associated with  $Mg^{2+}$  in a stoichiometric relationship. Complex **23** depicts  $S_N2$  attack of phosphorous by  $H_2O$  with formation of a trigonal bipyramid (TBP) transition state (TS). Compound **24** represents 5'-AMP as its inverted product. The indicated electronic charges conserve the net charge overall and across the TS. Panel B represents an overhead view of the atoms in the single plane of the TS which forms the common base for the two pyramids of the TBP system. Also shown is the proposed electrostatic potential map for the same atoms. Panel C shows a classical PDE III inhibitor ligand and the AM1 derived in-plane molecular electrostatic potential map of its imidazolone ring. Because of the very notable similarity between these two electrostatic potential maps, it has been proposed that these types of compounds, as well as several other heterocycles that have electron-rich hetero-atoms in analogous locations, act as TS inhibitors of PDE-III [404,493,494].

putational or theoretical approaches coupled to molecular modeling packages [411–414] except that the entire process would be based upon actual experimental data obtained in a real-time fashion, as the event actually occurred rather than by what we have only been able to so far catch experimental glimpses of at stabilized junctures or what we are able to imagine what such conversions may look like. For example, observing an actual trigonal bipyramid transition state for the phosphorous atom within c-AMP during its hydrolysis by a phosphodiesterase (Fig. 20) would certainly be a crowning analytical experimental achievement of the future, especially since today's sophisticated theoretical approaches cannot even provide a good cartoon version for this process due to collapse of such a species to lower energies during minimization. Likewise, observing the methylene portion of cyclopropyl dopamine actually crashing into the proposed molecular ceiling on the renal vasculature's dopamine receptor (Fig. 19) would be equally impressive since this bit of older SAR appears to have gradually become lost from the dopamine field due to lack of timely advances able to clarify its reality. Finally, observing that the conformationally redundant nature of endothelin's 3,11-disulfide bond (Fig. 21) actually serves to initiate its post-translational folding paradigm because that bond is easier (distance-wise) to form than the subsequent 1,15-disulfide link [415], represents just one of many older hypotheses that might be taken from the area of proteomics.



**Fig. 21** Proposed folding scheme for the endothelins (ETs) [415]. Positions 1, 3, 11, and 15 are cysteines. Note that formation of the 3,11-disulfide linkage is proposed to occur first given their closer proximity. Subsequent formation of the 1,15-disulfide can then occur more readily to finally adopt the tightly folded form depicted as **25**. At this juncture, the 3,11-disulfide may then represent a conformational redundancy that is not actually required in the final structure. This sequence of events is equally applicable to big endothelin and to pre-proendothelin. Structure **25** represents a molecular dynamics-derived minimum energy conformation for ET-1 after starting from an entry structure where residues 9-16 were initially constrained in an  $\alpha$ -helix [495]. Note that the  $\alpha$ -helix is retained and that His-16, Asp-18, and Trp-21 form a close triad wherein the His-16 and Asp-18 are probably internally hydrogen bonded [415].

## 9. SUMMARY

### 9.1 General points

Medicinal chemistry has been defined as a pure science that explores fundamental physical organic principles to understand the interactions of small molecular displays with the biological realm. Regardless of discipline or background, when investigators seek this level of understanding, they are embarking upon basic medicinal chemistry research. Using a variety of input data, medicinal chemistry's applications, in turn, become that of designing or selecting new drug candidates as well as providing molecular blueprints for improving the therapeutic profiles of existing drugs or of new pharmaceutical agent lead structures. Historically, medicinal chemistry has also been heavily involved with generating input data by designing and synthesizing probe molecules that can systematically test the roles being played by the various physical organic principles during a given interaction. More recently, medicinal chemistry has begun to utilize site-directed mutagenesis as an additional tool to understand these same types of interactions. Future developments in store for drug discovery are summarized in Table 10. The overall progression conveyed by Table 10 can be thought of as being driven by an ever-increasing accumulation of knowledge within the life science arena. Table 11 summarizes some key points relevant to chemical compound categories associated with drug discovery.

**Table 10** Bullet summary of future events predicted for drug discovery and development.

- 
- Genomics and especially proteomics will continue to unveil myriad new biomechanisms applicable to modification for therapeutic gain and applicable to better understanding processes associated with ADMET.
  - Biomechanistic systems lending themselves to crystallization followed by X-ray diffraction will be readily exploited by structure-based drug design.
  - BIOTECH will continue to evolve HTS/UHTS methodologies to assay therapeutic mechanisms and to assess ADMET properties as a front-line initiative.
  - For cases where structure-based drug design is not possible, combinatorial libraries along with both wild and genetically altered or elicited collections of “natural” materials will provide initial hits which will then be followed up by directed libraries and by ligand-based drug design.
  - Accumulating data in all areas will become well managed via a variety of databases including, in particular, an evolved level of 3D sophistication within chemoinformatics. The latter will ultimately provide the common language for the integration of information across all databases.
  - As ADMET information accumulates from preclinical models, which will indeed become validated relative to the human case, distinct structural motifs will arise that can be used with statistically derived confidence limits in a predictive manner during drug design.
  - UHTS of man-made libraries, directed analyses of nature’s mixtures, and importantly, rational exploitation of the newly elaborated and fully understood ADMET structural motifs will reveal synergistic combinations that involve more than one compound.
  - For each case of new drug design, a summation of the accumulated knowledge from efficacy testing, ADMET, and potential synergistic relationships will guide final tailoring of the clinical candidate drug or multi-drug combination. Whereas a reductionist approach toward achieving the most simple, single-molecular system possible will remain appealing, any combination of one or more agents wherein each member can independently use prodrug, soft drug, and multivalent strategies will be considered within the context of deploying whatever is envisioned to ultimately work the best for the clinical indication at hand.
  - As clinical successes unfold, a gradual move from experimental to virtual screening will occur. While this is already being done for initial lead finding by docking “drug-like” virtual compound libraries into pockets defined by X-ray, virtual methods should eventually be able to essentially replace the entire preclinical testing paradigm.
  - Palliative and curative targets will remain, the latter particularly for combating the ever-evolving populations of microorganisms and viruses, and the former for retaining the quality of life as the human lifespan continues to elongate. However, preventative and prophylactic treatment paradigms will gradually take on more significance and will eventually reside at the highest priority of life sciences research.
  - For all treatments, and especially for preventative and prophylactic paradigms, pharmacogenetics will define population subgroups that will then receive treatment protocols optimized for their individuality relative to the particular treatment that is being rendered. Testing to ascertain an individual’s pharmacogenetic profile will begin at birth and continue at periodic intervals throughout one’s life relative to the optimal deployment of preventative protocols. Such testing will also be conducted immediately prior to any treatment of a detected pathophysiology.
  - In the more distant future, the combination of nanotechnologies with bioengineering and biotechnology will allow instillation of devices not only for immediate diagnoses of any deviations from homeostasis, but also of programmable portals for user-friendly drug administration other than via the oral route. Likewise, this same mix of technologies will eventually allow for instillation of programmable exits for the controlled elimination of drugs with or without the need for metabolism. Such developments will, in turn, cause drug discovery to return primarily to the pursuit of only efficacy and toxicity issues.
  - Somewhere during gene therapy’s complete eradication of defective gene-based disease and bolstering of gene-linked defenses, along with the nanotechnology/bioengineering effort to reconstruct humans relative to improving health, public policies and opinions dealing with what other attributes might be manipulated to enhance the quality of life will need to be clarified by significant input from the nonbasic science disciplines. Thus, the social sciences, humanities and philosophy fields, along with religion and the lay public at large, should look forward to providing what will soon become desperately needed input into the continued directions that life sciences research is likely to take well before the end of the next century, let alone before the conclusion of the present millennium.
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## 9.2 Attributes of drug discovery libraries, compound hits, and lead compounds

Table 11 is important because it addresses a noteworthy concern, namely that today's trend to aggressively filter nondrug-like compounds out of the initial drug discovery HTS process may work against the accumulation of knowledge that will be vital toward continually improving the overall process. In other words, while it can be argued that a certain efficiency in the production of NCEs might already be obtainable at this juncture by engaging in this type of negative strategy, an overemphasis upon this approach runs the risk of having the drug discovery and development process becoming forever locked into just this point of evolution. Alternatively, Table 11 conveys how some of today's trends that pertain to the molecular attributes of discovery libraries, compound hits, and lead compounds, might be best deployed so as to allow the future developments conveyed in Table 10 to be derived from a truly solid base of accumulating knowledge.

At the front of the push to move forward remain the trends inspired by biotechnology. HTS has already led to the situation where there are now mountains of *in vitro* data available for input toward drug-related considerations. Within just the near term of the new millennium, the entire gamut of ADMET parameters can be expected to join efficacy surveys being conducted by HTS. Importantly,

**Table 11** Molecular attributes of discovery libraries, compound hits, lead structures, and final compounds.

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### Discovery libraries

- "Size" is less important than "diversity" (with allowance for structurally redundant series, e.g., Me, Et, etc.).
- "Diversity" is also much more important than "drug-like properties," e.g., presence of nondrug-like members can be extremely useful toward initially probing overall structural space.
- Alternatively, "assay likable properties" are mandatory, i.e., compound members must be able to be delivered (e.g., solubilized, etc.) according to demands of a given assay.

### Compound hits

- "Drug-like properties" are less important than "efficacy tolerance", i.e., flexibility for altering structure without altering efficacy (access to "neutral regions").

### Initial lead structures

- "Individual structures" are less important than a detailed description of the "pharmacophore" in terms of electrostatic surface potentials plus knowledge about structural space that is neutral or intolerable toward modifications relative to the measured biological parameter, e.g., efficacy.
- "Nondrug-like" features that may be present within certain members contributing to the overall pharmacophore should be "red-flagged" but not necessarily ruled out as potential building-blocks while the overall process of merging structural space across all parameters is continued, e.g., efficacy plus ADMET.

### Final lead compounds

- Optimal blend of efficacy and drug-like properties (nondrug-like features now completely removed or adequately modified according to experimentally ascertained criteria that have been validated for their correlation to the clinical response).
- At least one neutral region or prodrug/soft drug option remains such that unanticipated hurdles presenting themselves during further development might still be addressed by additional chemical modification.
- One or more back-up compounds having distinctly different molecular scaffolds while still fulfilling the overall ensemble of pharmacophore and drug-like patterns.

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Notice that while emphasis is placed upon defining a given pharmacophore to the maximum possible detail by deemphasizing the use of "drug-like property" parameters as an early filtering mechanism, components of the pharmacophore that are presumed to be undesirable should still be "red-flagged" as such. ADMET SAR can then be superimposed within the distinct molecular contexts of each identified pharmacophore so as to be more efficiently deployed as a filter and, importantly, in a proactive manner while initial lead structures move toward final lead compounds. This two-step approach will also allow for continued knowledge-building within all of the key parameters relative to various therapeutic areas.

during this period the latter's output will have also become validated in terms of predicting clinical correlates. The common link between these databases will be molecular structure as afforded by the probe compounds or compound library members that become deployed during a given assay. Molecular structure can be best appreciated by the precise language that medicinal chemistry has been learning since its formalization as a distinct discipline about 75 years ago. Thus, medicinal chemistry is obliged to also step to the forefront and assist in understanding and translating what the mountains of new data mean so that they might be optimally applied toward the development of new therapeutic agents.

Recognizing that we have not been very effective to date, the appropriate handling of 3D chemical structure within large databases represents a significant challenge that needs to be resolved by a cooperative effort between medicinal chemists, computational chemists, and both bioinformatic and chemoinformatic database experts as quickly as possible. That medicinal chemists have a good appreciation for the biological nature of the data within one mountain vs. that of another is an equally challenging interdisciplinary problem that will need to be addressed by cooperative efforts between medicinal chemists and investigators from all of the biochemical- and biological-related sciences. Resolving both of these challenges will eventually allow the *in vitro* data sets to be intermeshed so as to provide knowledge-generating assemblies that accurately predict the results that are eventually obtained *in vivo* and, ultimately, within the clinic.

### 9.3 Formalized instruction of medicinal chemistry

Faced with these immediate, critical roles for medicinal chemistry within drug discovery research, how should academia be preparing doctoral-level investigators to contribute as medicinal chemists of the new millennium? First and foremost should be to retain medicinal chemistry's emphasis upon the physical organic principles that define chemical behavior in any setting. This is fundamental to being a medicinal chemist. Such principles cannot be learned well by relying only upon textbook/E-instruction or even by predesigned laboratory outcome exposures. Thus, a laboratory-based thesis project that involves physical organic principles as the underlying variables of its scientific enquiries seems mandated. While several types of chemical problems might be envisioned to provide such a learning experience, the laboratory practices of synthetic and physical organic chemistry represent extremely useful tools to permanently drive home the principles associated with intra- and intermolecular behavior and chemical reactivity. Likewise, with regard to synthesis/compound production, it is also extremely important to first learn how to isolate and characterize pure materials. Combinatorial mixtures and biochemical manipulations that rely upon chemical kinetics and the process of natural selection to dictate their concentrations can then be better appreciated if approached at a later point in time. Finally, while a multistep synthesis of a complex natural product can instill fundamental chemical principles, it may be more effective for a budding medicinal chemist to prepare one or more series of probes wherein most of the members in the series are novel in structure but are (seemingly) still readily obtainable via reasonably close literature precedent according to short synthetic sequences, e.g., five or six steps to each template that is to be further derivatized. This positions the student closer to eventually appreciating structural trends and patterns that may reside within databases.

While this solid foundation is being derived from experimental lab work, graduate level exposures to various other fields and aspects of life science research will, instead, have to rely upon available courses, seminars or independent reading. Merging a student's chemical learning base with a specific biological area being targeted by the student's molecular probes, however, ought to be additionally feasible via actual experimentation without jeopardizing either subject's rigor. In the end, however, post-graduate, continuing education is probably the only way that an investigator intending to practice medicinal chemistry will be able to even purview the explosion of information occurring in all of the areas relevant toward assuming the roles needed to resolve the aforementioned challenges of the new millennium. That a practitioner may be able to have a head start along this learning path by initially pur-

suing a formalized medicinal chemistry curriculum rather than an organic chemistry curriculum, has recently been suggested by others [416].

It should be emphasized that the broader exposure to the life sciences is a critical component for a medicinal chemist's continuing education not because medicinal chemists should eventually attempt to independently pursue each of such endeavors, but because these exposures will allow them to more intelligently and meaningfully interact and collaborate with dedicated experts in each of the numerous other fields. Thus, the ability of medicinal chemists to participate in interdisciplinary research while serving as scientific "scholars" during their attempts to integrate knowledge across broad sets of data and scientific fields [417], are key operational behaviors that also need to be instilled early in the overall, graduate-level educational process. By their very nature, medicinal chemistry experiments often prompt fundamental questions or hurdles that may be related to a variety of other disciplines. For example, while in pursuit of dopamine receptor ligands having a cyclopropyl template (Fig. 19), it became necessary to devise a new chemical method for effecting the Curtius conversion under neutral conditions while preserving benzyl-protecting groups that were located on the catechol moiety [418]. A similar chemical hurdle pertaining to the formation of  $\beta$ -acetoxyoxetane systems relative to the paclitaxel studies was likewise encountered [239,240] as part of an earlier cited example. From the biological side, one of the first questions that a medicinal chemist cannot help but ponder immediately upon entry into the paclitaxel arena [175] is whether or not an endogenous material also exists, perhaps similar to but distinct from the microtubule-associated proteins, that normally interacts with the paclitaxel receptors purported to reside on intact microtubules in a stoichiometric manner [419]. Likewise, similar biological questions pertain to the results from probing the SAR associated with the Pgp MDR system. The latter appear to place the investigators in the middle of a "one versus two distinct Pgp binding sites" controversy [420]. In this case, further experimental clarification of this situation may eventually allow these medicinal chemists to pursue site-directed, selective Pgp ligands that are less prone to effect normal cells compared to cancer cells, or to pursue bivalent super ligands, well before the details for this controversy have become fully defined and resolved by genomic and proteomic approaches. Thus, *the interplay of the subject matter from various biological disciplines during medicinal chemistry research is as inherent to the broader medicinal chemistry intellectual process and notion of scholarship as is the practical requisite for a solid-based knowledge of fundamental physical organic principles.*

In the future, increasing numbers of formalized short programs pertaining to a given biological area are likely to be offered to practicing medicinal chemists at technical meetings, at academic centers, at home sites, and via e-instruction [421]. Given the interdisciplinary nature of the problems already at hand, along with the proposition that they will become significantly more complex as we progress further into the new millennium, it is likely that companies that encourage such interdisciplinary types of continuing education will also eventually become the leaders that are able to most effectively implement the new paradigm of drug discovery, i.e., not just toward generating more data faster while working on smaller scale, but toward producing knowledge systems that actually lead to better NCEs at a quicker pace while spending less money.

#### 9.4 Intellectual property considerations

Before closing this review it also becomes appropriate to consider how all of the aforementioned technical and operational possibilities could impact upon where medicinal chemistry may be headed in terms of pharmaceutical IP [422,423]. Comments in this area will be directed only toward small-molecule compounds and not toward biomolecules despite the noted turmoil that was initially created in the gene-related arena [424,425]. As indicated earlier, the highly interdisciplinary nature of today's life science research endeavors, coupled with the new paradigm in drug discovery, indicates that the small-molecule, composition of matter arena is no longer the exclusive domain of medicinal chemistry. Nevertheless, even though the appropriate list of inventors for any given case that has utilized HTS and combinatorial chemistry could become quite complex, with patience these situations should all be rec-



oncilable. Alternatively, there are some other issues that are also beginning to hit the IP arena for which answers and appropriate operational models may not be as clear. Given that the desirable goal of enhancing world trade has prompted the need to recognize (if not to completely harmonize) patents on a global basis [426,427], it is likely that the unique position held by the United States with regard to acknowledging notebook entries as the earliest dates of an invention's conception will ultimately give way to the more practical European process that simply acknowledges the first to file. However, this move will further encourage the filing of patents on technologies that are still very immature. For example, casting this possibility within the trends elaborated throughout this review, companies will need to resist the urge to file on complete compound libraries and instead focus upon claims that protect a reasonable family of leads for which several members have indeed been identified as being meritorious by both efficacy and selectivity and at least preliminary ADMET HTS, i.e., experimentally ascertained privileged structures. Unfortunately, an even worse scenario has already begun, namely in that applications appear to be pending and arguments are being directed toward the validity of patenting huge virtual libraries considered to be drug-like in their makeup. Emphasizing the notion that an actual reduction to practice is paramount for a patent, this author presently stands in opposition to the attempts to garner protection of virtual libraries. Along this same line, this author feels compelled to further note that the current motion to assign CAS numbers to virtual compounds also represents a step in the wrong direction. Finally, while patent protection of an existing scaffold that has experimentally demonstrated its utility in one or more therapeutic areas is certainly meritorious, in the future, companies will still need to refrain from over-elaborating these same scaffolds in an attempt to generate NCEs across several other therapeutic areas based solely upon already having secured IP protection within the context of compositions of matter. In other words, force-fitting a given scaffold via its array of appendage options, rather than by conducting an HTS survey of other structural systems across the complete profile of selective efficacy and ADMET parameters, could easily be taken as a step backwards in terms of both the molecular diversity and therapeutic quality that is ultimately being delivered to the marketplace down the road of the new millennium. A broader discourse on business and scientific ethics at this juncture is beyond the scope of this review even though the rapid biotechnology advances are certainly pressing the need for in-depth discussions in these areas and their fundamental ties with philosophy and religion [428].

### 9.5 Knowledge vs. diversity paradox

In this same regard, however, a seeming paradox will be created by the insertion of knowledge systems into the new drug discovery paradigm. Since medicinal chemistry will seek to define SXR in terms of 3D electrostatic potentials that become predictive of preferred ADMET and efficacy and selectivity behaviors so that their various assemblages can lead to privileged drug structural motifs (or to ensembles of privileged structural motifs that are deployed as drug teams), once this process begins to become effective, it will also play against molecular diversity. While this situation is not nearly as limiting as the situation conveyed in the preceding paragraph and while it will always be subject to an expansion of diversity based upon the uniqueness of the efficacy pharmacophoric components, enhanced ADMET knowledge in particular, will indeed work in a direction away from overall diversity. Hopefully, however, the saving factor in this evolution will remain the pursuit of therapeutically preferred arrangements and not the over utilization of a particular motif just because it has been able to garner an exceptionally favorable ADMET profile, perhaps accompanied by a strong patent position as well. Finally, while enhanced knowledge inherently leads to more credible and useful predictions, it is the overextrapolation, extra weight, or zeal that is sometimes placed upon a given prediction vs. other options including that of having no prediction, that can become problematic. Thus, even when all of the challenges cited in this review appear to be resolved, the various disciplines caught up in drug discovery, including that of medicinal chemistry, should all remain cognizant of the earlier days of "preconceived notions" while also recalling the old adage that "a little bit of knowledge can sometimes be dangerous" such that when

the ideal drugs/drug ensembles of the near-term future are constructed from experimental data, and those of the more distant future from virtual data, the subsequent, lab-based preclinical and clinical investigations, will still remain open to the possibility that, at any point along the way, anything might still be able to happen. Casting this last sentiment in a favorable direction, medicinal chemists of the future, no matter how knowledgeably and guided by wisdom the overall process of drug discovery may seem to have become, should always remain on the alert for serendipity. Toward this end, the following three quotes, already revived by others relative to recent developments important to medicinal chemistry, have been strung together as an apt closing for this review. Each is just as relevant today as it was when it was first pronounced.

“We have scarcely as yet read more than the title page and preface of the great volume of nature, and what we do know is nothing in comparison with that which may be yet unfolded and applied.”

—Joseph Henry, more than 100 years ago, as quoted recently by Madelein Jacobs [2]

And if we are indeed to go forth and “...see further, then it will be by standing on the shoulders of the giants...” as well as on the shoulders of the many others like us who have gone before and who have thus brought us to where we are now.

—Isaac Newton, as quoted recently by Randy Wedin [429] and as modified in tense so as to be used within the present context

For “...we shall not cease from exploration. And the end of all of our exploring will be to arrive where we started, and know the place for the first time.”

—T. S. Eliot, as recently quoted by the International Human Genome Sequencing Consortium while concluding their report on the analysis of a substantially complete version of the human genome sequence [430], a historic accomplishment also reported recently in a similar manner by a Celera Genomics led consortium [431]

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