

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act. 523 RESPUESTA Folios: 33

Señor Director  
**DIRECCIÓN DE NUEVAS CREACIONES**  
Superintendencia de Industria y Comercio  
E. S. D.

Trámite : 011  
Evento : 378  
Actuación : 523

JY

Referencia : Expediente No. **13.110.654**  
Asunto : Solicitud de patente: **"COMPOSICIONES PESTICIDAS QUE COMPRENDE DERIVADOS DE 3-(PIRAZOL-1-IL) PIRIDINA"**.  
Solicitante : DOW AGROSCIENCES LLC  
Fecha de solicitud : 2 de Mayo de 2013

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, me refiero al oficio No. **12642** notificado por fijación en lista el 7 de Octubre de 2014.

2. Mediante memorial del 21 de Noviembre de 2014 se solicitó oportunamente plazo para responder la acción oficial No. **12642**.

3. Mediante oficio No. **12642** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Las observaciones realizadas en el oficio se refieren a la claridad del título, a la presencia de reivindicaciones referentes a un uso o segundo uso, a la presencia de reivindicaciones relacionadas con materia exceptuada de patentabilidad, a la claridad del pliego reivindicatorio y al nivel inventivo de las reivindicaciones 1-44, 47 y 48 en vista de los documentos **D1**: WO2009149858 A1 y **D2**: US6218418 B1.

**"EXCELENCIA LEGAL EN UN MUNDO SIN FRONTERAS"**

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#### **4. Respuesta a las objeciones**

De este modo y con el objeto de atender las objeciones arriba mencionadas, se desea presentar las siguientes modificaciones, aclaraciones y argumentos:

##### **4.1. Modificación de una solicitud en trámite**

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar un nuevo pliego reivindicatorio conformado por 4 reivindicaciones.

Con el fin de atender a la objeción hecha por el señor examinador, se solicita el cambio de título de la presente solicitud de patente a: **“COMPOSICIONES PESTICIDAS QUE COMPRENDE DERIVADOS DE 3-(PIRAZOL-1-IL) PIRIDINA”**.

Se han introducido las siguientes modificaciones al capítulo reivindicatorio:

- Se han limitado de forma significativa las definiciones de los radicales R7, R8, R6 y A de la fórmula uno recitada en el pliego reivindicatorio. En particular, la definición de A se ha limitado a A2, aclarando y precisando aún más el objeto de la presente invención, mediante el énfasis en sus características esenciales. A este respecto, se aclara a su Despacho que los compuestos recitados en el nuevo pliego reivindicatorio se encuentran debidamente soportados en la descripción tal como fue originalmente presentada.
- La materia que ha sido eliminada del pliego reivindicatorio no puede ser considerada como un desistimiento de la misma y mi representada se reserva el derecho de volver sobre ésta durante el trámite de la presente solicitud de patente.
- Las reivindicaciones 45-46, 49 a 61 y 63 han sido eliminadas del nuevo pliego reivindicatorio y por lo tanto, las objeciones formuladas a este respecto por usos, segundos usos y excepciones de patentabilidad se deben tener por superadas.

Por lo anterior, las objeciones formuladas por el Examinador en cuanto a la presencia de reivindicaciones referentes al uso y de excepciones de patentabilidad, claridad y concisión del pliego reivindicatorio se ven superadas. En consecuencia, se solicita atentamente tener en cuenta este nuevo pliego reivindicatorio para el nuevo análisis de patentabilidad.

#### **4.2. Argumentos con respecto a la falta de Nivel Inventivo**

El artículo 18 de la Decisión 486 señala lo siguiente:

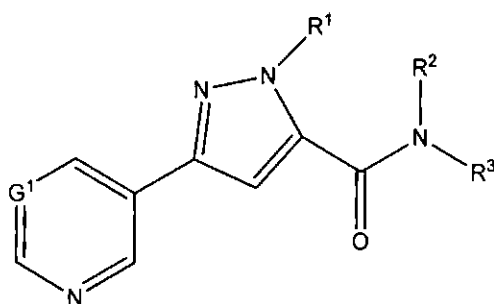
***“Artículo 18.-** Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica”.*

Una invención se considerará inventiva si la misma no hubiese resultado obvia a partir del arte previo para una persona del oficio normalmente versada en la materia. Esto a su vez implica que el Examinador a cargo de esta evaluación debe colocarse en el momento exacto en el que el inventor buscaba resolver el problema técnico contemplado en la solicitud y para el cual poseía la literatura y el conocimiento disponibles en dicho momento.

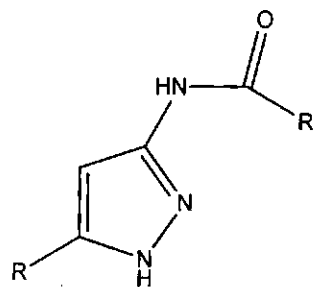
Siguiendo entonces los lineamientos de la Jurisprudencia aplicable al análisis del nivel inventivo de una solicitud de patente, se considera que una anterioridad o una combinación de dos anterioridades puede afectar dicho requerimiento de patentabilidad, si una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras que, a partir de un conocimiento medio en dicho campo, le permitan llegar de manera obvia a la invención reivindicada. Adicionalmente se considera que una mejora sustancial, un efecto inesperado o una ventaja con respecto al arte previo es un indicio de nivel inventivo, por cuanto aporta un salto tecnológico en la regla técnica.

A este respecto, respetuosamente manifestamos nuestro desacuerdo con el análisis llevado a cabo por el Examinador y con las conclusiones del mismo y solicitamos atentamente la reconsideración de las razones por las cuales se objeta el nivel inventivo, con base en la siguiente información:

Es evidente que ninguno de los dos documentos citados por el señor Examinador revela, sugiere o enseña el enlace C-N conectado el anillo de piridilo y el anillo de pirazolilo. D1 enseña que el anillo de piridilo tiene que estar en la tercera posición y la carboxamida necesita estar en la quinta posición del pirazolilo. Por su parte, D2 enseña que la acetamida necesita estar en la tercera posición y el grupo R, cicloalquilo a (C3-C6), necesita estar en la quinta posición de la pirazolilo. Tal y como se puede observar en las siguientes figuras:



(D1-Página 33, Esquema de reacción 6)



(D2 – Página 33)

Con base a los documentos citados por el señor Examinador, ninguno presenta una descripción, una enseñanza o alguna sugerencia, de que el grupo acetamida de D2 debe ser eliminado de la tercera posición del pirazolilo y ubicado en la quinta posición del pirazolilo de D1.

Adicionalmente, D2 enseña expresamente que un cicloalquilo (C3-C6) debe ser colocado en la quinta posición del pirazolilo, lo que se encuentra muy lejos del objeto que se busca proteger en la presente invención.

Como se puede observar en Anexos en los datos obtenidos por el doctor Pablo Bielzia, se utilizó *Bemisia tabaco*, toda vez que es la quinta especie de insectos más

resistente a pesticidas químicos. Como se observa, los resultados son contundentes, pues se evaluaron cuatro cepas diferentes de *Bemisia tabaco* y en todos los análisis el compuesto A1 obtuvo un resultado significativamente mejorado en comparación con los otros compuestos utilizados.

Así, en los argumentos arriba presentados se pueden identificar claramente un indicio de presencia de nivel inventivo de acuerdo con el numeral 2.13.5.3.1 de la "GUÍA PARA EXAMEN DE SOLICITUDES DE PATENTE DE INVENCION Y MODELO DE UTILIDAD" de su despacho:

- Efecto técnico sorprendente, ya que las composiciones reivindicadas en la presente solicitud presenta una actividad pesticida significativamente mejorada en comparación con las composiciones conocidas en el estado de la técnica.

Por lo tanto, se le debe otorgar una compensación a mi representada que demuestra nuevos hechos (efectos sorprendentes e inesperados) a las enseñanzas descritas en el estado de la técnica y contribuyen con el desarrollo de la tecnología.

Con respecto a la afirmación del Examinador, en cuanto a la obviedad de la presente invención en vista de lo divulgado por los documentos D1 y D2, manifestamos nuevamente nuestro desacuerdo y concluimos que el análisis realizado en la acción oficial No. 12642, se basó en un análisis retrospectivo o también conocido como "hindsight", el cual lo define la "GUÍA PARA EXAMEN DE SOLICITUDES DE PATENTE DE INVENCION Y MODELO DE UTILIDAD" de su Despacho, de la siguiente forma:

#### **Análisis ex post facto o retrospectivo o hindsight**

Es importante tener en cuenta que una invención reivindicada que, a primera vista, parece evidente, puede ser inventiva. Una vez formulada una nueva idea, a menudo se puede demostrar teóricamente el modo en el que se podría llegar a ella, a partir de algo conocido, a través de una serie de etapas aparentemente

fáciles. El examinador de patentes debe evitar el uso de un análisis ex post facto de este tipo.

Es decir, el estado de la técnica se debe examinar sin el beneficio del conocimiento ofrecido retrospectivamente por la invención reivindicada. La indicación o la sugerencia que permita llegar a la invención reivindicada deben proceder del estado de la técnica o de los conocimientos generales de la persona del oficio normalmente versada en la materia, y no basarse en la divulgación del solicitante.

La presente solicitud sí tiene nivel inventivo

El señor Examinador menciona que la presente invención carece de nivel inventivo argumentando que los compuestos de D1 y los compuestos de la presente invención pueden ser utilizados como insecticidas. Sin embargo, ese es un hecho irrelevante en el presente caso.

Cuando se realiza el análisis de nivel inventivo se debe tener en cuenta que una persona versada en la materia que estuviese enfrentada con el mismo problema habría tomado como una cuestión de rutina cualquier paso que lo llevara desde el arte previo al objeto reclamado en la presente invención. Así que partiendo de las enseñanzas de D1 y frente al problema de proporcionar un insecticida, no habría ninguna sugerencia ni indicio que llevara al experto en la materia a modificar la molécula de D1 tal y como se encuentra en las reivindicaciones de la presente invención, sobre todo, teniendo en cuenta que D1 ya revelaba compuestos que eran útiles como insecticidas. Por lo tanto, no existiría ninguna motivación para realizar la modificación a los compuestos de D1 con base al problema técnico.

Además, D1 revela compuestos con una disposición estructural diferente a la de los compuestos de la presente solicitud. De hecho, si una persona versada en la materia estuviera interesada en modificar los compuestos de D1, tampoco hubiese sido posible que modificara dichos compuestos como se encuentran reclamados en esta

invención, toda vez que existen numerosas modificaciones que podrían ser realizadas. Por ejemplo, como lo detalla el Doctor Peter Ertl en el artículo adjunto, existen 3,1 millones de sustituyentes.

Por consiguiente, no habría ninguna motivación para que una persona versada en la materia escogiera específicamente un grupo acetamida para reemplazar el grupo carboxamida en esa posición, tal y como es revelado en el compuesto en el documento D1.

Sin duda alguna, la elección de D1 y D2 hace parte de un análisis retrospectivo, pues como fue mencionado no existe ninguna motivación ni sugerencia en D1 para que una persona versada en la materia, decida reemplazar el grupo carboxamida por el grupo acetamida en esa posición específica con el objetivo de llegar a un compuesto con propiedades insecticidas. Adicionalmente, se debe tener en cuenta que el documento D2 se encuentra dirigido a controlar tumores en el cuerpo humano, lo que permite ver que se encuentra en un campo técnico totalmente diferente al aquí mencionado.

Por consiguiente, la presente solicitud posee la altura inventiva necesaria para que se le conceda el privilegio solicitado.

#### **4.3 Presentación de una solicitud divisional**

En virtud del Artículo 36 de la Decisión 486 mediante el cual se establece la posibilidad de dividir la solicitud en dos o más fraccionarias, se presenta en esta oportunidad una solicitud divisional, junto con un pliego reivindicatorio conformado por 1 reivindicación. La solicitud divisional va dirigida a compuestos que comprenden estructuras diferentes a las reclamadas en la solicitud parental.

Teniendo en cuenta que la nueva solicitud divisional (i) se presenta durante el trámite de la solicitud, (ii) la materia que protege no amplía la materia de la solicitud inicial, (iii) se presentan los documentos necesarios para formar su expediente y (iv) se presenta junto con el presente memorial comprobante de pago de la tasa correspondiente a la presentación de una nueva solicitud divisional, se solicita atentamente dar trámite a esta solicitud divisional.

#### **4.4 Concesión de Solicitudes equivalentes**

Aunque compartimos la opinión de su Despacho, en cuanto a que la concesión de una solicitud de patente en otros países, equivalente a la solicitud Colombiana, no obliga a su Despacho a otorgar el privilegio de patente para la misma invención, sí constituye un antecedente favorable para el estudio de patentabilidad que respetuosamente solicitamos tener en cuenta. Por lo tanto, informamos a su Despacho que la presente invención ha sido otorgada en la oficina de patente de Estados Unidos de América, Patente No. US 8. 815.271 B2

A este respecto, deseamos poner de presente que si bien cada país es autónomo de conceder o negar una solicitud luego de la realización del estudio de fondo, es claro que el hecho de que la novedad y el nivel inventivo de una invención hayan sido reconocidos por varias oficinas a nivel mundial, es un indicio de la patentabilidad de la misma toda vez que (i) el estudio de novedad y nivel inventivo en todas las Oficinas de Patentes del mundo es realizado por personas con conocimientos técnicos en el área de interés que son consideradas personas idóneas para emitir conceptos sobre la patentabilidad de una invención y que (ii) los resultados de los exámenes de novedad o de patentabilidad efectuados respecto a solicitudes extranjeras pueden ser reconocidos como suficientes para acreditar el cumplimiento de las condiciones de patentabilidad de la invención, tal como se señala en el artículo 46 de la Decisión 486:

***“Artículo 46.- La oficina nacional competente podrá requerir el informe de expertos o de organismos científicos o tecnológicos que se consideren idóneos, para que emitan***

*opinión sobre la patentabilidad de la invención. Asimismo, cuando lo estime conveniente, podrá requerir informes de otras oficinas de propiedad industrial.*

*De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederá de 3 meses, uno o más de los siguientes documentos relativos a una o más de las solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina:*

*a) copia de la solicitud extranjera;*

*b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera;*

*(...)*

*La oficina nacional competente podrá **reconocer los resultados de los exámenes referidos en el literal b) como suficientes para acreditar el cumplimiento de las condiciones de patentabilidad de la invención*** (Negrilla fuera del texto).

#### **4.5 Conclusión**

Por todo lo anterior, el documento D1, el documento D2, o su combinación, no resultan anterioridades válidas capaces de afectar el nivel inventivo de la invención de la presente solicitud.

Por lo tanto, consideramos que el Examinador está pasando por alto que una sola diferencia con respecto al estado de la técnica, permite concluir que el objeto reivindicado es nuevo. Además, está excluyendo el hecho de que el inventor en el momento de solucionar el problema técnico de la solicitud tuvo que emplear habilidad inventiva, pues la presente invención no resulta de la mera extrapolación de las enseñanzas del arte previo, como se afirma. Se está desconociendo el mérito investigativo empleado y que está aportando una ventaja al arte previo.

5. Puesto que se ha dado respuesta a todas las objeciones formuladas por el Examinador, se solicita atentamente proceder al otorgamiento de la solicitud de patente. En este sentido, respetuosamente recordamos al Examinador que la patente no podrá ser negada con base en objeciones diferentes a las expuestas en la acción oficial No. 12642,

toda vez que al no haber sido trasladadas a mi representada, dicha decisión violaría tanto el tenor literal del artículo 45 de la Decisión 486 como el derecho constitucional al debido proceso. En este evento, y con base en el inciso 2 del artículo 45, respetuosamente solicitamos al Examinador expedir una nueva acción oficial que permita a mi representada contra argumentar las mismas o modificar la solicitud con el fin de cumplir los requisitos de patentabilidad.

**6. Anexos**

- Nuevo pliego reivindicatorio conformado por 4 reivindicaciones.
- Comprobante de tasa por la solicitud divisional por valor de \$478.000
- Formulario por concepto de división de una solicitud de patente
- Capítulo descriptivo de la solicitud divisional.
- Pliego reivindicatorio de la solicitud divisional conformado por 1 reivindicación.
- Poder para la solicitud divisional.
- Sparks, T.; Nauen, R. *"IRAC: Mode of action classification and insecticide resistance management"*. Pesticide Biochemistry and Physiology. 2014.
- Ertl, P. *"Cheminformatics analysis of organic substituents: Identificación of the most common substituents, calculation of substituent properties, and automatic identification of drug-like bioisosteric groups"*. J. Chem. 2002.
- Resultados obtenidos por el por Doctor Pablo Bielza.
- Patente No. US8.815271 B2.

Señor Director,

  
**LUZ CLEMENCIA DE PÁEZ**

C.C. 35.456.344 de Usaquén

T.P.A. No. 23.555



4.

Datos del trámite

CONVERSION

Expediente \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
De: \_\_\_\_\_  
A: \_\_\_\_\_

DIVISION

Expediente : **13.110.654**  
De: \_\_\_\_\_  
A: \_\_\_\_\_

FUSION

Expediente \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
De: \_\_\_\_\_  
A: \_\_\_\_\_

5.

Comprobante de Pago No. 15-0010127

Fecha: 2015/01/27

6.

Anexos

☒

Comprobante de pago de la tasa de presentación solicitud por \$478.000.

☐

Comprobante de pago por reivindicaciones adicionales después de la décima reivindicación por

☒

Poder de **DOW AGROSCIENCES LLC**

☒

Documento que contiene la conversión, división o fusión de la solicitud

☐

Copia de la solicitud y sus anexos en formato magnético

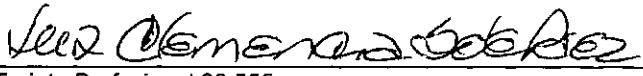
7. Firma

Nombre y apellidos

**LUZ CLEMENCIA DE PAEZ**

C.C. 35.456.344 DE Usaquén

Firma



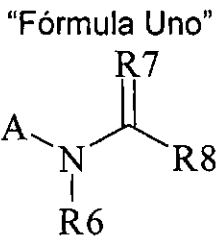
Tarjeta Profesional 23.555

**NOTA:** Esta es una solicitud de división de la materia contenida originalmente en la solicitud de patente No. **13.110.654**. La solicitud de división de la materia se hace como consecuencia de las observaciones hechas por ese Despacho y que fueron dadas a conocer al solicitante por medio del oficio No. **12642** notificado por fijación en lista del 07 de octubre de 2014. Por lo tanto pido que esta solicitud de división de materia sea tratada con el beneficio de presentación de la solicitud original, esto es 02 de mayo de 2013 y la prioridad que allí se reivindica el 03 de noviembre de 2010.

**Nota:** La copia básica original se encuentra en el expediente No. **13.110.654**

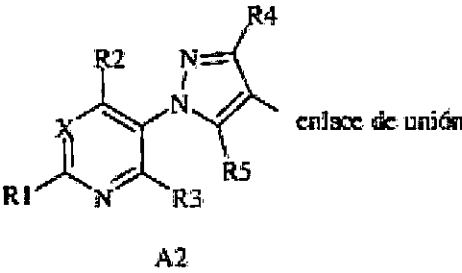
**REIVINDICACIONES MODIFICADAS**

1. Una composición que comprende la molécula de acuerdo con la Fórmula Uno:



en donde

- a) A es



- b) R1 es H;
- c) R2 es H;
- d) R3 es H;
- e) R4 es Cl;
- f) R5 es H;
- g) R6 es metil o etil;
- h) R7 es O;
- i) R8 es un (alquilo C<sub>1</sub>-C<sub>6</sub> sustituido o no sustituido)-S(O)<sub>n</sub>-(alquilo C<sub>1</sub>-C<sub>6</sub> sustituido o no sustituido) en donde los sustituyentes en dichos alquilos sustituidos son seleccionados de F, Cl, Br, I;
- j) n es 0, 1 o 2; y
- k) X es CR<sub>n1</sub> donde R<sub>n1</sub> es H o F.

2. Un composición de acuerdo con la reivindicación 1 en donde dicha molécula tiene una de las siguientes estructuras:

| Compuesto No. | Estructura |
|---------------|------------|
| 133           |            |
| 134           |            |

3. Una composición de acuerdo con la reivindicación 1 que, además, comprende:

- (a) uno o más compuestos que tienen acaricidas, algicidas, avicidas, bactericidas, funguicidas, herbicidas, insecticidas, moluscicidas, nematocidas, rodenticidas, o propiedades virucidas; o
- (b) uno o más compuestos que son antialimentarios, repelentes de aves, quicio-esterilizantes, aseguradores de herbicidas, atrayentes de insectos, repelentes de insectos, repelentes de mamíferos, interruptores del apareamiento, activadores vegetales, reguladores del crecimiento de los vegetales, o sinergistas; o
- (a) ambos (a) y (b).

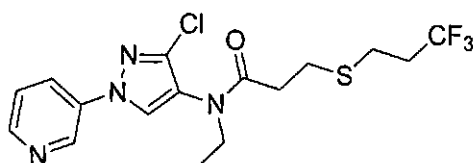
4. Una composición de acuerdo con la reivindicación 1 comprendiendo adicionalmente un vehículo agrícolamente aceptable.

### Pruebas:

El Dr. Pablo Bielza obtuvo los siguientes datos a nombre de Dow Agrosciences.

El Dr. Bielza es un científico de renombre mundial en el campo de la resistencia a los insecticidas. Es Profesor en la Universidad Politécnica de Cartagena, in Cartagena, España. El Profesor comparó los siguientes compuestos, el compuesto A1, contra *Bemisia tabaci* (mosca blanca) resistente.

Compuesto A1



El Compuesto A1 se ajusta a la reivindicación 1 actual.

En este estudio se utilizó *Bemisia tabaci* debido a la capacidad que tienen las moscas blancas para transportar y propagar enfermedades. Esta capacidad hace que las moscas blancas tengan amplio impacto en la producción alimenticia mundial. La *Bemisia tabaci* puede transmitir mosaico africano de la yuca, mosaico dorado del frijol, mosaico enano del frijol, mosaico cálico del frijol, rizado amarillo del tomate, jaspeado del tomate, y otros Begomovirus. En las regiones tropicales o subtropicales, las moscas blancas se han convertido en uno de los más graves problemas de protección de cultivos. Las pérdidas económicas se estiman en cientos de millones de dólares. Además, el control de la mosca blanca es difícil y complejo, ya que la mosca blanca adquiere rápidamente resistencia a los pesticidas químicos. Actualmente, es la quinta especie de insectos más resistentes. (Véase Thomas C. Sparks, Ralf Nauen, IRAC: Mode of action classification and insecticide resistance management, Pesticide Biochemistry and Physiology (2014), doi:10.1016/j.pestbp.2014.11.014)

Se prueban cuatro cepas diferentes de *Bemisia tabaci*:

(a) La cepa W1 es una cepa de laboratorio que se cultivó bajo presión de selección para que fueran resistentes a Pimetrozina. Esta cepa fue

seleccionada debido a la importancia de la Pimetrozina y su modo de acción distinto y novedoso en comparación con otras cepas de laboratorio;

(b) La cepa W2 es una cepa adquirida en campo que es resistente a Buprofezina, Imidacloprid, Pimetrozina, y Piridabeno;

(c) La cepa W3 es una cepa de laboratorio que se cultiva bajo presión de selección para que sea resistente a Imidacloprid. Esta cepa se selecciona debido a la importancia del Imidacloprid y sus modos de acción distintos y novedosos en comparación con otras cepas de laboratorio; y

(d) La cepa es una cepa de laboratorio que se cultiva bajo presión de selección para que sea resistente a Spirotetramat. Esta cepa se selecciona debido a la importancia del Spirotetramat y sus modos de acción distintos y novedosos en comparación con otras cepas de laboratorio.

#### **Resultados:**

1. Contra la Cepa W1, se encontró que el Compuesto A1 es **189% mejor** que Buprofezina y **12767% mejor** que Pimetrozina en el control de esta cepa.

2. Contra la Cepa W2:

(a) se encontró que el Compuesto A1 es **4367% mejor** en el control de esta cepa que la Pymetrozina;

(b) se encontró que el Compuesto A1 es **1714% mejor** en el control de esta cepa que la Buprofezina;

(c) se encontró que el Compuesto A1 es **368% mejor** en el control de esta cepa que el Imidacloprid; y

(d) se encontró que el Compuesto A1 es **4247% mejor** en el control de esta cepa que el Piridabeno.

3. Contra la Cepa 3, se encontró que el Compuesto A1 es **10104% mejor** que el Piridabeno y **3032% mejor** que el Imidacloprid en el control de esta cepa.

4. Contra la Cepa W4, se encontró que el Compuesto A1 es **1083% mejor** que el Spirotetramat en el control de esta cepa.



US008815271B2

(12) **United States Patent**  
Yap et al.

(10) **Patent No.:** US 8,815,271 B2  
(45) **Date of Patent:** \*Aug. 26, 2014

(54) **PESTICIDAL COMPOSITIONS AND PROCESSES RELATED THERETO**

(75) **Inventors:** Maurice C. H. Yap, Zionsville, IN (US); Ann M. Buysse, Carmel, IN (US); Daniel Knueppel, Zionsville, IN (US); Yu Zhang, Carmel, IN (US); Negar Garlzi, Westfield, IN (US); Noormohamed M. Niyaz, Indianapolis, IN (US); Christian T. Lowe, Westfield, IN (US); Ricky Hunter, Westfield, IN (US); Tony K. Trullinger, Westfield, IN (US); David A. Demeter, Fishers, IN (US); Dan Pernich, Indianapolis, IN (US); Carl Deamicis, Indianapolis, IN (US); Ronald Ross, Jr., Zionsville, IN (US); Timothy C. Johnson, Indianapolis, IN (US)

(73) **Assignee:** Dow AgroSciences, LLC., Indianapolis, IN (US)

(\*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 64 days.  
  
This patent is subject to a terminal disclaimer.

(21) **Appl. No.:** 13/285,595

(22) **Filed:** Oct. 31, 2011

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(51) **Int. Cl.**

A01N 25/08 (2006.01)  
A01N 25/28 (2006.01)  
A01N 25/32 (2006.01)  
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A01N 63/00 (2006.01)  
A01N 43/40 (2006.01)  
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A01N 43/56 (2006.01)  
A01N 47/36 (2006.01)  
A01N 47/18 (2006.01)  
C07D 401/14 (2006.01)  
A61K 45/06 (2006.01)

(52) **U.S. Cl.**

CPC ..... C07D 401/04 (2013.01); C07D 417/14 (2013.01); A01N 43/56 (2013.01); A01N 47/36 (2013.01); A01N 47/18 (2013.01); C07D 401/14 (2013.01); A61K 45/06 (2013.01)  
USPC ..... 424/417; 424/76.8; 424/78.09; 424/93.1; 424/93.2; 424/84; 424/405; 424/406; 424/408; 504/101; 504/103; 504/113; 504/116.1; 514/341

(58) **Field of Classification Search**

CPC ..... A01N 25/02; A01N 25/08; A01N 25/28; A01N 25/34; A01N 25/002; A01N 25/004; A01N 25/006; A01N 25/008; A01N 2300/00

USPC ..... 514/341  
See application file for complete search history.

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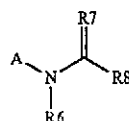
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Primary Examiner — Neil Levy

(74) *Attorney, Agent, or Firm* — Carl D. Corvin

(57) **ABSTRACT**

This document discloses molecules having the following formula ("Formula One"):



and processes related thereto.

19 Claims, No Drawings



US008815271B2

(12) **United States Patent**  
**Yap et al.**

(10) **Patent No.:** **US 8,815,271 B2**  
(45) **Date of Patent:** **\*Aug. 26, 2014**

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**A01N 47/36** (2006.01)  
**A01N 47/18** (2006.01)  
**C07D 401/14** (2006.01)  
**A61K 45/06** (2006.01)

(52) **U.S. Cl.**

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**USPC** ..... **424/417**; **424/76.8**; **424/78.09**; **424/93.1**; **424/93.2**; **424/84**; **424/405**; **424/406**; **424/408**; **504/101**; **504/103**; **504/113**; **504/116.1**; **514/341**

(58) **Field of Classification Search**

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**USPC** ..... **514/341**  
See application file for complete search history.

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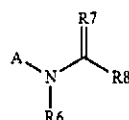
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*Primary Examiner* — Neil Levy

(74) *Attorney, Agent, or Firm* — Carl D. Corvin

(57) **ABSTRACT**

This document discloses molecules having the following formula ("Formula One"):



and processes related thereto.

**19 Claims, No Drawings**



# IRAC: Mode of action classification and insecticide resistance management

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## ABSTRACT

Insecticide resistance is a long standing and expanding problem for pest arthropod control. Effective insecticide resistance management (IRM) is essential if the utility of current and future insecticides is to be preserved. Established in 1984, the Insecticide Resistance Action Committee (IRAC) is an international association of crop protection companies. IRAC serves as the Specialist Technical Group within CropLife International focused on ensuring the long term efficacy of insect, mite and tick control products through effective resistance management for sustainable agriculture and improved public health. A key function of IRAC is the continued development of the Mode of Action (MoA) classification scheme, which provides up-to-date information on the modes of action of new and established insecticides and acaricides and which serves as the basis for developing appropriate IRM strategies for crop protection and vector control. The IRAC MoA classification scheme covers more than 25 different modes of action and at least 55 different chemical classes. Diversity is the spice of resistance management by chemical means and thus it provides an approach to IRM providing a straightforward means to identify potential rotation/ alternation options.

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## 1. Introduction

Insecticide resistance (see [1–3] for definitions) has been a major factor influencing insect control and pest management for more than half a century. The first paper documenting insecticide resistance was published 100 years ago and involved lime sulfur and the San Jose scale [4]. Thereafter, a few sporadic cases of insecticide resistance were reported through the mid-1940s (Fig. 1, [5]). The introduction of the synthetic organic insecticides (i.e. DDT, cyclodienes and organophosphorus insecticides) in the 1940s lead to great improvements in insecticidal efficacy and spectrum, with the

consequent large scale, expanded use of these new tools for pest insect control. Not surprisingly, there was also a rapid rise in the number of cases of resistance due to extensive, repeated use of these products. Since the late 1940s, the number of cases of insecticide resistance, and the number of species and compounds involved has been continually increasing (Figs. 1 and 2). The 1960s and 1970s saw the appearance of resistance to herbicides and fungicides (Fig. 2). However, the cases of insecticide resistance continue to far exceed the number of cases of herbicide and fungicide resistance (Fig. 2).

In light of its importance, approaches to studying insecticide resistance and insecticide resistance management (IRM) have been widely discussed (e.g. [6–14]). The crop protection industry has long recognized the importance of, and need for effective, proactive resistance management [15–22]. The time, effort, and increasingly very large costs involved in the discovery and development of new insecticides [23] dictate that the chances for the development of resistance be minimized as much as possible to ensure that the very substantial investment made to bring any new insecticide product or trait to the market is not wasted. Likewise, it is equally important to ensure minimize the chances of resistance developing for existing products, since in many instances alternative compounds that possess the same attributes or low cost may not be available. Thus, resistance management is of utmost importance and continues to be a critical concern for all stakeholders involved in modern applied pest control.

**Abbreviations:** AChE, acetylcholinesterase; APRD, Arthropod Pest Resistance Database; Bt, *Bacillus thuringiensis*; CC, chloride channel; CSI, chitin synthesis inhibitor; EcR, ecdysone receptor; GGCC, GABA gated chloride channel; GMO, genetically modified organism; IRAC, Insecticide Resistance Action Committee; IPM, Integrated Pest Management; IRM, Insecticide Resistance Management; JH-R, juvenile hormone receptor; MET, mitochondrial electron transport; MoA, mode of action; nAChR, nicotinic acetylcholine receptor; NTX, nereistoxin analogs; OA-R, octopamine receptor; Ox-Ph, oxidative phosphorylation; RNAi, RNA interference; Ry-R, ryanodine receptor; VGSC, voltage gated sodium channel; WG, working group; UN, unknown or uncertain mode of action.

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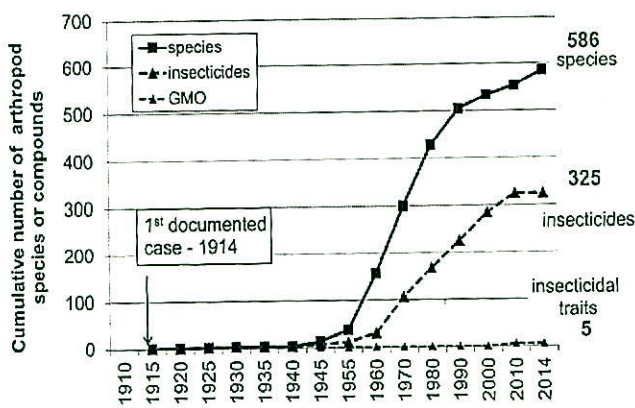


Fig. 1. Cumulative increase in (a) the number of species resistant to one or more insecticides, (b) number of insecticides for which one or more species has shown resistance, and (c) number of GMO traits for which resistance has been reported. Data adapted from: [2,3,47–50] and David Mota-Sanchez, Michigan State University, personal communication, 2014.

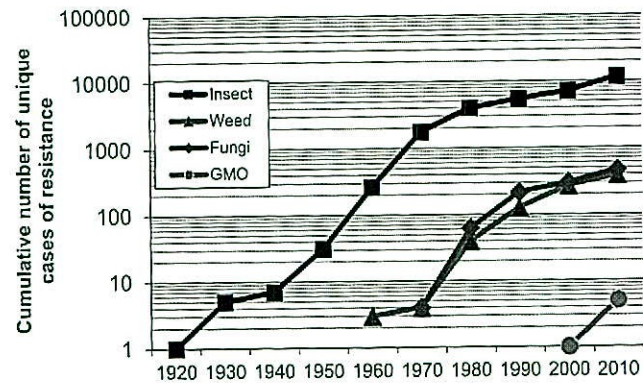


Fig. 2. Cumulative increase in the number of individual cases of resistance for insecticides, herbicides and fungicides. Herbicides and fungicide data adapted from [51,52]. Insecticide data kindly provided by Drs. David Mota-Sanchez, and Mark Whalon, Michigan State University.

## 2. Insecticide Resistance Action Committee (IRAC)

One response to the need for improved resistance management by the crop protection industry was first the formation of the Pyrethroid Efficacy Group and later on the Insecticide Resistance Action Committee (IRAC) [15,16,18,19,21,22] in 1984. IRAC, part of CropLife International, is a technical working group that focuses on providing a coordinated effort by the crop protection industry to prevent or delay the development of resistance in insect, mite and tick pests [22]. The mission of IRAC is twofold: (a) facilitate communication and education on insecticide and trait resistance, and (b) promote the development and facilitate the implementation of insecticide resistance management strategies to maintain efficacy and support sustainable agriculture and improved public health [1,22].

### 2.1. IRAC mode of action (MoA) classification

One of the key tools from IRAC is the MoA Classification Scheme. The MoA Classification Scheme provides state and government agencies, consultants, advisors, growers, universities and extension staff with guidelines for the selection of insecticides and acaricides when used in an alternation or rotation-based resistance management program (see below). Included in the MoA Classification is background information on resistance management and how the MoA Classification can be used for IRM. The MoA classification scheme is available in different formats such as posters (different language versions), a mini booklet and a smartphone App which are regularly updated (Fig 3).

The MoA Classification scheme is based on the best available evidence for the target-sites or MoA of currently available insecticides and acaricides (currently excludes nematocides). Details of the listing have been reviewed and approved by internationally recognized academic and industrial experts in insecticide toxicology, resistance and MoA. Currently the MoA Classification encompasses more than 25 different MoAs. A condensed listing of the chemistries currently covered by the MoA Classification is presented in Table 1; a more comprehensive listing is available on the IRAC website (<http://www.irac-online.org/>). In addition to data from the IRAC MoA classification scheme (main group and primary site of action, chemical subgroup/exemplifying active), Table 1 also provides additional information on the total number of compounds in each group/subgroup, the year the first compound in the group was introduced, and the 2013 end-user market value [24] for that group or subgroup.

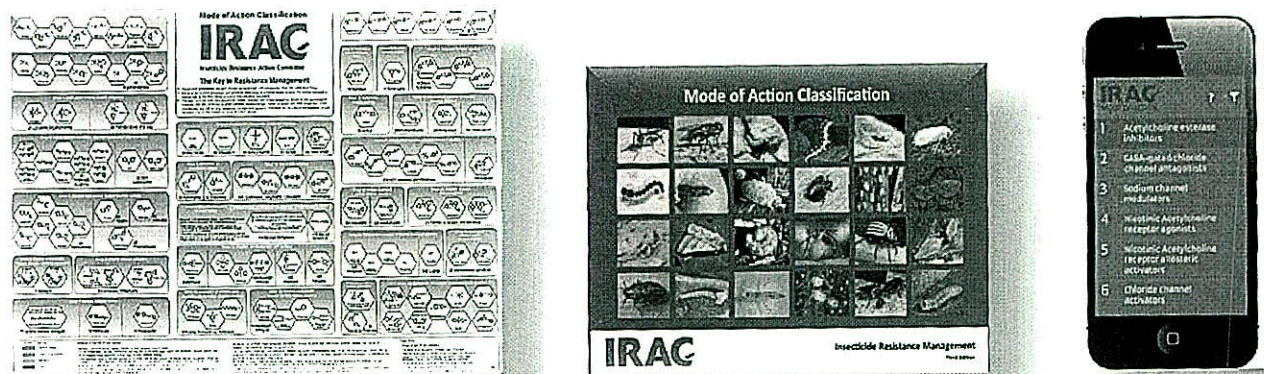


Fig. 3. Different formats of the MoA classification scheme available on the IRAC website include posters, a mini-booklet and a smartphone App (displayed with permission of IRAC).

**Table 1**  
Modes of action (based on IRAC MoA classification) for current insecticide groups.

| IRAC group                            | Primary site of action/MoA <sup>a</sup>            | Chemical subgroup/exemplifying active | 1st year <sup>b</sup> | No. of products <sup>c</sup> | Market <sup>d</sup> value |
|---------------------------------------|----------------------------------------------------|---------------------------------------|-----------------------|------------------------------|---------------------------|
| <b>Nerve and Muscle Targets</b>       |                                                    |                                       |                       |                              |                           |
| 1                                     | AChE inhibitor                                     | 1A carbamates                         | 1950                  | 30                           | \$667                     |
|                                       |                                                    | 1B organophosphates                   | 1944                  | 90                           | \$1794                    |
| 2                                     | GGCC antagonist                                    | 2A cyclodienes                        | 1950                  | 7                            | \$7                       |
|                                       |                                                    | 2B fiproles                           | 1990                  | 3                            | \$801                     |
| 3                                     | VGSC modulator                                     | 3A pyrethroids and pyrethrins         | 1977                  | 30                           | \$2777                    |
|                                       |                                                    | 3B DDT and analogs                    | 1944                  | 7                            | \$<1                      |
| 4                                     | nAChR agonist                                      | 4A neonicotinoids                     | 1990                  | 8                            | \$4650                    |
|                                       |                                                    | 4B nicotine                           | 1763                  | 1                            | –                         |
|                                       |                                                    | 4C sulfoximines                       | 2013                  | 1                            | \$8                       |
|                                       |                                                    | 4D butenolides                        | 2014                  | 1                            | –                         |
| 5                                     | nAChR allosteric                                   | Spinosyns                             | 1997                  | 2                            | \$401                     |
| 6                                     | CC activators                                      | Avermectins and milbemycins           | 1978                  | 4                            | \$1261                    |
| 9                                     | Modulators of chordotonal organs                   | 9B pymetrozine                        | 1994                  | 1                            | \$72                      |
|                                       |                                                    | 9C flonicamid                         | 2005                  | 1                            | \$112                     |
| 14                                    | nAChR blocker                                      | Nereistoxin analogs                   | 1965                  | 4                            | \$124                     |
| 19                                    | OA-R agonist                                       | Formamidines                          | 1971                  | 1                            | \$8                       |
| 22                                    | VGSC blocker                                       | 22A oxadiazines                       | 1997                  | 1                            | \$235                     |
|                                       |                                                    | 22B semicarbazones                    | 2007                  | 1                            | \$99                      |
| 28                                    | Ry-R allosteric                                    | Diamides                              | 2008                  | 5                            | \$1411                    |
| <b>Growth and Development Targets</b> |                                                    |                                       |                       |                              |                           |
| 7A                                    | JH-R agonist                                       | 7A juvenoids                          | 1973                  | 3                            | \$6                       |
|                                       |                                                    | 7B fenoxycarb                         | 1985                  | 1                            | \$12                      |
|                                       |                                                    | 7C pyriproxyfen                       | 1995                  | 1                            | \$56                      |
| 10                                    | MGI                                                | 10A clofentezine                      | 1983                  | 3                            | \$63                      |
|                                       |                                                    | 10B oxazoles                          | 1998                  | 1                            | \$44                      |
| 15                                    | CSI                                                | Benzoylureas                          | 1975                  | 14                           | \$441                     |
| 16                                    | CSI                                                | Buprofezin                            | 1984                  | 1                            | \$162                     |
| 17                                    | CSI                                                | Cyromazine                            | 1985                  | 1                            | \$14                      |
| 18                                    | EcR agonist                                        | Diacylhydrazines                      | 1993                  | 6                            | \$177                     |
| 23                                    | Acetyl CoA carboxylase                             | Tetronic/tetramic acids               | 2002                  | 3                            | \$456                     |
| <b>Respiration targets</b>            |                                                    |                                       |                       |                              |                           |
| 12                                    | ATP synthase                                       | 12A diafenthiuron                     | 1991                  | 1                            | \$44                      |
|                                       |                                                    | 12B organotin miticides               | 1968                  | 3                            | \$39                      |
|                                       |                                                    | 12C propargite                        | 1964                  | 1                            | \$47                      |
|                                       |                                                    | 12D tetradifon                        | 1954                  | 1                            | \$1                       |
| 13                                    | Ox-Ph uncouplers                                   | Chlorfenapyr                          | 1892                  | 3                            | \$81                      |
| 20A                                   | MET III inhibitors                                 | 20A hydramethylnon                    | 1977                  | 1                            | \$<2–3                    |
|                                       |                                                    | 20B acequinocyl                       | 1999                  | 1                            | \$43                      |
|                                       |                                                    | 20C fluacrypyrim                      | 2002                  | 1                            | \$22                      |
| 21                                    | MET I Inhibitors                                   | 21A MET I inhibitors                  | 1990                  | 6                            | \$274                     |
|                                       |                                                    | 21B rotenone                          | 1848                  | 1                            | \$<2–3                    |
| 24                                    | MET IV inhibitors                                  | 24A phosphine                         | –                     | 4                            | \$101                     |
|                                       |                                                    | 24B cyanide                           | 1877                  | 1                            | –                         |
| 25                                    | MET II inhibitors                                  | β-ketonitrile derivatives             | 2007                  | 2                            | \$50                      |
| <b>Midgut targets</b>                 |                                                    |                                       |                       |                              |                           |
| 11                                    | Midgut membr.                                      | 11A <i>Bacillus thuringiensis</i>     | 1970                  | 14                           | \$234                     |
|                                       |                                                    | 11B <i>Bacillus sphaericus</i>        | 1982?                 | 1                            | –                         |
| <b>Miscellaneous</b>                  |                                                    |                                       |                       |                              |                           |
| 8                                     | Miscellaneous non-specific (multi-site) inhibitors | 8A alkyl halides                      | 1932                  | –                            | \$327                     |
|                                       |                                                    | 8B chloropicrin                       | 1908                  | 1                            | \$285                     |
|                                       |                                                    | 8C sulfuryl fluoride                  | 2004                  | 1                            | \$44                      |
|                                       |                                                    | 8D borates                            | –                     | 1                            | –                         |
|                                       |                                                    | 8E tartar emetic                      | –                     | 1                            | –                         |
| <b>Unknown or Uncertain MoA</b>       |                                                    |                                       |                       |                              |                           |
| UN                                    | –                                                  | UN azadirachtin                       | 1995?                 | 1                            | \$–5–7 <sup>5</sup>       |
|                                       | –                                                  | UN benzoximate                        | 1971                  | 1                            | \$1                       |
|                                       | –                                                  | UN bifenazate                         | 1999                  | 1                            | \$42                      |
|                                       | –                                                  | UN bromopropylate                     | 1967                  | 1                            | \$<1                      |
|                                       | –                                                  | UN chinomethionat                     | 1960                  | 1                            | \$–8–9                    |
|                                       | –                                                  | UN cryolite                           | –                     | 1                            | \$8                       |
|                                       | –                                                  | UN dicofol                            | 1950                  | 1                            | \$2                       |
|                                       | –                                                  | UN pyridalyl                          | 2004                  | 1                            | \$118                     |
|                                       | –                                                  | UN pyrifluquinazon                    | 2010                  | 1                            | \$29                      |

<sup>a</sup> Abbreviations: AChE, acetylcholinesterase; GGCC, GABA gated chloride channel; CC, chloride channel; VGSC, voltage gated sodium channel; nAChR, nicotinic acetylcholine receptor; OA-R, octopamine receptor; Ry-R, ryanodine receptor; JH-R, juvenile hormone receptor; EcR, ecdysone receptor; CSI, chitin synthesis inhibitor; MET, mitochondrial electron transport; Ox-Ph, oxidative phosphorylation; UN, unknown or uncertain mode of action.

<sup>b</sup> First year (or approximate) of appearance of compounds in this class.

<sup>c</sup> Approximate number of products in each class (current and historic). Based, in part, on data from Alan Wood Compendium of Pesticide Common Names [40] ISO Common Names (<http://www.alanwood.net/pesticides/index.html>) and Cropnosis [53].

<sup>d</sup> 2013 sales (end user, millions USD) for the different IRAC Groups or subgroups of insecticides – data from Agranova ([24]).

The compound list for the MoA Classification Scheme is based, in part, on compounds appearing in the Pesticide Manual [25]. For new entries, a classification is provided for compounds registered in at least one country, or will soon be. The IRAC MoA Working Group (WG) is responsible for providing a classification for each compound. Companies interested in a classification for a new chemistry submit a request to the MoA WG for a classification and can suggest a potential grouping based on their research. Depending on the nature of the compound, a company requesting classification is typically asked to provide data to the MoA WG for review regarding the biochemistry and mode of action. As outlined in the IRAC MoA Classification document, companies may elect to provide internal data/information to support a classification request; however the preference is for data published in peer-reviewed journals.

2.2. Mode of action grouping and subgrouping

The MoA Classification scheme is principally based on the target site, and secondarily on novelty of the chemistry, differential action on the same target site and/or susceptibility to metabolic resistance mechanisms. A compound acting through a target site that is different from all others will be placed in a separate group (e.g. pyrethroids [Group 3] and neonicotinoids [Group 4]). Likewise, compounds acting at different sites in the same target (e.g. sodium channel modulators; pyrethroids [Group 3] and sodium channel blockers; indoxacarb and metaflumizone [Group 22]) [26,27] are also placed in different groups. Following a similar logic, compounds sharing a common target site, but representing very different types of chemistry (e.g. acetylcholinesterase inhibitors; carbamates [Group 1A] and organophosphates [Group 1B]) are placed in different subgroups because they can have distinctly different metabolic profiles minimizing the chances for metabolic cross-resistance. Similar examples exist for a number of other Groups (Table 2).

As outlined in the IRAC MoA Classification, rotation of compounds in the same Group, but in different subgroups (e.g. carbamates 1A and organophosphates 1B) is not recommended unless there are no other chemistries available that are in totally different groups (i.e. different modes of action). This recommendation is due to the increased chance of selecting for a common target site-based resistance mechanism thereby limiting the utility of both chemical classes of insecticides. Currently there are 25 specific MoAs listed in the MoA Classification along with some multi-site chemistries and a number that are either unknown or currently have insufficient data to formally classify them at this time (Table 2).

2.3. IRAC MoA classification and resistance management

Integrated pest management (IPM) in crop protection encompasses a range of approaches including biological control, cultural control, autocidal techniques, crop rotation, semiochemicals, host plant resistance, chemical control, and genetically modified (GMO) plants [28,29]. Among the tools on the horizon is sprayable RNAi [30,31], which provides a new approach to pest control with the potential of combining ease of spray application with a molecular targeting approach used in transgenic plants allowing for new modes of action and selectivity. As such sprayable RNAi is a conceptual bridge linking conventional chemical control, GMO crops and the older sprayable Bts. All of the above approaches seek to reduce pest pressure below economic damage thresholds on a crop. However, in spite of the many newer approaches available, for many specific cases of "crop, pest, locations", the use of chemical insecticides remains a primary tool. As such, preservation of the long term efficacy for current and new insecticides is essential since the availability of new, replacement insecticides may be very challenging given the time, increasing expense and increasingly stringent regulatory requirements [23]. One outcome associated with the increasing costs and rising regulatory requirements, has been a dramatic consolidation that has occurred in the agrochemical industry resulting in far fewer companies involved in pesticide discovery than a few years ago [23]. With fewer companies involved in insecticide discovery, the number of new insecticides with new modes of action may be limited in the future. As such, resistance management has become a critical consideration in seeking to preserve the future efficacy of existing and new insecticides. In some regions such as Europe it is even mandatory to provide documents covering resistance risk assessment for (re)registration purposes of pesticides [32].

IRM seeks to delay or prevent the evolution of resistance to insecticides. IRM can also aid in regaining susceptibility of a pest insect/ mite population that has already developed some degree of resistance to a particular chemistry. The primary means to accomplish these goals is to reduce the selection pressure directed toward any particular insecticide in a given crop or use. A number of approaches have been investigated on how best to use the available insecticide tools including alterations/rotations/sequences, mixtures, and mosaics [33].

Among these insecticide-based approaches, alteration/rotation/ sequences of insecticides are one of the more direct/simplest to execute having the fewest assumptions regarding the implementation [33,34]. A rotation approach often uses a "window" or block strategy [1,22] that is frequently defined by the length of a pest

Table 2  
Modes of action for future chemistries currently in various stages of development.

| Primary site of action/MoA <sup>a</sup> | Chemical class/exemplifying active | Example compound <sup>b</sup> | 1st year <sup>c</sup> | Reference |
|-----------------------------------------|------------------------------------|-------------------------------|-----------------------|-----------|
| GGCC allosteric                         | Isoxazolines                       | Fluralaner                    | 2010                  | [54]      |
| GGCC allosteric                         | Isoxazolines                       | Afoxolaner                    | 2014                  | [55]      |
| GGCC allosteric                         | Metadiazines                       | Broflanilide                  | 2013                  | [40]      |
| nAChR agonist                           | Cyclopyrim                         | Cyclopyrim                    | 2011                  | [56]      |
| nAChR                                   | Mesochorins                        | Triflumethoxypyrim            | 2013                  | [57]      |
| Ry-R allosteric                         | Diamides                           | Cyfluthrin                    | 2013                  | [40]      |
| Ry-R allosteric                         | Diamides                           | Tetraniliprole                | 2014                  | [40]      |
| UN                                      | Pyropenes                          | Afidopyropen                  | 2012                  | [58]      |
| UN                                      | Flometoquin                        | Flometoquin                   | 2011                  | [40]      |
| UN                                      | Fluhexafon                         | Fluhexafon                    | 2014                  | [40]      |

<sup>a</sup> Abbreviations: GGCC, GABA gated chloride channel; nAChR, nicotinic acetylcholine receptor; Ry-R, ryanodine receptor; UN, unknown.

<sup>b</sup> Example compound – example or representative member of this class of chemistry.

<sup>c</sup> First year (or approximate) of appearance of compounds in this class in the Alan Wood database (<http://www.alanwood.net/pesticides/index.html>) or in the literature.

generation or crop growth stages [35–37]. Such an approach has been effective in a number of instances as exemplified by experiences in Australia [35], Hawaii [36] and others [37], and involves rotating compounds with different MoAs according to a series of defined windows or blocks during the crop growing season to minimize selection for cross-resistance [1,37]. Always in such programs, local experts should be consulted for the best options for a particular pest–crop scenario.

The IRAC MoA Classification Scheme provides a means to select insecticide options for these types of rotation schemes by providing up-to-date information on the MoA of existing and newly registered insecticides. Compounds are assigned to MoA Groups that can then serve as simple means for selecting what compounds to put into an IRM program or rotation scheme. Depending on local conditions, typically one or more applications of a given insecticide may be acceptable within a window. However, it is critical that the next window or generation is not treated with a compound that is from the same MoA Group as the prior window/generation. The IRAC MoA Groups provide a ready means to identify compounds that have a different MoA relative to the insecticide just applied. In an increasing number of countries, the IRAC Group number is now on the product label (in some even mandatory) simplifying the process of determining if the next compound being considered for use has the same or different mode of action.

#### 2.4. Methods for resistance detection

Key to addressing insecticide resistance issues is the ability to reliably detect the presence of insecticide-resistant strains of pest insects. Some of the first standardized tests for insecticide resistance were developed by the World Health Organization in the 1950s for mosquito vectors of disease [6]. During the past 30 years, IRAC, through the Methods WG, has also developed and validated 30 standardized methods for resistance detection targeting a wide range of pest species, and primarily focused on crop insect and mite pests. The IRAC bioassay methods are characterized by being simple to perform, reliable, reproducible, and consistent in identifying susceptible versus resistant phenotypes [1]. In addition the Methods WG maintains a searchable reference database of nearly 160 other resistance bioassay methods that have been documented in scientific literature [1].

#### 2.5. Documentation and communication

For IRM to be effective, ready access to information along with education is needed; this role is central to IRAC's activities. The IRAC Communication & Education WG makes a variety of resources available to academia, industry, research groups, conferences, and growers regarding resistance management. A variety of material including monographs such as the vector manual, pamphlets, booklets, posters, references, and links are available covering for example IRM, test methods, and pest insect biology available on the IRAC website. Furthermore IRAC publishes resistance alerts on new resistance issues such as the recent *Myzus persicae* neonicotinoid target-site resistance alert (see [38]).

Another critical need in understanding and managing insecticide resistance is documentation of which pests and/or insecticides have had resistance developed. The Arthropod Pesticide Resistance Database (APRD) (<http://www.pesticideresistance.com/search.php>), available to the public, provides extensive listings of cases of insecticide resistance searchable by pest, year, and active ingredient [2]. The database documents insecticide resistance incidences from as early as 1914 through the present day. IRAC has had a long collaboration with Michigan State University to support, maintain and expand the APRD [2].

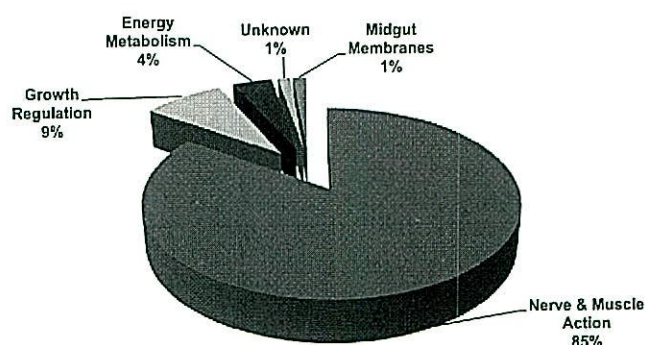


Fig. 4. Distribution of total insecticide sales (percent of total value) by broad mode of action. Total value = \$17016 million; excludes fumigants. Based on 2013 End-user sales data from Agranova [24], July 2014.

#### 3. Perspective

Among the more than 25 MoAs currently in the IRAC classification, 85% of the value of these MoAs is derived from insecticides that act on the insect nerve–muscle system (Fig. 3; for review see [39]). In contrast, insecticides altering growth and development account for only 9% of the total insecticides sales, while those disrupting energy production (respiration targets) account for only 4% (Fig. 4). Because small perturbations in the nervous system are quickly amplified, the insect nervous system has been and remains a prime target for new insecticides. Within the nerve–muscle acting insecticides, the neonicotinoids predominate with 27% of the market, nearly as much as the current organophosphates, carbamates and pyrethroids combined (31%) (Fig. 5). Although a relatively new class of chemistry, the diamides acting on ryanodine receptors now account for about 8% of total global end-user insecticide sales, a number that has been steadily increasing, and that is certain to continue to increase with the potential addition of other new diamides to the marketplace (Table 2). An interesting comparison is the number of compounds in each IRAC MoA Group or Subgroup (Table 2; includes current and historic compounds). There are in total 288 insecticidal compounds, excluding fumigants [40], and the number of organophosphate insecticides that became products (90; 31%) far exceeds any other Group or Subgroup, and yet today accounts for just 11% of the end-user sales. A similar situation exists

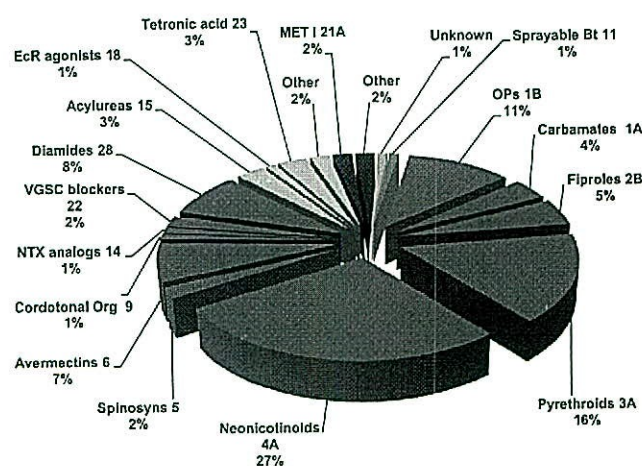


Fig. 5. Distribution of total insecticide sales (percent of total value) by IRAC MoA Group or Subgroup. Total value = \$17,016 million; excludes fumigants. Based on 2013 End-user sales data from Agranova [24], July 2014.

Table 3  
Top 12 resistant insect species.<sup>a</sup>

| Species                          | Common name                    | Order       | No. of compounds | No. of cases <sup>b</sup> |
|----------------------------------|--------------------------------|-------------|------------------|---------------------------|
| <i>Tetranychus urticae</i>       | Two-spotted spider mite        | Acari       | 93               | 414                       |
| <i>Plutella xylostella</i>       | Diamondback moth               | Lepidoptera | 91               | 576                       |
| <i>Myzus persicae</i>            | Green peach aphid              | Hemiptera   | 75               | 402                       |
| <i>Musca domestica</i>           | House fly                      | Diptera     | 58               | 303                       |
| <i>Bemisia tabaci</i>            | Sweet potato whitefly          | Hemiptera   | 54               | 555                       |
| <i>Leptinotarsa decemlineata</i> | Colorado potato beetle         | Coleoptera  | 54               | 279                       |
| <i>Aphis gossypii</i>            | Cotton aphid                   | Hemiptera   | 48               | 231                       |
| <i>Panonychus ulmi</i>           | European red mite              | Acari       | 48               | 197                       |
| <i>Helicoverpa armigera</i>      | Cotton bollworm                | Lepidoptera | 47               | 692                       |
| <i>Boophilus microplus</i>       | Southern cattle tick           | Ixodida     | 44               | 167                       |
| <i>Blattella germanica</i>       | German cockroach               | Blattodea   | 43               | 219                       |
| <i>Spodoptera litura</i>         | Mediterranean climbing cutworm | Lepidoptera | 38               | 457                       |

<sup>a</sup> Based on the number of different compounds for which resistance has been reported. Data from the APRD [50], July 2014.

<sup>b</sup> Number of unique instances of resistance reported for each species in the APRD [50]; July 2014.

<sup>c</sup> *Rhipicephalus*.

for the carbamates, and to a lesser extent, the pyrethroids (Table 1). In contrast, there are relatively few neonicotinoids in the marketplace (Table 2), and yet at present they account for a very sizable portion of the global insecticide sales (Fig. 5, Table 1).

In addition to existing (but still relatively new) MoAs, several new classes of insecticides targeting new or as yet undetermined target sites/MoAs are in varying stages of development (Table 2). At present, none of these potential new insecticides are registered crop protection products and thus too early to be considered for inclusion in the IRAC MoA Classification. However, these new, potential insecticides highlight the fact that the agrochemical industry is continuing to explore and develop new tools for pest arthropod control, therein providing new opportunities for developing or continuing IRM programs.

At the same time, due to the continuing expansion of insecticide resistance, regulatory and/or other considerations, many of the existing insect and mite control tools may not be as suitable or even available for use in future IPM and IRM programs. Also, the number of options available is pest–crop–region dependent. As such, many of the insecticide options in the 25 MoA Groups may, or may not be available or viable, with the result that in some crop systems the number of options may be very limited. Thus, any new insecticide options, especially those bringing forward new MoAs, should be treated as limited, finite resources that need to be used with care. If these new MoAs become over-used or mis-used with the resultant rapid development of resistance and consequent loss of efficacy and utility, all of agriculture will be the loser.

Such scenarios have been played out many times. For example when spinosad was introduced into Hawaii for control of the diamondback moth (*Plutella xylostella*) in 2000, the lack of suitable alternatives and the continuous weekly applications quickly (~2 years) led to resistance and a loss of efficacy and utility [41,42]. In a more recent example, resistance to chlorantraniliprole appeared to diamondback moth within 3 years of introduction in China due to its almost exclusive use for control in many regions [43]. Other historic examples of rapid resistance development include control of house flies with DDT [44], Colorado potato beetle control with a wide number of insecticides including the pyrethroids [5], and the control of horn flies with pyrethroids in cattle ear tags [45]. Some of the above insect pests and others including the diamondback moth, two-spotted spider mite, green peach aphid, cotton aphid, sweet potato whitefly, etc. (Table 3) have a history of developing resistance to insecticides with some species having developed resistance to more than 90 different insecticides (Table 3). Nearly all of the pests in Table 3 have 200 or more instances of resistance.

As also demonstrated by the experience with spinosad resistance in diamondback moth in Hawaii, attempting to reverse

resistance once it has developed is difficult. Even if initially successful, resistance reversal can be temporary [42,46] if the resistance selection has proceeded to the point where the frequency of the resistant alleles becomes high. As also exemplified by the diamondback moth, many of the pests in Table 3 have a short generation time, high fecundity, are highly mobile and attack crops where there may be few other control options or where little crop damage can be tolerated. As such, IPM and IRM programs involving these species deserve special consideration and planning when bringing a new insecticide tool into use due to their long history of resistance development.

4. Conclusions

Agrochemical industry responsibly addresses the importance of IRM as demonstrated by the activities and expanded agrochemical company membership of IRAC during the past 30 years. As noted above, the increasingly expensive and complex process of discovering new insect control products dictates that it is vital that the current and new insecticide tools be used in a rational manner in order to safeguard their long term efficacy and utility. Thus through its communication and education programs IRAC has been and continues to stress the importance of IRM inside and outside of the agrochemical industry, as well as the agricultural community. The IRAC-developed MoA Classification Scheme and the associated MoA labeling and IRM recommendations now common on the container labels for insecticides in many countries is just one demonstration of the agrochemical industry's IRM commitment. IRM is of paramount importance for growers, crop protection specialists, university and industry alike. As noted in past IRAC publications (e.g. [22]), and numerous presentations [1], IRM is not optional; it is essential to ensure that valuable, often scarce, insect control tools are not mis-used or over-used, and continue to be available to address the expanding global need for the production of food and fiber as well as for improved public health.

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## Cheminformatics Analysis of Organic Substituents: Identification of the Most Common Substituents, Calculation of Substituent Properties, and Automatic Identification of Drug-like Bioisosteric Groups

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A large set of more than 3 million molecules was processed to find all the organic substituents contained in the set and to identify the most common ones. During the analysis, 849 574 unique substituents were found. Extrapolated to the number of known organic molecules, this result suggests that about 3.1 million substituents are known. Based on these findings the size of virtual organic chemistry space accessible using currently known synthetic methods is estimated to be between  $10^{20}$  and  $10^{24}$  molecules. The extracted substituents were characterized by calculated electronic, hydrophobic, steric, and hydrogen bonding properties as well as by the drug-likeness index. Various possible applications of such a large database of drug-like substituents characterized by calculated properties are discussed and illustrated by reference to a Web-based tool for automatic identification of bioisosteric groups.

### INTRODUCTION

The concept of organic substituents and their influence on molecular properties is one of the pillars of modern organic chemistry as well as a basis of QSAR analysis. Prominent examples from this area are the pioneering contribution of Hammett with regard to the effect of substituents on reactivity (including the introduction of substituent  $\sigma$  constants characterizing the electron donating and accepting power of substituents), the reaction mechanism theory of Ingold (including the definition of mesomeric and inductive effects of substituents), the QSAR concept of Hansch (including the definition of substituent hydrophobicity  $\pi$  constants and the application of substituent constants in QSAR<sup>1</sup>), and the ideas of Craig and Topliss concerning the influence of substituent properties on biological activity applied in early drug design.<sup>2,3</sup> The whole combinatorial chemistry is also based on the concept of substituents, acting in this case under the name building blocks.

The present study focuses on organic substituents from the point of view of cheminformatics and tries to answer questions about the total number of substituents in known organic chemistry space and the implications of this number for the size of virtual organic chemistry space. The characterization of substituents by calculated properties is also discussed, including a procedure for calculating substituent drug-likeness based on a comparison of the distribution of substituents in a large database of drugs versus a large database of nondrugs. Finally an example of the application of a large database of drug-like substituents with calculated properties is presented—a Web-based tool for automatic identification of bioisosteric groups.

### IDENTIFICATION OF MOST COMMON SUBSTITUENTS, THE NUMBER OF KNOWN ORGANIC SUBSTITUENTS

To estimate the number of substituents and identify the most common organic substituents, we processed a large in-house database of commercially available molecules containing 3 043 941 entries. Structures stored as SMILES strings were processed, and all substituents up to 12 non-hydrogen atoms were extracted. Any group of atoms connected by a single chemically activated (breakable) nonring bond to the rest of the molecule was considered a “substituent”. Charged groups were neutralized when possible. Only substituents containing “organic” atoms (including Si, P, and Se) were collected. The whole molecular manipulation and processing was done using an in-house molecular development kit written in Java.

Analysis of the molecular database yielded 849 574 unique substituents. The substituents with the highest frequency in the database are shown in Figure 1. The size of the database processed is large enough for generalization, so we can claim that substituents displayed in this figure are the most common organic substituents.

Out of all 849 574 substituents found, however, only a very small fraction, namely 50, may be considered to be truly “common”, i.e., present in more than 1% of all molecules in the database, while 438 substituents are present in more than 0.1% of all molecules. About 64% of all substituents found are singletons (i.e., they are present only in a single molecule in the whole database processed). A similar frequency distribution of fragments in molecules from the Derwent World Drug Index was also obtained in a study by Lewell et al.<sup>4</sup>

Figure 2 shows the dependence of the total number of substituents identified on the number of molecules processed

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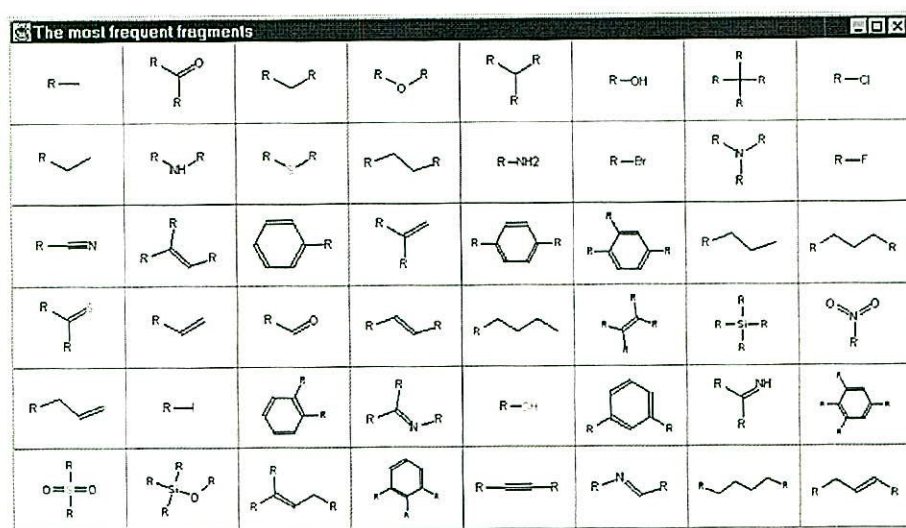


Figure 3. The most common fragments obtained by decomposition of 849 574 substituents.

example neglect of symmetry of the X scaffolds). Nevertheless, we believe the results presented here may be a useful approximation of the overall size of virtual organic chemistry space.

#### CALCULATION OF SUBSTITUENT PROPERTIES

An analysis of the substituents described hitherto produced a large database of about 850 000 substituents. To use this database in practical applications, the substituents need to be classified in some way. For applications in drug design, a classification based on substituent physicochemical properties is more useful than a simple classification based on structural similarity. In this study, we used substituent size, hydrophobicity, electronic properties (donating/accepting power), and hydrogen bonding characteristics. Steric substituent properties were characterized simply by topological size (number of non-hydrogen atoms) and maximum topological length. Substituent hydrophobicity ( $\pi$  constant) was calculated using the Ghose-Crippen atom contribution method.<sup>7</sup> The interdependence between calculated and experimental  $\pi$  constants for 256 common substituents (Figure 4) is quite acceptable. For the calculation of substituent electronic properties (Hammett  $\sigma$  constant) we used methodology based on quantum chemical parameters developed in-house. Since the method has been described in detail in the original paper,<sup>8</sup> the description here is confined to its basic features. The method is based on attaching a small model system (probe) to the substituent. Atomic charges on the probe are then calculated using a semiempirical quantum chemical method. The charges are of course influenced by the attracting or donating power of the substituent. In a training process these calculated charges were correlated with experimental  $\sigma$  constants for a set of substituents. Various probes, semiempirical Hamiltonians, and calculation protocols were tested to find a model with the best predictive power. Correlation between experimental and calculated  $\sigma$  constants for 368 substituents is shown in Figure 5. The correlation in this case is influenced by a low reliability of experimental  $\sigma$  constants for substituents that are not so common.<sup>8</sup> And as a final parameter, hydrogen bonding substituent properties were generated by a simple approach taking into account the

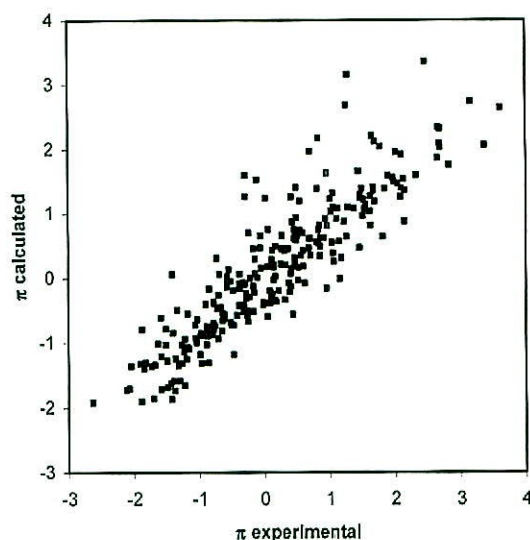


Figure 4. Correlation between calculated and experimental hydrophobicity  $\pi$  constants for 256 substituents.

topological distance of the hydrogen bond donor and acceptor centers from the substituent root.

A two-dimensional view (hydrophobicity versus electronic properties) of this four-dimensional substituent property space for more than 850 000 substituents is shown in Figure 6. This graph is actually nothing more than a well-known Craig plot<sup>2</sup> with the number of points, however, slightly larger than usual.

#### MOST COMMON SUBSTITUENTS IN DRUGS AND CALCULATION OF SUBSTITUENT DRUG-LIKENESS

To use the substituent database in drug design, not only substituent properties are important but also a characteristic known as drug-likeness or drugability. This may be defined as an ability of the substituent to generally increase the probability that its parent molecule is a drug. To identify the most common substituents in drugs, we performed an analysis of molecules in the World Drug Index database.<sup>9</sup> The most common substituents identified by this procedure are shown in Figure 7. A similar analysis of substituents for

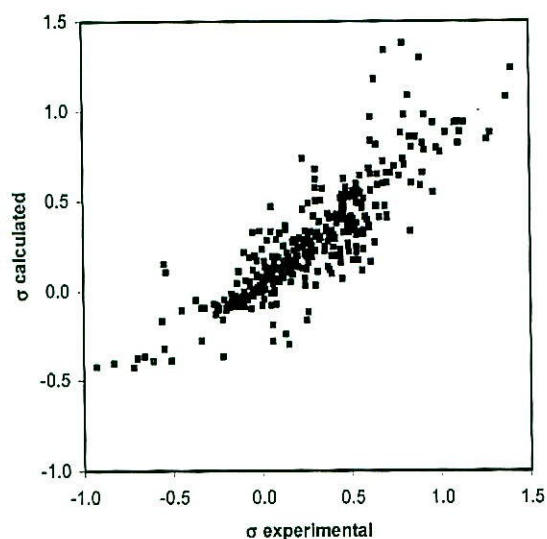


Figure 5. Correlation between calculated and experimental Hammett  $\sigma$  constants for 368 substituents.

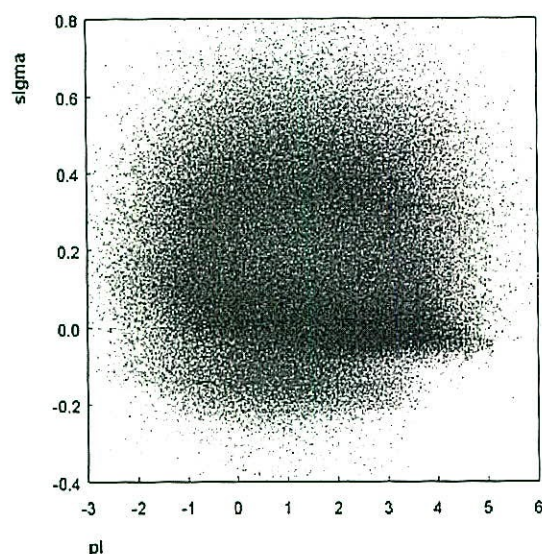


Figure 6. Distribution of calculated hydrophobic ( $\pi$  constant) and electronic ( $\sigma$  constants) properties for about 850 000 substituents (points representing aliphatic carbon substituents are blue, aromatic carbon ones violet, nitrogen green, oxygen red, and sulfur yellow).

5090 molecules from the Comprehensive Medicinal Chemistry database was published recently<sup>10</sup> and despite a slight difference in the definition of "sidechains" used in this study and definition of substituents in our analysis, the results of these two studies are very similar.

A comparison of most common substituents found in drugs (Figure 7) and most common substituents identified in average organic molecules (Figure 1) reveals quite a marked overlap between these two sets. For example, out of 500 most common substituents in both sets 243 are common. We also analyzed a large database of molecules with toxic effects, and the most common substituents identified here (not shown) were again similar to those presented in Figures 1 and 7. These functionalities are simply the most common organic substituents and will be found at the top after analyzing any large collection of molecules. The list of substituents presented in Figure 7 is therefore not the

information needed when looking for substituents with drug-like properties. To identify substituents which beneficially influence the drug-likeness of their parent molecules one needs to identify substituents with *relatively* higher distribution in drugs than in nondrugs. A similar approach of identifying the substructure motifs present more frequently within a specific therapeutic class than in the whole World Drug Index has been described by Lewell et al.<sup>4</sup>

To find substituents with the highest drug likeness, we compared the distribution of substituents in two large databases of molecules: the database of nondrugs (or rather the reference set of average organic molecules) used in our earlier studies (about 3 000 000 molecules) and a subset of the World Drug Index.<sup>9</sup> The World Drug Index database was preprocessed by removing various "helper" molecules (imaging, radioprotecting, or dental agents, etc) as well as organometallic structures to leave 36 482 molecules which may be termed "true drugs".

Substituent drug-likeness index was calculated according to the following formula

$$f_i = \log(nact_i / ninact_i * ninact_{total} / nact_{total})$$

where  $nact_i$  is the number of drugs which contain substituent  $i$ ,  $ninact_i$  is the number of nondrugs which contain substituent  $i$ ,  $nact_{total}$  is the total number of drugs, and  $ninact_{total}$  is the total number of nondrugs processed.

In several in-house studies we compared the performance of various indices for separating drugs and nondrugs, and the simple index described above provided the best results. This index ranked very well also in the analysis of Ormerod et al.<sup>11</sup> Statistical significance of results was checked by contingency analysis at the 95% level. This ensured that rare substituents with possibly random distribution were not considered in the analysis.

Examples of substituents with high drug-likeness are shown in Figure 8. These substituents (or their derivatives in the proper reactive state) may be used as reagents in drug optimization processes or as building blocks in the design of drug-like combinatorial libraries. At the same time, our analysis also provided a list of substituents with a high negative drug-likeness index, examples of which are shown in Figure 9. The statistical analysis, of course, does not provide any reasons for these groups to be in the "bad" list. They have been identified solely based on the fact that they are present with significantly lower frequency in drugs than in average organic molecules. Therefore groups in this list should be checked manually to identify substructures with potential toxic effects, too reactive groups or metabolic weakpoints. Such groups should be avoided in synthesis planning, because products containing them would very probably be molecules with poor drugability. Such "negative lists" may also be used as exclusion criteria in virtual screening.

#### A WEB-TOOL FOR AUTOMATIC IDENTIFICATION OF BIOISOSTERIC SUBSTITUENTS

A large database of drug-like substituents/building blocks characterized by calculated properties may be used with advantage in various drug design applications, ranging from "classical" use in QSAR studies or molecular design by hand, through selection of building blocks for synthesis of com-

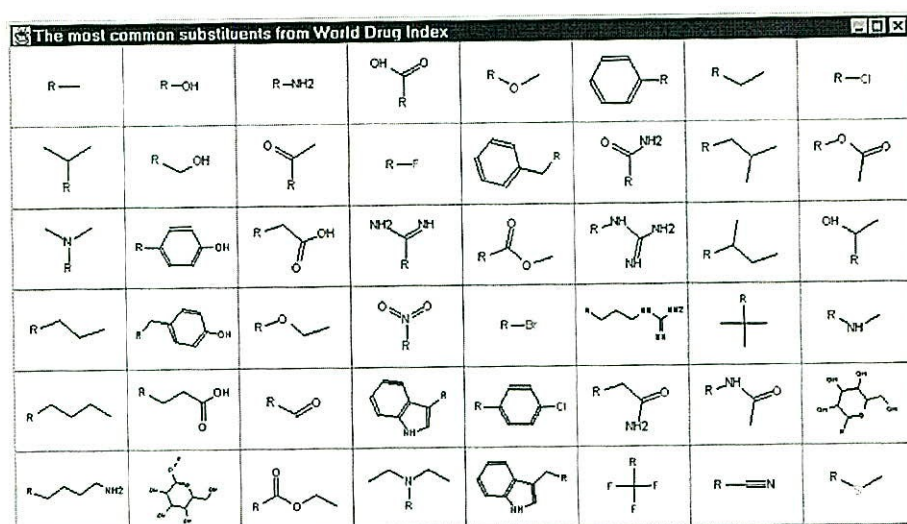


**Figure 7.** The most common substituents from the World Drug Index.

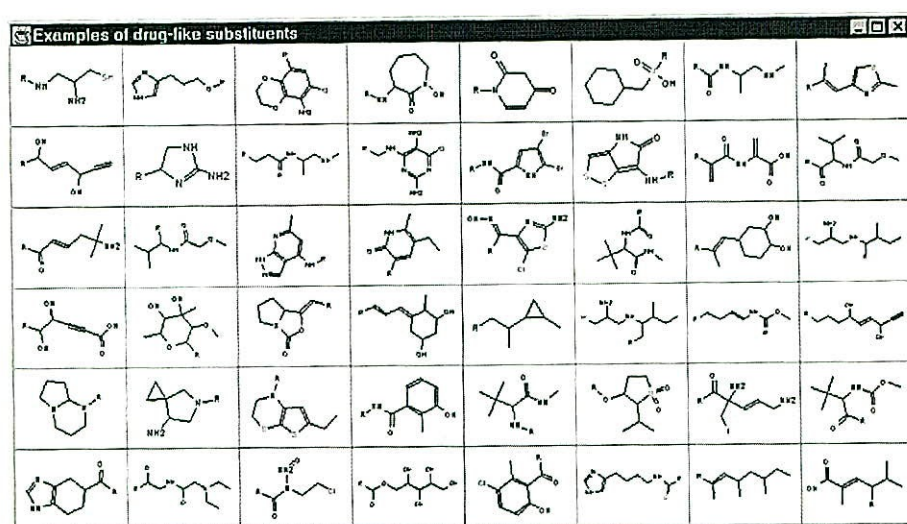


**Figure 8.** Examples of substituents with the highest drug-likeness index.

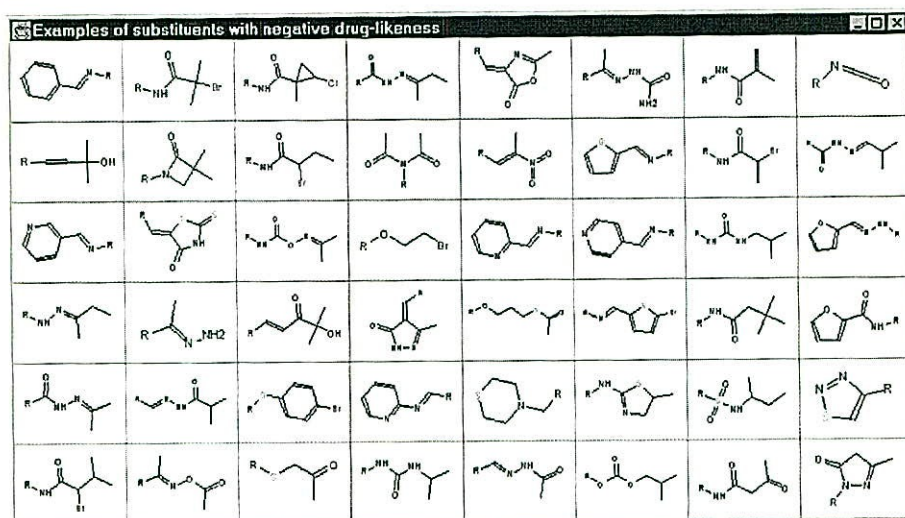


**Figure 9.** Examples of substituents with negative drug-likeness index.

binatorial libraries with desired characteristics, to automatic design of molecules with optimal properties by evolutionary

algorithm. As an example of such applications, a Web tool for automatic identification of bioisosteric functional groups,

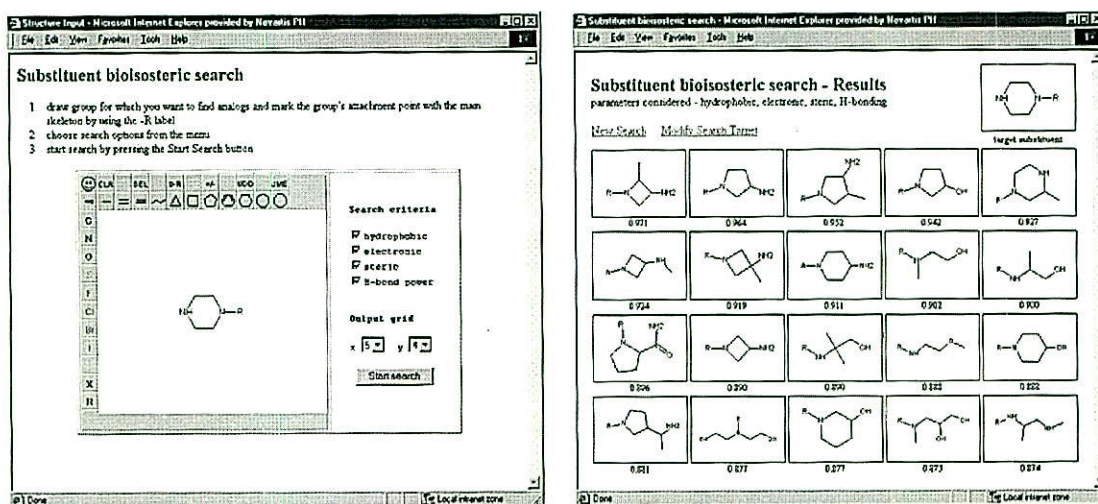


Figure 10. Web-based system for identification of bioisosteric substituents.

which is installed on the Novartis cheminformatics intranet,<sup>12–14</sup> is presented here.

Bioisosteric replacement is one of the standard techniques used in medicinal chemistry.<sup>15</sup> It can be defined as the replacement of a functional group in a bioactive molecule by another functionality of similar size and physicochemical properties. Bioisosteric transformations are used in the process of drug optimization to improve the properties of drug candidates, such as bioactivity, selectivity, and transport characteristics, and to remove unwanted side effects such as toxicity or an excessively rapid metabolism. Bioisosteric replacement is also used to design molecules more easily to synthesize or avoid patented structural features. Classical textbook examples of bioisosterically equivalent groups are phenyl and thiophenyl or carboxylic group and tetrazole. To find bioisosteric analogues of more complex groups, however, is not so easy. It requires a lot of experience, and even then the identification of a group with an optimal balance of steric, hydrophobic, electronic, and hydrogen-bonding properties, all of which influence ligand–receptor interactions, usually calls for a demanding procedure of trial and error.

That is the reason that a tool for automatic identification of substituent and linkers bioisosteric with the given target was developed. The tool presented here is an updated and modernized version of a Web application briefly presented earlier.<sup>16</sup> The heart of the system is a database of about 10 000 drug-like substituents characterized by calculated hydrophobic, electronic, steric, and hydrogen-bonding properties. When performing a search, the substituent for which analogues are to be identified must be entered into the system. This may be done easily with help of a Java molecular editor applet<sup>17</sup> incorporated directly into the Web page (Figure 10). After search options are chosen, the search is started. Substituents having properties compatible with those of the target are identified in the substituent database and displayed. Such lists of bioisosteric groups may serve as an “ideas generator” for bench chemists, helping them to design new bioactive molecules. The advantage of this approach is that it facilitates the identification not only of traditional analogues but also of nonclassical bioisosteric

analogues, i.e., groups which are structurally different but are compatible in terms of their physicochemical properties.

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