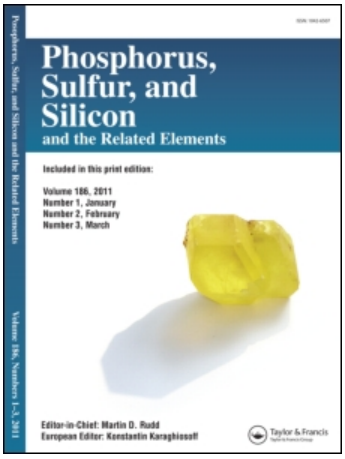

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Dehlinger, Peter J.(1996) 'Making the Most of Inventive Discoveries in the Phosphorus Chemistry Field: Implications of a Probability Model of Invention', Phosphorus, Sulfur, and Silicon and the Related Elements, 109: 1, 369 — 372
To link to this Article: DOI: 10.1080/10426509608545167
URL: http://dx.doi.org/10.1080/10426509608545167

Phosphorus, Sulfur, and Silicon, 1996, Vols. 109–110, pp. 369–372
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Making the Most of Inventive Discoveries in the Phosphorus Chemistry Field: Implications of a Probability Model of Invention

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Abstract A probability model of invention is discussed. The model is used to show how to identify the scope of invention, and support claims commensurate with this scope.

INTRODUCTION

To make the most of an inventive discovery, an inventor needs to be able to recognize the full scope of an invention, and know how to support claims commensurate with this scope. This paper presents a probability model of invention which can guide an inventor on these issues.

THE MODEL

We start with the premise that an invention contains novel information. By applying this premise to some simple probability notions, we are led to two conclusions that will be developed in the course of the paper: (i) an invention is patentable (nonobvious) if the novel information suggests further improvements; and (ii) the scope of the invention includes the invention and its suggested improvements.

To illustrate the probability model with an example from the field of phosphonate compounds, consider an invention for a competitive NMDA (N-methyl-D-aspartate) receptor antagonist compound[1]. One of the first NMDA antagonist compounds discovered was D-α-AA (D-α-aminoadipic acid), an analog of L-aspartate acid that contains an additional two methylene groups in its α-carbon side chain. The information contained in this invention is that "increasing the size of the α-carbon side chain by two methylene groups converts the NMDA agonist L-aspartate to an NMDA competitive antagonist."

How can this information be used? Before the inventive discovery, the logical

search space for finding an NMDA receptor antagonist is the space containing all possible L-aspartate analogs (excluding known agonists, such as L-glutamate and NMDA). Once the D-α-AA discovery is made, however, the search for new antagonists is logically confined to those L-aspartate analogs having side chains with additional methylene groups in the side chain (FIGURE 1). The constrained search leads to the identification of two additional NMDA antagonists, D-α-AP (D-α-aminopimelic acid) and D-α-AS (D-α-aminosuberic acid) containing 3 and 4 additional methylene groups, respectively, in the side chain.

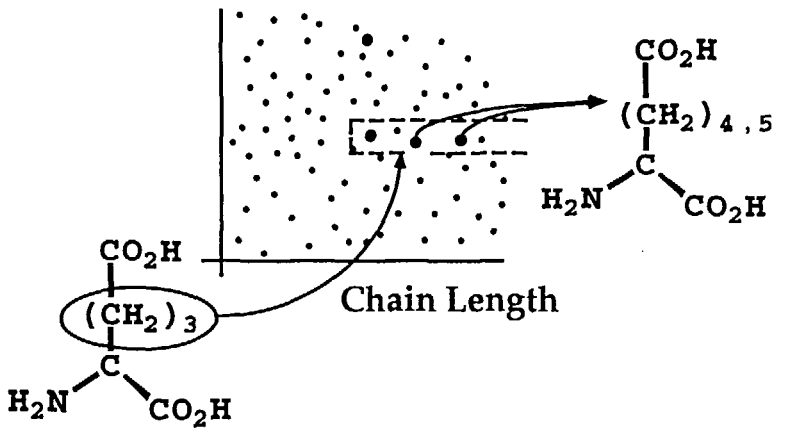

FIGURE 1 What D-α-AA suggests

The D-α-AA discovery has converted a relatively low-probability event--identifying D-α-AP or D-α-AS as an NMDA antagonist-- to a high probability event. We can say that the parent discovery has "suggested" the improvements by confining the search for improvements to a narrow region of the total search space-- namely the space of L-aspartate analogs with additional methylene groups in the α-carbon side chain. The ability to suggest further improvements not previously suggested provides a simple test for patentability, i.e., nonobviousness.

Note that under this test, the improvements D-α-AP and D-α-AS would not be independently patentable, because they don't suggest further modifications not already suggested by D-α-AA.

The scope of the D-α-AA invention would encompass all improvements

suggested by the compound. It is therefore useful to ask whether D-α-AA suggests other analogs, for example, AP-5 (D-2-amino-5-phosphonopentanoic acid), a second-generation NMDA antagonist that differs from D-α-AA in the substitution of a δ phosphono group for a δ carboxy group (FIGURE 2). Although D-α-AA does suggest confining the search space to analogs with extended α-carbon chains, there is nothing about the D-α-AA discovery to specifically guide the search among L-aspartate analogs to the chain-terminal acid group, or to a phosphono group in particular. For this reason, the discovery of D-α-AA as an NMDA antagonist hasn't significantly increased the probability of finding the δ carbon phosphono analog over any other analog containing three-methylene side chains. Thus, D-α-AA cannot be said to suggest AP-5, and AP-5 would not be within the scope of the D-α-AA invention.

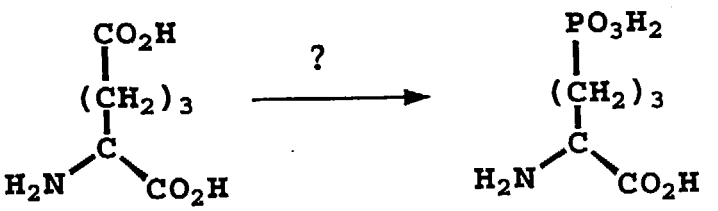

FIGURE 2 First-to-second generation NMDA antagonists

In summary, the scope of invention will include the invention itself and the improvements suggested by the invention, i.e., improvements for which constraints imposed by the invention convert a low-probability discovery event to a high-probability one. Now, to obtain claims whose scope is commensurate with the scope of the invention, the inventor must further establish a reasonable basis for predicting that the suggested improvements are enabled, that is, can be made and used.

To illustrate the latter point, the cyclic phosphono NMDA antagonist CGS 19755 (FIGURE 3) would logically suggest any R-group substitution that preserves the basic features of the invention of a piperidine ring with an "α" carboxy group and a phosphono R-group attached to the ring. The range of these substitutions would represent the scope of the invention, i.e., improvements whose discovery is significantly enhanced by the parent discovery.

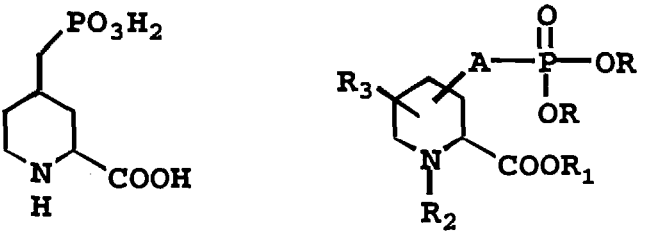

FIGURE 3 Scope of an invention

To support claims of this scope, the inventor must show, by selected examples, that various combinations of R-groups within the scope of the invention can be synthesized and retain NMDA antagonist activity[2].

OTHER IMPLICATIONS OF THE MODEL

The invention model discussed above establishes a link between nonobviousness and claim scope, which may be useful in examining various stretegies employed in medicinal chemistry research. SAR and pharmacophore modeling studies are designed to yield information that can be used to predict the structure of novel, high-activity compounds. If the modeling information is highly predictive, the information will lead to the discovery of such compounds with high probability. In this case, the information is inventive, and the scope of the invention includes the suggested high-activity compounds. By the same token, a weakly predictive model will not significantly enhance the probability of finding high-activity compounds, and the modeling information will be of limited patent value.

We can contrast SAR or pharmacophore modeling with small-molecule combinatorial library screening, which has the inherent capability of generating highly predictive information, because of the large number of data points considered. In fact, this approach, perhaps for the first time, may allow inventors to claim novel compounds in terms of search constraint information, rather than structural features.

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1. J.C. WATKINS and R.H. EVANS, Ann. Rev. Pharmacol. Toxicol., 21, 165 (1981).
2. U.S. PATENT NO. 4,746,653.