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STRATEGIES FOR ANTIFILARIAL DRUG DEVELOPMENT

M. A. Kron, L. A. Kuhn*, P. C. Sanschagrin*, M. Hartlein†, Morten Grotli‡, and S. Cusack§
Division of Infectious Diseases, Michigan State University, East Lansing, Michigan 48824. *e-mail: michael.kron@ht.msu.edu*

ABSTRACT: Drug development for most important tropical parasitic diseases, such as lymphatic filariasis, has been orphaned by pharmaceutical companies because it has been considered as not having enough profit potential. The question is not whether new antiparasite drugs are needed for human applications but rather how one can justify the enormous expense involved in new drug discovery. Modern preclinical drug discovery uses a number of complementary techniques to identify lead compounds. To illustrate these approaches, we use the example of a search for antifilarial aminoacyl-tRNA synthetase inhibitors. High-throughput screening of synthetic chemical and natural product libraries uses recombinant enzyme to search for structurally unique enzyme inhibitors. Solving the atomic structure of inhibitor–enzyme complexes yields detailed information on the chemistry of ligand interactions that can be used to enhance inhibitor chemistry and to predict better drug design. Once an enzyme structure is solved, structure-based computational methods are available to predict additional ligands and to optimize the selectivity, affinity, and pharmacological properties of a promising lead compound. Inhibitors thus identified can be tested for effects on parasites maintained in short-term culture. Novel enzyme inhibitors with the best binding and pharmacological properties are selected for large-scale organic synthesis and future clinical phase studies in animals or humans.

MANDATE FOR ANTIPARASITIC DRUGS

The challenge

In September of 2000, the National Institute of Allergy and Infectious Diseases (NIAID) convened the Summit on Development of Infectious Disease Therapeutics to address the state of development of new therapeutics for infectious diseases. Tropical parasitic disease treatments were an important part of these discussions. Conclusions from the NIAID summit highlighted pressing needs for investment in therapeutic, preclinical research for infectious parasitic diseases, innovative partnering with industry, encouragement of international capacity building, mentoring of academics by established industry drug development organizations, and piggy-backing onto existing therapeutic infrastructures for parasite drug discovery.

Filariasis

Human filarial diseases caused by the nematode parasites *Onchocerca volvulus*, *Brugia malayi*, and *Wuchereria bancrofti* affect more than 100 million persons worldwide. The social and economic burden of human filarial diseases, such as loss of productivity in the workforce, physical disfigurement, and social stigmata, e.g., blindness, reaches into the hundreds of millions of dollars annually (Kron et al., 2000). Yet, drug development for most important tropical parasitic diseases has been orphaned by pharmaceutical companies because it has been considered as not having enough profit potential. In the United States, the cost of new drug discovery, from preclinical identification through Food and Drug Administration approval, is estimated to be in the range of 500 to 800 million dollars during a minimum 12- to 15-yr time commitment. Unless a new pharmaceutical company has the potential to recover these costs, i.e., create a billion dollar market, the pharmaceutical industry is often hesitant to invest capital on "novel" molecular targets and their prerequisite new medicinal chemistry infrastructure. Antiinfectives that target known biochemical pathways are therefore more straightforward to develop. For these reasons, there are relatively few drugs that are approved for treatment of human filariasis. Most of the currently available drugs for human usage are first- or second-generation antihelminthics used in veterinary medicine and are chemotherapies discovered decades ago.

Present drugs for filariasis

During World War II, an estimated 15,000 servicemen in the South Pacific acquired acute lymphatic filariasis from exposure to *B. malayi* and *W. bancrofti* (Coggeshall, 1946). In 1947, Hewitt et al. identified a nontoxic piperazine molecule, diethylcarbamazine (84L, *N, N*,-diethyl-4-methylpiperazine-1-carboxamide [DEC]), by in vitro screening using the cultured rat filaria *Litomosoides carinii* (Mackenzie and Kron, 1985). Diethylcarbamazine was then found to be active against human filaria, and it rapidly became the standard oral chemotherapeutic agent to combat most forms of human filariasis because of its chemical stability. However, side effects of DEC induced by treatment of infected subjects and the adult parasites' relative insensitivity to DEC made it necessary to continue the search for antifilarial drugs.

Two groups of antihelminthics in use today act on ligand-gated ion channels in the filarial nematode nervous system (Lazdins and Kron, 1999). Avermectins are irreversible agonists of glutamate-gated chloride channels. Levamasole exerts its effects on the nicotinic acetylcholine receptor (nAChR). Imidazoles exert their effects by targeting tubulin. Benzimidazole and newer fluorinated derivatives bind filarial tubulin.

As research advances our knowledge of filarial biochemistry, a number of new molecular targets have been proposed for antifilarial drug development. Given the enormous costs of drug discovery, it is important to consider which molecular targets might be most appropriate (Table I).

"Ideal" characteristics for an antifilarial drug

In 1998, the World Health Organization sponsored an interdisciplinary meeting to discuss and evaluate new molecular targets for filariasis drug discovery. A consensus opinion on ideal characteristics for a new antifilarial drug addressed both preclinical and clinical needs. A "good target" should be readily available for in vitro testing, such as a recombinant or highly purified enzyme, with an inhibition assay suitable for use in high-throughput screening (HTS). In parallel with HTS, studies involving computer mod-

* Department of Biochemistry and Molecular Biology, Michigan State University, Lansing, Michigan 48824.
† Deuteration Laboratory, Institute Max von Laue-Paul Langevin (ILL), Grenoble, France.
‡ University of Göteborg, Göteborg, Sweden.
§ European Molecular Biology Laboratory, Grenoble Outstation, Grenoble, France.

TABLE I. Partial list of proposed molecular targets in human filarial worms.*

Proposed drug targets in human filarial parasites	Effects
Trehalose	Energy utilization
Prolyl hydoxylase	Cuticle
Glutahione-S-transferase	Detoxification
Ecdysone receptors	Molting, maturation
Retinol-binding proteins	Various biochemical pathways
Aminoacyl-tRNA synthetases	Protein synthesis

* Lazdins and Kron (1999).

eling and atomic structural analysis of target–ligand complexes would complement in vitro and HTS efforts. For widespread use in impoverished countries, drugs should be inexpensive, administered orally, and have a low incidence of side effects. A target may be novel but not so novel as to preclude support from the pharmaceutical industry. Ideally, the drug would kill adult worms after a few doses or at least result in sterilization of female worms. Thus, the molecular target should be present in adult parasites of both sexes and in microfilariae and infective larvae. If the mechanism of action were different from that of presently available drugs, then the new medication could be used to treat parasites resistant to presently available drugs.

Aminoacyl-tRNA synthetases

Aminoacyl-tRNA synthetases (AARS) are a family of enzymes that exemplify a paradox of structure and function. In 1953, Crick postulated the existence of AARS as critical regulatory elements for protein translation in his "Adaptor Hypothesis" of protein assembly (Ibba, 2000). As originally stated, this hypothesis predicted the existence of a unique AARS for each amino acid. The primary function of AARS is to correctly aminoacylate or charge isoacceptor tRNA with the correct amino acid. This is accomplished in a 2-step reaction that involves the formation of an aminoacyl–adenosine monophosphate (aa-AMP) intermediate.

$$ATP + aa_x \leftrightarrow aa_x - AMP$$

$$aa_x - AMP + tRNA^x \rightarrow tRNA^{aa_x} + AMP$$

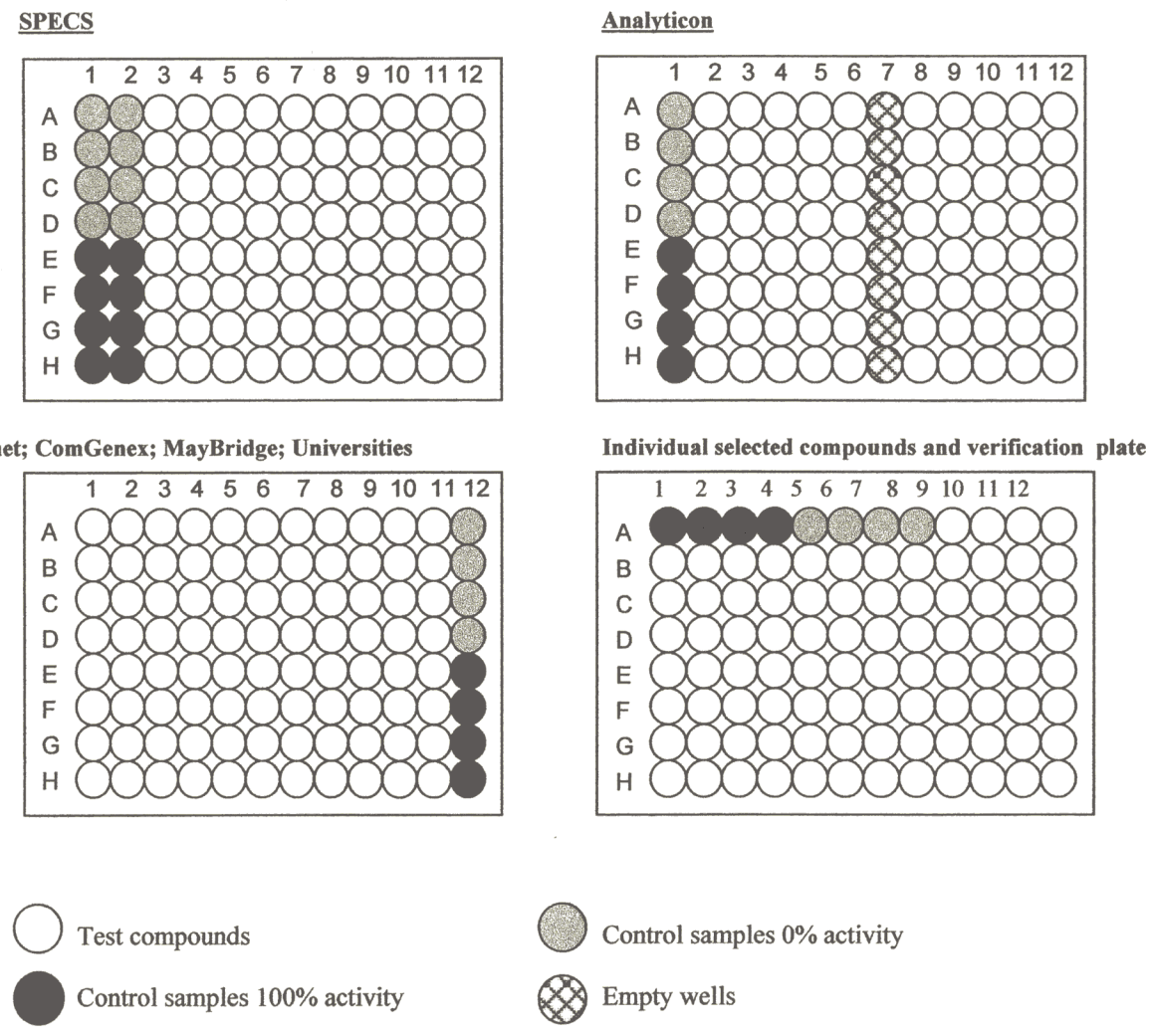

FIGURE 1. Layout of commercial 96-well plates containing low–molecular weight chemicals used in high-throughput screening. Each well contains 5 or more different chemicals.

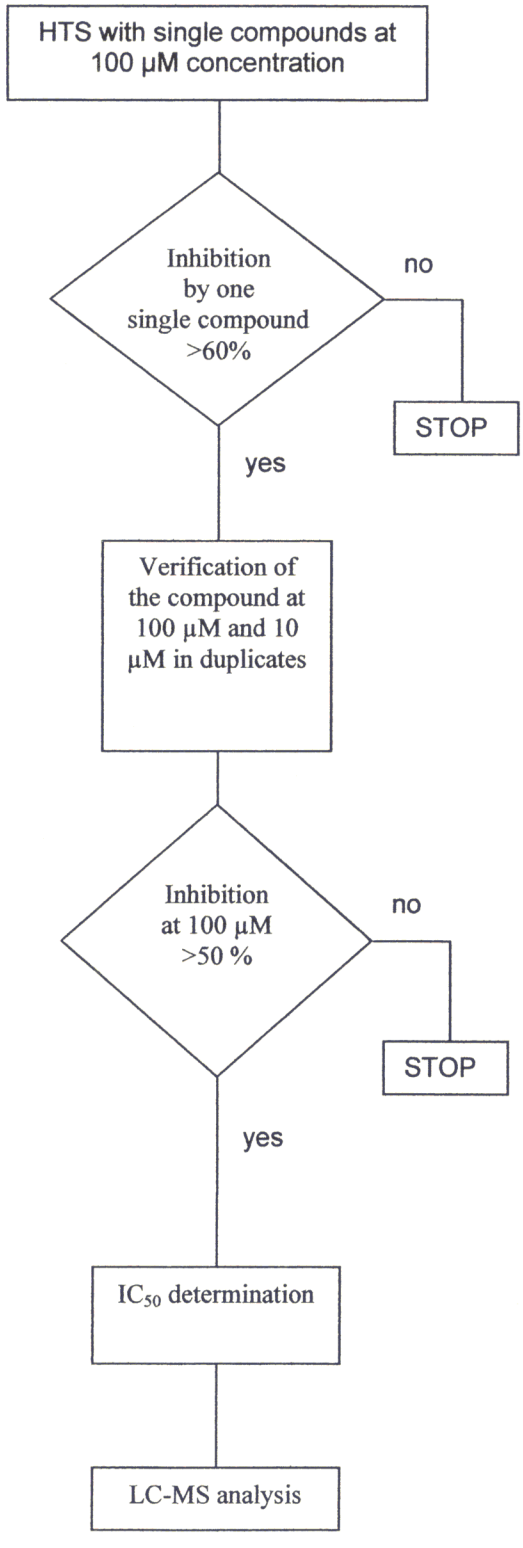

FIGURE 2. Algorithm for definition and selection of potential enzyme inhibitors in a high-throughput–screening scheme.

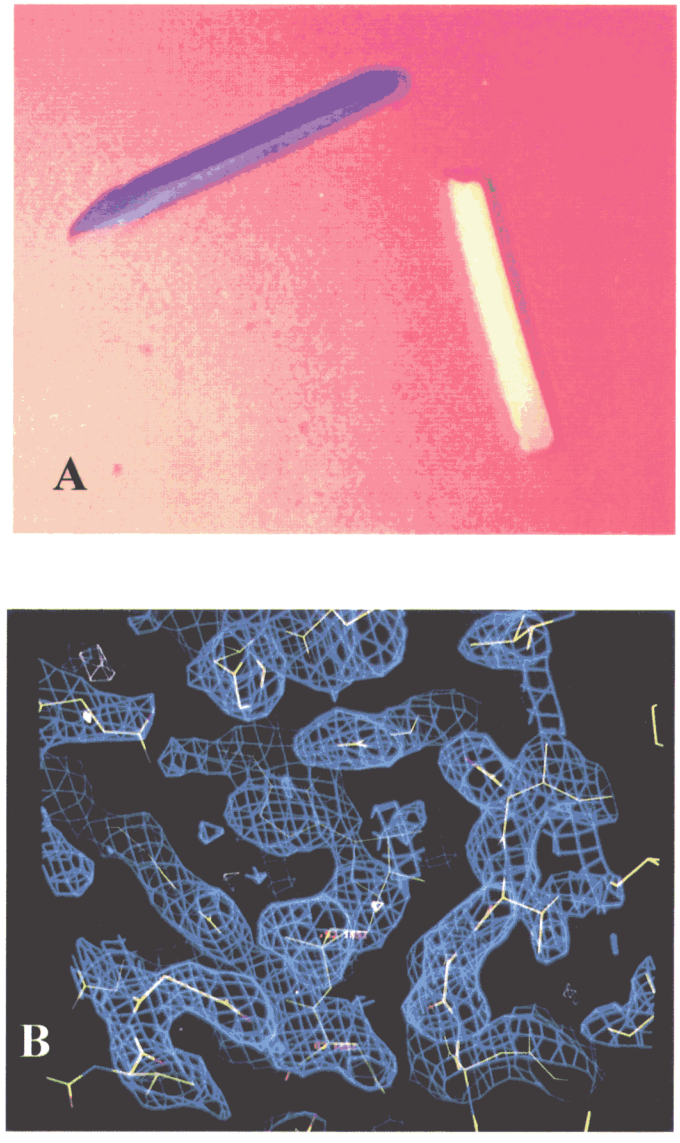

FIGURE 3. (**A**) Crystals of *Brugia malayi* AsnRS complexed with asparagine-sulfamoyl adenylate. (**B**) Electron density map (blue) generated by enzyme crystals in panel A using the European synchrotron radiation source in Grenoble, France. Central structure (green) in catalytic site pocket represents the asparagine sulfamoyl adenylate.

Understanding exactly how such a diverse enzyme family can share a common primary function and yet maintain extraordinary specificity and the ability to discriminate subtle differences between tRNAs and amino acids remains an area of intense interest to structural and evolutionary biologists. The picture grew more complex as structural and functional homologs of AARS were identified using the vastly expanding protein databases. Weiner (1999) suggested that as primordial class I and class II enzymes have evolved over time, catalytic domains have "broken loose" to perform unexpected catalytic and regulatory functions. This was favored by AARSs being among the very first proteins that evolved because they are required for synthesizing other proteins; their subunits thus provided early building blocks to evolve new functions.

Cusack et al. (1990) solved the atomic structure of the *Escherichia coli* seryl-tRNA synthetase, the first example of an AARS, whose catalytic site did not contain the conformation of a common nucleotide-binding motif, the Rossmann fold.

With rare exceptions, all AARS from prokaryotes, eukaryotes, and archae can be classified as either class I (Rossmann Fold) or class II enzymes (antiparallel beta fold) on the basis of their catalytic site topology. The class II enzymes include asparaginyl-tRNA synthetase (AsnRS) and are active as α_2 homodimers or $\alpha_2\beta_2$ tetramers. Each AARS displays up to 3 conserved 9- to 11-residue class-specific motifs that play a role in recognition of the adenylate intermediate, ATP, and maintenance of quaternary structure. Unmodified synthetic aminoacyl adenylate analogs, e.g., amino acid sulfamoyl adenylates, can inhibit both microbial and human AARS; to become good candidates as drug leads, they require further optimization to achieve specificity for the microbial enzyme, relative to the human enzyme.

With the recent rapid accumulation of primary sequences of AARS in various genomes, it is apparent that often there are distinct structural differences detectable in the primary sequence between the same AARS from organisms in Archaea, Eubacteria, and Eukarya. Several exceptions to the classic rule of 2 AARS classes have been documented. For example, lysyl-tRNA synthetase is normally a class II enzyme. However, in the archaebacterium *Methanococcus jannaschii* and the spirochete *Borrelia burgdorferi*, there is a novel class I lysyl-tRNA synthetase. Up to 4 of the 20 AARS are missing in the genomes of some archaebacteria, revealing alternative pathways for amino acid utilization. Prolyl-tRNA synthetase (ProRS) is a class II synthetase that occurs in 1 or 2 quite distinct structural architectures, i.e., prokaryotelike and eukaryote-archaeon–like (Yaremchuk et al., 2000). Asparaginyl-tRNA synthetase is another class IIa synthetase that is believed to be an evolutionarily more recent enzyme. Bacteria that lack a dedicated AsnRS use an alternative pathway involving a heterotrimeric amidotransferase enzyme, gatCAB, to form Asn-tRNA^{Asn} from an AspRS that does not discriminate between the isoacceptor tRNAs of asparagine and aspartic acid (Becker et al., 2001). The filarial parasite, *B. malayi*, clearly possesses a multicopy AsnRS gene (Nilsen et al., 1988; Kron et al., 1995), but the *Wolbachia* endosymbionts within the filaria, which are similar to archaea, exhibit the aminotransferase pathway for amino acid utilization (H. Hartlein and M. Kron, unpubl. data).

AARS as targets for new antiinfectives

Aminoacyl-tRNA synthetases are active targets for antibacterial and antifungal drug design being pursued by several major pharmaceutical companies. Aminoacyl-tRNA synthetases have been acknowledged as a rational target for antiinfective drug development (Schimmel et al., 1998) because they

- Function in important primary functions (aminoacylation of isoacceptor tRNA) or secondary functions within prokaryotic and eukaryotic species. These enzymes are essential for the viability of the organism.
- Demonstrate primary and secondary sequence heterogeneity although sharing a common catalytic site topology, which is critical to recognition of inhibitors that block the synthesis or release of the aminoacyl adenylate.

The idea of AARS as novel molecular targets for antifilarial drug discovery was first suggested 17 yr ago at a Burroughs Wellcome Filariasis Seminar (Walter, 1986). The experimental antihelminthic compound, CGP8065, demonstrated weak effects on the arginyl-, lysyl- and seryl-tRNA synthetases of the dog filaria *Dirofilaria immitis*, and the human filaria *Onchocerca volvulus*. Because of toxicity issues, unknown mechanism of action, and the absence of any purified sources of filarial AARS in 1985, this dithiocarbamate derivative of amoscanate was abandoned as an antifilarial drug. Presently, because of many advances in our knowledge of AARS structure and function during the last 15 yr, filarial AARS can be revisited as novel molecular targets for drug development. In particular, filarial AsnRS may be a good target for drug development because in *B. malayi*, AsnRS is expressed in both sexes, adults, bloodborne microfilariae, and in the infective larvae (L3) (Nilsen et al., 1988; Kron et al., 1995). Asparaginyl-tRNA synthetase is well characterized biochemically and structurally in several species, and both filarial and human AsnRS can be expressed recombinantly in biologically active forms (Kron et al., 1995; Beaulande et al., 1998).

Many examples of novel and enzyme-specific or species-specific AARS inhibitors have been identified. The natural product, pseudomonic acid (mupirocin, produced by strains of *Pseudomonas fluorescens*), was the first FDA-approved AARS inhibitor (Baines et al., 1984). Pseudomonic acid is specific for the *Staphylococcus aureus* isoleucyl-tRNA synthetase, with an approximately 8,000-fold selectivity for pathogen against mammalian isoleucyl-tRNA synthetase (Hughes and Mellows, 1987). Other known natural product inhibitors of tRNA synthetases include borrelidin (against the threonyl enzyme) (Nass et al., 1969), furanomycin (against isoleucyl RS) (Tanaka et al., 1969), granaticin (against leucyl RS) (Ogilvie et al., 1975), indolmycin (against tryptophanyl RS) (Werner et al., 1976), ochratoxin A (against phenylalanine RS) (Konrad and Roschenthaler, 1977), and cispentacin (Konishi et al., 1989).

MATERIALS AND METHODS

The same complementary methods used by the preclinical discovery laboratories of the pharmaceutical industry seeking new antibacterial and antifungal AARS inhibitor can be pursued by academic collaborations to search for and evaluate novel inhibitors of filarial AARS.

High-throughput screening

High-throughput screening of chemical libraries for AsnRS inhibitors uses a stable in vitro aminoacylation assay with recombinant AsnRS and radiolabeled asparagine. Technological advances such as the use of robotics and miniaturization of assay volumes raise the capacity of HTS to evaluate tens of thousands of compounds per day. In collaboration with Discovery Technologies Ltd. (Basel, Switzerland), a collection of 11,000 low–molecular weight synthetic chemicals was selected from various commercial sources to search for filarial AsnRS inhibitors (Fig. 1).

The specific enzyme activity (in %) was calculated using the following equation:

$$E_a = \frac{V - B}{C - B} \times 100$$

where

E_a: Specific activity in %

V: Measured value (cpm) for test compound

C: Mean cpm of 100% activity

B: Mean cpm of 0% activity.

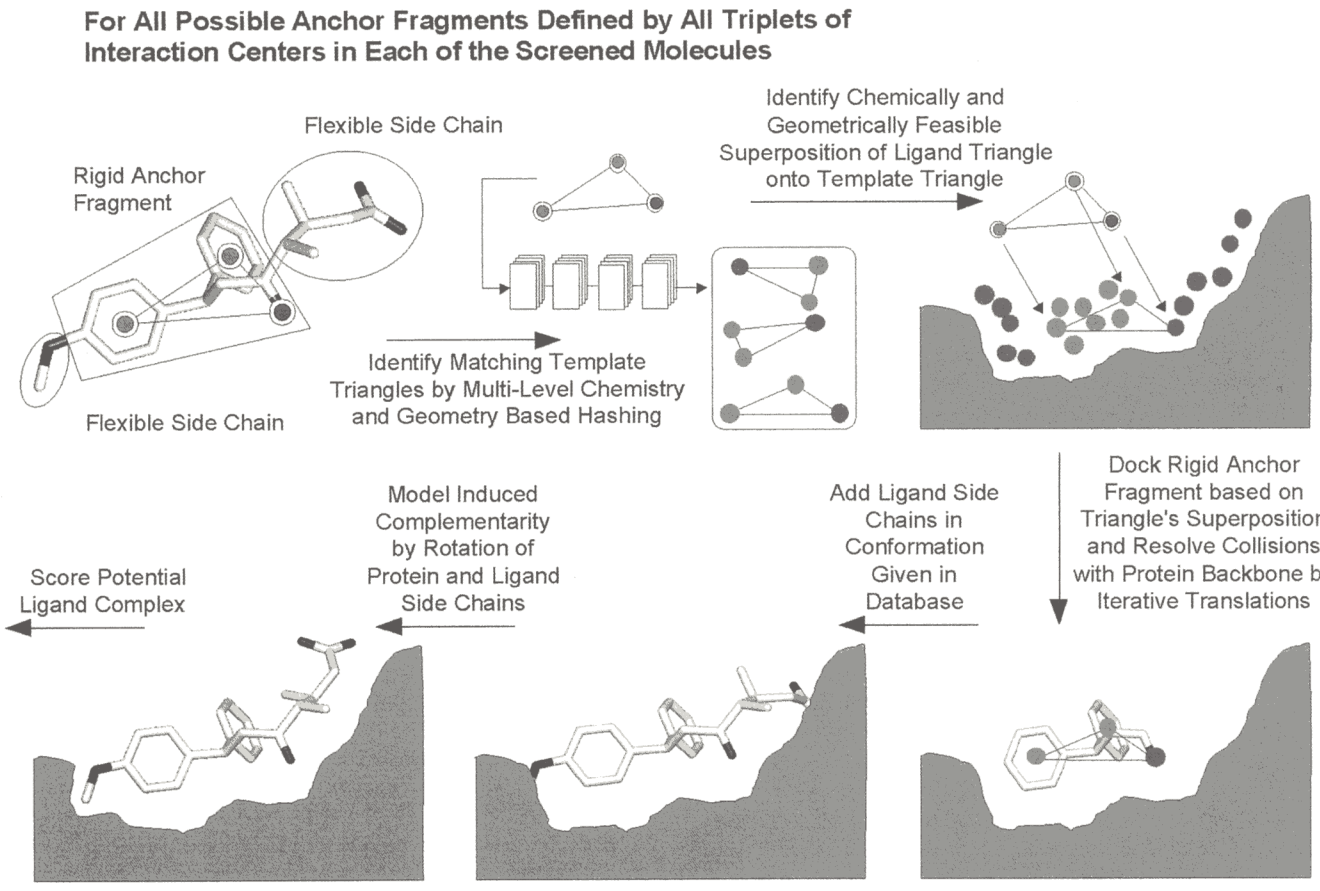

FIGURE 4. Diagram outlining the steps used by the structure based computational screening method, SLIDE. Catalytic site templates can be generated using the native enzyme structure (unbiased) or by making use of an inhibitor–enzyme complex (biased template).

TABLE II. Results of high-throughput screening. IC_{50} values measured with *Brugia malayi* enzyme (Bm) are compared with human enzyme (Hs). All 16 compounds identified had IC_{50} values lower with parasite enzyme. Activity values represent the residual enzyme activity after incubation with potential inhibitors.

Hit no.	ID	Activity at 100 μM (%)	Activity at 10 μM (%)	Bm IC_{50} (μM)	Purity of compound*	Hs IC_{50} (μM)	IC_{50} ratio
1	0107228	38	59	29	70%	1,810	63
2	0113011	29	64	109	Good	910	8
3	0115790	−14	44	14	80%	201	14
4	0117496	10	47	50	Good	1,656	33
5	0118041	38	72	97	80%	203	2
6	0118994	22	83	69	80%	807	12
7	0134321	12	59	14	80%	571	40
8	0134763	0	52	16	70%	61	4
9	0134901	37	66	115	80%	503	4
10	0139248	5	50	102	70%	554	5
11	0139260	−16	31	8	Good	157	20
12	0139386	−18	40	33	70%	830	25
13	0139410	46	69	170	Good	8,096	48
14	0139411	−2	30	7	80%	183	28
15	0213336	15	84	63	Good	108	2
16	0001366	31	73	22	80%	125	6
17	Positive control	0	0	4.5	100%	1.7	0.4

* "Good" = 50–70%.

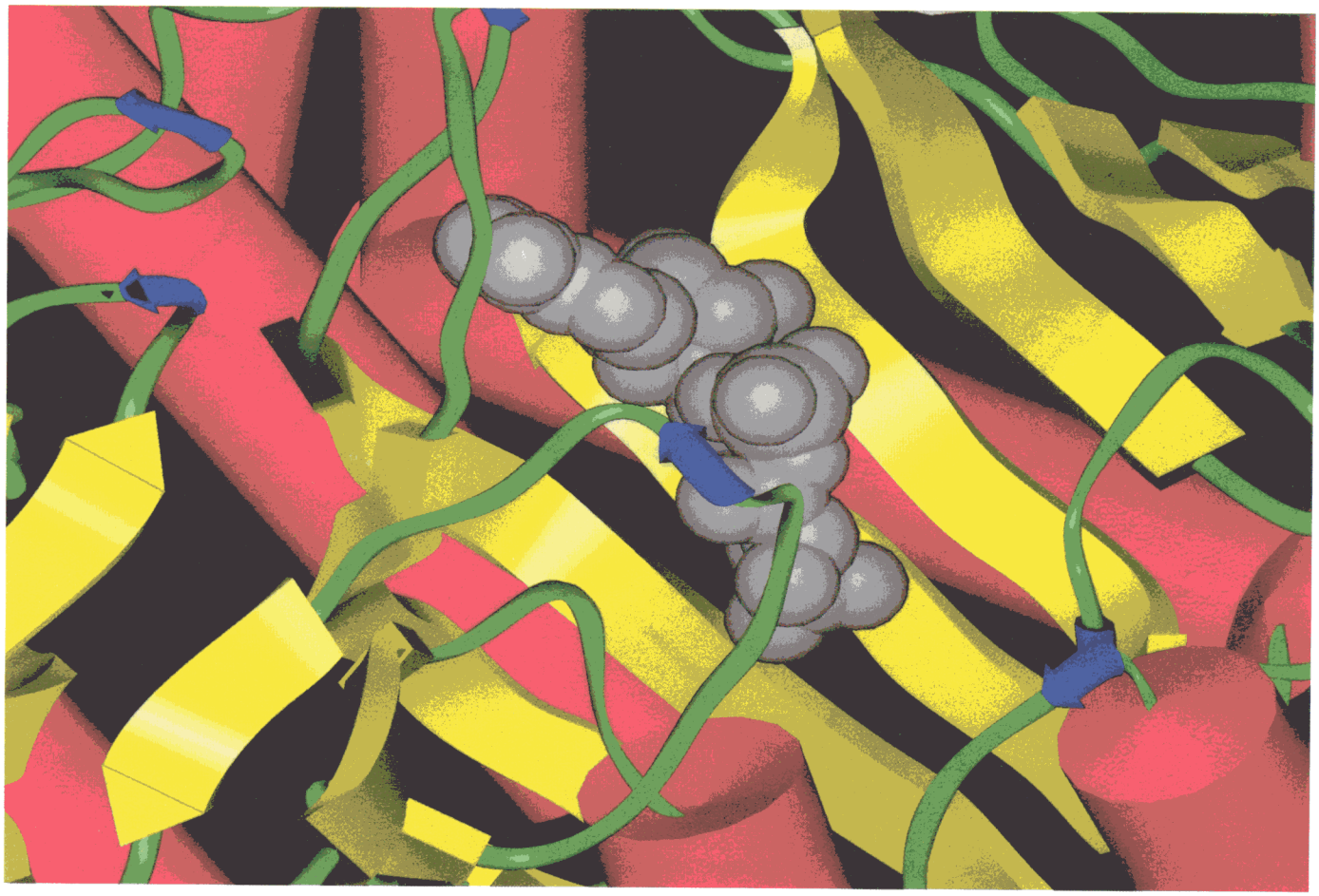

FIGURE 5. Atomic structure of the cytoplasmic *Brugia malayi* AsnRS. The enzyme displays general structural features characteristic of class IIa synthetases. The location of the adenylate binding is indicated by a gray beaded structure.

The inhibition of asparagine aminoacylation activity is calculated as follows. The percentage of counts inhibited by a chemical sample is compared with a control included in each run where percentage inhibition = ([cpm with control − cpm with test compound]/cpm with control) × 100. Test compounds were stored in dimethyl sulfoxide (DMSO) in standard 96-well microtiter plates under an N_2 atmosphere until ready for use. Solvent insensitivity of the recombinant AsnRS was confirmed before HTS.

Primary screening of compounds follows a preestablished methodology that includes an important decision on the drug concentration for screening (Fig. 2). Significant inhibition was defined as >50% inhibition. After identification of possible leads in primary screening, single compounds were diluted in DMSO to give the original and one-tenth of the original screening concentration in the verification assay. Activity was determined in duplicate, with controls on each plate and evaluated as described above. A liquid chromatography–mass spectrometry analysis was performed to check the identity and purity of the reported compounds. Hit compounds were subjected to IC_{50} analysis at 300/100/33/11/3.6 and 1.2 μM, respectively, in duplicate.

Atomic structures of target–ligand complexes

A variety of sophisticated techniques, e.g., nuclear magnetic resonance, X-ray and synchrotron high-energy diffraction of crystals, deuteration, and neutron scattering, have been developed to obtain information on the 3-dimensional structures of chosen drug targets (Cusack et al., 1990; Chayen et al., 1996; Bon et al., 1999; Langan and Schoenborn, 1999). Ideally, if an enzyme can be crystallized in the proper form, then one can use these crystals to generate high-energy diffraction patterns, i.e., electron density maps, to reveal the atomic structure of the enzyme. If similar crystals can be produced in the presence of an inhibitor, then catalytic site topology can be studied for residues making critical ligand–enzyme interactions (Fig. 3).

Structure-based computational methods in drug design

Once the structure of a molecular target has been solved, computational methods can be used to identify new druglike inhibitors. Structure-based drug design (Doucet and Weber, 1996) has led to the development of potent and specific new drugs, such as the widely used nonsteroidal anti-inflammatory Celebrex and human immunodeficiency virus (HIV)–protease inhibitors such as Viracept. Computational or virtual screening is attractive for identifying new molecular scaffolds and substituents for drug design and for screening analogs, and computational screening typically has a higher hit rate for identifying inhibitors than in vitro screening. It is also a useful tool for focusing in vitro screening toward appropriate molecular scaffolds and substituents because virtual screening incorporates knowledge of the 3-dimensional characteristics of the protein site being targeted. Whereas in vitro library screening does not provide insights into the way compounds bind, computational screening using docking provides a direct, atomic model of the protein–ligand interaction that can guide further experimentation and lead optimization.

In one study, 34% of potential ligands identified by the computational screening tool DOCK (Shoichet et al., 1999) showed inhibitory activity, compared with a 0.03% hit rate for in vitro high-throughput screening. Whereas DOCK has the advantage of having been in development and use since the mid-1980s, the virtual screening tool SLIDE, developed at collaborator Dr. Leslie Kuhn's laboratory, has the potential to perform better because of its ability to include active-site flexibility and solvation in the screening and docking steps. SLIDE has been shown to appropriately mimic protein and ligand conformational changes, al-

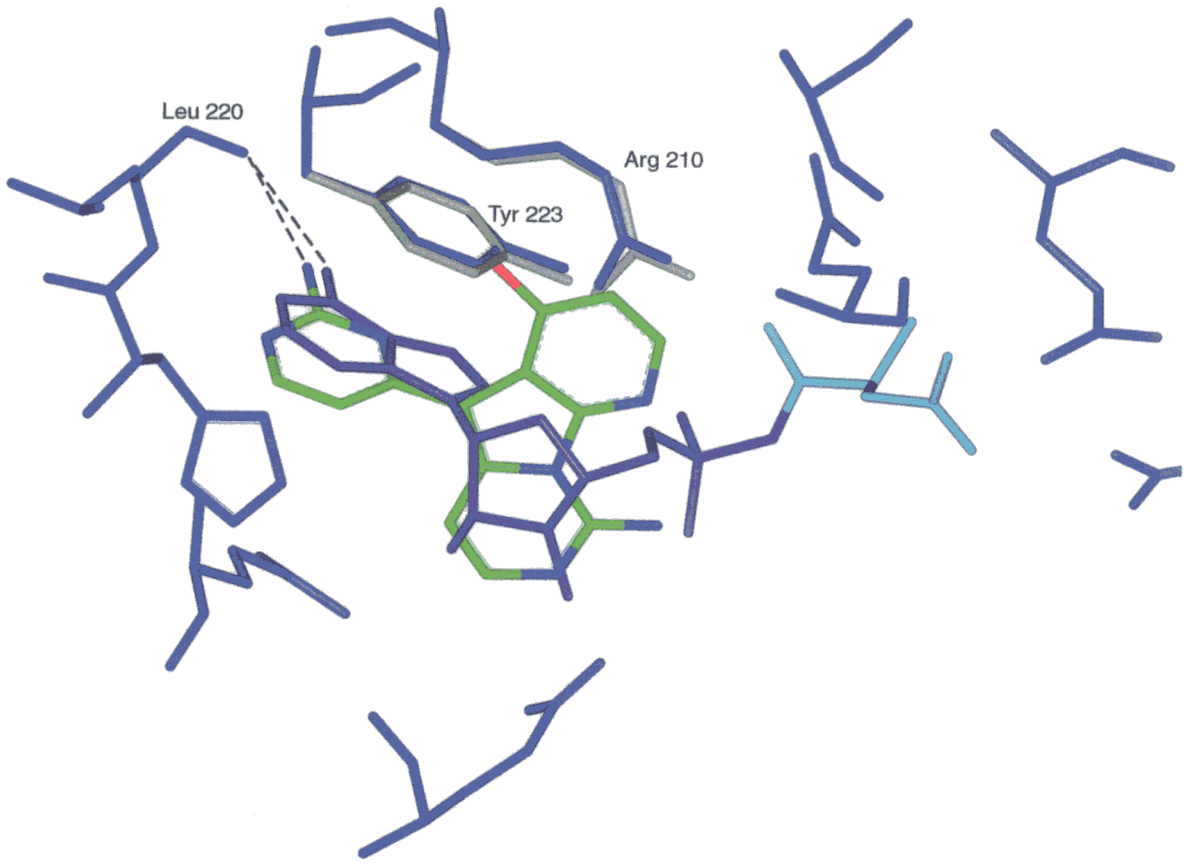

FIGURE 6. The structure of a tricyclic chemical (shown by the atom-colored tubes at center) docked by SLIDE into the crystal structure of *Brugia malayi* AsnRS (active-site side chains shown in dark blue). The position of the adenosyl portion of the predicted ligand (purple tubes) from the *B. malayi* AsnRS crystal structure is shown superimposed with the docked orientation of the predicted ligand (atom-colored tubes) for comparison of their binding modes. Side chains rotated by SLIDE during docking are indicated in gray, and a hydrogen bond conserved between the AMP and predicted ligand interactions with AsnRS are shown by dashed lines.

though correctly docking and giving high protein–ligand complementarity scores to known ligands for diverse proteins. Some applications to date include thrombin, HIV protease, glutathione S-transferase, estrogen receptor, subtilisin, uracil-DNA glycosylase, rhizopuspepsin, and dihydrofolate reductase (Schnecke et al., 1998; Schnecke and Kuhn, 1999). Recent isothermal titration calorimetry results on 15 SLIDE ligands (of 200,000 screened) led to the discovery of 2 new ligands for another target, thrombin (M. L. Zavodszky and L. A. Kuhn, pers. comm.). With a high-resolution crystal-derived structure of *Brugia* AsnRS, SLIDE can be used to predict new AsnRS inhibitors that can be verified in vitro. An additional advantage of virtual screening is to enable prioritization of scaffolds and substituents in library screening so that the screening and assays can be focused on shapes and chemistries most compatible with the tRNA synthetase–binding sites (Fig. 4).

In vitro drug testing in cultured parasites

Most filarial species can be maintained for at least several days in laboratory culture media. This time is sufficient for examining the effects of lead compounds. This rather crude screening method tests also for penetration of the filarial cuticle by underivatized lead compounds.

RESULTS

High-throughput screening

Using the definition of a hit as >50% inhibition, 16 compounds were identified. The IC50 values of each hit were determined using both recombinant *B. malayi* and human AsnRS. IC50 ratios were calculated as an indicator of the relative affinity of the inhibitors for parasite and human enzymes (Table II).

Atomic structure of filarial AsnRS

Crystals of *B. malayi* AsnRS were produced from the recombinant enzyme, and these crystals diffracted well using the high-energy synchrotron radiation source at the European Molecular Biology Laboratories Grenoble Outstation (Cusack et al., 2001). These crystals yielded a high-resolution structure (1.9 Å) of the enzyme complexed with a synthetic asparagine adenylate intermediate (Fig. 5).

Structure-based focusing

Using the high-resolution structure of filarial AsnRS, a computer model of the catalytic site–adenylate interactions were generated. This template was used to screen the Cambridge Structural Database of 80,000 compounds for novel compounds that mimic the binding characteristics of the adenylate (Fig. 6). Binding modes were also predicted for the 16 compounds identified by in vitro HTS.

Effects of hits on adult female parasites in vitro

Adult female *B. malayi* parasites were grown in the presence of hit compounds for 96 hr to determine whether any unmod-

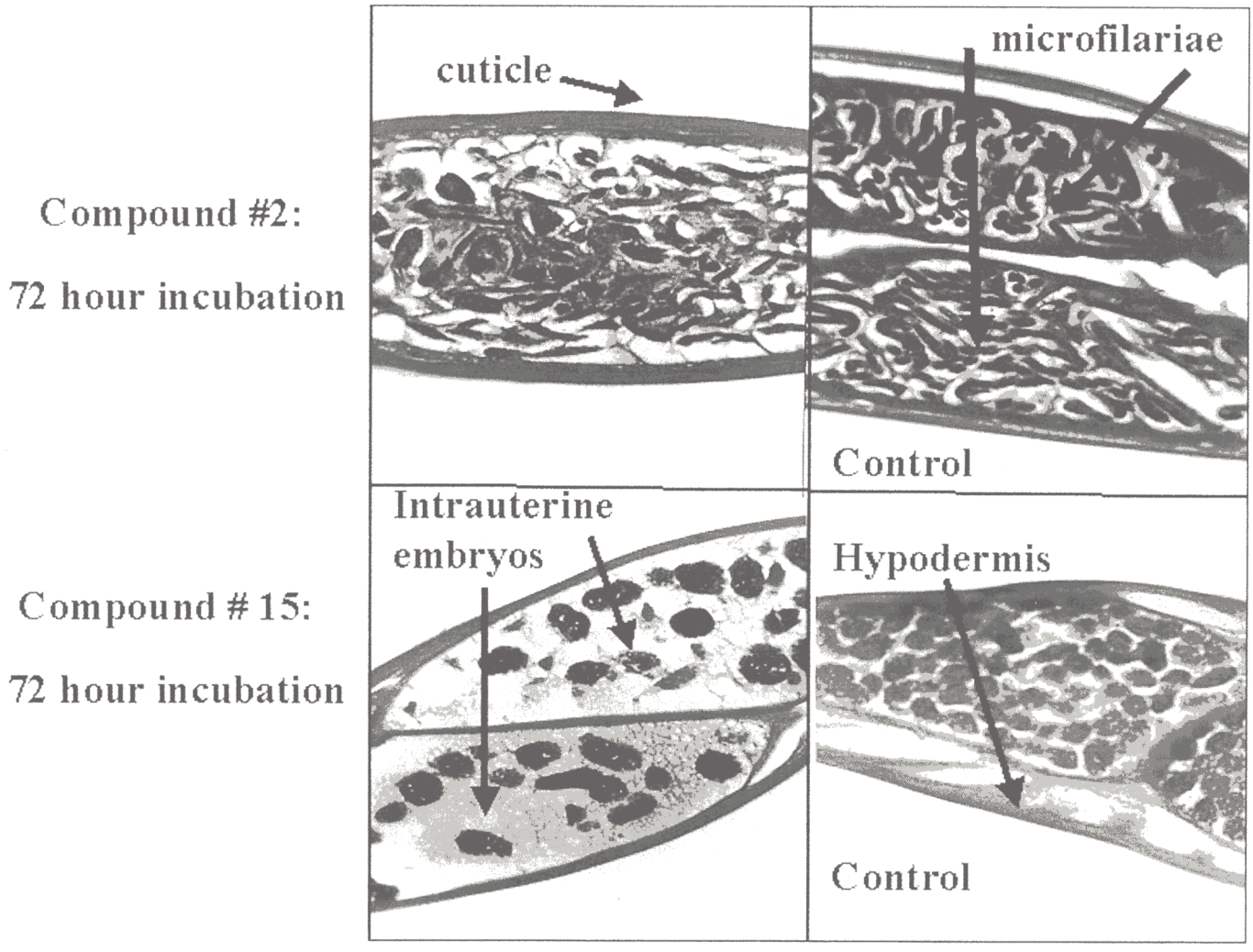

FIGURE 7. Photomicrographs of adult female *Brugia malayi* after exposure to 2-hit compounds (left panels) compared with controls (right panels) containing DMSO alone. At 72 hr, all parasites exposed to compounds #2 and #15 (100 μM) are dead and intrauterine forms are disintegrating. Controls and parasites incubated with the other 14 compounds from Table II all appear normal. After just 24 hr, the motility of parasites exposed to #2 and #15 is grossly abnormal and slow. Magnification of photomicrographs is ×100.

ified chemicals demonstrated obvious physiological effects on the parasite (Fig. 7). Two compounds produced significant toxic effects on intrauterine developing forms and resulted in 100% parasite death by 72 hr. In contrast, control female worms (DMSO alone) were 100% viable at 72 hr.

DISCUSSION

The results of preclinical drug discovery efforts to identify filarial AARS inhibitors are intended to identify novel enzyme inhibitors and not new antifilarial drugs. Rather, the information gleaned from detailed studies of enzyme–inhibitor activity can guide future efforts at designer drug synthesis. High-throughput screening identifies compounds that consistently inhibit enzyme activity, but this does not necessarily imply a uniform mechanism of action. Each hit must be individually tested for mechanism of inhibition and pharmacokinetics. One must be aware of the concept of "frequent hitters" in HTS. Certain chemical structures appear to inhibit many different types of enzymes. They can be identified by anomalies in the concentration dependence of ligand inhibition of the target and thus may be disregarded as viable lead drug candidates (Roche et al., 2002). Because statistical modeling tools help evaluate lead compounds before large scale synthesis, QSAR (for "quantitative structure–activity relationships") and ADMET (for "absorption, distribution, metabolism, excretion, and toxicity") can also be used to select lead compounds for further cell culture and animal testing, followed by human clinical trials. At some point, one must ask the question, "What is an acceptable IC50 ratio for a drug"? In the case of the antibiotic naldixic acid, the compound from which modern day quinolone antibiotics are derived, modifications of the base structure raised the pathogen enzyme selectivity (IC50 ratio) from 17 to over 3,000 in clinically useful drugs.

Structure-based focusing methods have improved significantly during the past 5 yr. Especially when based on atomic structures of the enzyme target, computational methods have the capacity to lead HTS by restricting chemical libraries to defined subsets. But no matter how low the hit rate is brought

down, i.e., from 0.01 to 10%, each potential enzyme inhibitor must be tested in vitro to confirm a mechanism of action.

Successful efforts to solve atomic structures of the enzyme target can generate extraordinary new insights into understanding the mechanism of inhibitor action. However, in the case of AARS, to make the most of atomic structure data and the computational methods based on them, the full set of atomic structures desirable includes the native enzyme plus enzyme complexes including ATP, amino acid, tRNA, the adenylate intermediate, and any other prototype inhibitors.

CONCLUSIONS

Modern drug discovery is an enormously expensive process that also requires many years of commitment. Therefore, the most logical approach to antiparasite drug development may be derived from "piggy back" projects linked to preexisting preclinical discovery programs and by research in such related fields as veterinary medicine, animal health products, and anticancer drug discovery. One can never, however, control the occasional serendipitous discovery of novel target inhibitors. Therefore, continued research into parasite-specific biochemical pathways, proteomics, and genomics are critically important endeavors that will provide the infrastructure for new parasite control discoveries.

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