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The discovery of novel auxin transport inhibitors by molecular modeling and three-dimensional pattern analysis

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SUMMARY

Molecular modeling techniques and three-dimensional (3D) pattern analysis have been used to investigate the chemical and steric properties of compounds that inhibit transport of the plant hormone auxin. These compounds bind to a specific site on the plant plasma membrane characterized by its affinity for the herbicide *N*-1-naphthylphthalamic acid (NPA). A 3D model was derived from critical features of a set of ligands for the NPA receptor, a suggested binding conformation is proposed, and implications for the topographical features of the NPA receptor are discussed. This model, along with 3D structural analysis techniques, was then used to search the Abbott corporate database of chemical structures. Of the 467 compounds that satisfied the criteria of the model, 77 representative molecules were evaluated for their ability to compete for the binding of [^{3}H]NPA to corn microsomal membranes. Nineteen showed activity that ranged from 16 to 85% of the maximum NPA binding. Four of the most active of these, representing chemical classes not included in the original compound set, were also found to inhibit polar auxin transport through corn coleoptile sections. Thus, this study demonstrates that 3D analysis techniques can identify active, novel ligands for biochemical target sites with concomitant physiological activity.

INTRODUCTION

Molecular modeling techniques have proven useful in aiding the identification and design of bioactive compounds [1–3]. In such studies, consideration of relative activity, along with evaluation of the chemical and steric properties of a series of compounds, has been used to develop a model of the pharmacophore and active site for the set of ligands [4]. Typically, the pharmacophore model includes a description of the chemical moieties necessary for binding to the active site

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and a set of required geometrical relationships among the important groups. Computational tools that use the three-dimensional (3D) structural information obtained in modeling studies have recently become available [5]. One such promising method is the searching of databases of 3D molecular structures for specified patterns of atoms. This method, referred to as 3D pattern analysis or 3D database searching, originated in the well-established technique of 2D substructural searching [6]. In 3D pattern analysis, however, search queries consist of a geometric and spatial description of the target, as well as a set of chemical requirements. Recently, 3D database searching has been used successfully in identifying new lead structures in several compound design efforts [7]. The focus of this work is the application of 3D pattern analysis to the identification and design of novel herbicides and plant growth regulators that act by inhibiting polar transport of the plant hormone auxin.

Most auxin transport inhibitors bind to a specific site on the plant plasma membrane, defined by its affinity for the herbicide naptalam, *N*-1-naphthylphthalamic acid (NPA) [8]. Structure–activity principles for these compounds have been elucidated by Katekar and Geissler [9]. The objective here is to identify and analyze the features of ligands for the NPA receptor, based on a reference set of seven compounds (Fig. 1), in order to probe the chemical and steric properties of the pharmacophore for these compounds. A model of the receptor binding site is proposed, and 3D database searching techniques are used to evaluate the pharmacophore characteristics. Representative compounds identified from searching are then evaluated in physiological and biochemical assays.

MATERIALS AND METHODS

NPA binding experiments and auxin transport

In-vitro activities of predicted auxin transport inhibitors were compared by measuring their ability to displace [3H]naphthylphthalamic acid from its binding site on membranes from etiolated corn coleoptiles (*Zea mays* L., cv. WF9 × Bear 38), as described previously [10,11]. Centrifugation binding assays were carried out in triplicate, and a representative experiment is shown. 'Specific' binding in these experiments is the binding of 10^{-9} M [^{3}H]NPA that is abolished by higher concentrations of nonradioactive NPA or competing substance. The experimental variability within an experiment was about 2%.

Auxin transport was directly measured through etiolated corn coleoptile sections [12] of the same variety, precisely as described by Gardner and Sanborn [11]. The sections were placed on a receiver block of agar containing the test compound at 10^{-5} M. A donor block containing 10^{-7} M [^{3}H]indoleacetic acid (IAA) was placed on top of the sections, and basipetal transport (apex to base) was carried out for 90 min. Nonspecific, primarily diffusional, acropetal transport (base to apex) was determined in a similar way by inverting the coleoptile sections. Each transport test with ten sections was carried out in duplicate. Specific (net) polar transport was calculated by subtracting from the radioactivity in the basipetal receiver block the amount in the receiver block of the acropetal control.

[2,3,4,5-^{3}H]NPA (54.8 Ci/mmol) was purchased from Research Products International Corp. (RPI, Elk Grove, IL). The specific activity was diluted to 20 Ci/mmol and was used from a 2×10^{-7} M stock solution in 95% (*v*/*v*) ethanol. [5-(*n*)-^{3}H]indoleacetic acid was also purchased from RPI; for these experiments, the original specific activity of 25 Ci/mmol was diluted to 250 mCi/mmol.

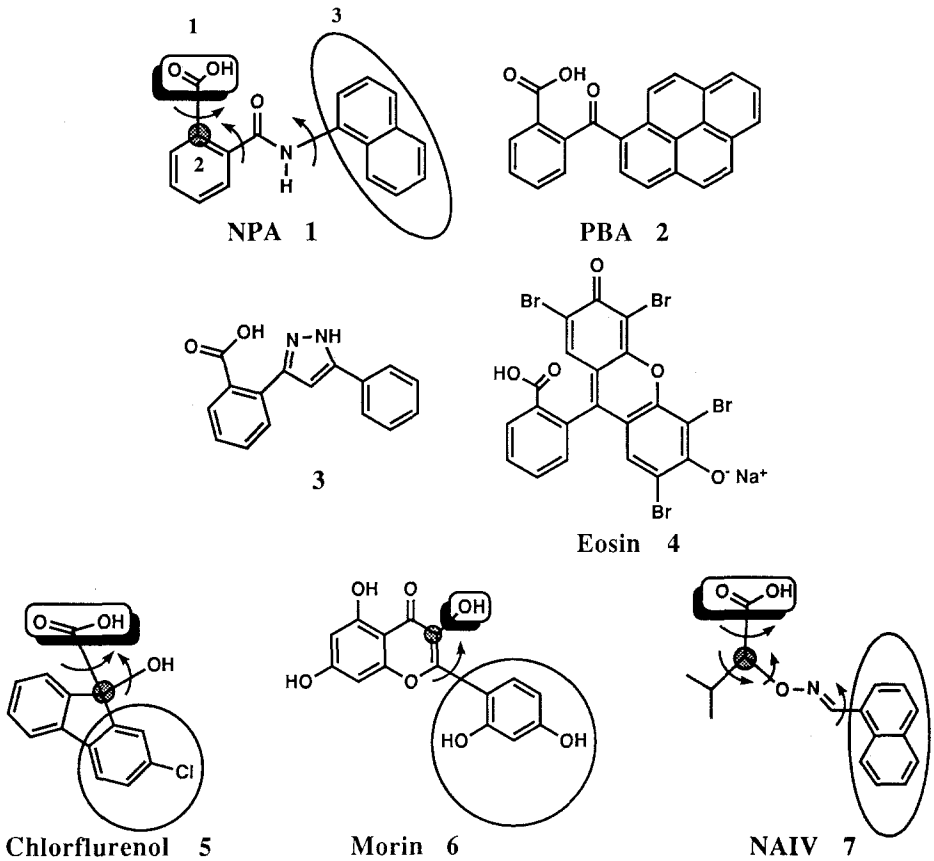

Fig. 1. Chemical structures of the reference auxin transport inhibitors examined in this study: Compound **1**, *N*-1-naphthylphthalamic acid (NPA); Compound **2**, pyrenoylbenzoic acid (PBA); Compound **3**, a pyrazole benzoic acid; Compound **4**, eosin; Compound **5**, chlorflurenol; Compound **6**, morin; and Compound **7**, 2-([1-naphthyl]methyleneaminooxy)isovaleric acid (NAIV). A representation of torsional flexibility is shown for Compounds **1,5,6,7**. For each compound, a conformational analysis was performed by systematically studying the rotation of the bonds noted with an arrow. Also illustrated are the proposed pharmacophore points necessary for inhibition of auxin transport for the reference Compounds **1,5,6,7**. The points are: (1) an acidic functionality (highlighted rectangle); (2) a sterically bulky or aromatic center (shaded circle); and (3) an aromatic system (circled). The pharmacophore points for Compounds **2–4** (not shown) are analogous to those for NPA, Compound **1**.

Structural analysis

The modeling study used Abbott Laboratories' molecular modeling package, SWAMI [13], and several commercial software programs, as noted below. The initial 3D structures for the compound set (Fig. 1) were obtained from CONCORD, a program for the rapid generation of high-quality approximate structures [14]. Analysis of the flexibility of the structures reveals that a conformational analysis is required. For example, Compounds **1–4** consist of several planar fragments connected by the rotatable bonds denoted in Fig. 1. The *s-trans* conformation of the carboxylic acid was used for all compounds. A complete conformational search was executed, using distance geometry [15], by systematically varying the torsion angles shown in Fig. 1. This resulted

in the identification of several low-energy conformations for each structure. A geometry optimization was performed on each conformation generated, using MOPAC and the MNDO Hamiltonian [16], and the energy of the relaxed conformation was noted.

RESULTS AND DISCUSSION

Pharmacophore model

As indicated above, structure–activity principles for auxin transport inhibitors have been elucidated by Katekar et al. [9,17]. These require that active compounds possess a carboxylic acid function attached to an aromatic ring, which is connected at the *ortho* position to a second aromatic ring. In addition, the aromatic rings may be separated by a conjugated or planar system of atoms. These principles do not fully account for properties of known ligands that bind to this site. First, the morphactins such as chlorflurenol bind to the same receptor site, inhibit auxin transport, cause abnormal root geotropism, and do not fit Katekar's structural criteria [18]. Second, the carboxyl group can be replaced by an acidic proton. For example, the flavonoids morin (Compound **6**, 3,5,7,2′,4′-pentahydroxyflavone) and quercetin compete for NPA binding in vitro though they lack a free carboxyl group [11,19]. Third, the aromatic ring to which the carboxyl group is bound is not necessary, provided that a bulky substituent (isopropyl in the case of the α-aminooxyisovalerates) is present to position the carboxyl group appropriately [11].

In light of these observations, we describe the pharmacophore as a three-point model: (1) an acidic functionality (e.g., carboxylic acid, acidic hydroxyl); attached to, (2) a tertiary, quaternary, or aromatic center; which is connected to, (3) an aromatic system. As in Katekar's model, points 2 and 3 can be separated by a planar or conjugated system. The selection of the fragments corresponding to these pharmacophore points in the carboxylic acids (Compounds **1–5, 7**) is straightforward. In morin (Compound **6**), the hydroxyl group alpha to the carbonyl moiety was selected as the acidic functionality because of its attachment to a highly conjugated system and its adjacency to a carbonyl group. Utilization of a pK_a estimation algorithm [20] corroborated this selection. The third pharmacophore point is the chlorophenyl fragment in chlorflurenol (Compound **5**) and the 2′,4′-dihydroxyphenyl ring in morin (Compound **6**). These pharmacophore points are illustrated in Fig. 1.

The seven compounds were superimposed, using chlorflurenol (Compound **5**) as a template, in an orientation and conformation which achieves maximum overlap of the pharmacophore points. The rotatable bonds in each structure were then adjusted to give the best overall match for the entire compound set. Special attention was given to maximize the overlap and coplanarity of pharmacophore region 3 – an aromatic system. In each case, the energy of the conformation used in the model is within 5 kcal of the minimum-energy conformation identified. Stereo pairs of the best superpositions found for the compound set are shown in Fig. 2A. A stereo-pair representation of the union molecular surface (at the van der Waals radius of each atom) for the compound set in this suggested binding conformation is shown in Fig. 2B.

In Fig. 2, first note that for each compound the acidic functionality is directly superimposed, including the acidic hydrogen. A body of evidence [18] suggests that this group is necessary for receptor binding, and its importance is reflected in the model. This site may be involved in a hydrogen-bonding or, if deprotonated, a charge–charge interaction with the receptor binding site (see below). In the region of the second pharmacophore point a variety of moieties with different

topographical features appears to be tolerated. This region, along with its associated conjugated group may serve to orient the acidic functionality and the hydrophobic area in conformations necessary for good receptor binding affinity. The third pharmacophore region consists of aromatic ring systems that are approximately coplanar. In addition, this region is non-coplanar with the plane defined by the atoms of the acidic functionality. Thus, for this set of compounds, a requirement for receptor binding may be that the plane of the acidic functionality is at some non-zero angle to the plane of the hydrophobic region.

3D pattern analysis

A proposed pharmacophore model can be described in chemical and steric terms, which in turn can be used to search databases of 3D structures to identify compounds that contain the characteristics necessary to fit the model [5]. The compounds found in the search ('hits') can then be tested for biological activity, such as receptor binding affinity, and the results can be used to validate and refine the model.

In this study ALADDIN [7], a computer program for identifying and designing compounds that fit certain chemical, geometric, and steric requirements, was used to search two large 3D databases, the Abbott Laboratories' corporate database and the Fine Chemicals Directory (FCD) database. The Abbott corporate database contains the structures of ca. 80 000 organic compounds, of which ca. 70 000 each have one computationally determined 3D structure. The FCD is a database of ca. 65 000 commercially available organic compounds [21]. Abbott's 3D FCD database contains ca. 55 000 3D structures. The 3D structures in these two databases were generated by the program CONCORD [14]. Compounds found in searching the FCD database were being tested at the time of writing; therefore, complete results are only available for searches on Abbott's corporate database. Three ALADDIN searches, differing in the description of the three pharmacophore points and in the geometric requirements, were performed on Abbott's corporate database. The ALADDIN description of the pharmacophore points for all searches is summarized in Table 1.

The objective of the first search was to use simple pharmacophore point definitions in order to see what types of compounds would be found as hits. Hence, pharmacophore point 1 was described as a carboxylic acid or hydroxyl group attached to an aromatic system. Point 2 was defined as a tertiary carbon center, excluding an aromatic center in this search. Point 3 was defined simply as an aromatic atom. Note that these pharmacophore point definitions resemble those in Katekar's model (vide supra). The geometric requirements imposed were a set of ranges defining the allowed distance between each point, such that the distance from point 1 to point 2 equaled 2.7–3.7 Å; point 2 to point 3, 4.9–5.9 Å; and point 1 to point 3, 4.6–6.8 Å. The ranges were selected by taking the minimum and maximum distance, plus a 0.2 Å tolerance, of the corresponding pharmacophore point-to-point distances for each structure in the compound set.

The first ALADDIN search resulted in 204 hits, and examples of each structural class within that group were chosen for in-vitro testing. If the supply of a chosen compound had previously been exhausted, a substructure search for close analogues was carried out in the original database, and the activity of the selected analogues was determined. From the first search results, 35 compounds were tested for their ability to compete for NPA binding sites. Of these, ten showed moderate to good activity, i.e., the displacement of [^{3}H]NPA by the compound at 10^{-5} M was 16–85% of that displaced by the same concentration of non-radiolabeled NPA.

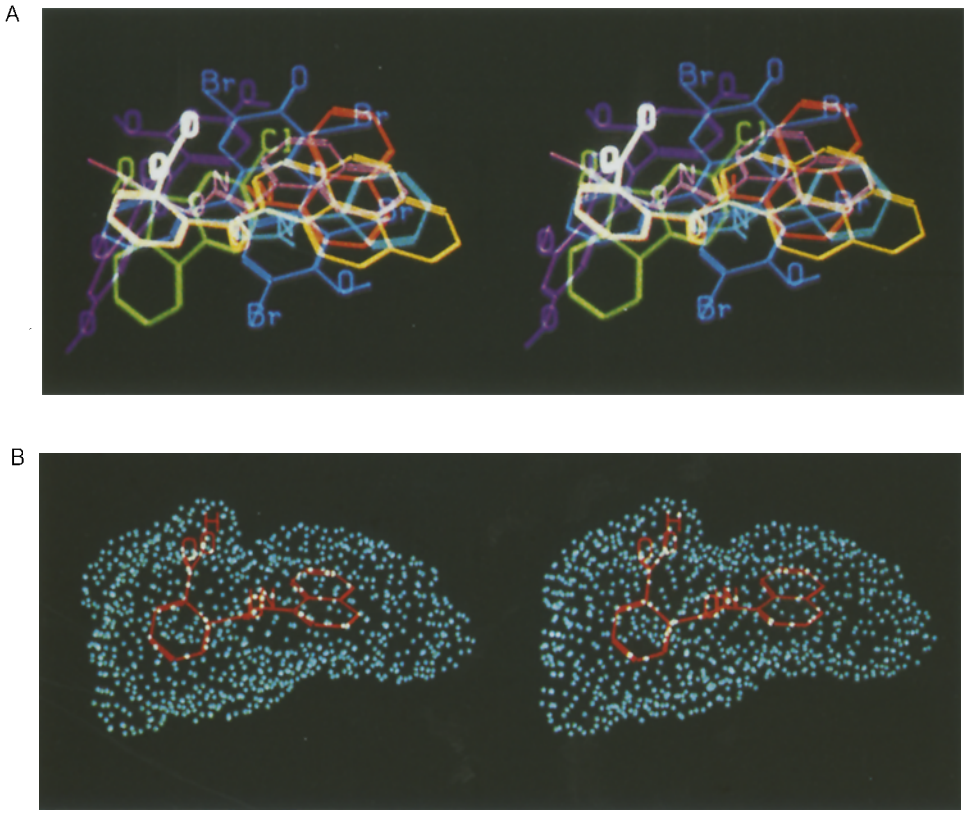

Fig. 2. Stereo-pair diagrams of the proposed bioactive superpositions for the reference auxin transport inhibitors, **1–7**. A: NPA (Compound **1**, red) is compared with PBA (Compound **2**, yellow), Compound **3** (light blue), eosin (Compound **4**, dark blue), chlorflurenol (Compound **5**, green), morin (Compound **6**, purple), and NAIV (Compound **7**, pink). B: The union molecular surface (at the van der Waals radius of each atom) of Compounds **1–7** in their proposed bioactive superposition, with NPA as a point of reference. For clarity, hydrogen atoms on carbon centers are not displayed, and hydrogen atoms on non-carbon centers are displayed as a bond only.

In the second search the definitions of pharmacophore points 1 and 2 were less restrictive. Point 1 was defined as a carboxylic acid attached to any atom, a hydroxyl group attached to an aromatic system, or an aryl or aliphatic sulphonic acid. For point 2 both a tertiary and quaternary carbon atom were permitted. Again, point 3 was defined as an aromatic atom and the distance ranges were the same as used in the first search. Thus, search one is a subset of search two. In the second search, 135 new hits were identified. Of these, 27 compounds were selected and tested, with six showing moderate activity. No sulphonic acids showed activity.

Based on the first two searches, a third search, corresponding to a full description of the model, was performed. In this search, the least restrictive of the three, the acidic functionality, was that used in the second search. Pharmacophore point 2 was expanded to any atom with three or four non-hydrogen attachments or an aromatic atom. Point 3 was defined more generally as the center of mass of a six-membered aromatic (including heteroaromatic) ring. Last, the distance ranges were adjusted slightly, as shown in Table 1.

TABLE 1
ALADDIN DESCRIPTION OF THE PHARMACOPHORE POINTS FOR EACH SEARCH

ALADDIN	ALADDIN pharmacophore description		
Search number	Point 1	Point 2	Point 3
1	HOOC-Ar	3 °C	aromatic
	HO-Ar		atom
	Distance ranges (Å):	(1–2): 2.7–3.7	
		(2–3): 4.9–5.9	
		(1–3): 4.6–6.8	
2	HOOC-Ar	3 °C	aromatic
	HOOC-R	4 °C	atom
	HO-Ar		
	HO-SO_2Ar		
	HO-SO_2R		
	Distance ranges:	(same as in No. 1)	
3	(same as in No. 2)	3° atom	center of mass of
		4° atom	6-membered aromatic ring
		aromatic atom	
	Distance ranges (Å):	(1–2): 2.9–3.4	
		(2–3): 5.7–7.3	
		(1–3): 4.9–7.0	

The proposed pharmacophore model is described as a three-point array, where each point represents a feature important to receptor binding. Three searches were performed, with a successively expanded target definition in each case. Pharmacophore point 1 is an acidic functionality, and includes such groups as carboxylic acids and phenolic hydroxyls. Tertiary, quaternary, and aromatic centers comprise pharmacophore point 2, a sterically bulky region. The aromatic/hydrophobic region, pharmacophore point 3, is defined as either an aromatic atom or the center of mass of a six-membered aromatic ring. The proposed geometric relationship necessary for receptor binding is imposed on the pharmacophore points as a set of point-to-point distance ranges. These distance ranges were determined by considering the corresponding pharmacophore point distances in the set of reference inhibitors (Compounds **1–7**, Fig. 1). Distances are measured atom-to-atom (or point-to-point); for point 1 the measurement is made from the atom underlined.

In the third search, 128 new hits were found. Fifteen compounds were selected for testing and three of these exhibited moderate to good binding activity.

In total, the three ALADDIN searches on the Abbott database resulted in the identification of 467 compounds which met the criteria for the proposed pharmacophore model. Of these compounds, 77 were screened in the NPA receptor binding assay with 19 showing a moderate to good level of activity. Four of the most active of these 19 compounds are shown in Fig. 3. Two of these, Compounds **8** and **9**, were identified in the first ALADDIN search, one (Compound **10**) was a close analogue of a compound identified in the second search, and one (Compound **11**) was found in the third search.

It is important to note that this work represents an initial attempt to describe a pharmacophore for a full set of ligands that bind to the NPA receptor. Accordingly, a relatively simple three-point model was formulated as a reasonable starting point for 3D pattern analysis. The success of

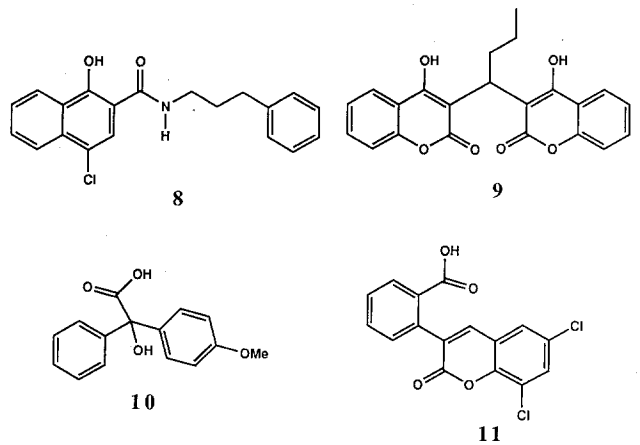

Fig. 3. The structures of four of the most potent (competition for NPA binding) compounds identified from 3D searching, using the program ALADDIN, on the Abbott corporate structural database.

searches performed with this model shows that this was a good place to start. In more refined models, based on the results reported here, it may prove useful to include additional geometric constraints such as angular ranges between selected pharmacophore points or dihedral angle ranges between the plane of the acidic functionality and that of the hydrophobic region. Naturally, inclusion of these additional constraints could be expected to increase search time, while reduc-

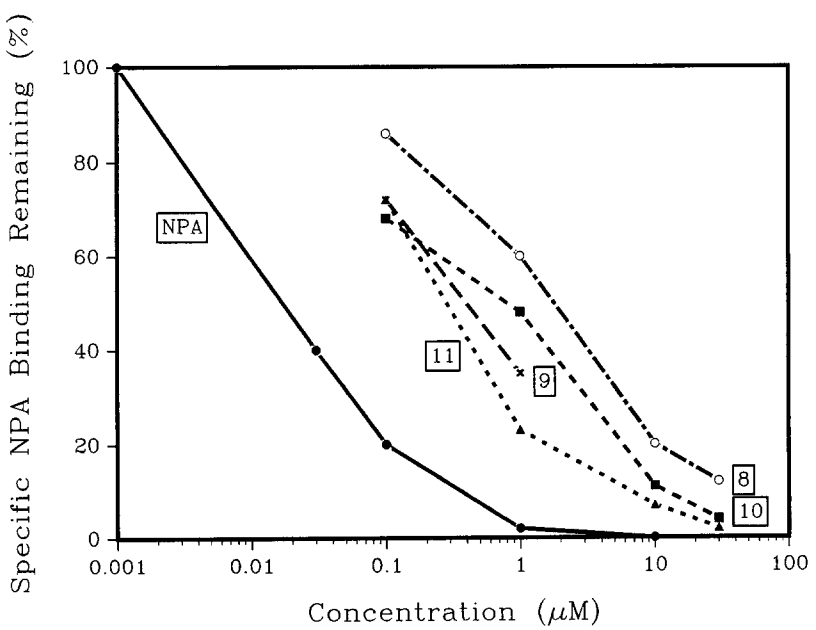

Fig. 4. Competition for NPA binding sites on corn microsomal membranes by the four compounds shown in Fig. 3, identified by the ALADDIN search of the Abbott corporate chemical-structure database. All samples contained 10^{-9} M [^{3}H]NPA. Specific binding is the amount of [^{3}H]NPA that is displaced by the non-radioactive compound relative to that displaced by a saturating concentration of non-radioactive NPA.

ing the total number of compounds found to match the new criteria. At the same time, however, 3D searching using a more rigorous model may result in identifying proportionally more compounds with the desired biological activity. Indeed, an increase in the proportion of active, potent compounds identified would be a measure of the validity of a more robust model.

Turning again to the results of the searches, the four compounds shown in Fig. 3 were selected for further evaluation. Dose–response curves which compare these compounds with NPA for the ability to compete for NPA binding sites are shown in Fig. 4. An estimation of the binding affinity (est. K_d) is given by the concentration of non-radioactive ligand required to displace 50% of the maximum specific binding. In this experiment, the est. K_d for NPA was 2×10^{-8} M. Compounds **9** and **11** were about an order of magnitude less active than NPA (est. $K_d = 4 \times 10^{-7}$ M and 3×10^{-7} M, respectively), Compound **10** was next with an est. K_d of 8×10^{-7} M, and Compound **8** was two orders of magnitude less active than NPA (est. $K_d = 2 \times 10^{-6}$ M).

Since the physiological consequence of binding of a ligand to the NPA receptor is the inhibition of polar auxin transport, these four compounds were also examined for their ability to inhibit [^{3}H]IAA movement through maize coleoptile sections (Fig. 5). Compound **11** was also the most active of the 4 in this assay, inhibiting 92% of the auxin flux at 10^{-5} M as compared with 96% inhibition by NPA. Compounds **8** and **10** were intermediate, with 53% and 35% inhibition, respectively, and Compound **9** was the least active of the group, with 24% inhibition. Thus, these four compounds represent four novel classes of ligands that show significant activity, without structural optimization, in both biochemical and physiological assays associated with this target site.

Each of these compounds (Fig. 3) was also used to search the FCD for related structures. Several close analogues of Compound **9** were found (available from Aldrich Chemical Co.), and one, dicumarol, showed binding affinity comparable to Compound **9** (results not shown). This observation independently confirms activity in this class of molecules.

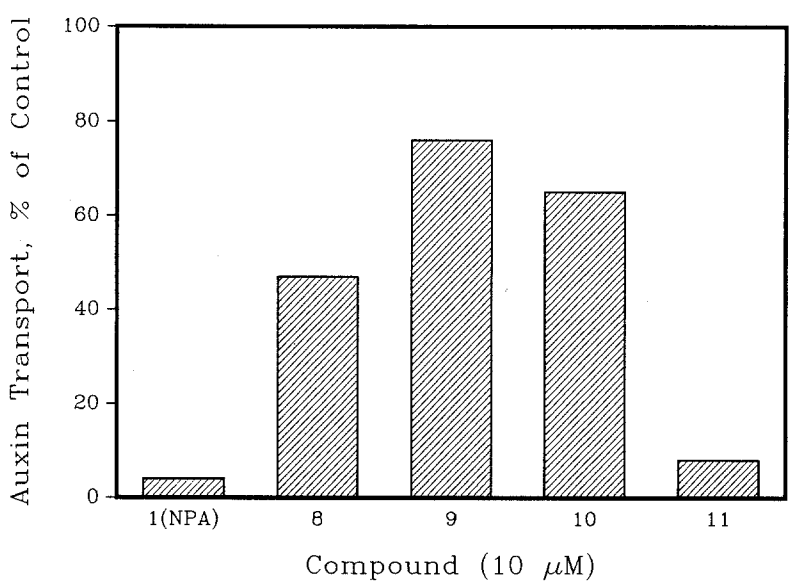

Fig. 5. Inhibition of net polar auxin transport in corn coleoptiles by NPA and the four compounds shown in Fig. 3. Donor blocks contained 10^{-7} M [^{3}H]indoleacetic acid, and the test compounds were evaluated at 10^{-5} M.

A conformational analysis (vide supra) was performed on Compounds **8–11**, and a proposed bioactive conformation for each was identified. The compounds were then superimposed on the model; a stereo-pair diagram of the superposition for each compound is shown in Fig. 6, compared with NPA. It is important to note that Compounds **8–11** have not been optimized for auxin transport inhibition. Accordingly, the compounds' fit to the model, as illustrated in Fig. 6, would not necessarily be as good as the reference auxin transport inhibitors (Fig. 2).

Consequences of the model

We have extended the modeling work of Katekar et al. [9,17,22] by including three additional classes of compounds, i.e., flavonoids (e.g., Compound **6**), morphactins (e.g., Compound **5**), and α-aminooxyisovalerates (e.g., Compound **7**), in our analysis. This resulted in a model of the suggested binding conformation with several fundamental steric differences to that proposed by Katekar et al. [9,17,22], as discussed below.

The best overall superposition for the entire compound set could be achieved when a nonplanar conformation for the benzoic acid portion of Compounds **1–4** was used. Specifically, the conformation selected for structures **1–4** was one in which the carboxylic acid group is rotated out-of-plane relative to the aromatic ring to which it is attached. This conformation was necessitated by compounds that cannot adopt a planar conformation in the region of the carboxylic acid fragment due to excessive steric hindrance, as in chlorflurenol (Compound **5**) and NAIV (Compound **7**). In contrast, the proposed binding conformation for benzoic acids in Katekar's model [17,22] is one in which the carboxylic acid and the aromatic ring to which it is attached are nearly coplanar. Although the relative orientation in space of these two pharmacophore regions differs, the present study and the work of Katekar et al. suggest that a specific steric relationship between the acidic functionality and the aromatic/hydrophobic region is necessary for receptor binding. Further work, especially with conformationally rigid analogues of active compounds, is needed to better describe the preferred relationship between these critical pharmacophore regions.

The present work has also further characterized the tolerated chemical and steric properties of the acidic functionality and of the region to which it is attached. Compounds such as chlorflurenol (Compound **5**), NAIV (Compound **7**), and Compound **10** show that the presence of an aryl

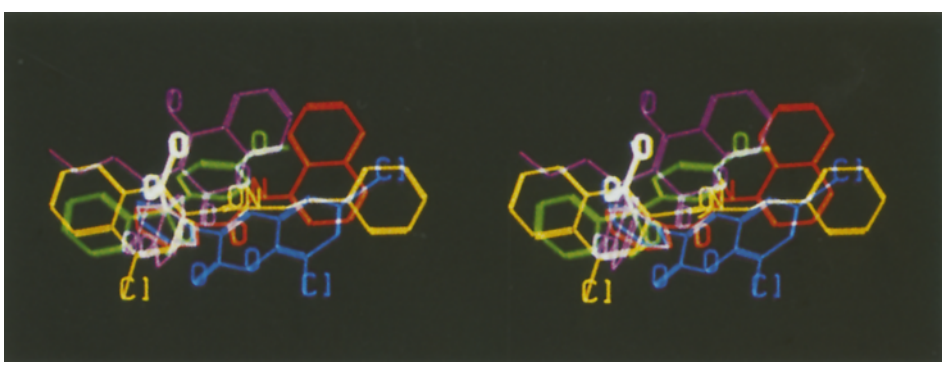

Fig. 6. Stereo-pair diagrams of the proposed binding orientation of the 4 most potent compounds (**8–11**) identified from the ALADDIN searches. NPA (Compound **1**; red) is compared with Compound **8** (yellow), Compound **9** (magenta), Compound **10** (green), and Compound **11** (blue).

carboxylic acid is not an absolute requirement for auxin transport inhibition. Rather, it appears that the acidic group can be attached to a variety of centers. Perhaps more importantly, the carboxylic acid can be replaced by other acidic functionalities such as the acidic hydroxyl moiety in morin (Compound **6**) and in Compounds **8** and **9**. However, compounds containing an acidic functionality other than a carboxylic acid generally show only moderate binding affinity and functional acitivity compared to compounds containing a carboxylic acid group (see Figs. 4 and 5). Estimation of the acidity of carboxylic acid inhibitors (e.g., Compounds **1–5, 7, 10, 11**) shows that these compounds are approximately 3–5 pK_a units more acidic than compounds in which the acidic functionality is an aryl hydroxyl group (e.g., Compounds **6, 8, 9**) [20]. Therefore, there may be an optimum pK_a range of the acidic functionality necessary to achieve maximal receptor binding and auxin transport inhibition. Future plans include the identification and design of new inhibitors that will aid in determining the optimum acidity range.

CONCLUSION

Using 3D database searching techniques in the evaluation of the proposed model, we were able to identify several different types of compounds that displayed moderate to good NPA receptor binding affinity and auxin transport inhibition. Each of the 4 examples in Fig. 3 provides further confirmation that several different classes of compounds, in addition to the traditional benzoic acid inhibitors (e.g., NPA, Compound **1**), can act as auxin transport inhibitors. Compound **10**, which is an open ring analogue of the morphactin chlorflurenol (Compound **5**), illustrates that the acidic functionality need not be directly attached to a benzene ring. Compounds **8** and **9**, which do not contain a carboxylic acid group, show that an acidic hydroxyl group can apparently serve as the necessary acidic functionality. Compounds **8–11** share similar structural features with the compounds used to build the proposed pharmacophore model, thus lending validity to the suggested binding orientation.

This study shows that molecular modeling and 3D database searching can be applied successfully to the analysis of the chemical and steric properties common to a set of plant growth regulators, resulting in the identification of new classes of bioactive molecules. In future work, we hope to use the insight gained to aid in the design and optimization of novel auxin transport inhibitors with practical utility.

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