Journal of Computer-Aided Molecular Design, 1 (1987) 243–256
ESCOM

J-CAMD 019

Designing novel nicotinic agonists by searching a database of molecular shapes

Robert P. Sheridan and R. Venkataraghavan

Medical Research Division, Lederle Laboratories, Pearl River, NY 10965, U.S.A.

Received 13 October 1987
Accepted 26 October 1987

Key words: Nicotinic agonist; Cambridge Crystallographic Database; Pharmacophore; Shape

SUMMARY

We introduce an approach by which novel ligands can be designed for a receptor if a pharmacophore geometry has been established and the receptor-bound conformations of other ligands are known. We use the shape-matching method of Kuntz et al. [J. Mol. Biol., 161 (1982) 269–288] to search a database of molecular shapes for those molecules which can fit inside the combined volume of the known ligands and which have interatomic distances compatible with the pharmacophore geometry. Some of these molecules are then modified by interactive modeling techniques to better match the chemical properties of the known ligands. Our shape database (about 5000 candidate molecules) is derived from a subset of the Cambridge Crystallographic Database [Allen et al., Acta Crystallogr., Sect. B,35 (1979) 2331–2339]. We show, as an example, how several novel designs for nicotinic agonists can be derived by this approach, given a pharmacophore model derived from known agonists [Sheridan et al., J. Med. Chem., 29 (1986) 889–906]. This report complements our previous report [DesJarlais et al., J. Med. Chem., in press], which introduced a similar method for designing ligands when the structure of the receptor is known.

INTRODUCTION

For most receptors associated with a particular biological activity, nothing is known about the structure at atomic resolution. The traditional approach to designing a new ligand (agonist, antagonist, allosteric effector) for a receptor has been to make small chemical variations on a known ligand. A newer approach is to deduce the geometry of the 'pharmacophore', a three-dimensional arrangement of essential chemical groups common to a set of known ligands, and then to design de novo a new molecule which can exhibit the pharmacophore. In the pharmaceutical industry, a new ligand must not only be biologically active but also 'novel', i.e. sufficiently different from any

previously known to be patentable. The number of truly novel ligands that can be designed by either of the above approaches is rather limited, however. In the first approach, the new ligands are necessarily close in chemical structure to the known one. In the second approach, the ligands are novel, but, because it is hard to invent chemical structures to fill a three-dimensional volume, the number of new designs is usually small. Moreover, a prejudice toward designs resembling known ligands is likely.

In a previous report [1], we presented a strategy by which novel ligands can be designed when the structure of the receptor is known. This strategy has two steps. In the first step, we use the shape-matching algorithm of Kuntz et al. [2] to search a large database of molecular shapes for a candidate that makes a good steric fit with the receptor. In the second step, we can modify the candidate so that it complements the receptor in chemical properties as well as in shape. In this paper, we extend the strategy so that novel ligands can be designed if the receptor-bound conformations are established for a set of ligands which are known to bind to the receptor. The structure of the receptor itself need not be known. We show, as an example, how to use this extension to find molecules which fit the combined volume of known nicotinic agonists in their receptor-bound conformations and which contain interatomic distances compatible with the nicotinic pharmacophore. A significant fraction of these molecules can then be used as starting points for the design of novel nicotinic agonists.

METHODS

Our approach depends on having a valid binding site model for a given receptor. When the structure of the binding site is not known, we must construct a model from a set of known ligand molecules. The model has two important features:
(1) a pharmacophore; and (2) a binding site volume.
The 'pharmacophore' is a specific arrangement of essential chemical groups common to active molecules. For example, for three groups A, B, and C, the equivalent of A (A_1, A_2, A_3, ...A_M), B, and C must appear in each of M molecules and a three-dimensional arrangement of A, B, and C common to all molecules, the 'pharmacophore geometry', must be attainable. Given enough conformationally-constrained active and inactive ligands, one can often deduce the pharmacophore geometry. Several methods for doing this have already been described [3–6]. It is often possible to decide which of the low-energy conformations of each ligand that can attain the pharmacophore geometry is the 'receptor-bound' conformation. We define an 'ensemble' as a set of active ligands, each in its receptor-bound conformation; these conformations are docked together so that the essential groups are superimposed (that is, A1, A2, A3 ... are close in space; B1, B2, B3 ... are close, etc.). The volume of the ensemble defines a minimum 'binding site volume', the space that an active ligand can occupy on the receptor.

Once a binding site model is constructed, new ligands are designed in four steps:
(1) Construct a database of molecular shapes.
This need be done only once; the database can be used for many receptors.
(2) Characterize the shape of the ensemble.
(3) Search the database for molecules with shapes which fit inside the ensemble volume and which have atoms disposed in a geometry close to the pharmacophore geometry.
(4) Design new ligands by modifying the molecules with the best fit.

Construction of the shape database

The construction of a database of molecular shapes from crystal structures in the Cambridge Crystallographic Database [7] has been discussed in our previous report [1]. The database we use for this work consists of 5008 candidate molecules, each candidate represented as a list of coordinates for the non-hydrogen atoms.

Characterization of the shape of the ensemble

There are two shapes to be characterized, the binding site and the receptor. (In the 'lock and key' analogy, these volumes would correspond to the keyhole and the lock, respectively.) Since the true shape of the binding site is unknown, we must approximate the shape of the binding site (keyhole) by the shape of the ensemble (the union of the volumes of all the known keys) and approximate the receptor (lock) as the volume surrounding the ensemble.

The characterization of either shape begins with a calculation of the molecular surface of the ensemble using a program developed by Connolly [8–10]. A spherical solvent 'probe' of radius 1.4 Å is conventionally used. The surface is represented as a series of 'dots', each of which lies either on the van der Waals surface of an atom (when the probe is touching one atom) or on the van der Waals surface of the probe (when the probe is touching two or more atoms). Each dot has a vector associated with it that indicates the location of the probe center when the dot was generated. The surface is usually calculated using only non-hydrogen atoms, with the van der Waals radii slightly expanded to compensate for the absence of explicit hydrogens.

There are two ways to represent the ensemble shape. The first is to generate a set of 'receptor spheres' inside the surface, each sphere characterized by a radius and the location of its center, such that the surface of the spheres mimics the surface of the ensemble. The subroutines for generating the spheres from the Connolly surface are described by Kuntz et al. [2]. Alternatively, we can use the ensemble atoms directly as the sphere centers.

We generate a single layer of 'receptor atoms' surrounding the ensemble in the following way: For each dot of the Connolly surface, we calculate the position of the probe center and assign it as an atom position. To reduce such receptor atoms (typically a thousand or more) to a manageable number, we save a subset of the atoms such that no two atoms are less than 1.4 Å apart. It is obvious that the volume defined by the receptor atoms exactly encloses the volume defined by the receptor spheres.

Location of pharmacophore atoms

In the ensemble the known ligands are docked together so that the equivalent chemical groups (usually atoms) are superimposed. For instance for three groups A, B, and C, we define the idealized location of 'pharmacophore atom' A as the mean position of A_1, A_2, A_3,..., A_M for M ligands. Similarly for B and C.

Shape-search algorithm

The algorithm to test each candidate molecule for shape-complementarity to the ensemble and to test it for a potentially correct pharmacophore geometry is summarized as follows:

1. Read in the coordinates for the receptor spheres, the receptor atoms, and the pharmacophore atoms. Calculate the distances between the sphere centers.
2. For each candidate in the database:
    - 2.1 Read the coordinates of the atoms.
    - 2.2 Calculate the distances between the atoms.
    - 2.3 Find all sets of atom-sphere pairs that are allowed as 'matches' (see next paragraph).
    - 2.4 For each match:
        - 2.4.1 Orient the candidate as determined by the match (see next paragraph).
        - 2.4.2 If there is not at least one atom of the candidate within a small distance of each of the pharmacophore atoms, skip to the next match. Otherwise go to step 2.4.3.
        - 2.4.3 If the candidate in this orientation makes a forbidden steric overlap with the receptor, skip to the next match. Otherwise, score the steric-fit of this orientation.
        - 2.4.4 Save the orientation in a list of N orientations if its score is higher than the lowest score in the list.
3. Write the coordinates of the N orientations with the highest scores.

The geometrically possible ways to orient each candidate in the binding site (step 2.3) are found by a method of systematic distance matching [1,2,11]. Each atom i in the candidate is systematically paired with each receptor sphere k. A second pair, atom j with sphere l, is accepted if the distances obey the condition:

$$\text{abs}[d(i,j) - d(k,l)] \leq C$$

where C is a parameter set by the user. Additional pairs are assigned until no further pairs meet the condition. The minimum number, N_{min}, of atom-sphere pairs needed for a 'match' to be saved can be set by the user, although at least four pairs are necessary to determine a unique docking. In effect, a match maps a subset of the candidate's atoms into a subset of pockets (each pocket defined by a sphere center) that can receive them. A complete combinatorial matching is not feasible. Instead, the matching routine is biased toward considering the longest atom-atom distances first.

For each match we use the least-square algorithm of Ferro and Hermans [12] to obtain a rotation/translation matrix that will best superimpose each atom onto its paired receptor sphere (step 2.4.1). The matrix is then applied to all the atoms of the candidate to generate an 'orientation', i.e. a set of coordinates for the candidate positioned in the binding site.

In previous steps, orientations were generated by considering only the receptor spheres. In step 2.4.2, we check whether there is at least one atom in the orientation within 0.5 Å of the location expected for each pharmacophore atom. In step 2.4.3, we measure how each orientation interacts with the receptor atoms. First, we discard any orientation in which any atom in the candidate is within 2.5 Å of any receptor atom. This has the effect of removing from consideration all orientations that have significant steric overlaps with the receptor, i.e. which extend far outside the ensemble volume. For the remaining 'allowed' orientations, the steric-fit score is calculated from the number of receptor-candidate contacts:

$$\text{Score} = \sum_{i}^{\text{receptor atoms}} \sum_{j}^{\text{candidate atoms}} F(i,j)$$

where $F(i,j) = 1.0$ if $d(i,j) \leq 4.0$ Å
$F(i,j) = 0.0$ otherwise.

Since the receptor and each candidate are represented only as shapes at this point, all atoms are treated as equivalent.

Modifying the candidates to design new ligands

A true ligand must fit the binding site in terms of physical and chemical properties (hydrophobicity, hydrogen bonding, electrostatic potential, etc.) as well as in shape. At this point, we generate a molecular 'framework' by reintroducing the bonds connecting the atoms in the candidate and then modify the framework so that the final design for a ligand should have the following properties:

(1) Each atom in the framework closest to a pharmacophore atom should have the same properties as the pharmacophore atom (be a charged center, hydrogen-bond acceptor, etc.).

(2) The conformation of the designed ligand that exhibits the pharmacophore geometry must be an energetically accessible one.

(3) No ligand-receptor steric overlaps should be introduced.

During the design process we use interactive modeling techniques to inspect the fit of the designed ligand inside the ensemble volume. Because the design operation depends heavily on chemical intuition, it cannot yet be automated.

As a final step, the designed ligands must be energy-minimized by some molecular mechanics method. This is to check that there is a minimum-energy conformation near the 'framework' conformation that obeys conditions (2) and (3).

RESULTS

We present one test case in detail: the design of novel nicotinic agonists. We recently [3] deduced that the nicotinic pharmacophore consists of three groups: a cationic center (A), an electronegative atom (B) that can accept a hydrogen bond, and an atom (C) that defines the direction of hydrogen bonding around B; the distances between these groups are approximately (± 0.3) 4.8 (A–B), 4.0 (A–C), and 1.2 Å (B–C). We were also able to suggest a unique receptor-bound conformation for each agonist in the study and suggest a specific disposition of 'agonist volume' relative to the pharmacophore 'triangle'. The ensemble constructed in that study, which we use here, is composed of seven agonists: (−)-nicotine, (+)-nicotine, (−)-muscarone, (+)-muscarone, (−)-ferruginine methiodide, (−)-cytisine, and half of *trans*-3,3′-bisQ.

We took the locations of the receptor spheres as the location of the ensemble atoms (88 in all). Then we generated 123 receptor atoms from the Connolly surface of the ensemble. We considered only pharmacophore atoms A and B for the search. In some known nicotinic agonists, atom C does not correspond to a real atom but only to a 'dummy' that helps define a dipole with B (e.g., C would be along the angle bisector for an ether oxygen, aromatic nitrogen, etc.). Since the can-

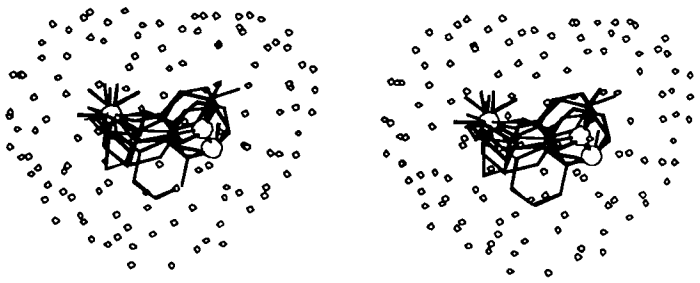


Fig. 1. The model for the nicotinic agonist binding site. The non-hydrogen atoms (shown connected by bonds) of the agonists: (−)-nicotine, (+)-nicotine, (−)-muscarone, (+)-muscarone, (−)-ferruginine methiodide, (−)-cytisine, and *trans*-3,3′-bisQ define the shape of the binding site and are used as receptor spheres. (The symmetrical structure of *trans*-3,3′-bisQ implies a symmetrical binding site that can accommodate two sets of pharmacophore atoms. We represent only half of this site and truncate *trans*-3,3′-bisQ accordingly.) A layer of receptor atoms (small circles) surrounds the ensemble of agonists. The idealized locations of three pharmacophore atoms A, B, and C are shown as large circles. A is toward the left and B points down. Only A and B were used in the shape-search. This and the following stereo plots were produced by the plotting routines of CHEM-X[17].

didates would not necessarily have a ready-made atom in the corresponding position, we thought that requiring them to have the equivalent of C would be unduly restrictive. As will be shown later, the omission of C was not critical. Fig. 1 shows the receptor spheres, the receptor atoms, and the pharmacophore atoms.

Search for candidates with good steric fit and suitable pharmacophore geometry

We set the match parameters $C = 1.0$ Å and $N_{min} = 6$. In this example, these parameters strike a good balance between generating too few orientations per candidate (in which case some allowed orientations are missed) and generating too many orientations (which take a great deal of computer time to process). Since our ensemble is fairly small in size, we ran the search against only the 3926 candidates in the data base with fewer than 25 non-hydrogen atoms. A total of 2 948 324 orientations were examined, of which 2877 had approximately correct pharmacophore geometries and which made no forbidden steric contacts with the receptor atoms. Among these allowed orientations, the steric-fit scores ranged from 27.0 to 191.0 with a mean of 89.9. We then repeated the search using the *enantiomers* of the 3926 candidates. This time there were 2813 allowed orientations for which the scores varied from 27.0 to 184.0 with a mean of 89.2. Each search took approximately 12.5 CPU hours on our VAX 8650.

For each search, we kept a list of the 100 allowed orientations with the highest scores. These are presumably the orientations that make the best contact with the receptor. Each list contained more than one orientation for the same candidate. We therefore filtered the lists further by keeping for each distinct candidate only the one orientation with the highest score. The high-score orientations, pooled from the two lists, are shown in Table 1.

Despite the fact that we omitted the requirement that the candidates have the equivalent of pharmacophore atom C, at least half of the candidates in Table 1 have an atom in the proper position or an angle bisector around B near the proper B→C direction. Pictures of some selected candidates which meet that condition are shown in Fig. 2.

TABLE I
CANDIDATE MOLECULAR SHAPES WITH THE HIGHEST STERIC-FIT SCORES

Candidate No.	Non-hydrogen atoms	Score	Cambridge Refcode	Candidate No.	Non-hydrogen atoms	Score	Cambridge Refcode
507[a]	18	191.0[b]	CICKAA[c]	1340	15	151.0	FRCTNI
4189*[d]	18	184.0	CABZEK	225*	14	150.0	CEWHER
733*	16	181.0	CIGTIV	1757*	16	150.0	COBROA
861*	14	180.0	CIJTIY	2712	14	150.0	PHENBD
1143	17	179.0	CIPGIR	2712*	14	150.0	PHENBD
862	14	173.0	CIJTOE	3714*	14	150.0	BUCKEP
2717	15	168.0	PILOCP	4076	15	150.0	BUWXIA
3959	18	168.0	BURRAH	4537*	14	150.0	CASVOH
3696	15	167.0	BUBNER	4698	15	150.0	CBABMO
2718*	15	166.0	PILOCP	1757	16	149.0	COBROA
2717*	15	165.0	PILOCP	2642*	14	149.0	COWSIG
4066*	16	164.0	BUWSER	3483	15	149.0	BOHJIR
622	14	162.0	CIFDEA	224	14	148.0	CEWHAN
3117*	16	159.0	CENKOV	655	16	148.0	CIFRIS
826*	15	158.0	CIJFOQ	1179	15	148.0	CIPVEC
3870	15	158.0	BULNEB	2454	15	148.0	COSYEO
275*	15	157.0	CEXMAT	2974*	15	148.0	CEKPAJ
1005*	17	156.0	CILZOM	3372*	15	148.0	ZZZKVU
2907*	16	156.0	CEJPEW	4188*	14	148.0	CABZAG
3617*	15	156.0	BOXCOG	4499*	14	148.0	CARPAM
2959*	14	155.0	CEKJUX	3193	14	147.0	CEPSUL
3118*	16	155.0	CENKUB	3881	14	147.0	BULYOW
4295*	16	155.0	CAGTIN	4499	14	147.0	CARPAM
1405*	15	154.0	BAMTAK	1981	14	146.0	COHPIY
2668	16	154.0	COXBIA	2749	14	146.0	BIFRUD
1005	17	153.0	CILZOM	2959	14	146.0	CEKJUX
1340*	15	153.0	FRCTNI	3854	16	146.0	BUKYUB
3012	15	153.0	CELBUQ	3483*	15	145.0	BOHJIR
3881*	14	153.0	BULYOW	531*	16	144.0	CICWEQ
4631*	15	153.0	CAWNUJ	559*	16	144.0	CIDHOM
4110	14	152.0	BUYBEC	927*	15	144.0	CIKSEU

[a]Refers to the order of the candidate in the database of molecular shapes.
[b]Highest score among the orientations of this candidate.
[c]Cambridge Crystallographic Database entry from which the candidate was extracted.
[d]A '*' indicates the enantiomer of this candidate. An enantiomer is listed only if its shape is not nearly superimposable with the original candidate.

Design of novel agonists

We have already discussed our model for the chemical properties of nicotinic agonists. In Fig. 3 we show, for each of the candidates in Fig. 2, one design for a novel nicotinic agonist derived from the candidate. Other designs are possible, of course. In each case, we transformed the candidate atom (A') closest to the pharmacophore atom A to a cationic group (quaternary or basic ni-

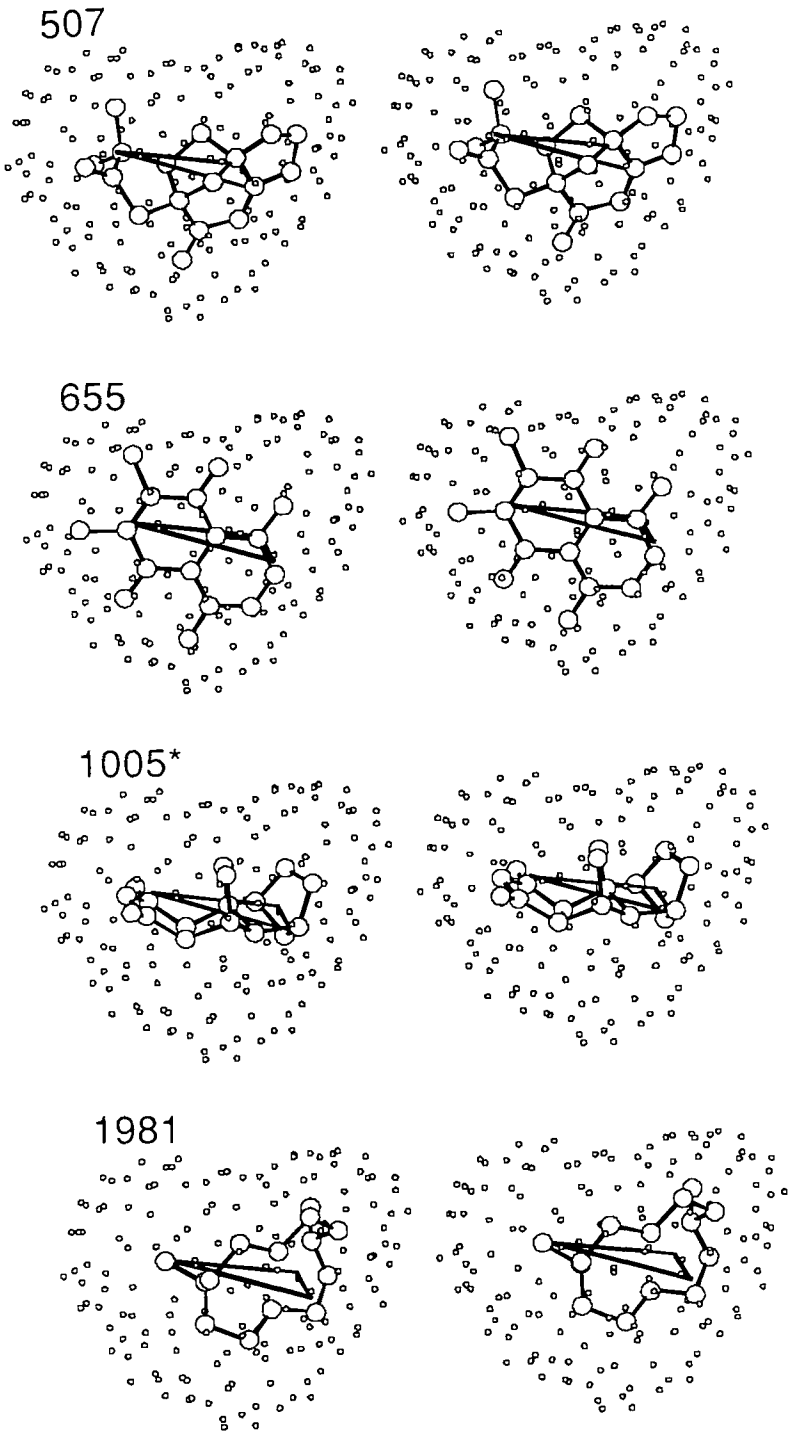
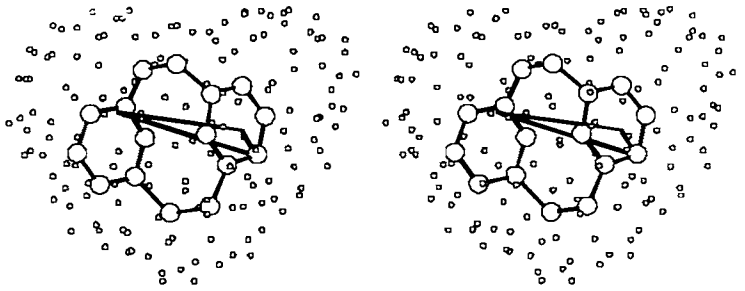
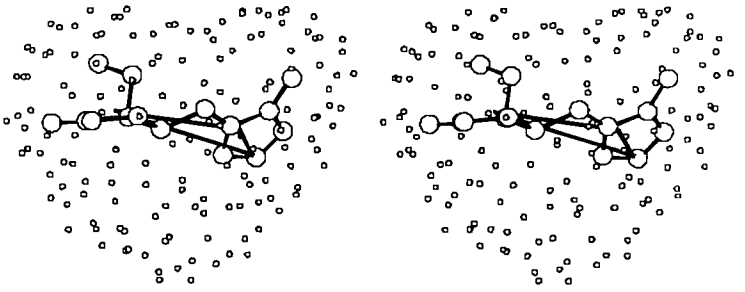


Fig. 2. Selected candidates from Table 1 which have atoms within 0.5 Å of pharmacophore atoms A and B and which have either an atom close to pharmacophore atom C or an angle bisector at B nearly parallel to the B→C direction. (The candidates were not required in the shape-search to have the equivalent of C.) The triangle formed by the pharmacophore atoms is shown. The molecular surface of the ensemble volume is indicated by the small dots. (Continued on pp. 251—252.)

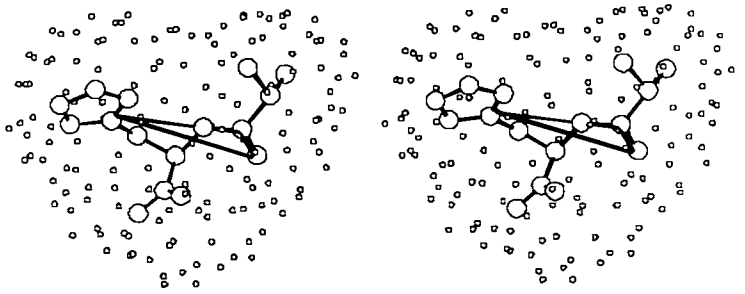
2668



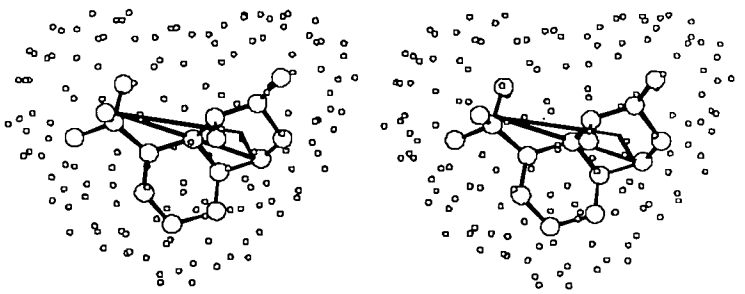
2718



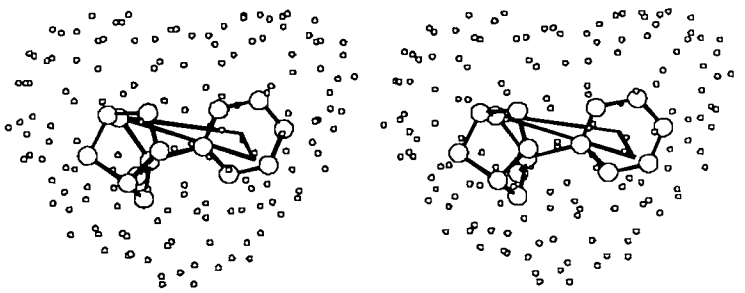
2907*



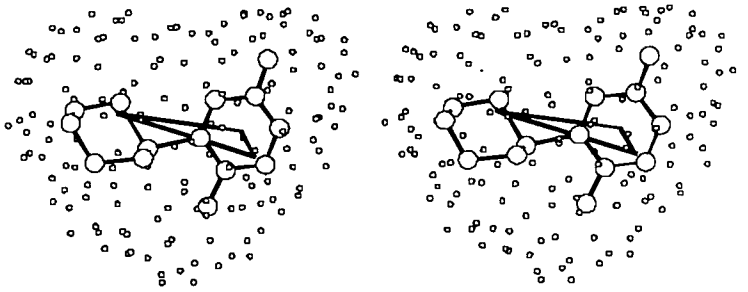
3117*



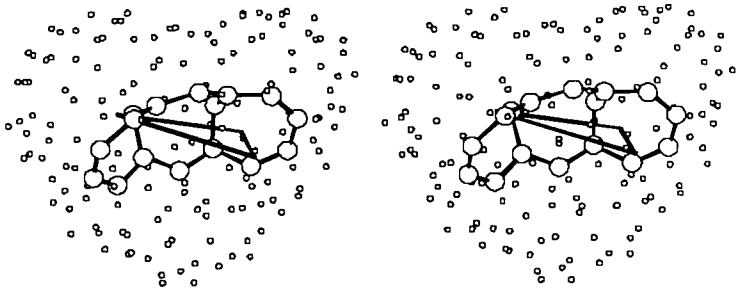
3617*



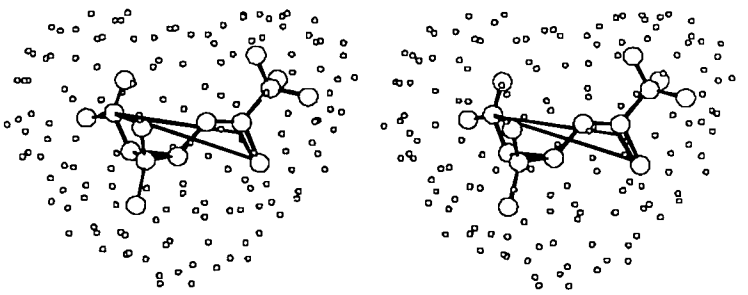
3714*



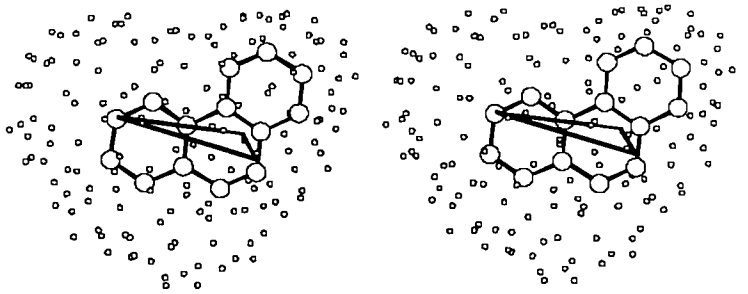
3854



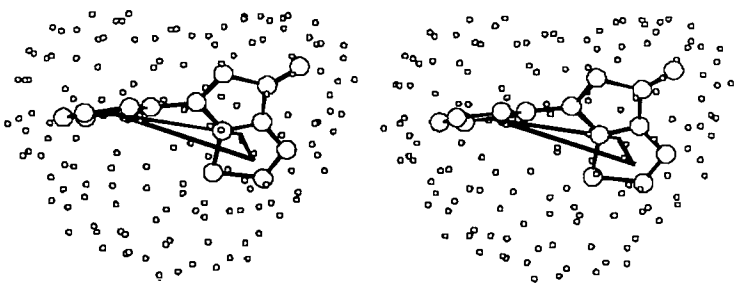
4076



4499



4631*



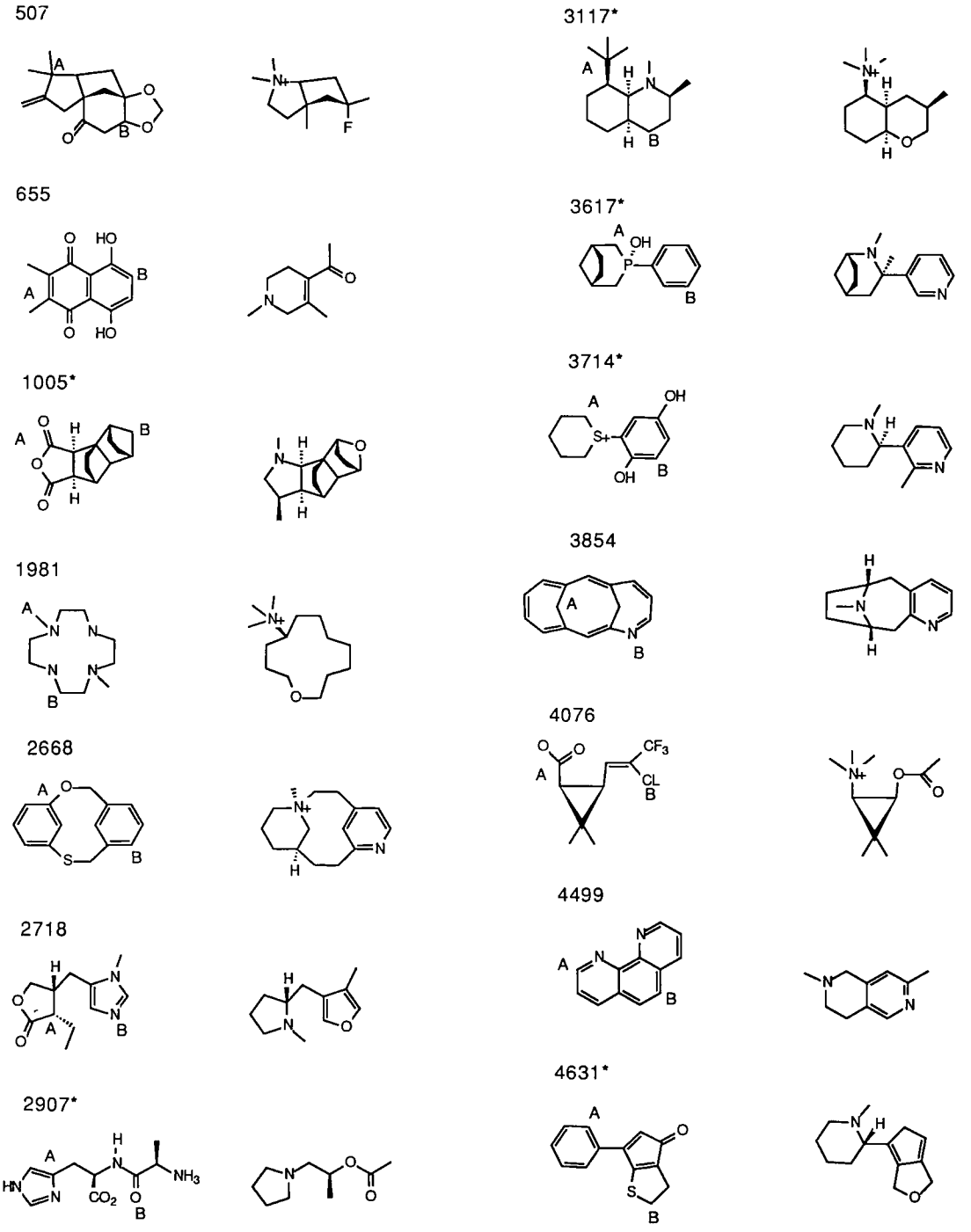


Fig. 3. Novel nicotinic agonists. In the left columns are shown the candidates from Fig. 2 with their original element types and bond orders. The candidate atoms closest to pharmacophore atoms A and B in Fig. 2 are indicated. In the right columns, are possible designs for nicotinic agonists based on the candidate 'framework'.

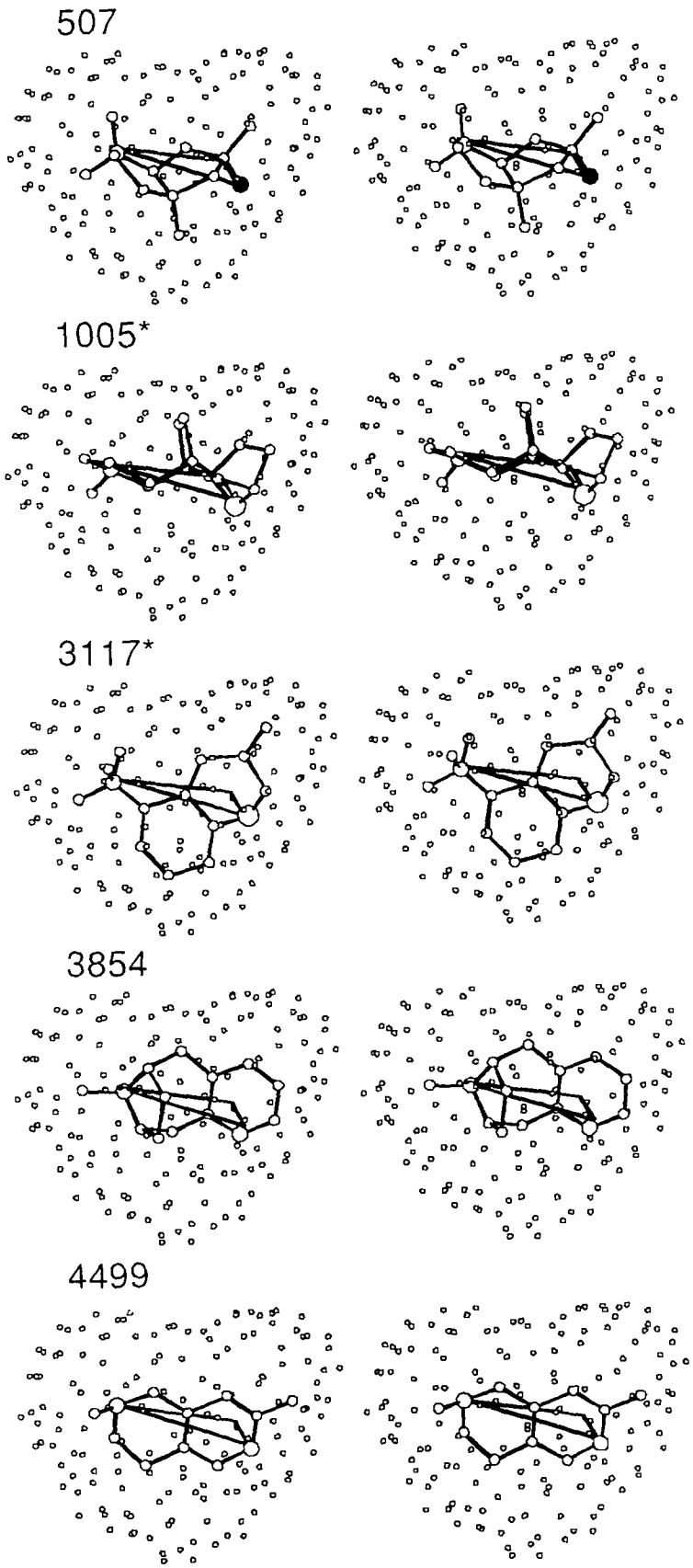


Fig. 4. Selected agonist designs, after energy-minimization, docked onto the binding site. Atom types are indicated: carbon, small circles; nitrogen, open medium circles; fluorine, filled medium circles; oxygen, large circles. Although explicit hydrogens were added for the minimization, these are omitted for clarity.

trogen) and the candidate atom (B′) closest to B to an electronegative atom capable of accepting a hydrogen bond. All other atoms in the designs were assumed to be carbons. The steric-overlap cutoff used in the search (2.5 Å) is intended to be slightly permissive. For some orientations allowed by that cutoff, there will be one or two atoms which overlap the receptor at a more realistic (3.0 Å) cutoff. These atoms were omitted from the designs.

It is interesting to note that some designs resemble compounds which are known to bind to the nicotinic receptor. Design 655 resembles isoarecolone, a potent agonist [13]. Design 4076 resembles *cis*-ACTM, a weakly-binding agonist [14]. Designs 2718, 3617*, and 3714* resemble anabasine [15, 16], an analog of nicotine. Design 2907* is an analog of acetylcholine.

A few designs are especially interesting because they are conformationally constrained: 507, 1005*, 3117*, 3854, and 4499. Coordinates for these designs were produced by modifying the corresponding frameworks using CHEM-X [17]. Explicit hydrogens were added and each design was energy-minimized for 50 cycles. In some cases, a dummy atom C′, was added to the energy- minimized structure 1.2 Å from B′ along the angle bisector. The energy-minimized structure was then docked by rigid body superposition of the atoms A′, B′, and C′ onto the idealized pharmacophore triangle A, B, and C. We found that some of our original designs produced minimum energy structures in which A′, B′, and C′ were not properly disposed or in which there was a steric overlap with the receptor. This caused us to modify those designs until they were acceptable. Pictures of some final designs in the binding site are shown in Fig. 4 .

DISCUSSION

Our approach is to find novel chemical 'frameworks' which are similar in shape to the receptor-bound conformations of known ligands and which have atoms in approximately the same location as the pharmacophore atoms in those ligands. We then use these frameworks as starting points from which to design new 'leads' for further study as novel ligands. The power of our approach is in the ability of shape-search algorithm to generate novel, varied, and valid starting points for design. The subsequent design step uses well-known principles of chemical intuition and is not really new. The novelty and variety of the generation step depends on the database, in which the candidates generally have no chemical relationship to any known ligand or to each other. The validity is a result of the selection imposed by the criteria in the shape-search algorithm which define an acceptable orientation.

It is worth reviewing the requirements and assumptions under which our approach operates. Most importantly, since the goal of the approach is to find new ligands to fit a particular receptor, our success will depend on having a complete and valid pharmacophore model for that receptor. In order to construct such a good model, we need to know enough semi-rigid ligands to define the pharmacophore geometry uniquely. When there are two or more conformations that can attain the pharmacophore geometry, we need to define one receptor-bound conformation for each ligand. Motoc et al. [18] discuss a procedure to test the validity of pharmacophore models.

We assume that we should first match the shape of the ensemble, and then match the pharmacophore geometry. Thus, the candidates are initially oriented by matches between candidate atoms and receptor spheres, and the pharmacophore geometry is checked subsequently. We chose this sequence as a direct extension of our previous algorithm [1] in which only shape was considered. An alternative scheme, in which candidates are oriented by matches between candidate atoms and pharmacophore atoms (so that the pharmacophore geometry is checked first), might also be useful.

Currently, we can include only those pharmacophore groups that are explicit atoms. Many pharmacophore models include geometric points (e.g., the center of phenyl rings) for which a corresponding atom would not normally appear in the candidates. Fortunately, as shown in our example, having to leave out these points does not preclude the use of our method.

Our shape-search method is constrained in the types of shapes that are acceptable. One constraint is that we consider only one shape for each candidate (the crystal conformation) and for the receptor; i.e., we ignore the possibility of 'induced fit'. Our definition of the receptor shape, an 'excluded volume' into which ligands cannot extend, adds an additional constraint. Although it is possible to locate small regions of the true receptor from data on inactive compounds which can attain the pharmacophore geometry (see Marshall et al. [6]), there is hardly ever enough data to locate enough of the receptor for this application. Thus, we must construct an imaginary receptor that is exactly complementary to the ensemble volume. Since we can never know about all possible ligands, the ensemble volume always represents a *minimum* volume that can be occupied by ligands. Thus when we discard candidates that extend outside this volume, we probably are discarding some that might be compatible with the true receptor shape. Fortunately, since for our purpose we need only *some* candidate shapes that can suggest new designs (rather than *every* acceptable shape), the over-conservative nature of the search method is not a problem.

Finally, the design process uses molecular modeling and can consider only those aspects which are easily modeled. The in vivo activity of ligands depend on factors (transport, metabolism, toxicity, etc.) which cannot be predicted from modeling. These factors become especially significant as the designs depart from known ligands. In balance, we note that the ligands designed by our method, being based on an explicit pharmacophore model, provide a rigorous test for that model.

REFERENCES

1 DesJarlais, R.L., Sheridan, R.P., Seibel, G.L., Dixon, J.S., Kuntz, I.D. and Venkataraghavan, R., J. Med. Chem. (in press).

2 Kuntz, I.D., Blaney, J.M., Oatley, S.J., Langridge, R. and Ferrin, T.E., J. Mol. Biol., 161 (1982) 269–288.

3 Sheridan, R.P., Nilakantan, R., Dixon, J.S. and Venkataraghavan, R., J. Med. Chem., 29 (1986) 899–906.

4 Schulman, J.M., Sabio, M.L. and Disch, R.L., J. Med. Chem. 26 (1983) 817–823.

5 Crippen, G.M., J. Med. Chem., 22 (1979) 988–997.

6 Marshall, G.R., Barry, C.D., Bosshard, H.E., Dammkoehler, R.A. and Dunn, D.A., In Olson, E.C. and Christoffersen, R.E. (Eds.) Computer-Assisted Drug Design, ACS Symp. Ser. 112, American Chemical Society, Washington, D.C., 1979, pp. 205–226.

7 Allen, F.H., Bellard, S., Brice, M.D., Cartwright, B.A., Doubleday, A., Higgs, H., Hummelink, T., Hummelink-Peters, B.G., Kennard, O., Motherwell, W.D.S., Rodgers, J.R., and Watson, D.G., Acta Crystallogr., Sect. B, 35 (1979) 2331–2339.

8 Connolly, M.L., Ph.D. dissertation, University of California, 1981.

9 Connolly, M.L., J. Appl. Crystallogr., 16 (1983) 548–558.

10 Connolly, M.L., Science, 221 (1983) 709–713.

11 DesJarlais, R.L., Sheridan, R.P., Dixon, J.S., Kuntz, I.D. and Venkataraghavan, R., J. Med. Chem., 29 (1986) 2149–2153.

12 Ferro, D.R. and Hermans, J., Acta Crystallogr., Sect. A, 33 (1977) 345–347.

13 Spivak, C.E., Gund, T.M., Liang, R.F. and Waters, J.A., Eur. J. Pharmacol., 120 (1986) 127–131.

14 Chiou, C.-Y., Long, J.P., Cannon, J.G. and Armstrong, P. J., Pharmacol. Exp. Ther., 166 (1969) 243–248.

15 Eldefrawi, M.E. and Eldefrawi, A.T., J. Environ. Sci. Health, 1318 (1983) 65–88.

16 Williams, M. and Robinson, J., J. Neurosci., 4 (1984) 2906–2911.

17 CHEM-X, created by E.K. Davies, Chemical Crystallography Laboratories, Oxford University, developed and distributed by Chemical Design Ltd., Oxford.

18 Motoc, I., Dammkoehler, R.A., Mayer, D. and Labanowski, J., Quant. Struct.-Act. Relat., 5 (1986) 99–105.