ISSUES IN SMALL ORGANIC MOLECULES

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571-272-0616

Overview

- Small Molecule Examples – "Markush" claims.
- Combinatorial Chemistry-small molecule libraries
- Search Strategy – difficulties in searching broad "Markush" claims.
- Examination Issues/35 U.S.C. 112 first and second paragraph
- Issues with Method of Use/Pharmaceutical Composition Examples

Definition

- Small organic molecules
- Usually excludes:
  - Biomolecules
 - DNA, proteins
  - Polymers

Generic variation presents complexity in searching Markush compound claims

"One of the major problems with Markush structures, besides their inherent variability and complexity, is the representation of generic groups [homology, position and frequency variation] and the matching of these against specific examples of them."

"A generic group can be considered as one which cannot be shown by a single atom-bond connection table, and examples include expressions like "alkyl", "heterocyclic" and "cycloalkyl: In some cases the expression may have no direct association with structural features, like "electron-withdrawing group."

Barnard et al. "Use of Markush structure analysis techniques for descriptor generation and clustering of large combinatorial libraries"   J Mol Graphics Vol 18 452-463 August-October 2000

4

Four Types of Variation in a Markush Structure
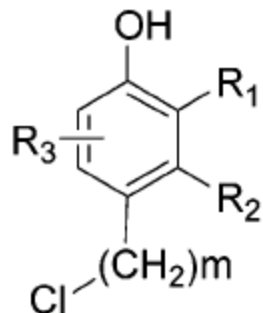
Substituent Variation: R1 is methyl or ethyl
Homology Variation: R2 is alkyl
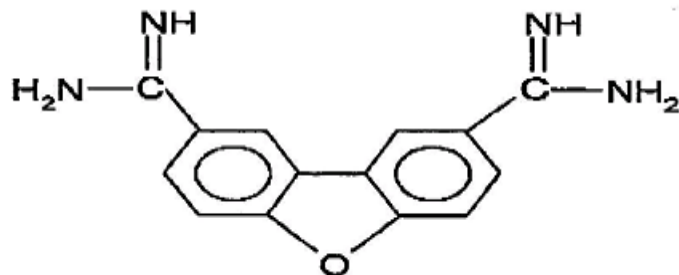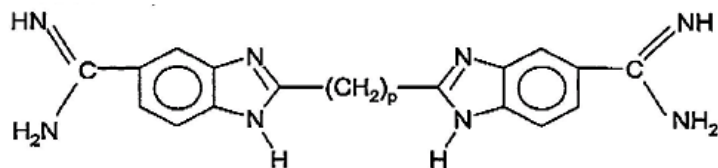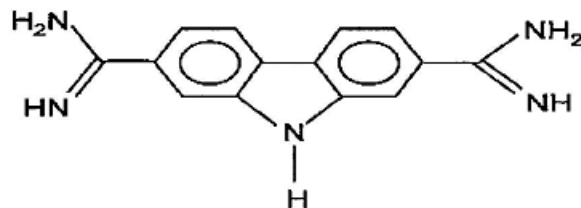Position Variation: R3 is amino
Frequency Variation: m is 1-3

"….the substitution variation is essentially the only form of variation found in real combinatorial libraries…."

MacLean et al
On the Representation of Combinatorial Libraries
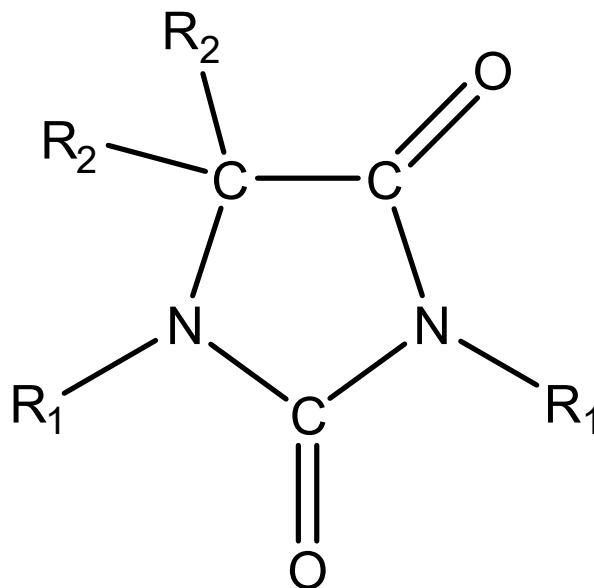Journal of Combinatorial Chemistry Vol 6(1) 1-10, 2004.

Small Molecule Examples - Species

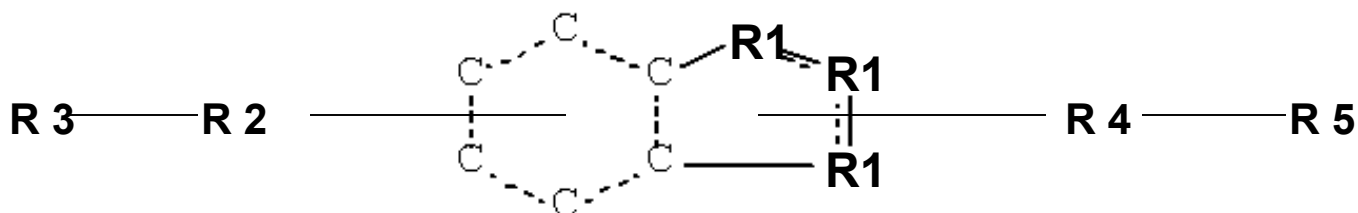# Small Molecule Examples (cont.)

A compound of formula:

R1 = HYDROGEN / HALOGEN;

R2 = HYDROGEN / ALKYL.

Small Molecule Examples (cont.)

A compound of Formula (II):

$$R3 - R2 - \text{(ring structure)} - R1, R1, R1 - R4 - R5$$

wherein:

R1 is C, O, S, or N;

R2, R3, R4, and R5 is independently hydrogen, substituted or unsubstituted straight or branched alkyl, alkoxy, halo, carbonyl, amino, alkyl-$S(O)_m$, alkyl-aryl, alkoxy-aryl, alkyl-heterocyle, alkoxy-heterocycle, substituted or unsubstituted C_{3-10}-aryl, substituted or unsubstituted 5-12 membered heteroaryl containing one or more heteroatoms selected from O, N, or S, wherein R2, R3, R4, or R5 may be optionally substituted by one or more R1, R2, or R3.

Small Molecule Examples (cont.)

Claim 1: A compound of formula:

$$A\text{-}B\text{-}C\text{-}D\text{-}E\text{-}F$$

A is:
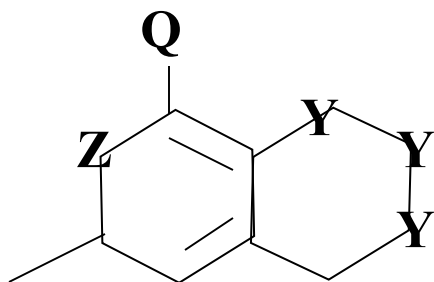
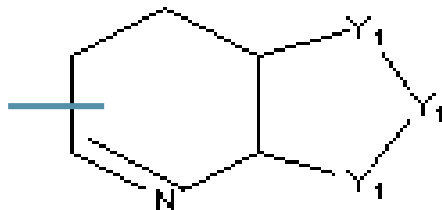wherein, Z is CH_2, O, S, or NH;
Y is CH_2, O, S or NH
Q is a 5-6 membered carbocyle or heterocycle;

B is alkylene;

C is isoquinoline, pyrrolidine, piperidine or indole;

D is CH_2, O, CHOH or CCl_2;

E is   wherein Y_1 is NH or CH_2;

and

F is naphthalene optionally substituted by 1-3 substituents.

Small Molecule Examples (cont.)

A compound of formula (I):

$$\textbf{X-Ar}^1\textbf{-Ar}^2\textbf{-L}^1\textbf{-L}^2\textbf{-Ar}^3\textbf{-L}^3\textbf{-Y}$$

wherein

X is a leaving group;

L^1, **L**^{2}, and **L**^{3} are a bond or a divalent linker having a main chain of 1 to 10 atoms, or represented by the formula Q-R-S, wherein Q is O, S, N, and C; R is independently a bond, hydrogen, alkyl, alkylene, alkynyl, aryl, and alkylaryl; S is is independently C, S, N, SO, and O(C R_3R_4)m, <u>provided that L^1 and L^2 are not simultaneously a bond</u>.

Ar^1, **Ar**^{2}, and **Ar**^{3} are independently, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-8} cycloakane, C_{1-8} alkylaryl, -C(O)C_{1-8} alkyl, -C(O)OC_{1-8} alkyl, C_{1-8} alkylcyloalkane, $(CH_2)_n$C(O)OR_5, $(CH2)_n$NSO$_2$ R_1R_5, and $(CH2)_n$NSO$_2R_5$, wherein each of the alkyl, alkenyl, aryl are each optionally substituted with one to five groups independently selected from C_{1-8} alkyl, C_{2-8} alkenyl, phenyl, and alkylaryl, and wherein L^1, L^2, may be taken together and with the nitrogen atom to which they are attached or with 0, 1, 2, or 3 atoms adjacent to the nitrogen atom to form a nitrogen containing heterocycle with may have 1 or 2 substituents independently selected from R_1, <u>provided that when L^1 is a bond and L^2 is phenyl, Ar^2 and Ar^3 are not phenyl</u>, and

Y is a basic group, or a pharmaceutically acceptable salt thereof.

"Combinatorial" Chemistry?

- In combinatorial technology there is no good set of terms that can cover every scenario.

  - Commonly seen terminology: "combinatorial", "library", "collection", "plurality", "array", "linker", "resin", "bead", "diversity", "tag", "solid support/supported", "high-throughput", "iterative", "deconvolution"..

- <u>Absent evidence to the contrary</u>,

  - "A combinatorial library can be defined as any ensemble of molecules"

  Janda, K. D. PNAS, 1994

Markush Structures in Combinatorial Chemistry

"The generic or Markush structure is the primary tool used to condense the structural representation of sets of compounds. Generic structures can depict on a single page libraries that would fill a book if fully enumerated. This compression is possible as a result of the regulatory of the library."

"Generic structures have a long history of use in patents and are ubiquitous in combinatorial chemistry publications. They consist of the common core structure of the library with one or more 'superatoms' attached (often represented by R, for 'residue' or 'radical') indicating the existence of variable substituents at that location."

Maclean et al "On the Representation of Combinatorial Libraries." Journal of Combinatorial Chemistry Vol 6(1) 10 1-10. 2004.

Factors that Complicate Generic Representations

A number of factors can complicate the use of generic representations: libraries may have multiple cores, ring forming attachments or correlated sets of substituents.

Maclean et al "On the Representation of Combinatorial Libraries."
Journal of Combinatorial Chemistry Vol 6(1) 10 1-10. 2004.

Dependent variation may be inaccurate

"In their simplest form, Markush structures assume that each R-group is independent of the others. There may be situations in which, for synthetic feasibility or other reasons, some alternatives for R1 cannot occur with some alternatives for R2- in other words, the library is not strictly combinatorial but it is non-regular. Simple Markush structure may therefore give misleading or inaccurate representations of product sets…"

Barnard et al. "Use of Markush structure analysis techniques for descriptor generation and clustering of large combinatorial libraries"   J Mol Graphics Vol 18 452-463   August-October 2000

"Combinatorial" Chemistry

- Anticipation and Obviousness

A case for prima facie obviousness

If the parent molecule in a series is known; and

substituents and the substitution pattern claimed are established in the prior art,

Obviousness to make the library becomes the question.

"Combinatorial" Chemistry

Obviousness

"The goals of combinatorial organic synthesis are to create populations of molecular structures" in order to search them for more potent derivatives of known pharmacophores.

– Gordon et al. J. Med. Chem., 1994

The fact that properties rely on a number of variables "precludes the truly rational design…and provides a clear invitation to use the power of combinatorial chemistry to accelerate discovery".

– Francis et al. "Combinatorial libraries of transition-metal complexes, catalysts and materials", Cur. Opin. Chem. Biol., 1998 [16]

Search Strategy

CHEMICAL SUBSTANCES, INCLUDING:

MOLECULAR STRUCTURES, CHEMICAL REACTIONS

Basically two means of searching:
 - CHEMICAL COMPOUND SEARCHING USING THE US CLASSIFICATION SYSTEM-BASED ON STRUCTURE - CLASSES 532-570
 (various heterocycles, etc.)
- REGISTRY, BEILSTEIN, MARPAT, CASREACT

BIBLIOGRAPHIC,   OR   **TEXT** SEARCHES

- CHEMICAL ABSTRACTS   BIBLIOGRAPHIC FILES, NAPRALAERT
- USPATFULL
- WPI, DPCI, JICST
- BIOSIS, MEDLINE, EMBASE, AGRICOLA, FSTA, FROSTI, JAPIO

Search Strategy (cont.)
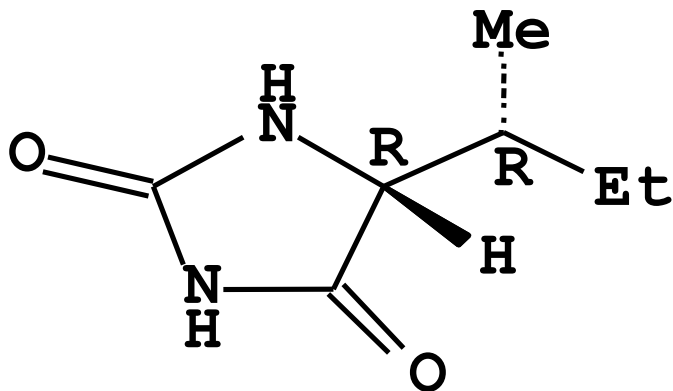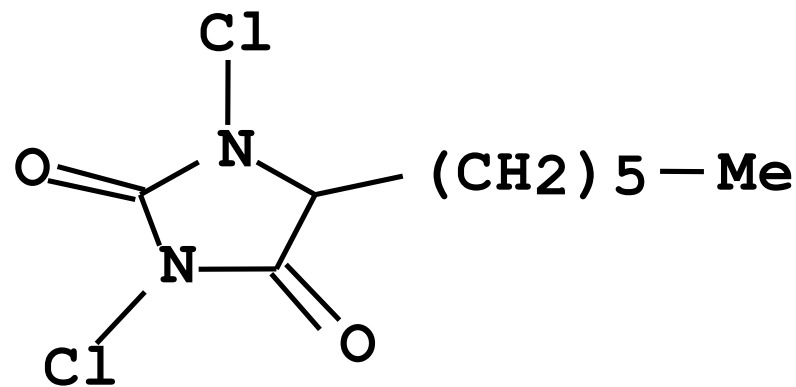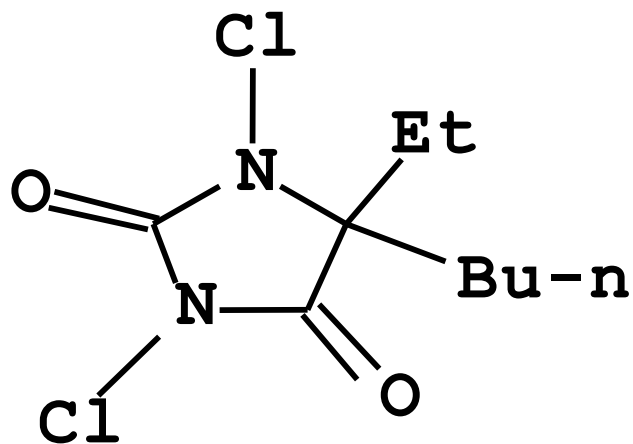
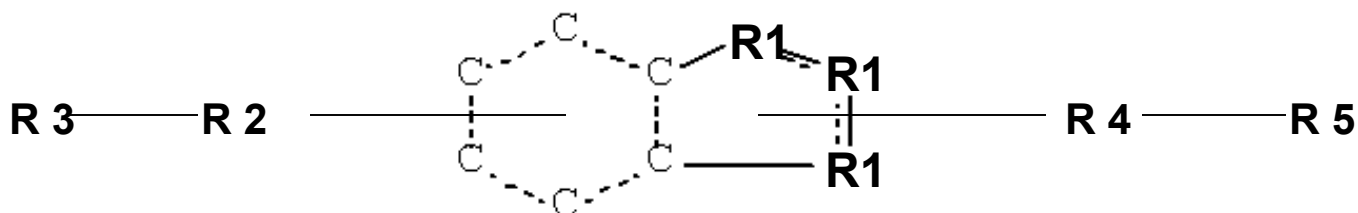## Simple structure
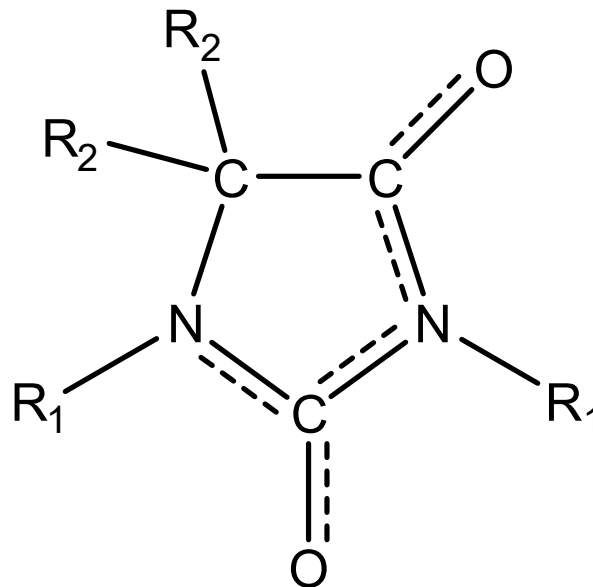
R1 = HYDROGEN / HALOGEN

R2 = HYDROGEN / ALKYL

Search Strategy (cont.)

EXAMPLES OF HITS RETRIEVED
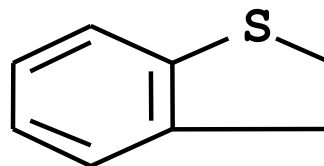
Search Stratecy (cont.)

A compound of Formula (II):

$$R3 - R2 - \text{[benzene ring with } R1, R1, R1 \text{ substituents]} - R4 - R5$$

wherein:

R1 is C, O, S, or N;

R2, R3, R4, and R5 is independently hydrogen, substituted or unsubstituted straight or branched alkyl, alkoxy, halo, carbonyl, amino, alkyl-$S(O)_m$, alkyl-aryl, alkoxy-aryl, alkyl-heterocyle, alkoxy-heterocycle, substituted or unsubstituted C_{3-10}-aryl, substituted or unsubstituted 5-12 membered heteroaryl containing one or more heteroatoms selected from O, N, or S, wherein R2, R3, R4, or R5 may be optionally substituted by one or more R1, R2, or R3.

Search Strategy (cont.)

TOTAL POSSIBLE STRUCTURES: 353,917
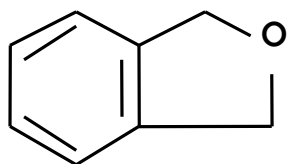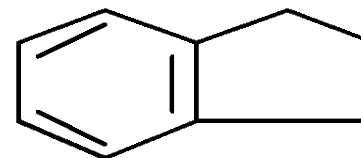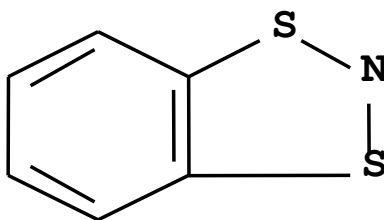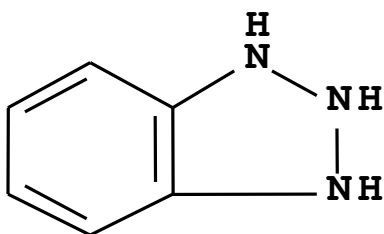
EXAMPLES OF STRUCTURES RETRIEVED

Search Strategy (cont.)

EXPENDITURE FOR SEARCH OF MARKUSH CLAIMS

TIME:

- APPROXIMATELY **5 HOURS** FOR AN

EXPERIENCED SEARCHER

COST:

- **$900 - $1200**

Search Strategy (cont.)

METHOD OF USE FOR KNOWN COMPOUND

RN **127266-56-2** REGISTRY
CN Tricyclo[3.3.1.13,7]decane-1-carboxamide, N-[2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]-
CN **Adatanserin**
CN Adatensin
CN N-[2-[4-(2-Pyrimidinyl)-1-piperazinyl]ethyl]-1-adamantanecarboxamide
CN **Wy 50324**
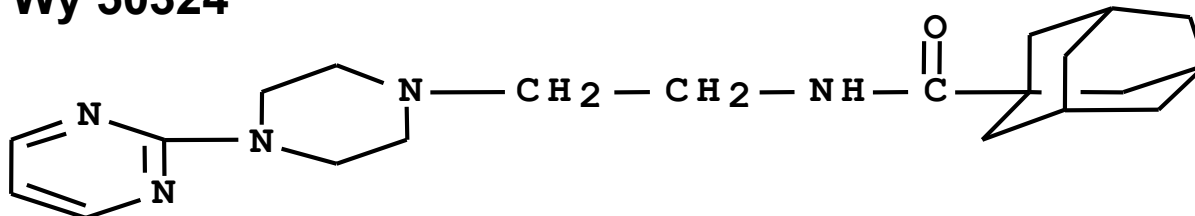
BIBLIOGRAPHIC FILE SEARCH FOR REFERENCES
 FILE HCAPLUS
 L2   **17 S L1**
 L3   **5 S ADATANSERIN?**
 L4   0 S ADATENSIN?
 L5   **14 S WY50324 OR WY()(50324 OR 50 324)**
 L6   **20 S L2,L3,L5**

Search Strategy (cont.)

FIRST KNOWN REFERENCE FOR THIS COMPOUND - CHEMICAL ABSTRACTS

TI   Preparation of N-[(4-arylpiperazino)alkyl]adamantanecarboxamides and analogs as psychotropic agents
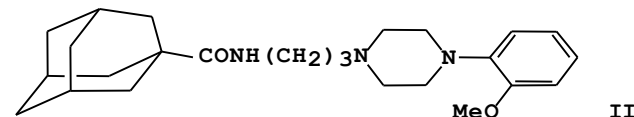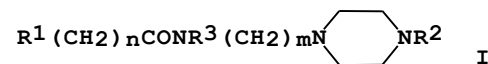
SO **Brit. UK Pat. Appl., 39 pp.**

PI   **GB 2218988   A1 19891129   GB 1989-11912 19890524**

             •

        US 5254552   A 19931019   US 1992-852119 19920316

        US 5380725   A 19950110   US 1993-91495 19930714

PRAI US 1988-197890   19880524

             •

       US 1992-852119   19920316

$$R^1(CH_2)_nCONR^3(CH_2)_mN\text{—}NR^2 \quad \text{I}$$

$$\text{adamantyl}\text{—}CONH(CH_2)_3N\text{—}N\text{—}C_6H_4\text{—}MeO \quad \text{II}$$

AB   The title compds. [I; R1 = 1-adamantyl, 3-methyl-1-adamantyl, 3-noradamantyl, (un)substituted 2- or 3-indolyl, 2- or 3-benzofuranyl; R2 = (un)substituted Ph, PhCH2, pyridyl, pyrimidinyl, pyrazinyl; R3 = H, alkyl; n = 0, 1; m = 2-5] were prepd.

RN   **127266-56-2** HCAPLUS

CN   Tricyclo[3.3.1.13,7]decane-1-carboxamide, N-[2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]- (9CI) (CA INDEX NAME)

$$\text{pyrimidinyl}\text{—}N\text{—}N\text{—}CH_2\text{—}CH_2\text{—}NH\text{—}\overset{O}{\underset{}{C}}\text{—}\text{adamantyl}$$
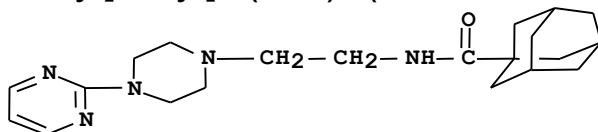
Search Strategy (cont.)

BIOSIS CONFERENCE LITERATURE
EARLIEST REFERENCE FOR SAME COMPOUND

TI   BEHAVIORAL CHARACTERIZATION OF THE NOVEL ANXIOLYTIC-
      ANTIDEPRESSANT AGENT **WY-50324**.

SO 19TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE,
      PHOENIX, ARIZONA, USA, **OCTOBER 29-NOVEMBER 3, 1989**.
      SOC NEUROSCI ABST. (1989) 15 (1), 852.

DT Conference
CC   General Biology - Symposia, Transactions and Proceedings of Conferences,
      Congresses, Review Annuals 00520
      Behavioral Biology - Animal Behavior *07003
      Biochemical Studies - General 10060
      Pathology, General and Miscellaneous - Therapy   *12512
      Nervous System - Pathology *20506
      Pharmacology - Neuropharmacology *22024
      Pharmacology - Psychopharmacology *22026
      Laboratory Animals - General   28002
BC   Muridae 86375

Examination Issues - Indefiniteness

- Evaluation of the claim language depends on whether one of skill in the art would understand what is claimed, in light of the specification

- Questions of indefiniteness are determined on a case-by-case basis

Examination Issues - Indefiniteness

- Relative Language-examples: large, high, etc.

- The fact that claim language-including terms of degree- may not be precise, does not automatically render the claim indefinite under 112(2). The specification must be considered.

Examination Issues - Indefiniteness

Metabolite(s)

"A compound of formula I … and its metabolites or salts thereof."

Residue

- – "B is a residue capable of binding to a compound."
- – "Y is a residue of an azole compound, solvates or salts thereof."

Examination Issues - Indefiniteness

- Analogues thereof
- Derivatives thereof
- Derived from
  - "A compound of formula II…and its pharmaceutically acceptable salts or derivatives thereof."
  - "A is derived from a group…"

Examination Issues - Indefiniteness

- Prodrugs
- Functional derivatives
  - "A compound of formula III … and its prodrugs, functional derivatives or pharmaceutically acceptable salts thereof."

Examination Issues - Indefiniteness

- Precursor(s)
- Linking group(s)
- Organic moiety
  - "A Ketorolac compound and its precursors"
  - "X is a linking group or an organic moiety"
  - A substituent that binds receptor X

Examination Issues - Enablement

1. A pharmaceutical composition for preventing cancer comprising compound A.

2. A prophylactic pharmaceutical composition to mediate a delta opioid receptor comprising compound A.

Examination Issues - Enablement

1. A method of treating cancer in a patient comprising administering to said patient a daily unit dose of compound A of 10 mg/kg of body weight for at least 7 consecutive days.

2. A method of the treatment and prevention of liver necrosis, obesity, diabetes, depression, cardiovascular disorders, CNS disorders, and asthma comprising administering compound A in an effective amount.

THANK YOU!

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