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Patents of bio-active compounds based on computer-aided drug discovery techniques

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1. ABSTRACT

In recent times, there has been an increased use of Computer-Aided Drug Discovery (CADD) techniques in Medicinal Chemistry as auxiliary tools in drug discovery. Whilst the ultimate goal of Medicinal Chemistry research is for the discovery of new drug candidates, a secondary yet important outcome that results is in the creation of new computational tools. This process is often accompanied by a lack of understanding of the legal aspects related to software and model use, that is, the copyright protection of new medicinal chemistry software and software-mediated discovered products. In the center of picture, which lies in the frontiers of legal, chemistry, and biosciences, we found computational modeling-based drug discovery patents. This article aims to review prominent cases of patents of bio-active organic compounds that involved/protect also computational techniques. We put special emphasis on patents based on Quantitative Structure-Activity Relationships (QSAR) models but we include other techniques too. An overview of relevant international issues on drug patenting is also presented.

2. INTRODUCTION

Whilst there are few connections between Computer-Aided Drug Discovery (CADD) and the legal system, the latter does have and continues to have an impact on drug discovery. Indeed, the relationship between CADD and the law spans a wide range of different issues including intellectual property (e.g. patents, trademarks, trade secrets), licensing (e.g. licensing patents, intellectual property of software), legislation, regulation, product development as well as corporate legal issues (1). CADD encompasses the use of tools and techniques from three separate disciplines; molecular biology (the source of the data to be analyzed), computer science (the hardware to run the analysis and the networks to communicate the results), and data analysis algorithms, which strictly define CADD tools (2). The development of CADD software is a challenge for the future; the software facilitates the research and the science fosters the development of new bioinformatics software businesses (3). CADD can not to

all intents and purposes evolve without software development. In any case, even when CADD tools are final products *per se*, the ultimate goal of all Bio-Pharmaceutical industry is the discovery of new compounds, which may be introduced in the market as a new product at the service of society. In the center of this picture, which lies in the frontiers of legal, chemistry, and biosciences, we found CADD-based bio-active compound patents. We refer here to patents that claims new drug candidate compounds and recognized/claim as well CADD techniques used in the discovery process. We refer to techniques like molecular Docking, Molecular Modeling, Molecular Dynamics, but we put special emphasis on Quantitative Structure-Activity Relationships (QSAR) models. For an exhaustive explanation on CADD techniques, including QSAR and others, the reader may refer for instance to recent special issues guest-edited by Gonzalez-Diaz (4-40). These issues contain many reviews published by prominent researchers. In this sense, this article aims to review prominent cases of patents of bio-active organic compounds that involved/protect also computational techniques with special emphasis on patents based on QSAR models but we include other techniques too. In order to put the paper in the correct background we offer an overview of relevant international issues on drug patenting as well.

3. CADD BIO-ACTIVE COMPOUNDS PATENTS

Different software and/or CADD methods may be used as auxiliary tools in drug discovery and patenting. The patents generated in such a way may protect not only the new organic compounds and their biological activity but also the CADD techniques or software used to discover them (see section 4) (23). In Table 1 we depict some of these patents that protect new bio-active compounds and/or the CADD techniques used. At follows we discuss some examples of these patents with more detail.

3.1. Compounds & Computational method

3.1.1. Aziridinyl quinone antitumor agents

A large number of aziridinyl quinones represented by Series 1-9 were studied with respect to their DT-diaphorase substrate activity, DNA reductive alkylation, cytostatic/cytotoxic activity, and in vivo activity. As a result generalizations have been made with respect with respect to the following: DT-diaphorase substrate design, DT-diaphorase-cytotoxicity QSAR, and DNA reductive alkylating agent design (41). A saturating relationship exists between the substrate specificity for human recombinant DT-diaphorase and the cytotoxicity in the human H460 non-small-cell lung cancer cell line. The interpretation of this relationship is that reductive activation is no longer rate limiting for substrates with high DT-diaphorase substrate specificities. High DT-diaphorase substrate specificity is not desirable in the indole and cylopent[b]indole systems because of the result is the loss of cancer selectivity along with increased toxicity. We conclude that aziridinyl quinones of this type should possess a substrate specificity (V_{max}/K_M) < $10x10^{-4}$ s^{-1} for DT-diaphorase in order not to be too toxic or nonselective. While some DNA alkylation was required for cytostatic and cytotoxic activity by Series 1-9, too much alkylation results in loss of cancer selectivity as well as increased in vivo toxicity. They conclude that relatively poor DNA alkylating agents (according to our assay) show the lowest toxicity with the highest antitumor activity.

3.1.2. Chalcones for neoplastic disorders

The invention relates to the use of 1,3-bis-aromatic-prop-2-en-1-ones (chalcones), 1,3-bis-aromatic-propan-1-ones (dihydrochalcones), and 1,3-bis-aromatic-prop-2-yn-1-ones for the preparation of pharmaceutical compositions for the treatment or prophylaxis of a number of serious diseases including i) conditions relating to harmful effects of inflammatory cytokines, ii) conditions involving infection by Helicobacter species, iii) conditions involving infection by viruses, iv) neoplastic disorders, and v) conditions caused by microorganisms or parasites. The invention also relates to novel chalcones and dihydrochalcones (especially alkoxy substituted variants) having advantageous substitution patterns with respect to their effect as drug substances, and to methods of preparing them, as well as to pharmaceutical compositions comprising the novel chalcones (42). Moreover, the present invention relates to a method for the isolation of Leishmania fumarate reductase, QSAR methodologies for selecting potent compounds for the above-mentioned purposes.

3.1.3. Steroid acting over DNA replication

The present invention relates to an in vitro mammalian DNA replication system and to a method for identifying agonists and antagonists of DNA replication. The method comprises contacting in vitro a plasmid with a mixture comprising nuclear or cytoplasmic extracts from HeLa cells, the drug and a mixture of nucleotides, assessing the stimulation or the inhibition of initiation of DNA replication and the elongation of nascent DNA produced by the drug, and identifying the essential structures of the drug by QSAR analysis deriving relationships between the structural features of the drug and biological responses produced by the binding of the drug to the target receptor. The plasmid has a target receptor and comprises a specific mammalian origin of DNA replication (43).

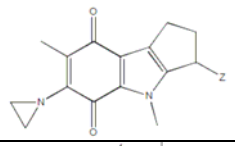
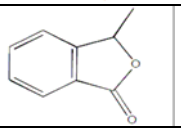
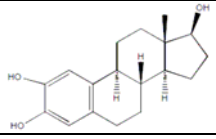
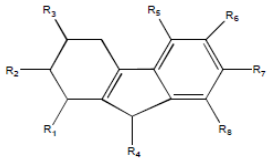
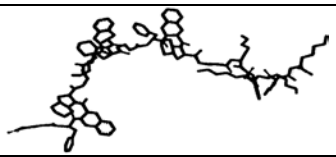
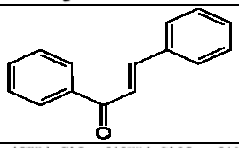
3.1.4. Drugs suppressing appetite

Compounds of formula I are useful for suppressing appetite, and for altering macronutrient preferences, where the R2-R9 substituents are so selected as to meet a defined quantitative structure activity relationship (QSAR) quantity relating to the partition coefficient of the compound, the net charge on the ring nitrogen, and the radical superfdelocalizability at the position-8 ring carbon (44).

3.1.5. Anti-microbial peptidomimetic compounds

This invention encompasses synthetic antimicrobial peptide analogs having certain un-natural amino acids, including the un-natural amino acids hydrophobic tetrahydroisoquinolinecarboxylic acid (Tic) and octahydroindolecarboxylic acid (Oic), incorporated into the polypeptide backbone (45). These antimicrobial peptides (AMPs) are useful to treat infection in humans and other mammals of such bacteria as Gram positive bacteria,

Table 1. Some patents protecting potential drugs and/or drug-discovering computational models

Patent	Main Claims	Compounds	Ref.	Owner [a] (Country)
Compounds & Computational method				
US2003 139609	Aziridinyl quinone antitumor agents		(41)	Authors (US)
US2003 065039	Chalcones for neoplastic disorders, viral and parasite infections, etc.		(42)	Statens Serum Institut (DK)
WO992 8496	In vitro assay & QSAR to identify steroid agonists and antagonists of DNA replication.		*(43)*	Univ. Mcgill (CA).
US51 69852	Drugs suppressing appetite & QSAR model to predict them.		(44)	Neurex Corp (US)
US2009291898	Novel anti-microbial peptidomimetic compounds		(45)	US ARMY (US)
WO9900114	Biologically Active 1,3-Bis-Aromatic-Prop-2-En-1-Ones		(46)	Authors (DK)
WO0244686	Predictive method for polymers	$(CH_3)_3SiO—[(CH_3)_2SiO]_a—[(CH_3)(R^1)SiO]_b—Si(CH_3)_3$	(47)	Procter & Gamble
Computational method alone				
US2006 206269	1D QSAR models	-	(48)	PDD (US)
US53 07287	CoMFA	-	(49)	Tripos (US)
US62 08942	Molecular Hologram QSAR	-	(50)	Tripos. Inc. (US)
US2002 123848	Polymers QSAR	-	(51)	Authors (US)
US2010 010955	Molecule Fragmentation	-	(52)	Vlife Sci. Tech. Pv
CN101673321	predicting organic pollutant	-	(53)	Univ. Dalian Tech.
WO2009 11409	Searching databases	-	(54)	Authors(US)
US2006 080073	3D-QSAR	-	(55)	Authors (US)
WO0025106	Pharmacophore ingerprinting	-	(56)	Glaxo Group (US)
US2003149554	data segmenting techniques	-	(57)	Authors (US)

[a] PDD means Pharm. Drug. Discov.

Gram negative bacteria and Mycobacterium. Many of the AMPs also exhibit the property of reduced hemolytic activity.

3.1.6. Biologically active chalcones

The invention relates to the use of 1,3-bis-aromatic-prop-2-en-1-ones (chalcones), 1,3-bis-aromatic-propan-1-ones (dihydrochalcones), and 1,3-bis-aromatic-prop-2-yn-1-ones for the preparation of pharmaceutical compositions for the treatment or prophylaxis of a number of serious diseases including i) conditions relating to harmful effects of inflammatory cytokines, ii) conditions involving infection by Helicobacter species, iii) conditions involving infections by viruses, iv) neoplastic disorders, and v) conditions caused by microorganisms or parasites. The invention also relates to novel chalcones and dihydrochalcones (especially alkoxy substituted variants) having advantageous substitution patterns with respect to their effect as drug substances, and methods of preparing them, as well as to pharmaceutical compositions comprising the novel chalcones.; Moreover, the present invention relates to a method for the isolation of Leishmania fumarate reductase, QSAR methodologies for selecting potent compounds for the above-mentioned purposes (46).

Table 2. Copyright, use, price and other details for some software used in medicinal chemistry

Software	Authors and/or *Copyright details* (web)	Date	Input [a]	Output [b]
Data Analysis				
Statistica 6.0	*StatSoft inc.*	1984-2002	RD	QSAR
WEKA			RD	QSAR
CODESSA + AMPAC	Katritzky A. and Karelson M. *Semichem, Inc.* (http://www.semichem.com/)	2007	Mol	QSAR, O.S.
Molecular Modeling & Structure Optimization				
Hyper Chem	*Hyper Cube* (http://www.hyper.com/)	2007	Mol	O.S.
Chem3D Pro	*Cambridge Soft* (http://www.cambridgesoft.com)	2007	Mol, PDB	O.S., 3DI, TIs
Cerius	*Accelrys* (http://accelrys.com/)	2007	Mol	O.S.
Drug-Target Docking				
Auto Dock 4.	GNU General Public License (http://autodock.scripps.edu/)	2007	Mol, PDB	O.S.
Gold	CCDC (http://www.ccdc.cam.ac.uk)	2007	Mol, PDB	O.S.
MOE	*Chem. Comput. Group Inc.*(http://www.chemcomp.com)	2007	Mol, PDB	O.S., 3DIs, TIs
Calculating Molecular Descriptors for QSAR				
TOMO COMD	Marrero-Ponce, Y. *et al.*(http://www.uv.es/yoma/)	2003-2007	Mol	TIs
MODES LAB	Estrada, E. *MODesLab.com* (http://www.modeslab.com)	2002-2007	Mol, Smi	3DIs, TIs
E-Calc	Kier L.B. & Hall L.H.	1999-2007	Mol	3DIs, TIs
DRAGON	Todeschinni, R. *Talete srl, Milano, Italy* (http://www.talete.mi.it)	2003-2007	Mol + Smi	3DIs, TIs
MARCH INSIDE	Gonzalez-Diaz, H. *et al.* (*see footnotes*)[c]	2003-2007	Mol, Smi, Seq, CT, PDB	3DIs, TIs

[a] In Inputs: RD refers to Raw Data of biological activity and molecular descriptors; Mol. to structure of small molecules; Smi to SMILE codes; PDB to Protein Data Bank files; Seq to Protein and DNA sequences and CT to secondary structures of RNAs b In Outputs: QSAR refers to predictive models, O.S. to Optimized Structures; 3DIs to 3D Molecular indices, and TIs to topological indicesc Homepage of the main author: *http://gonzalezdiazh.googlepages.com/cvsummary* (contain links to copyright owners webs and published papers).

3.1.7. Predictive method for polymers

The present invention relates to a computational method for predicting a desired property and/or performance of polymers, and/or identifying and designing polymers that provide said desired property and/or performance, wherein the desired property can be provided by the neat, undiluted polymers, or diluted polymers in a composition. The method is QSAR approach wherein the descriptors used are structural descriptors which are experimentally generated and/or derived from one or more analytical methods (47).

3.2. Registry & patents only with CADD method

Different software can be used to predict new compounds in CADD. These computer programs may be registered in order to protect them by means of copyright issues (see section 4) (23). In Table 2 we depict some useful software for CADD research and their registration details. In addition, other software and/or CADD methods may be protected by means of patents. At follows we discuss some examples of patents that protect only software and/or CADD methods and not compounds.

3.2.1. One-dimensional QSAR models

A set of molecules, the members of which have the same type of biological activity, are represented as one-dimensional strings of atoms (48). The one-dimensional strings of all members of the set are aligned, in order to obtain a multiple alignment profile of a consensus active compound. The one-dimensional multiple alignment profile is used in deriving a one-dimensional QSAR model to identify other compounds likely to have the same biological activity, and also may be used to derive a three-dimensional multiple alignment profile of the molecules in the set.

3.2.2. Comparative molecular field analysis

Comparative Molecular Field Analysis (CoMFA) is an effective computer implemented methodology of 3D-QSAR employing both interactive graphics and statistical techniques for correlating shapes of molecules with their observed biological properties. For each molecule of a series of known substrates the steric and electrostatic interaction energies with a test probe atom are calculated at spatial coordinates around the molecule. Subsequent analysis of the data table by a partial least squares (PLS) cross-validation technique yields a set of coefficients which reflect the relative contribution of the shape elements of the molecular series to differences in biological activities. Display in three dimensions in an interactive graphics environment of the spatial volumes highly associated with biological activity, and comparison with molecular structures yields an understanding of intermolecular associations (49). CoMFA will also predict the biological activity of new molecular species.

3.2.3. Molecular hologram QSAR

A new computer implemented method for discovering structure-activity relationships has been discovered which utilizes weighted 2D fingerprints in conjunction with the PLS statistical methodology (50). This method produces a robust QSAR technique that can be automated. In addition, the MOLECULAR HOLOGRAM

QSAR technique generates high quality QSAR models that are in many cases as good as or better than models arising from use of more complex and time consuming techniques such as CoMFA or Apex-3D.

3.2.4. Predictive method for polymers

The present invention relates to a computational method for predicting a desired property and/or performance of polymers, and/or identifying and designing polymers that provide said desired property and/or performance, wherein the desired property can be provided by the neat, undiluted polymers, or diluted polymers in a composition. The method is a QSAR approach wherein the descriptors used are structural descriptors which are experimentally generated and/or derived from one or more analytical methods (51).

3.2.5. Molecule fragmentation scheme

Group based QSAR method (G-QSAR) is reported which uses descriptors evaluated only for the substituent groups or molecular fragments rather than whole molecule for generating QSAR (52). In addition, cross terms are calculated from product of descriptors at different substituent sites or fragments and used as descriptors to improve the QSAR models. This method provides QSAR models with predictive ability similar or better to conventional methods and in addition provides hints for sites or fragments of improvement in the molecules. The descriptor ranges for substituents or fragments are used to search for new groups/fragments leading to design of novel molecules with improved activity/property.

3.2.6. Method for predicting organic pollutants

The invention discloses a method for fast predicting organic pollutant n-caprylic alcohol/air distribution coefficient based on molecular structure, belonging to the technical field of quantifying structure/active relationship (QSAR) facing to the environmental risk evaluation (53). The method is characterized of comprising the steps of: adopting the molecular structure of atomic center fragment characterization compound; and screening the atomic center fragment combination by means of stepwise regression and partial least-squares regression, to build a group contribution model for predicting KOA. The internal authentication and the external authentication improves that the built KOA group contribution model has stability and predicting capability, and a range and distance method and a probability density method express the application domain of the group contribution model, thereby defining the application range of the model and guaranteeing the predict accuracy. The method has the effects and benefits of being capable of fast predicting the KOA of the high flux compound, obtaining the KOA with low cost, being helpful for obtaining the high flux KOA data, and having a significant meaning for the environment supervision and the risk evaluation of chemicals.

3.2.7. Searching compound databases

A CoMFA 3D QSAR shape analysis may be performed on molecules arising from the same activity series that may be decomposed / viewed as assemblies of discrete identifiable subunits. The disclosed method provides for identifying in databases of whole molecules those molecular subunits that possess the same shape or shape and feature characteristics as the subunits of molecules used to perform the CoMFA analysis (54). Additionally, the method provides for estimation of the likely biological activity of molecules assembled from the subunits identified in the molecular database.

3.2.8. A 3D-QSAR method

A three-dimensional quantitative structure-activity relationship method has process B1 of calculating the coordinates of the respective atoms contained in the plural molecules thus superposed in the virtual space, process B2 of calculating inter-atomic distances between each atom and other atoms and identifying the shortest inter-atomic distance among thus calculated inter-atomic distances and two atoms constituting the shortest inter-atomic distance; process B3 of deleting the two atoms having the shortest inter-atomic distance from the three-dimensional space and generating an atom which represents the two atoms in the weighted average coordinates of the two atoms to delete, when the shortest inter-atomic distance thus calculated is equal to or smaller than a predetermined threshold value; process B4 of returning to the second process B2 after the third process B3 and executing the second process B2 including the atoms formed during the third process B3; and process B5 of terminating the process B when the shortest inter-atomic distance thus calculated is exceeds the predetermined threshold. This method enables strikingly reducing the memory zone and amount of computation required for 3D QSAR analysis (55).

3.2.9. QSAR & pharmacophore fingerprinting

This invention provides an improved format for pharmacophore fingerprints as well as improved methods of generating and using fingerprints (56). A specific embodiment provides a structure-activity relationship derived with the aid of pharmacophore fingerprints. A pharmacophore fingerprint for a chemical compound may specify a collection of individual pharmacophores that match the structure of the compound. Preferably, the fingerprint includes distinct pharmacophores that match distinct energetically favorable conformations. Some pharmacophores may match a first conformation but not a second conformation. Other pharmacophores may match the second conformation but not the first. Yet, the two conformations may each make significant contributions to the compound's activity. So the fingerprint should identify pharmacophores matching any appropriate conformation. The present invention also provides apparatus and methods for identifying, representing and productively using high activity regions of chemical space. Many representations of chemical space have been used and may be envisioned. In a preferred embodiment of this invention, at least two representations provide valuable information. A first representation has many dimensions defined by a pharmacophore basis set and one or more additional dimensions representing defined chemical activity (*e.g.*, pharmacological activity). A second representation may be one of reduced dimensionality, where the coordinates can be derived from the first representation by a suitable

mathematical technique such as, for example, the principle components produced by Principle Component Analysis using pharmacophore fingerprint/activity data for a collection of compounds.

3.2.10. Fast computer data segmenting techniques

Versions of the invention are directed to computer-based methods, apparatus and software (programs) for fast, dynamic programming and recursive partitioning techniques to segment data, especially real-world data, into data structures for display as nodal trees (57). These techniques and displayed data in segmented form have numerous applications, especially for the analysis and understanding of real-world data. Some particular applications are in the area of computational high throughput screening of molecular drug (or pharmaceutical) candidates using a quantitative structure activity relationship (QSAR) approach. Another particular application is in the areas of pharmacogenomics and pharmacogenetics.

4. LEGAL ISSUES RELATED TO CADD

4.2. Short notes on Copyright protection

Copyright laws operate under the territoriality principle. These usually provide protection only for a country's nationals or for works first published in that country. Conventions and bilateral agreements address the availability of protection and grant it to foreign authors under the principles of national treatment or formal reciprocity. In general, under the principle of national treatment, a country will grant the same protection to works of foreign authors as it grants to works of its own nationals. In the same way, under the principle of formal reciprocity, a country will grant the same protection to works of authors from another country as it grants to works of its own nationals, but only if a country determines that the works of its own nationals, are granted some minimum degree of protection in the other country (58-71). The most significant international treaties relating to copyright protection are the Berne Convention, the Universal Copyright Convention (72) and certain provisions of the TRIPS (Trade- Related Aspects of Intellectual Property Rights) agreement (73). Copyright protection is formality-free in countries party to the Berne Convention, which means that protection does not depend on compliance with any formalities, such as registration or deposit of copies. Under the Berne Convention, software is likened to literary works for protection, and thus receives the full extent of the same treatment. Recent experiences within the European Union have shown promise in terms of developing a coordinated and improved global copyright framework. In order to compete effectively in an international market, the EC was forced to develop a harmonized approach for intellectual property; covering computer software, semi-conductors, and biotechnology products (74). This was achieved amongst countries which did not even share a single author's rights or common law copyright approach.

4.3. A Short note on patent protection

A patent is an exclusive right granted for an invention, which is a product or a process that provides a new way of doing something, or offers a new technical solution to a problem. Patents require an inventive step, an assessment of industrial applicability and should undergo an examination procedure (61). The law relating to the patentability of software is still not harmonized internationally, though many countries have to some extent embraced the patentability of software-related inventions. There is a worldwide trend in favor of adopting patent protection for software-related inventions, mainly because a patent is valid against everyone in that country, who makes use of or sells the patented invention, even if the infringer invented it independently (58). Patent law protects the underlying idea, provided the idea is within the statutory categories of patentable subject matter and is not so fundamental that it constitutes a law of nature (60), whereas copyright law only protects the expression of an idea. The most widely followed doctrine governing the scope of patent protection for software related inventions is the "technical effects" doctrine that was first promulgated by the European Patent Office (EPO). This doctrine holds that software is generally patentable if the application of the software has a "technical effect." Thus, for example, software that controls the timing of an electronic engine is patentable under this doctrine, whereas software that detects and corrects contextual homophone errors (*e.g.*, "there" to "their") may not be patentable (58).

5. CONCLUSIONS

There are multiple interactions between Medicinal Chemistry, Computational Chemistry, Bioinformatics and Law. This article has touched upon three aspects. There is no one solution to protect software but there are many forms of legal protection available. International software taxation practices reveal the growing importance that software has on different economies. Payments designated royalties need to be harmonized, though it is recognized that is a complex issue. The competing interests of countries needs to be taken account of - perhaps through determining the boundary between "business income" and "royalties". Finally, the validation and legal acceptance of computational models and methods in Medicinal Chemistry, in particular with respect to QSAR has been given a large impetus following the impact of REACH. A growing, but still insufficient, interaction between Law and Computational Medicinal Chemistry has been shown. This is a very important shift in order for tools and methodologies in the field of science to be legally recognized. This interaction may be given an important place next to the so-called "hard sciences".

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