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Rational and efficient geometric definition of pharmacophores is essential for the patent process

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The geometric description of pharmacophores suffers from approximations. No consensus has been clearly established, despite the increasing interest in using pharmacophores in drug design and in patent applications. We therefore propose an original definition of a pharmacophore using spherical coordinates. These coordinates give a precise description of each point using three parameters: distance to a geometric origin and two angles. If necessary, these parameters can be easily and rapidly converted to cartesian coordinates. Our method can guaranty, to the patent applicant, the safe protection of his intellectual property by both improving markedly the readability of a pharmacophore definition and bringing, to the person who is skilled in the art, enough information to understand easily the essence of the invention.

Introduction

The concept of a 'pharmacophore' is not recent. It was first introduced by Paul Ehrlich in 1909 as ''a molecular framework that carries (phoros) the essential features responsible for a drug's (pharmacon's) biological activity'' [1]. This definition was further updated in 1977 by Peter Gund to ''a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity'' [2]. More recently, the official IUPAC recommendation from 1997 has summarized the concept as follows: ''A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response'' [3].

In modern computational chemistry and drug design, pharmacophores are used commonly in various applications. For example, they can be used to extract, from a database of chemically diverse compounds, molecules sharing similar physicochemical features that fit with the property defined by the pharmacophore. They are also implemented in several molecular modeling algorithms that are used to align molecules onto a reference molecule, to dock virtual compounds into a receptor-binding pocket or to generate *de novo* a virtual compound library, among others (reviewed in Ref. [4]).

In addition to these applications, pharmacophores are founds in many patent applications. The importance of pharmacophores in the protection of intellectual property became apparent early on. Indeed, the intellectual property of any molecule that fits with a special patented pharmacophore falls, *de facto*, under the intellectual property protection of the pharmacophore patent. From this point of view, the concept of the pharmacophore is really attractive to extend the life time of a patent filed for a lead compound that might fail in clinical trial. It is, however, still not simple to patent a pharmacophore.

If one accepts that the utility of pharmacophores in drug design is well established, their description in patent applications remains problematic with respect to their general acceptance as inventions by international patent offices. The main problem is that the geometric description of the pharmacophores by the inventors

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is often inadequate, particularly when the number of pharmacophore centers or points is as many as five or six. Then, the complexity of the classical pairwise matrix of distances of a pharmacophore increases markedly with the number of points and the pharmacophore definition has to be completed by geometric plans and angles to define the relative spatial position of a set of points. The patent officer, who has to give the status of invention to a patent application, is thus unable to appreciate the intellectual value of the invention and is constrained to deny the status of 'invention'. It is obvious that a clear geometric definition is needed because it has to be understood by a person who is skilled in the art, in addition to anyone who wants to reproduce the invention for his purpose. Furthermore, if based on a classical pharmacophore definition, the description of chirality for a set of isomeric compounds showing different interesting and patentable activities is a hard task.

We thus propose the use of spherical coordinates as an alternative to the current trend that defines a pharmacophore with a set of distances and angles between pharmacophore points. The advantage of this new definition is to bring four geometric parameters – namely, an origin, a distance from the origin and two angles – for the description of one pharmacophore point. Each point is thus described alone in spherical reference coordinates, and a complex set of vectors, angles and planes is no longer necessary. In addition, it becomes easy to define, in one table and one or two figures, the optimal hydrogen-bond vector, electrostatic field or hydrophobic volume that is claimed for each pharmacophore point by using the same spherical space.

Patentability of pharmacophore claims

A recent report in *Nature Biotechnology* [5] summarizes the main points of the debates held at a conference in Austria, where the European Patent Office (EPO), the United States Patent and Trademark Office (USPTO) and the Japan Patent Office (JPO) commented on the patentability of protein 3D structural data and pharmacophores designed by *in silico* screening methods. This conference highlighted the necessity of a clear pharmacophore definition and established the commitments that an applicant has to meet for publishing pharmacophore patent claims.

Several types of claim based on the discovery of pharmacophore models can be found in patent applications [6]. First, some claims concern an *in silico* screening method of a drug candidate molecule using a pharmacophore model. Second, some claims are related to a compound obtained by the latter screening method and specified by a pharmacophore model. Third, some claims concern a compound that is specified by the combination of both pharmacophore model and pharmacological effect (e.g. an agonist or antagonist specified by a pharmacophore model). Last, sometimes a composition for treating a disease containing a compound specified by the pharmacophore is put forward in the patent claims.

If the first two types of claim are recognized to show utilization of a law of nature and can therefore be patented under patent law, it is more difficult to accept that a person with ordinary skill in the art can judge whether the remaining types of claim (which are those that most commonly included in patent applications) meet patentability. Thus, careful descriptions of the pharmacophore have to be made in the patent application to convey sufficient clarity to the examiners to enable them to make a rational judgment. Indeed, even if a pharmacophore model is recognized to have value as a property, a pharmacophore model itself is the 'creation of a technical idea utilizing a law of nature', which is not included in the concept of an invention in the legal sense [6]. A compound specified by a pharmacophore model for a special pharmacological activity is only partially structurally defined, because the overall structure is not specified but replaced by steric and electronic pharmacophore points.

Thus, the concept of a pharmacophore made in virtual reality has to be transposed clearly in the real world of physical reality to enable the examiners adequately to understand. This aspect is important because there is also the possibility that one might enlarge the intellectual property from known compounds incorporated in the patent file to compounds that have not yet been made but will be later synthesized, with respect to the pharmacophore, and included in claims of compounds containing the pharmacophore of interest. This paradox is interesting to the applicant, because protection through the pharmacophore, as we mentioned earlier, can increase the lifetime intellectual property protection of drugs made on the basis of the actual patented pharmacophore.

Patent attorneys, scientists and pharmaceutical companies who want to patent a pharmacophore often encounter some difficulties in the definition of their pharmacophore. The patent examiners are sometimes very severe on pharmacophore definitions that use the classical pairwise distance matrix method, which is considered by many to be a mere representation. Some otherwise good patents have been denied as a result of such criticism.

Classical pharmacophore definition in patent claims

Because humans prefers to rationalize the world surrounding them in terms of straight lines and planes, they commonly use illogical linear and square models of the Universe, such as the four corners of the wide, wide world with their nonexistent fixed top and bottom coordinates [7,8]. The classical geometric definition of a pharmacophore uses a pairwise distance matrix between the pharmacophore points [9,10]. Angle values, defined by two vectors linking three points, are often included in the description. The classical definition of a pharmacophore lacks accuracy because a significant number of different arrangements in the 3D space of the pharmacophore points can lead to the same geometric parameters. Furthermore, the distance matrix rapidly becomes complex when the number of pharmacophore points increases, rendering the reading of patent files tedious, even for a person skilled in the art.

Figure 1a shows a simple representation of a four-point pharmacophore. If all four points are in the same plane, the pharmacophore is defined by six distances and four angles. Most of the time, pharmacophores are represented by several limited distances between some pharmacophore points that the authors consider as important with respect to pharmacological activity. For an exhaustive description in the patent file, however, the pairwise distance matrix has to contain all possible distances linking all pairs of pharmacophore points. If one of the points of the pharmacophore represented in Figure 1a is placed out the plane, the geometric definition of the whole pharmacophore increases in complexity.

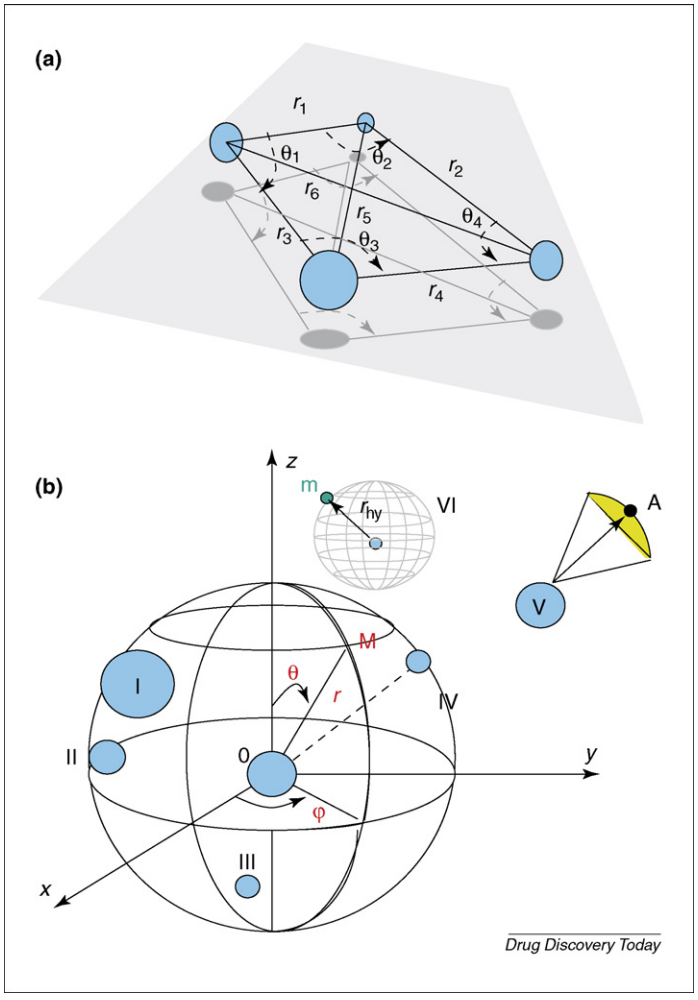

FIGURE 1

New geometrical definition of a pharmacophore. **(a)** Classical 'distance matrix' pharmacophore definition. **(b)** New pharmacophore definition in spherical coordinates. See Box 1 for definitions of the parameters. M represents any pharmacophoric point, such as I, II, III and so on.

Projection of the out-of-plane-pharmacophore point will lead to the definition of at least one or two supplementary angles.

Rationale behind the new pharmacophore definition

Before 3000 BC, the Babylonians believed that the Earth was a flat disk floating in an endless ocean. Later, Aristotle (384–322 BC) showed that the Earth was spherical and provided the foundations of the science of geodesy. A coordinate reference system (datum) was subsequently developed and has been further modified through the centuries to reach a submetric degree of precision with the use of satellites to describe geographic positions for surveying, mapping and navigation. Thanks to Aristotle, the 'shape of the earth' was refined from 'flat-earth models' to 'spherical models' [11]. Geodesy datums can be transposed to the pharmacophore geometric definition to improve the commonly used 'flat-pharmacophore pairwise distance matrix' definition.

Placed in the center of a sphere, an individual can feel the inherent order on his surrounding Universe that is omnidirectional, where people and things are moving apart and toward him. We do not live in and experience either a one-dimensional linear world or a two-dimensional infinitely extended planar world. Our proposed method facilitates transformation of the 'flat-pharmacophore' definition into a 'spherical-pharmacophore' one by using spherical coordinates to define the spatial position of each pharmacophore point. Polar coordinates and radial distribution functions have been used interestingly in drug design and chemoinformatics [12,13]. They were specially developed for aligning several structurally disparate molecules that show a common bioactivity [12]. However, Richmond *et al.* [12] did not succeed in adapting spherical coordinates in their 'similar atom' matching algorithm for superimposing molecules and instead used a 2D (polar coordinates) shape-matching method. Hence, they did not propose the use of spherical coordinates for describing and defining a pharmacophore.

The spherical coordinates consist in a set of three parameters – one distance r and two angles, θ and φ – as defined geometrically in Figure 1b. The origin of the x, y and z axes is placed at the center of a sphere arbitrarily positioned in the geometric center or 'nucleus' of the pharmacophore. The geometric parameters of curvilinear coordinates are natural for describing positions on a sphere or a spheroid. The azimuthal angle in the xy plane from the x axis is $\varphi \in [0,2\pi)$, θ is the polar angle from the z axis or co-latitude with $\theta \in [0,\pi)$, and $r \in [0,\infty)$ is the distance (radius) from a point to the origin. The angles are independent of the object size and absolutely generalized. Interconversion from spherical to cartesian

BOX 1

Pharmacophore geometric parameters

Each pharmacophoric point (Figure 1b, main text, points I–VI) and their relative spatial distribution can be defined by two types of coordinates:

Cartesian coordinates

$$x = r \sin\theta \cos\varphi \quad \text{[Eqn I]}$$

$$y = r \sin\theta \sin\varphi \quad \text{[Eqn II]}$$

$$z = r \cos\theta \quad \text{[Eqn III]}$$

Spherical coordinates

$$r = \sqrt{x^2 + y^2 + z^2} \quad \text{[Eqn IV]}$$

$$\theta = \cos^{-1}\left(\frac{\mathbf{z}}{\mathbf{r}}\right) \quad \text{[Eqn V]}$$

$$\varphi = \tan^{-1}\left(\frac{\mathbf{y}}{\mathbf{x}}\right) \text{ if } x > 0 \quad \text{[Eqn VI]}$$

$$\varphi = \tan^{-1}\left(\frac{\mathbf{y}}{\mathbf{x}}\right) + 180 \text{ if } x < 0 \quad \text{[Eqn VII]}$$

Angle θ lies in the range 0° to 180°. To determine the correct value of angle φ it is necessary to look at the signs of x and y to see in which quadrant φ has to be. The value of φ is obtained after adding or subtracting 180° (or π in radians) as in equations (6) and (7). We always choose r to be positive. 'Quadrants' 1, 2, 3 and 4 (Figure 1b, green, main text) determine the sign of angle φ, as shown in Table I.

TABLE I

The sign of the azimuthal angle

Sign of x	Sign of y	Quadrant	Sign of φ
+	+	1	+
–	+	2	+
–	–	3	+
+	–	4	–

coordinates can be performed by simple equations (Box 1). This definition avoids a long list of distances linking couples of pharmacophore points used in the classical definition.

For patent drafting, the geometric description of the pharmacophore is thus summarized in one file containing all pharmacophore points and, if necessary, the corresponding values of their cartesian and spherical coordinates. To facilitate manipulations of the pharmacophore in three dimensions (3D), a second file written in Protein Data Bank (PDB) format containing the cartesian coordinates of all pharmacophore points and those of the arbitrary origin can be added. This second file can be directly imported into Insight II graphical software (Accelrys, http://www.accelrys.com/products/insight/) and submitted to a molecule alignment process for database screening.

Adding in hydrogen-bond vectors and hydrophobic volumes

Most patent applications relating to a pharmacophore mention only the pharmacophore points and their physicochemical nature in their description. No information is specified on the orientation of hydrogen-bond vectors pointing from the hydrogen-bond donor or acceptor centers toward the virtual receptor. An accurate description of the 3D orientation of such interactions has to be detailed in a patent claim, because it can influence markedly, for example, the quality of database screening for a compound. Indeed, the superposition of a molecule on a pharmacophore can lead to a perfect match between the position and physical nature of all the pharmacophore points and can identify essential chemical groups in the molecule. Although the fit might be perfect, however, the orientation of the hydrogen-bond vectors pointing from the hydrogen-bond donor or acceptor centers of the pharmacophore might be radically different from those of the molecule. This strongly depends on the nature of the chemical groups on which the pharmacophore points were defined. Figures 1b and 2a show, for example, that at a hydrogen-bond donor center the heteroatom bound to the proton is usually taken as a pharmacophore point. The vector pointing towards the putative hydrogen-bond acceptor center of the receptor can be also described in terms of spherical coordinates. Furthermore, the binding of a ligand to a receptor does not necessarily result in ideal hydrogen bonding but sometimes deviates and binds in a zone of the 3D space that can be defined by a spherical cap [14].

Figure 2a–d shows the geometric definition of the hydrogen-bond donor and acceptor pharmacophore points *R* and *O*, respectively. The ideal hydrogen bond follows the vector **H–A** or **O–A**, where A is the position of the putative contact with the receptor. The surface *S* of the spherical cap represents the possible deviation of the hydrogen-bond interaction around the center A. The surface *S* can be calculated by using the geometric parameters in Figure 2a, b (Boxes 2, 3). In the patent draft, point A is defined by spherical and cartesian coordinates and surface *S* can be pasted in the same file below each concerned pharmacophore point. In the PDB format file, point *A* defined in cartesian coordinates enables the easy measurement of *r* and *h* within a computer graphical interface and calculation of *S*.

The description of hydrophobic volumes is also important in a patent application. It provides the possibility of increasing the diversity of compounds selected during database screening, because hydrophobic volumes can accommodate some variability without altering the activity of the selected compounds. This is due to the isotropic nature of the van der Waals non-bonded interactions that hydrophobic volumes and surfaces establish when they interact together. These interactions differ from hydrogen bonds, which are anisotropic in 3D space and need precision in the topology of their interactions. Hydrophobic interactions have been represented by volumes in some software dedicated to drug design (e.g. Catalyst 4.9, Accelrys, http://www.accelrys.com/products/catalyst/); however, the representations used are not described in spherical coordinates and are always combined, in scientific publications, with the classical pairwise distance matrix pharmacophore definition, which obviously lacks accuracy and does not meet the commitments needed to claim intellectual property on a pharmacophore.

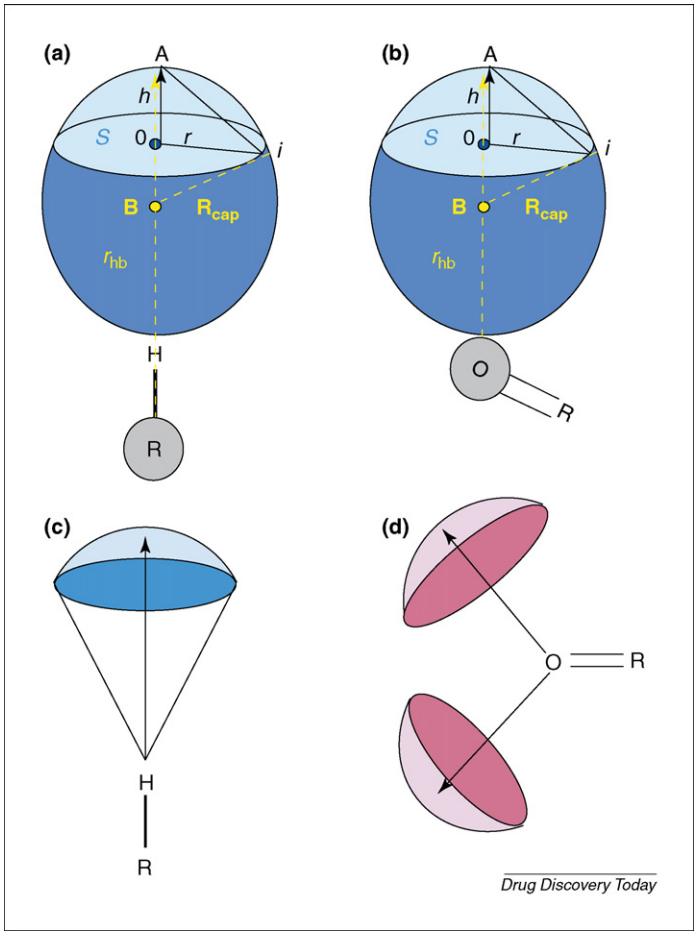

FIGURE 2

Geometrical definition of the hydrogen-bond interaction surface. **(a,b)** Geometrical parameters needed to calculate the spherical cap surface *S* (light blue) corresponding to the interaction surface between a hydrogen-bond donor (R–H) and a putative hydrogen-bond acceptor (a) and between a hydrogen-bond acceptor (R═O) and a putative hydrogen-bond donor (b). O and R represent a hydrogen-bond acceptor and a hydrogen-bond donor pharmacophoric center respectively. **(c,d)** Graphical representations of hydrogen-bond spherical cap surfaces after calculations that are currently included in the patent definition of a pharmacophore. O indicates an oxygen atom, as an example of a bidirectional hydrogen-bond acceptor pharmacophoric center.

BOX 2

Hydrogen bonds and hydrophobic volumes geometric definition

The definition of the two system coordinates – namely, hydrophobic volume and hydrogen-bond vector – are shown in Figure 1b (main text). Hydrophobic volume around a hydrophobic center can be defined with the help of point m, which is used to calculate the radius of the hydrophobic sphere, which in turn is the norm of the vector $\mathbf{r_{hy}}$. Hydrophobic volume is easily defined as:

$$V_{hy} = 4/3\pi\mathbf{r}_{\mathbf{hy}}^3(\text{Å}^3) \quad \text{[Eqn I]}$$

Points A allow the definition of the vector pointing in the direction of an ideal hydrogen bond from a hydrogen-bond donor or acceptor pharmacophoric point to, respectively, a hydrogen-bond acceptor or donor atom of the interacting molecule or receptor (Figure 2, main text). Point A is located on the van der Waals surface of this atom. The extremity A of the hydrogen-bond vector can deviate from this ideal position (the pharmacophoric point extremity of the vector being fixed) and can define a 'spherical cap' (Figure 2, main text) corresponding to the surface *S*, where a hydrogen bond between the pharmacophoric point and the putative interacting molecule atom is still possible:

$$S = 2\pi\mathbf{R}_{\mathbf{cap}}h(\text{Å}^2) \quad \text{[Eqn II]}$$

Point *B* is the middle of a sphere (Figure 2a,b, dark blue; main text) corresponding to the volume occupied by the orbital of a putative interacting hydrogen-bond acceptor atom containing a pair of electrons (Figure 2c, main text) or to the volume occupied by the orbital of a hydrogen-bond acceptor pharmacophoric center containing a pair of electrons (Figure 2d, main text). The O of R═O (Figure 2, main text) influences the geometry of the hydrogen-bond network of a hydrogen-bond acceptor pharmacophoric center. It can be replaced by any other heteroatom and depends on the chemical structure of compounds that are used to define the pharmacophore.

The surface *S* (Figure 2a,b, light blue, main text) is dependent on the height *h*, which is set by the angle defined by the two vectors **B–A** and $\mathbf{R_{cap}}$. Point *B* is the middle of vector **A–H** in the case of a hydrogen-bond donor pharmacophoric center, or the middle of vector **A–O** in the case of a hydrogen-bond acceptor pharmacophoric center. The orthogonal projection of point *i* on the vector **B–A** is point *O*, which delimits the base of the spherical cap. The distance **O–A** is equal to *h*.

The hydrophobic volume can be calculated around a hydrophobic pharmacophore center (Figure 1b). A point m and its corresponding two systems of coordinates are added in the same file as pharmacophore points and point A. Point m represents the radius of the hydrophobic sphere r_{by}. The volume ofthe sphere is rapidly calculated using a very simple formula (Boxes 2, 3).

Tolerance in the position of pharmacophore points

In the classical definition of a pharmacophore, tolerance in the geometric parameters is always mentioned and is usually represented by an average value and a standard deviation for all distances and angles of the pharmacophore. This average corresponds to the authorized geometric space where the bioactivity can be defined by the pharmacophore. This crude representation is poorly informative, lacks accuracy, and must be revised to meet the commitments required for a patent application.

In the classical definition of a pharmacophore, the authorized frame of euclidian distances between two pharmacophore points concerns only the position of a couple of points relative to each other. If the distance is elongated, are the two points moving apart? Or is one point moving towards the other, which is fixed? If the distance varies within the authorized frame, the position of the vector between those two points can be set in any position in the 3D space. Furthermore, because each point of a pharmacophore is interdependent in the pairwise distance matrix, for each authorized distance for each couple of points, the positions, distances and angles for all of the other points should also be defined. Such definition would lead to a non-understandable and complex description of a pharmacophore. The classical 2D pharmacophore definition is thus reductive.

In our proposed method, each point is easily localized inside a sphere because the point refers to the geometric origin and there is no need to describe its position relative to the other points. Instead of proposing an average position separately for the three geometric parameters r, θ and φ, the authorized frame for the spherical coordinates of each point is defined by a sphere centered on the average position of the point. This enables the three geometric parameters to vary interdependently. The radius of the 'frame sphere' can be also defined in spherical coordinates and implemented inside a table with the other parameters.

Pharmacophores and chirality

Our pharmacophore definition can be extended to the notion of chirality. Indeed, chiral technologies [15,16] represent a real trend that drug discoverers and patent attorneys must examine for drug design development and intellectual property protection. In therapeutics, chiral effects can be exploited in two ways: by chiral switching – that is, by developing single-enantiomer versions of approved racemic drugs; and by discovering distinct therapeutic uses for enantiomers of chiral drugs. Thus, it is of paramount importance to include chirality and racemic molecules in the pharmacophore definition of the filed patent.

A pharmacophore cannot be chiral owing to the lack of defined bonds and thus the impossibility of applying the rules of Cahn, Ingold and Prelog that are used to name enantiomers and diastereomers. However, establishing two pharmacophores for the same molecule can facilitate the definition of two different bioactivities, where each pharmacophore is obtained after the alignment of a series of chemical compounds with the two isomers of the same molecule. The 3D spatial distributions of the pharmacophore points of the two isomers can be clearly individualized in a patent file by using spherical coordinates, even if the two pharmacophores vary only by one point (Figure 3).

Chirality can be defined in every conceivable dimension: as far as principles go, chirality is not related to the third dimension in any way. If describing chirality is simpler in the 2D case, however, the description requires sufficient accuracy to fulfill the recommendations of the USPTO, JPO or EPO. Thus, chirality has to be described in 3D for efficient and precise definition within a pharmacophore. Indeed, the patent application must contain sufficient information to enable any individual skilled in the art, using his common general knowledge, to execute the whole invention without undue burden or inventive skill. The distance matrix definition of a pharmacophore has formed the

BOX 3

Pharmacophore spherical coordinates and its 3D representations

Table I lists the pharmacophoric and accessory points with their respective two systems of coordinates. A file containing the *x*, *y* and *z* coordinates of those points can be used to represent in 3D the pharmacophore by a graphical interface. The group of accessory points contains the origin, the points *A* and point m.

Figure 3 (main text) shows an example of the geometric definition of two enantiomeric pharmacophores. After superposition of the two mirror images, fitting points are places in the center of the sphere. Because they are mirror images (Figure 3a, main text), the points of a pair of the two enantiomeric pharmacophores have a similar co-latitude (value of angle θ) and *r* value (Figure 3b, main text). They differ in the value of their azimuthal angle, φ (Figure 3d, main text) because they are located in a different quadrant. Figure 3 (main text) represents the extreme case in which all of the pharmacophoric points are affected by chirality. Our definition and procedure can be also applied when one or two points are affected.

TABLE I

Two coordinates systems conversion table

Pharmacophoric and accessory points	*x*	*y*	*z*	*r* (Å)	θ (°)	φ (°)	*S* (Å^2)	V_{hy} (Å^3)
I H-bond donor	−0.186	1.385	1.385	1.97	45.10	97.6	4	–
II H-bond donor	2.528	5.073	0.025	5.67	89.70	63.5	3	–
III H-bond acceptor	0.306	−1.172	2.067	2.40	30.50	−75.4	5	–
IV H-bond acceptor	1.328	1.682	4.265	4.77	26.70	51.7	6	–
V H-bond donor	−5.411	−4.479	2.280	7.38	71.90	219.6	4	–
VI hydrophobic volume	−5.647	1.999	0.232	6.00	87.6	160.5	–	50
Origin	0.000	0.000	0.000	0.000	0.000	0.0	–	–
A–I	−0.837	3.193	0.695	3.37	78.0	104.7	–	
A–II	3.708	6.546	−2.409	7.90	107.80	60.5	–	–
A–III	−0.697	−2.615	3.022	4.06	41.9	255.1	–	–
A–IV	0.652	3.176	5.781	6.63	29.20	78.4	–	–
A–V	−5.001	−4.947	0.379	7.04	86.90	224.7	–	–
m–VI	−6.958	2.951	−1.040	7.63	97.60	157.0	–	–

basis of criticisms about the classical pharmacophore definition. Indeed, patent offices have considered the classical definition as a mere presentation of information that does not support sufficiently the characterization of the active compounds and does not satisfy patent eligibility. Because geometric parts of the pharmacophore signature are determined by types of center and inter-center distances, many pharmacophores are achiral.

Our definition allows the clear and simultaneous definition of two enantiomers of a racemic mixture. Figure 3 shows the superposition of two such enantiomers within a sphere. Some of the pharmacophore points are common and have the same spherical coordinates. The set of different points can be distinguished by differences in spherical coordinates. The azimuthal angle is intrinsically different for the two enantiomeric forms of the same pharmacophore point, leading to negative and positive values. A definition using only cartesian coordinates is sometimes insufficient to obtain a 3D image of a pair of enantiomers. Indeed, algorithms implemented in graphical interface packages often attribute erroneously the stereoisomers in a system by using only reference cartesian coordinates.

Applications of the new pharmacophore definition

In addition to their use in patent files, spherical coordinate systems can be extended to other applications. One of their immediate applications is to the definition of a 'chiral pharmacophore' model from molecular field analyses of two enantiomers using one of the most popular 3D quantitative structure–activity relationship (3D-QSAR) methods such as 'comparative molecular field analysis' (CoMFA) [17,18] or the GRID program [19]. The description of two enantiomers (in a single, active conformation) of the same chiral molecule in spherical coordinates is easy because the isomers give two different molecular fields. It is rather more difficult for achiral molecules that become chiral inside a chiral environment because these molecules are thought to produce only one molecular field. In fact, placed in a known binding site or chiral environment, they can generate different molecular interacting fields like a chiral molecule. An example is serotonin or 5-hydroxytryptamine (5-HT), which does not contain any asymmetric carbon. The binding mode of 5-HT is greatly altered, however, if the conformation of the ethylamine side chain of 5-HT is changed inside the binding site of the 5-HT receptor subtype [20]. Thus, 5-HT behaves like a chiral molecule. This behavior is of prime importance in the design of rational 5-HT reuptake inhibitors [21].and agonists or antagonists of 5-HT receptors [22].

The need for an accurate definition of chirality is essential and chirality-sensitive 2D descriptors for QSAR analysis have been proposed to define enantiomers and to quantify chirality [23]. After superposition of the two enantiomers, field vectors generated with a specific probe used to map the surface of the enantiomers can be defined with spherical coordinates and easily transferred to QSAR analysis by using statistical tools such as partial least squares analysis or a neural network.

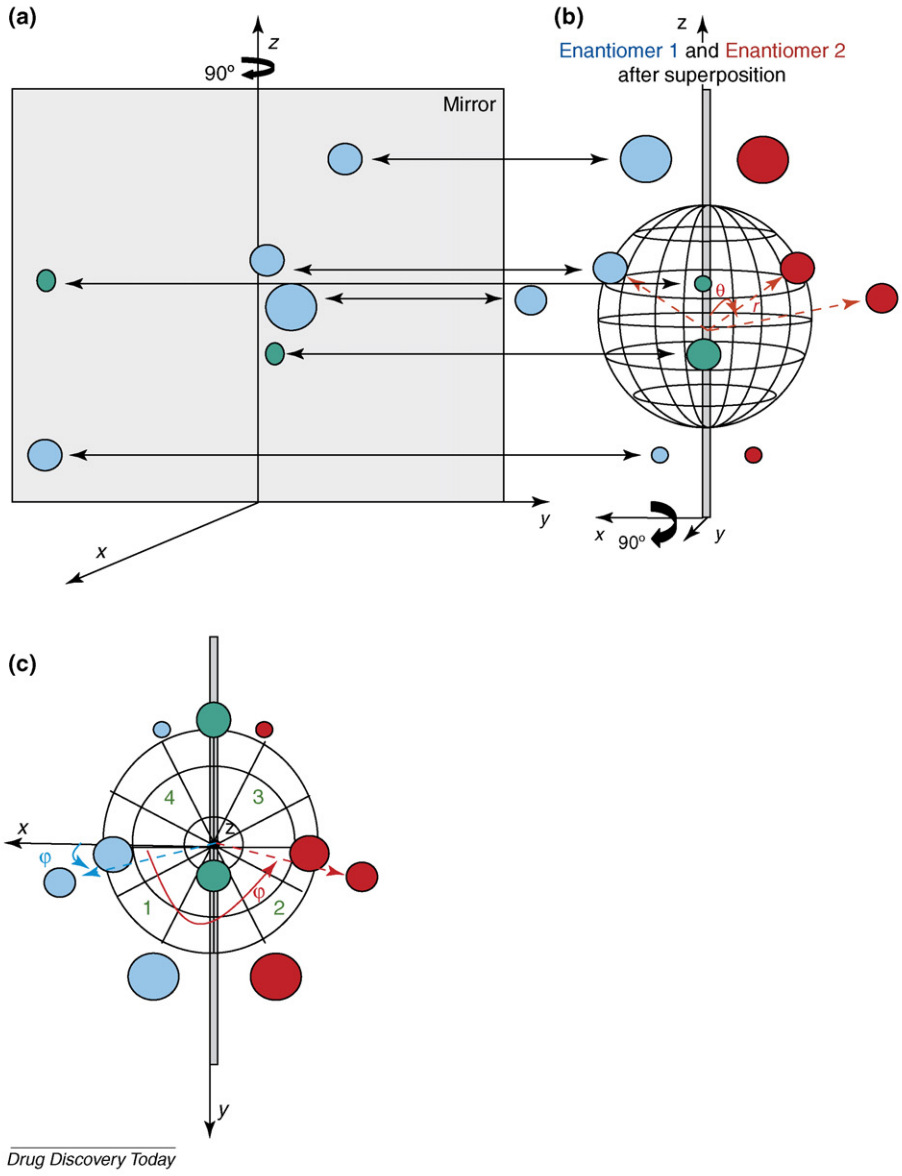

FIGURE 3

Geometrical definition of chirality. **(a)** A pharmacophore (blue spheres) and its image are separated by a mirror. Two points in the plane of the mirror (green) correspond to the fitting point of the two enantiomeric pharmacophores after alignment. **(b)** After a 90° rotation around the *z* axis, the two aligned pharmacophores (blue and red) are placed in a sphere. Each point is defined in spherical coordinates. Angle θ and distance *r* are similar for a pair of image points. **(c)** After 90° rotation around *x* axis, pairs of image points are distributed in different quadrants and differ by their azimuthal angle, φ.

Another chief application concerns crystal engineering and the patenting of crystal structures of either small organic compounds or ligand–protein complexes [24]. The three known types of chiral drug crystal that are marketed as 'racemate' (racemic conglomerate, racemic compound, and pseudo-racemate) have to be carefully defined in the patent draft. Crystal structures can be obtained by X-ray crystallography and *ab initio* crystal structure prediction [25]. The latter technique involves a sophisticated analysis of the crystal lattice energy hyper-surfaces, using intermolecular interaction terms such as 'distributed multipole-based intermolecular potential' and 'hydrogen-bond anisotropic potential'. Water molecules contribute to crystal stability through their ability to form multidirectional hydrogen bonds, which link the drug molecule to form a crystal. Each drug crystal contains unit cells with a specific network of hydrogen bonds that can be described using our spherical coordinate method.

The new definition can be also extended to the degree of similarity between a pharmacophore and hits extracted from a database of chemical compounds [26,27]. In spherical coordinates, similarity can be measured more accurately and, in addition, molecule superposition methods using mathematical formulae based on matching scores or goodness of fit are more efficient than are cartesian coordinates. Indeed, spherical coordinates give precise information about the relative orientation of equivalent points from two similar molecules. Furthermore, they enable the definition of the spatial distribution of two points to

be superposed, relative to mass or geometric centers, and enable distance minimizing algorithms to reach convergence more quickly. These features are facilitated by the omnidirectionality of the reference coordinate and the transferable isotropic vector matrices of the two superposed objects that enable the two spheres to be moved and aligned on their center. With cartesian coordinates, the distance to minimize between two points is always constant in 3D space, and several relative positions of the two points exist and can lead to the same matching score. The application of spherical coordinates will be important here, especially for the superposition of candidate molecules on different enantiomers of the same reference molecule.

Conclusion

We have demonstrated that our geodesic spherical coordinate system can be efficiently transposed to the definition of a pharmacophore. This transposition has been achieved by reconsidering our perception of a pharmacophore placed inside an omnidirectional microenvironment. Surprisingly, although those individuals involved in molecular modeling and drug design are supposed to be familiar with manipulation of the virtual world and mathematics of 3D and higher dimensions, the geometric definition of pharmacophores in patent applications has been relatively neglected and poorly documented until now. A few patent applications involving pharmacophores have been launched, despite the great interest in the pharmacophore concept. We hope that our geodesic definition of pharmacophores will reactivate the interest in pharmacophores as a valuable tool for protecting intellectual property.

We are currently implementing our definition in a computer algorithm dedicated to drug design. Special attention will be given to the definition of a non-static pharmacophore. This concept will be used for flexible-pharmacophore alignment-based screening of chemical compound databases. Indeed, most pharmacophore-based screening is currently performed with the aid of a static pharmacophore, but in fact a pharmacophore is not static at all because it is extracted from an alignment of vibrating molecules that are able to accommodate a particular conformation during binding to their macromolecular target. Our technique will enable both the molecule and the pharmacophore to remain flexible during the alignment procedure.

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