

Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 01-002407-A-00000-0000

Delegatura de Prop

Fecha: 2001-01-15 00:00:00 Dep. 2020 DIR.NUEVASCR
Tra. 2 PATENTES Eve. 1 REGDEPOSITO
Act. 411 PRESENTACION Folios: 1

División de Nuevas Creaciones

INVENTARIO

SOLICITUD

PATENTE DE INVENCION

01-2407A

21. EXPEDIENTE No.

54. TÍTULO

4-AMINOPICOLINATOS Y SU USO COMO HERBICIDAS

CLASIFICACIÓN INTERNACIONAL

SOLICITANTE

DOW AGROSCIENCES LLC

DOMICILIO

INDIANA, ESTADOS UNIDOS DE AMERICA

74. APODERADO

EMILIO FERRERO

C.C. 438.019 de Usaquén

22. BOGOTÁ, D. C.,



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 01-002407-A-00000-0000

Fecha: 2001-01-15 00:00:00 Dep. 2020 DIR.NUEVASCR
Tra. 2 PATENTES Eve. 1 REGDEPOSITO
Act. 411 PRESENTACION Folios: 1



01 2407

CION

02 EVENTO 01 ACTUACION 411

DATOS DEL SOLICITANTE

(71) Nombres y Apellidos o Razón Social

DOW AGROSCIENCES LLC.

Constituida bajo las leyes de Delaware, Estados Unidos

Nº de Identificación

Representante Legal (Persona Jurídica)

País de Domicilio

Estados Unidos de América

Departamento o Estado

Indiana 46268

Dirección

9330 Zionsville Road

Ciudad

Indianapolis

Teléfono

(74) DATOS DEL APODERADO

Nombre

EMILIO FERRERO

Dirección y Domicilio

Carrera 4 No. 72-35

Ciudad

Bogotá, Colombia.

Teléfono 3-47-36-11

DATOS DEL INVENTOR

(72) Nombre del inventor(es)

- 1- Stephen Craig FIELDS
- 3- Ann Marie BUYSE
- 5- Christian Thomas LOWE
- 7- Anita Lenora ALEXANDER
- 9- Renee Joan KEESE
- 11- John Sanders RICHBURG III

- 2- Terry William BALKO
- 4- Karl Leopold KRUMEL
- 6- James Melvin RUIZ
- 8- Leslie Anne BJELK
- 10- William CHI-LEUNG LO

Identificación

- 1- 12341 H Springside Lane North, Indianápolis, Indiana 46260, Estados Unidos
- 2- 1410 Bowman Drive, Greenfield, Indiana 46140, Estados Unidos
- 3- 1212 Golfview Drive Apt. A, Carmel, Indiana 46032, Estados Unidos
- 4- 1614 Shorefront Circle, Midland, Michigan, 48640, Estados Unidos

Ciudad

Continúa al respaldo...

DATOS DE LA PATENTE DE INVENCIÓN

(54) Título de la Invención

4-AMINOPICOLINATOS Y SU USO COMO HERBICIDAS

PRIORIDAD REIVINDICADA

SI ☒ NO ☐ TIPO DE PRIORIDAD ANDINA ☐ UNIONISTA ☒

(33) País

(32) Fecha

(31) No. Solicitud

US

14 de Enero de 2000

60/176.720

Convención de París

Para Publicar a los ☐ 6 meses ☐ 12 meses ☒ 18 meses a partir de la fecha de la presente solicitud

Colo: 10975-801-006-9-MLR/mrm-ID.66

(51) CLASIFICACION INTERNACIONAL

A 01 N 0 43 40

15 ENE 2001

RESUMEN CON EL OBJETO Y LA FINALIDAD DE LA INVENCION

La presente invención se relaciona con ácidos 4-aminopicolínicos, que tienen halógeno, alcoxi, alquiltio, ariloxi, heteroariloxi o sustituyentes de trifluorometilo en las posiciones 3, 5 y 6, y sus aminas y derivados de ácido que son potentes herbicidas que demuestran un espectro amplio de control de malezas.

Domicilios Inventores:

- 5- 4813 North Broadway, Indianápolis, Indiana 46205, Estados Unidos.
- 6- 4747 Woods Edge Drive, Zionsville, Indiana 46077, Estados Unidos.
- 7- 829 North Lesley Avenue, Indianapolis, Indiana 46219, Estados Unidos.
- 8- 8521 Williams Cove Court, Indianapolis, Indiana 46260, Estados Unidos.
- 9- 985 Arrowwood Drive, Carmel, Indiana 46033, Estados Unidos.
- 10- 6938 Bluffgrove Circle, Indianápolis, Indiana 46278, Estados Unidos.
- 11- 103 East Bloomfield Lane, Westfield, Indiana 46074, Estados Unidos.

ANEXOS DE LA SOLICITUD

Certificado de Existencia y Representación Legal cuando el solicitante sea Persona Jurídica ☒

Los poderes debidamente otorgados, o mención de su protocolización ante la SIC ☒

Recibo de la tasa respectiva *por v/r de \$608.000.000* ☒

Recibo de la tasa por concepto de excedente de palabras en la publicación ☐

Si se reivindica prioridad Andina: ☐

Copia de la primera solicitud ☐

Traducción oficial ☐

Si se reivindica prioridad Unlonista: ☐

Copia certificada de la primera solicitud: ☐

Nota: Debe presentarse dentro de los tres (3) meses, contados a partir de la fecha de radicación de la solicitud posterior

Traducción simple ☐

Capítulo descriptivo ☒

Dibujos, planos necesarios ☐

Capítulo reivindicatorio ☒

Tarjeta archivo propietarios según formato ☒

Tarjeta archivo temático según formato ☒

Extracto para publicación según formato ☒

Arte final 12 x 12 cms y 6x6 cms ☐

Otros Documentos ☐

SOLICITO LA CONCESION DE LA PATENTE DE INVENCION Y DECLARO QUE LA INVENCION ES NUEVA Y DE MI PROPIEDAD

FIRMA

Emilio Ferrero

NOMBRE EMILIO FERRERO

438.019 de Usaquén

T.P.No. 31.929

**Industria y Comercio**

SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación

FORMULARIO ÚNICO DE CONVERSIÓN, DIVISIÓN Y FUSIÓN DE SOLICITUDES

1			SOLICITUD DE:		
☐ Conversión.			☒ División		
☐ Fusión					
☐ Patente de Invención			☐ Patente de Modelo de Utilidad		
☐ Registro de Diseño Industrial			☐ Esquemas de Trazado para Circuitos Integrados		
2 SOLICITANTE (71)		Nombre: DOW AGROSCIENCES LLC Sociedad constituida y existente bajo las leyes del Estado de Indiana, Estados Unidos de América. Dirección: 9330 Zionsville Road, Indianápolis, Indiana 46268, Estados Unidos de América Domicilio: Indianápolis, Indiana 46268, Estados Unidos de América Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@camyp.com		IDENTIFICACIÓN C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____	
3 REPRESENTANTE O APODERADO		Nombre: EMILIO FERRERO Dirección: Carrera 4ª. No. 72-35 Teléfono: 347 36 11 Fax: 217 92 11 E-mail: clientes@camyp.com.		IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>438.019</u> T.P <u>31.929</u>	
4 CONVERSIÓN Expediente No: _____ De: _____ A: _____		5 DIVISIÓN Expediente No: <u>01.002.407</u> No. de Divisionales: <u>1</u>		6 FUSIÓN Expediente No: _____ Expediente No: _____	
7 Comprobante de pago No.: <u>07-46,924</u> Fecha: <u>12 de junio de 2007</u> <u>07-44,836</u> <u>4 de junio de 2007</u>					
8 Anexos ☒ Comprobante de pago de la tasa por \$ 482.000.00 ☒ Comprobante de pago por la reivindicación de prioridad. ☒ Poderes, si fuere el caso ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas. ☒ Copia de la Solicitud Divisional.					

9

Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : 

C.C. 438.019 de Usaquén T.P. 31.929

MSM

Esta es una solicitud de división de la materia contenida originalmente en la solicitud de patente No. 01.002.407. 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. 3641 notificado por fijación en lista del 22 de marzo de 2007. Por lo tanto pido que esta solicitud de división de materia sea tratada con el beneficio de la fecha 15 de enero de 2001.

De acuerdo con el artículo 36 de la Decisión 486, el solicitante aclara que la materia de la presente solicitud queda cubierta por la prioridad US. No. 60/176.720 del 14 de enero de 2000.

Nota: La copia básica original se encuentra en el expediente No. 01.002.407.

Documento de Traspaso, Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales registradas o pendientes de registro, licencias.

Assignment with Representation and Power-of-Attorney with notarial authentication and Apostille of granted or pending patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

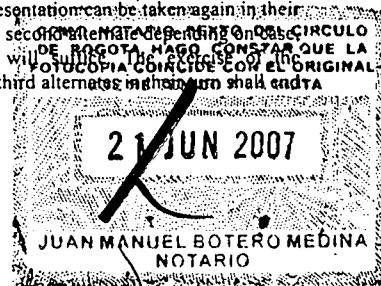
DOCUMENTO DE TRASPASO,
REPRESENTACION Y PODERASSIGNMENT WITH REPRESENTATION AND
POWER OF ATTORNEYYo, (nosotros), abajo firmado (s) ZENECA INC.domiciliado (s) en 1800 Concord Pike,
Wilmington, Delaware 19897, E.U.A.aquí llamado (s) CEDENTE(s), propietario(s) de la(s) marca
(s) en Colombiano sigue:
TROPHY, Reg. 122.558, clase 5;declara(n) por el presente instrumento que cede(n) la(s) dicha (s)
marcaa DOW AGROSCIENCES LLCsociedad organizada y existente bajo las leyes del Estado de
Delaware, Estados Unidos de Américadomiciliada en 9330 Zionsville Road,
Indianapolis, Indiana 46268, E.U.A.

(aquí llamada la CESIONARIA). Por el presente acto, la CESIONARIA acepta dicho traspaso y nombra a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª N° 72 35, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

I (we), the undersigned ZENECA INC.of 1800 Concord Pike,
Wilmington, Delaware 19897, U.S.A.hereinafter the ASSIGNOR(s) owner of the trademarkin Colombia as follows:
TROPHY, Reg. 122.558, class 5;declares by this document that assigns the mentioned
trademarkto DOW AGROSCIENCES LLCa corporation organized and existent under the laws of State of
Delaware, United States of Americaand domiciled in 9330 Zionsville Road,
Indianapolis, Indiana 46268, U.S.A.

(which in this document will be called the ASSIGNEE). The ASSIGNEE accepts the said assignment and in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª N° 72 35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate representative, and the mere fact of its exercise will constitute the exercise of the representation by the first, second or third alternate mentioned shall end at such time.

J. Colina
(Authorised Signatory)



Además, confiero (conferimos) poder a los abogados arriba nombrados; para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas de servicio, lemas comerciales, nombres comerciales, enseññas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa o judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

Dado y firmado hoy Nov. 27, 2001

en Indianapolis, Indiana 46268 U.S.A.

In addition, we grant a Power of Attorney in favor of the above named attorneys-at law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection of the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters may substitute this Power of Attorney, compromise, conciliate, admit facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Given and signed this 7/11/01

in Brockton

ZENECA INC.

Cedente

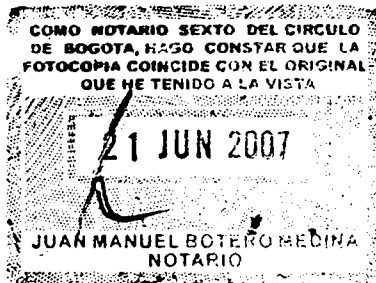
Assignor

DOW AGROSCIENCES LLC

Cesionario

Assignee

C. Joe Miller, Attorney-in-Fact



CERTIFICADO NOTARIAL (INDIVIDUO)

A los 7 días del mes de Noviembre
de 2001 ante mí, Notario Público o Funcionario Autorizado
de Diana Jane Collins
compareció(eron) personalmente _____

a quien(es) doy fe de conocer y me consta que es(son) la(s)
persona(s) firmante(s) del documento que precede, y quien(es)
tiene(n) capacidad legal para otorgarlo

Notario Público o Funcionario Autorizado --Notary Public or Attesting Official

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy 7 de Noviembre de 2001
Compareció(eron) ante mí
Diana Jane Collins
quien(es) conozco personalmente y que firma(n) este
documento en representación de la Sociedad/compañía
denominada ZENECA INC.

Certifico:

1. Que he visto los siguientes documentos: *
A. LOS DE CONSTITUCION PRESENTADOS CON
E. SECRETARIO DE ESTADO EL 22 ABRIL, 1971.

2. Que dichos documentos prueban lo siguiente:

2.1. Que ZENECA INC.

es una Sociedad/Compañía legalmente constituida y existente
de acuerdo con las leyes de 1 Estado de Delaware,
Estados Unidos de América

2.2. Que el domicilio de dicha Sociedad/Compañía es _____
1800 Concord Pike,
Wilmington, Delaware 19897, E.U.A.

Que el objeto u objetos para los cuales se otorga el presente
poder están comprendidos dentro del objeto social de la
mencionada Sociedad/Compañía.

Que el(los) Sr.(Sres.) Collins

está(n) autorizado(s) para otorgar el presente Poder.

Ciudad Blackwell

Estado Inglaterra

Hoy 7 Noviembre de 2001

Notario Público o Funcionario Autorizado --Notary Public or Attesting Official

* Los documentos deben identificarse con fecha y origen

© CAVELIER ABOGADOS
WPP0DE01-182 (MINUTA 12.1.2.6 USA)

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this 7th day of November
2001 before me, a Notary Public or Attesting Official of
DIANA JANE COLLINS
personally appeared _____

to me known, and known to me to be the person(s) who
executed that foregoing document, and who has(have) legal
capacity to execute it.

NOTARIAL CERTIFICATE (CORPORATION)

On this 7th day of Novemb 2001
appeared before me
DIANA JANE COLLINS
who(m) I know personally and who(m) signed this document as
representative(s) of the Corporation/Company named _____
ZENECA INC.

I certify:

1. That I have seen the following documents: *

Certificate of Incorporation which was
filed with the Delaware Secretary of State
on April 22, 1971

2. That the above documents duly prove the following:

2.1. That ZENECA INC.

is a Corporation/Company legally constituted and in existence
in accordance with the laws State of Delaware,
United States of America

2.2. That the domicile of said Corporation/Company is _____
1800 Concord Pike,
Wilmington, Delaware 19897, U.S.A.

2.3. That the purpose or purposes for which the present Power
of Attorney is granted are comprised within the corporation
purposes set forth in the charter of the mentioned
Corporation/Company.

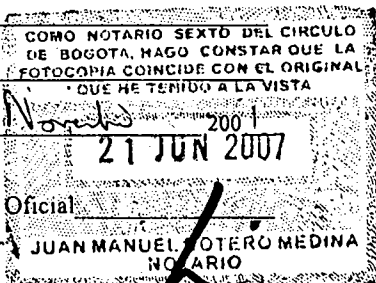
2.4. That Mr.(Messrs.) COLLINS

is(are) authorized to grant the present Power of Attorney.

City Blackwell

State England

This 7th day of November 2001



NOTARY PUBLIC
Blackwell
England

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country:
This public document

2. has been signed by

3. acting in the capacity of

4. bears the seal/stamp of

Certified

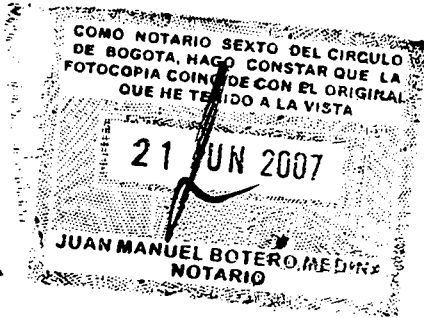
5. at6. the

7. by

8. No.

9. Seal/stamp10. Signature

.....



APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Country:
This public document
2. has been signed by
3. acting in the capacity of
4. bears the seal/stamp of

APOSTILLE

(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by A Brooker
a été signé par
3. Acting in the capacity of Notary Public
agissant en qualité de
4. Bears the seal/stamp of The Said Notary Public
est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres

6. the/le 12 November 2001

by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No G956004

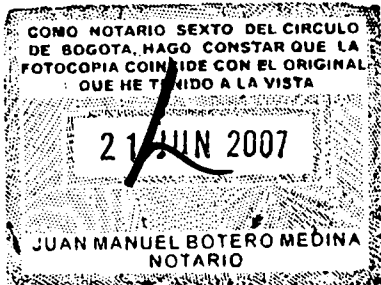
9. Stamp:
timbre:

10. Signature: J. Garbrah



J. Garbrah

For the Secretary of State / Pour le Secrétaire d'Etat



SECRETARY OF STATE
STATE OF INDIANA



Sue Anne Gilroy
Secretary of State

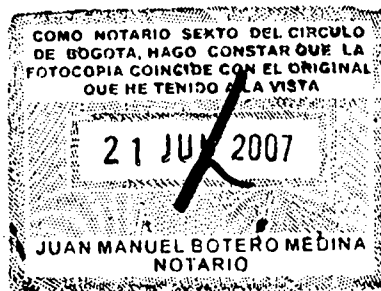
APOSTILLE

(Convention de la Haye du 5 Octobre 1961)

1. Country: United States of America
2. This public document has been signed by *Kathryn A. Broshous*
3. acting in the capacity of Circuit Court Clerk In & For *Marion County*
4. and bears the seal/stamp of Circuit Court Clerk In & For the State of Indiana

Certified

5. at Indianapolis, Indiana
6. the *Twenty-ninth Day of November, 2001*
7. by Secretary of State of Indiana
8. No. A2001- 10429



9. Seal/Stamp:



10. Signature:

Sue Anne Gilroy

Sue Anne Gilroy
Indiana Secretary of State

CERTIFICADO NOTARIAL (INDIVIDUO)

A los _____ días del mes de _____
de 200_____ ante mí, Notario Público o Funcionario Autorizado
de _____
compareció(eron) personalmente _____

a quien(es) doy fe de conocer y me consta que es(son) la(s)
persona(s) firmante(s) del documento que precede, y quien(es)
tiene(n) capacidad legal para otorgarlo

Notario Público o Funcionario Autorizado --Notary Public or Attesting Official_____

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy 27 de Noviembre de 2001
Compareció(eron) ante mí
C. Joe Miller

quien(es) conozco personalmente y que firma(n) este
documento en representación de la Sociedad/compañía
denominada DOW AGROSCIENCES LLC

Artículo:

1. Que he visto los siguientes documentos:*
- CERTIFICACION DE CONSTITUCION, 1 JULIO, 1997,
CERTIFICADO DE MODIFICACION, 1 OCTUBRE, 1997
RESOLUCION DE LA JUNTA, 23 OCTUBRE, 1991,
CONSENTIMIENTO ESCRITO DE LA JUNTA, 1 JULIO, 1997
2. Que dichos documentos prueban lo siguiente:

2.1. Que DOW AGROSCIENCES LLC

es una Sociedad/Compañía legalmente constituida y existente
de acuerdo con las leyes del Estado de Delaware,
Estados Unidos de América

2.2. Que el domicilio de dicha Sociedad/Compañía es _____
9330 Zionsville Road,
Indianapolis, Indiana 46268, E.U.A.

2.3. Que el objeto u objetos para los cuales se otorga el presente
están comprendidos dentro del objeto social de la
mencionada Sociedad/Compañía.

2.4. Que el(los) Sr.(Sres.) _____
está(n) autorizado(s) para otorgar el presente Poder.

Ciudad Indianapolis

Estado Indiana 46268 EEU

Hoy 27 Nov. de 2001

Notario Público o Funcionario Autorizado -- Notary Public or Attesting Official_____

* Los documentos deben identificarse con fecha y origen

© CAVELIER ABOGADOS
WPP0DE01-182 (MINUTA 12.1.2.6 USA)

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this _____ day of _____
200_____ before me, a Notary Public or Attesting Official of _____
personally appeared _____

to me known, and known to me to be the person(s) who
executed that foregoing document, and who has(have) legal
capacity to execute it.

NOTARIAL CERTIFICATE (CORPORATION)

On this 27 day of November 2001
appeared before me
C. Joe Miller

who(m) I know personally and who(m) signed this document as
representative(s) of the Corporation/Company named _____
DOW AGROSCIENCES LLC

I certify:

1. That I have seen the following documents:*
- Certificate of formation, dated July 1, 1997
Certificate of amendment, dated October 1, 1997
Board resolution, dated October 23, 1991
Board written consent, dated July 1, 1997
2. That the above documents duly prove the following:

2.1. That DOW AGROSCIENCES LLC

is a Corporation/Company legally constituted and in existence
in accordance with the laws of State of Delaware,
United States of America

2.2. That the domicile of said Corporation/Company is _____
9330 Zionsville Road,
Indianapolis, Indiana 46268, U.S.A.

2.3. That the purpose or purposes for which the present Power
of Attorney is granted are comprised within the
purposes set forth in the charter of the
Corporation/Company.

2.4. That Mr.(Messrs.) _____
is(are) authorized to grant the present Power of Attorney.

City Indianapolis

State Indiana 46268 U.S.A.

This 27 day of November 2001

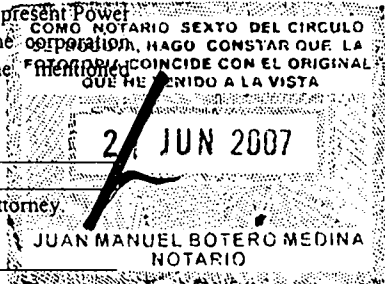
Notario Público o Funcionario Autorizado -- Notary Public or Attesting Official_____

* Documents must be identified with date and origin

Kathryn A. Broshous

KATHRYN A. BROSHOUS
NOTARY PUBLIC
STATE OF INDIANA

My Commission Expires: July 31, 2008
Residing in Marion County



APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Country:
This public document

2. has been signed by

3. acting in the capacity of

4. bears the seal/stamp of

Certified

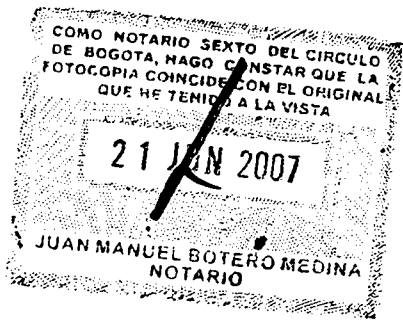
5. at 6. the

7. by

8. No.

9. Seal/stamp 10. Signature

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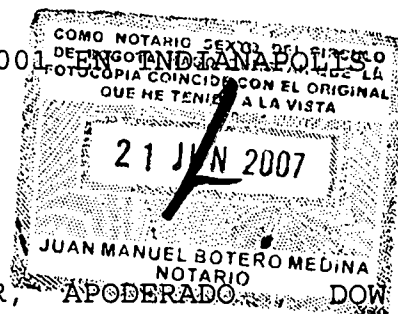
TRADUCCIÓN OFICIAL 135/2001 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL, REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL APROBADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 POR EL MINISTERIO DE JUSTICIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE LA REPÚBLICA DE COLOMBIA Y MEDIANTE EL CUAL ZENECA INC., EMPRESA DOMICILIADA EN 1800 CONCORD PIKE, WILMINGTON, DELAWARE 19897, ESTADOS UNIDOS DE AMÉRICA, AQUÍ LLAMADO EL CEDENTE, PROPIETARIO EN COLOMBIA DE LA MARCA SIGUIENTE : TROPHY, REG 122.558, CLASE 5 DECLARA POR EL PRESENTE QUE CEDE DICHA MARCA A DOW AGROSCIENCES LLC, EMPRESA CONSTITUIDA Y EXISTENTE BAJO LAS LEYES DEL ESTADO DE DELAWARE, ESTADOS UNIDOS DE AMERICA, DOMICILIADA EN 9330 ZIONSVILLE ROAD, INDIANAPOLIS, INDIANA 46268, ESTADOS UNIDOS DE AMERICA, AQUI LLAMADA LA CESIONARIA, QUE POR EL PRESENTE ACEPTA DICHO TRASPASO Y OTORGA PODER A EMILIO FERRERO, TPA 31929, GONZALO PERDOMO, TPA 831; LUZ CLEMENCIA DE PAEZ TPA 23555 Y A GERMÁN CAVELIER, TPA 832.

EXPEDIDO Y FIRMADO HOY 27 DE NOVIEMBRE DE 2001 EN INDIANAPOLIS, INDIANA 46268, ESTADOS UNIDOS DE AMERICA.

FIRMADO: CEDENTE, FIRMA ILEGIBLE, ZENECA INC.

FIRMADO: CESIONARIO, FIRMA: C. JOE MILLER, APODERADO,

AGROSCIENCES LLC.



CERTIFICADO NOTARIAL EN INGLÉS Y EN ESPAÑOL POR EL CUAL SE

CERTIFICA LA COMPARECENCIA DE DIANA JANE COLLINS, PARA FIRMAR

ESTE DOCUMENTO EN REPRESENTACIÓN DE ZENECA INC, ASÍ COMO LA EXISTENCIA LEGAL DE DICHA FIRMA Y SU DOMICILIO Y LA CAPACIDAD DE DIANA J COLLINS PARA OTORGAR ESTE PODER. BLACKWELL, INGLATERRA, 7 DE NOVIEMBRE DE 2001.

SELLO REALZADO FIJADO SOBRE PLÁSTICO DE COLOR ROJO EN FORMA DE ESTRELLA, EN CUYO CENTRO HAY UNA LEYENDA QUE REZA: NOTARIO PÚBLICO Y UN NOMBRE ILEGIBLE.

APOSTILLA:

(Convención de La Haya del 5 de octubre de 1961)

1. Estados Unidos de América

Este documento público

2. ha sido firmado por A. BROOKER

3. quien actúa en su calidad de NOTARIO PÚBLICO

4. lleva el sello de dicho NOTARIO PÚBLICO

CERTIFICADO

5. en LONDRES

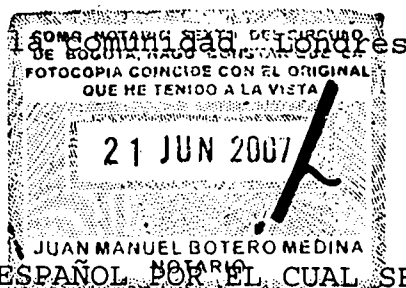
6. el 12 de noviembre de 2001

7. por el Secretario de estado principal de Su Majestad para Asuntos Extranjeros y de la Comunidad

8. Número G956004 ✓

9. Sello: Oficina extranjera y de 150ms Notario 848 de Londres

10. Firma: J. Garbrah.



CERTIFICADO NOTARIAL EN INGLÉS Y EN ESPAÑOL POR EL CUAL SE

CERTIFICA QUE C. JOE MILLER COMPARECIÓ ANTE MI Y FIRMÓ ESTE DOCUMENTO EN SU CALIDAD DE REPRESENTANTE DE LA EMPRESA LLAMADA DOW AGROSCIENCES LLC; QUE LA FIRMA DOW AGROSCIENCES LLC ES UNA EMPRESA LEGALMENTE CONSTITUIDA Y EXISTENTE DE ACUERDO CON LAS LEYES DEL ESTADO DE DELAWARE, ESTADOS UNIDOS Y SU DOMICILIO. ADEMÁS SE CERTIFICA QUE C. JOE MILLER ESTÁ AUTORIZADO PARA OTORGAR ESTE PODER. INDIANAPOLIS, INDIANA 46268, ESTADOS UNIDOS DE AMÉRICA, 27 DE NOVIEMBRE DE 2001.

Firmado: Kathryn A. Broshous, notario público, estado de Indiana.
 Mi cargo vence el 31 de julio de 2008. Residente en el condado
 Marion.

SECRETARIA DE ESTADO, ESTADO DE INDIANA

SUE ANNE GILROY, SECRETARIA DE ESTADO

THE STATE HOUSE, INDIANAPOLIS, INDIANA 46204, (317) 232-6531. FAX
 (317) 233-3283

APOSTILLA:

(Convención de La Haya del 5 de octubre de 1961)

1.Estados Unidos de América

Este documento público

2.ha sido firmado por KATHRYN A. BROSHOUS

3.quien actúa en su calidad de SECRETARIA DE LA CORTE DEL
 CIRCUITO PARA EL CONDADO DE MARION

4.lleva el sello de SECRETARIA DE LA CORTE DEL CIRCUITO PARA
 EL ESTADO DE INDIANA

CERTIFICADO

5. en Indianapolis, Indiana

6. el 29 de noviembre de 2001

7. por el Secretario de estado de Indiana

8. Número A2001-10429 ✓

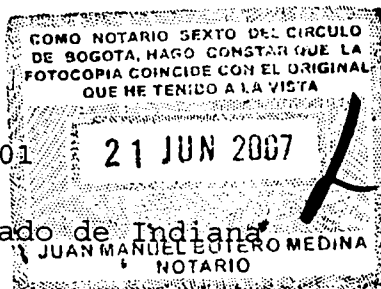
9. Sello realizado fijado sobre papel dorado brillante en forma
 de estrella en cuyo centro se lee: Sello del estado de
 Indiana, 1816 y donde hay también un paisaje rural

Firma: Sue Anne Gilroy, secretario de estado de Indiana

COLO-10975-704-001-8

WPCL002G ID 2934

Bogotá, 17 de diciembre de 2001



SECRETARIA DE LA CORTE DEL CIRCUITO PARA EL CONDADO DE MARION
 KATHRYN A. BROSHOUS
 21 JUN 2007

Eduardo Calado N.
 Eduardo Calado Noque
 'TRADUCTOR OFICIAL'
 INGLES - ESPAÑOL - INGLES
 Reg. 541, febrero de 1977

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA. HAGO CONSTAR QUE LOS ANTERIORES FIRMA(S) PUESTA(S) POR

Pablo Menendez Barajas

IDENTIFICADOS CON C.C. No.(s)

ES(SON) AUTENTICA(S)

SANTAFE DE BOGOTA, 18 DIC. 2001

NOTARIA S.A.

PABLO MENDEZ BARAJAS

Notario Sexto Encargado

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2001 DEC 18 A 11:42

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

11 JUN 2007

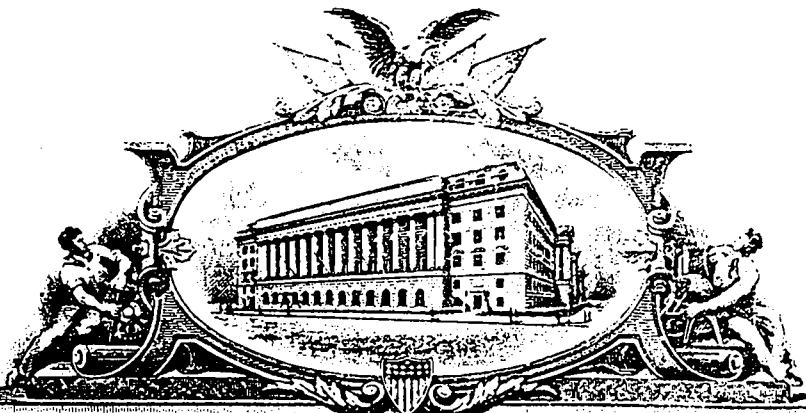
JUAN MANUEL BOTERO MEDINA NOTARIO

MINISTERIO DE RELACIONES EXTERIORES

Cedrosch

3450720

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

November 22, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/176,720

FILING DATE: *January 14, 2000*



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

L. Edelen

L. EDELEN
Certifying Officer

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U.S. PATENT AND TRADEMARK OFFICE

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(b)(2).

Docket Number		50,669 PROV1		Type a plus sign (+) inside this box----->	+
INVENTOR(s)/APPLICANT(s)					
Last Name	First Name	Middle Initial	Residence (City and either State or Foreign Country)		
Fields	Stephen	C.	1235 Ridge Road, Carmel, Indiana 46033		
Alexander	Anita	L.	829 N. Lesley, Indianapolis, Indiana 46219		
Balko	Terry	W.	1410 Bowman Drive, Greenfield, Indiana 46140		
Bielk	Leslie	A.	8521 Williams Cove Court, Indianapolis, Indiana 46260		
Buyse	Ann	M.	1212 Golfview Drive Apartment A, Carmel, Indiana 46032		
Keese	Renee	J.	985 Arrowwood Drive, Carmel, Indiana 46033		
Krumel	Karl	L.	614 Shorefront Circle, Midland, Michigan 48640		
Lo	William	C.	6938 Bluffgrove Circle, Indianapolis, Indiana 46278		
Lowe	Christian	T.	4813 North Broadway, Indianapolis, Indiana 46205		
TITLE OF THE INVENTION (280 characters max)					
4-AMINOPICOLINATES AND THEIR USE AS HERBICIDES					
CORRESPONDENCE ADDRESS					
Dow AgroSciences LLC 9330 Zionsville Road Indianapolis					
State: Indiana		Zip Code: 46268		Country USA	
ENCLOSED APPLICATION PARTS (check all that apply)					
☒ Specification		Number of Pages: 55		☐ Small Entity Statement	
☐ Drawing(s)		Number of Sheets: None		☐ Other (specify)	
METHOD OF PAYMENT (check one)					
A check or money order is enclosed to cover the Provisional Filing fees				PROVISIONAL FILING FEE	
☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: 04-1529				AMOUNT \$150.00	

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE

Craig E. Mixan

Date

January 14, 2000

TYPED OR PRINTED NAME

Craig E. Mixan

REGISTRATION NO: 32,709

TELEPHONE: 317/337-4812

☐ Additional inventors are being named on separately numbered sheets attached hereto

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PROVISIONAL APPLICATION FILING ONLY

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16

4-AMINOPICOLINATES AND THEIR USE AS HERBICIDES

Background of the Invention

5 This invention relates to certain novel 4-aminopicolines and their derivatives and to the use of these compounds as herbicides.

A number of picolinic acids and their pesticidal properties have been described in the art. For example, U.S. Patent 3,285,925 discloses 4-amino-3,5,6-trichloropicolinic acid derivatives and their use as plant growth control agents and herbicides. U.S. Patent 3,325,272 discloses 4-amino-3,5-dichloropicolinic acid derivatives and their use for the control of plant growth. U.S. Patent 3,317,549 discloses 3,6-dichloro-picolinic acid derivatives and their use as plant growth control agents. U.S. Patent 3,334,108 discloses chlorinated dithiopicolinic acid derivatives and their use as parasiticides. U.S. Patent 3,234,229 discloses 4-amino-polychloro-2-trichloromethylpyridines and their use as herbicides. In *Applied and Environmental Microbiology*, Vol. 59, No. 7, July 1993, pp. 2251-2256, 4-amino-3,6-dichloropicolinic acid is identified as a product of the anaerobic degradation of 4-amino-3,5,6-trichloropicolinic acid, the commercially available herbicide picloram.

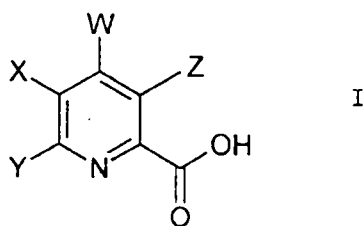
25 While picloram is recommended for the control of woody plants and broadleaf weeds in certain applications, its properties are not ideal. It would be highly desirable to discover related compounds that are more potent, more selective or of broader spectrum in their herbicidal activity and/or that have improved toxicological or environmental properties.

27

Summary of the Invention

It has now been found that certain 4-amino-
picolinic acids and their derivatives having selected
substituents in the 3-, 5-, and 6-positions are potent
5 herbicides with a broad spectrum of weed control and
excellent crop selectivity. The compounds further possess
excellent toxicological or environmental profiles.

The invention includes compounds of Formula I:



10 wherein

X represents H, halogen, C₁-C₆ alkoxy, C₁-C₆
alkylthio, aryloxy, cyano or trifluoromethyl;

Y represents halogen, C₁-C₆ alkoxy, C₁-C₆
15 alkylthio, aryloxy, cyano or trifluoromethyl;

Z represents halogen, C₁-C₆ alkoxy, C₁-C₆
alkylthio, aryloxy, cyano or trifluoromethyl;

W represents -NR₁R₂, -N=CR₃R₄ or -NHN=CR₃R₄

where

20 R₁ and R₂ independently represent H, C₁-C₆ alkyl,
C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl, heteroaryl, hydroxy, C₁-
C₆ alkoxy, amino, C₁-C₆ acyl, C₁-C₆ carboalkoxy, C₁-C₆
alkylcarbamyl, C₁-C₆ alkylsulfonyl, C₁-C₆ trialkylsilyl or
C₁-C₆ dialkyl phosphonyl or R₁ and R₂ taken together with N

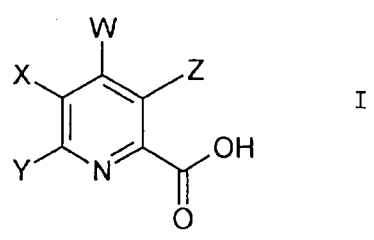
represent a 5- or 6-membered saturated or unsaturated ring which may contain additional O or N heteroatoms; and

R₃ and R₄ independently represent H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl or heteroaryl or R₃ and R₄ taken together with =C represent a 5- or 6-membered saturated ring; and

agriculturally acceptable derivatives of the carboxylic acid, with the proviso that when X represents H or Cl, then Y and Z are not both Cl.

10 Compounds of Formula I wherein X represents H or F, wherein Y represents F, Cl, or Br, wherein Z represents Cl and wherein R₁ and R₂ represent H or C₁-C₆ alkyl are independently preferred.

15 The invention includes herbicidal compositions comprising a herbicidally effective amount of a 4-amino-picolinate of Formula I:



wherein

20 X represents H, halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, cyano or trifluoromethyl;

Y represents halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, cyano or trifluoromethyl;

25 Z represents halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, cyano or trifluoromethyl;

W represents $-NR_1R_2$, $-N=CR_3R_4$ or $-NHN=CR_3R_4$

where

5 R₁ and R₂ independently represent H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl, heteroaryl, hydroxy, C₁-C₆ alkoxy, amino, C₁-C₆ acyl, C₁-C₆ carboalkoxy, C₁-C₆ alkylcarbamyl, C₁-C₆ alkylsulfonyl, C₁-C₆ trialkylsilyl or C₁-C₆ dialkyl phosphonyl or R₁ and R₂ taken together with N represent a 5- or 6-membered saturated or unsaturated ring which may contain additional O or N heteroatoms; and

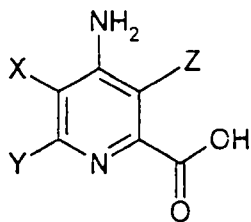
10 R₃ and R₄ independently represent H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl or heteroaryl or R₃ and R₄ taken together with =C represent a 5- or 6-membered saturated ring; and

15 agriculturally acceptable derivatives of the carboxylic acid, with the proviso that when X represents Cl, then Y and Z are not both Cl

in admixture with an agriculturally acceptable adjuvant or carrier. The invention also includes a method of use of the compounds and compositions of the present invention to
20 kill or control undesirable vegetation by application of an herbicidal amount of the compound to the vegetation or to the locus of the vegetation as well as to the soil prior to emergence of the vegetation. The use of the compounds to kill or control woody plants and broadleaf weeds in grass
25 crops is a preferred utility and post-emergent application of the compounds to the undesirable vegetation is a preferred method of application.

Detailed Description of the Invention

30 The herbicidal compounds of the present invention are derivatives of 4-aminopicolinic acids:



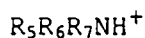
These compounds are characterized by possessing halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, cyano or trifluoromethyl substituents in the 3-position with
 5 chlorine being preferred; by possessing hydrogen, halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, cyano or trifluoromethyl substituents in the 5-position with hydrogen being preferred; and by possessing halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, cyano or trifluoromethyl
 10 substituents in the 6-position with fluorine, chlorine or bromine being preferred.

The amino group at the 4-position can be unsubstituted or substituted with one or more C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl, heteroaryl, hydroxy, C₁-
 15 C₆ alkoxy or amino substituents. The amino group can be further derivatized as an amide, a carbamate, a urea, a sulfonamide, a silylamine, a phosphoramidate, an imine or a hydrazone. Such derivatives are capable of breaking down into the amine. An unsubstituted amino group or one
 20 substituted with one or more alkyl substituents is preferred.

The carboxylic acids of Formula I are believed to be the compounds that actually kill or control undesirable vegetation and are typically preferred. Analogs of these
 25 compounds in which the acid group of the picolinic acid is derivatized to form a related substituent that can be transformed within plants or the environment to a acid group possess essentially the same herbicidal effect and are within the scope of the invention. Therefore, an
 30 "agriculturally acceptable derivative", when used to describe the carboxylic acid functionality at the 2-

position, is defined as any salt, ester, amide or any other acid derivative well known in the art which (a) does not substantially affect the herbicidal activity of the active ingredient, i.e., the 4-aminopicolinic acid, and (b) is or
 5 can be hydrolyzed in plants or soil to the picolinic acid of Formula I that, depending upon the pH, is in the dissociated or the undissociated form.

Suitable salts include those derived from alkali or alkaline earth metals and those derived from ammonia and
 10 amines. Preferred cations include sodium, potassium, magnesium, and aminium cations of the formula:



wherein R_5 , R_6 , and R_7 each, independently represents hydrogen or C_1 - C_{12} alkyl, C_3 - C_{12} alkenyl or C_3 - C_{12} alkynyl,
 15 each of which is optionally substituted by one or more hydroxy, C_1 - C_4 alkoxy, C_1 - C_4 alkylthio or phenyl groups, provided that R_5 , R_6 , and R_7 are sterically compatible. Additionally, any two of R_5 , R_6 , and R_7 together may represent an aliphatic difunctional moiety containing 1 to
 20 12 carbon atoms and up to two oxygen or sulfur atoms. Salts of the compounds of Formula I can be prepared by treatment of compounds of Formula I with a metal hydroxide, such as sodium hydroxide, or an amine, such as ammonia, trimethylamine, diethanolamine, 2-methylthiopropylamine,
 25 bisallylamine, 2-butoxyethylamine, morpholine, cyclo-dodecylamine, or benzylamine. Amine salts are often preferred forms of the compounds of Formula I because they are water-soluble and lend themselves to the preparation of desirable aqueous based herbicidal compositions.

30 Suitable esters include those derived from C_1 - C_{12} alkyl, C_3 - C_{12} alkenyl or C_3 - C_{12} alkynyl alcohols, such as methanol, iso-propanol, butanol, 2-ethylhexanol, butoxyethanol, methoxypropanol, allyl alcohol, propargyl alcohol or cyclohexanol. Esters can be prepared by
 35 reacting the corresponding acid chloride of a picolinic

acid of Formula I with an appropriate alcohol or by reacting the corresponding picolinic acid of Formula I with an appropriate alcohol in the presence of an acid catalyst. Suitable amides include those derived from ammonia or from

5 C₁-C₁₂ alkyl, C₃-C₁₂ alkenyl or C₃-C₁₂ alkynyl mono- or di-substituted amines, such as but not limited to trimethylamine, diethanolamine, 2-methylthiopropylamine, bisallylamine, 2-butoxyethylamine, morpholine, cyclododecylamine, or benzylamine. Amides can be prepared by reacting the

10 corresponding picolinic acid chloride of Formula I with ammonia or an appropriate amine.

The terms "alkyl", "alkenyl" and "alkynyl", as well as derivative terms such as "alkoxy", "acyl", "alkylthio" and "alkylsulfonyl", as used herein, include

15 within their scope straight chain, branched chain and cyclic moieties. Unless specifically stated otherwise, each may be unsubstituted or substituted with one or more substituents selected from but not limited to halogen, hydroxy, alkoxy, alkylthio, C₁-C₆ acyl, formyl, cyano,

20 aryloxy or aryl, provided that the substituents are sterically compatible and the rules of chemical bonding and strain energy are satisfied. The terms "alkenyl" and "alkynyl" are intended to include one or more unsaturated bonds.

25 The term "aryl" refers to a phenyl or naphthyl group. The term "heteroaryl" refers to a 5- or 6-membered aromatic ring containing one or more heteroatoms, viz., N, O or S; these heteroaromatic rings may be fused to other aromatic systems. The aryl or heteroaryl substituents may

30 be unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, cyano, aryloxy, formyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, halogenated C₁-C₆ alkyl, halogenated C₁-C₆ alkoxy, C₁-C₆ acyl, C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl, C₁-C₆

35 alkylsulfonyl, aryl, C₁-C₆ OC(O)alkyl, C₁-C₆ NHC(O)alkyl, C(O)OH, C₁-C₆ C(O)Oalkyl, C(O)NH₂, C₁-C₆ C(O)NHalkyl, or C₁-C₆

C(O)N(alkyl)₂, provided that the substituents are sterically compatible and the rules of chemical bonding and strain energy are satisfied.

Unless specifically limited otherwise, the term
5 halogen includes fluorine, chlorine, bromine, and iodine.

The compounds of Formula I can be made using well-known chemical procedures. The required starting materials are commercially available or readily synthesized utilizing standard procedures.

10 4-N- amide, carbamate, urea, sulfonamide, silylamine and phosphoramidate amino derivatives can be prepared by the reaction of the free amino compound with, for example, a suitable acid halide, chloroformate, carbamyl chloride, sulfonyl chloride, silyl chloride or
15 chlorophosphate. The imine or hydrazone can be prepared by reaction of the free amine or hydrazine with a suitable aldehyde or ketone.

6-Bromo analogs can be prepared by the reduction of several key intermediates, e.g., the corresponding 6-
20 bromo-4-azido, 6-bromo-4-nitro, and 6-bromo-4-nitro pyridine N-oxide analogs. These intermediates, in turn, can be prepared either by nucleophilic displacement of 6-bromo-4-halo analogs with NaN₃ or by electrophilic nitration of the corresponding 6-bromopyridine-N-oxides.
25 Alternatively, such analogs can be prepared by direct amination of the corresponding 4,6-dibromo analogs.

6-Fluoro analogs can be prepared by direct amination of the corresponding 4,6-difluoro analog.

3- and 5-Alkoxy and aryloxy analogs can be
30 prepared by reduction of the corresponding 4-azido derivatives, which in turn can be prepared by nucleophilic displacement of the corresponding 4-bromopyridines with

NaN₃. The required 3- and 5-alkoxy-4-bromopyridines can be prepared according to literature procedures.

6-Alkoxy, alkylthio and aryloxy analogs can be prepared by nucleophilic displacement with alkoxide or thioalkoxide on the appropriate 6-halopyridine.

3- and 5-Alkylthio analogs can be prepared by lithiation of the appropriate chloropyridines at low temperature and sequential treatment with alkyl disulfides and carbon dioxide. Reaction of the resulting picolinic acids with ammonium hydroxide gave the desired products.

6-Cyano analogs can be prepared by amination of the appropriate 4-halo-6-cyanopicolinate. 4-Halo-6-cyanopicolinate can be prepared by action of TMSCN on the appropriate pyridine N-oxide, which can be prepared by hydrogen peroxide mediated oxidation of the corresponding pyridine.

3- and 5-Cyano analogs can be prepared by action of KCN on the appropriate fluoropyridine at high temperature.

6-Trifluoromethyl analogs can be prepared by amination of readily available methyl trifluoromethylpicolinate (oxidative halogenation of the 4-position followed by displacement with ammonia or an amine equivalent) followed by chlorination of the 3- and 5-positions.

3- and 5-Trifluoromethyl analogs can be prepared by standard manipulations known to those skilled in the art starting from the known compounds 2-fluoro-3-chloro-5-trifluoromethylpyridine and 2,5-dichloro-3-trifluoromethylpyridine.

25

Substituted 4-amino analogs can be prepared by reacting the corresponding 4-halopyridine-2-carboxylate with the substituted amine.

5 The compounds of Formula I, obtained by any of these processes, can be recovered by conventional means. Typically, the reaction mixture is acidified with an aqueous acid, such as hydrochloric acid, and extracted with an organic solvent, such as ethyl acetate or dichloro-
10 methane. The organic solvent and other volatiles can be removed by distillation or evaporation to obtain the desired compound of Formula I, which can be purified by standard procedures, such as by recrystallization or chromatography.

15 The compounds of Formula I have been found to be useful pre-emergence and post-emergence herbicides. They can be employed at non-selective (higher) rates of application to control a broad spectrum of the vegetation in an area or at lower rates of application for the selective control of undesirable vegetation. Areas of
20 application include pasture and rangelands, roadsides and rights of ways, and crops such as corn, rice and cereals. It is usually preferred to employ the compounds post-emergence. It is further usually preferred to use the compounds to control a wide spectrum of broadleaf weeds,
25 including Dock species (*Rumex* spp), Canada thistle (*Cirsium arvense*), pigweed species (*Amaranthus* spp.), Senna species (*Cassia* spp.), spurge species (*Euphorbia* spp), ragweed species (*Ambrosia* spp.), Sida species (*Sida* spp.), field bindweed (*Convolvulus arvensis*), and knapweed
30 species(*Centaurea* spp.), among others. Use of the compounds to control undesirable vegetation in grassy areas is especially indicated. While each of the 4-aminopicolinate compounds encompassed by Formula I is
35 within the scope of the invention, the degree of herbicidal activity, the crop selectivity, and the spectrum of weed control obtained varies depending upon the substituents

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present. An appropriate compound for any specific herb-
icidal utility can be identified by using the information
presented herein and routine testing.

5 The term herbicide is used herein to mean an
active ingredient that kills, controls or otherwise
adversely modifies the growth of plants. An herbicidally
effective or vegetation controlling amount is an amount of
active ingredient which causes an adversely modifying
effect and includes deviations from natural development,
10 killing, regulation, desiccation, retardation, and the
like. The terms plants and vegetation include germinant
seeds, emerging seedlings and established vegetation.

Herbicidal activity is exhibited by the compounds
of the present invention when they are applied directly to
15 the plant or to the locus of the plant at any stage of
growth or before planting or emergence. The effect
observed depends upon the plant species to be controlled,
the stage of growth of the plant, the application
parameters of dilution and spray drop size, the particle
20 size of solid components, the environmental conditions at
the time of use, the specific compound employed, the
specific adjuvants and carriers employed, the soil type,
and the like, as well as the amount of chemical applied.
These and other factors can be adjusted as is known in the
25 art to promote non-selective or selective herbicidal
action. Generally, it is preferred to apply the compounds
of Formula I postemergence to relatively immature
undesirable vegetation to achieve the maximum control of
weeds.

30 Application rates of about 1 to about 500 g/Ha
are generally employed in postemergence operations; for
preemergence applications, rates of about 10 to about 1000
g/Ha are generally employed. The higher rates designated
generally give non-selective control of a broad variety of
35 undesirable vegetation. The lower rates typically give

selective control and can be employed in the locus of crops.

The herbicidal compounds of the present invention are often best applied in conjunction with one or more
5 other herbicides to obtain control of a wider variety of undesirable vegetation. When used in conjunction with other herbicides, the presently claimed compounds can be formulated with the other herbicide or herbicides, tank
10 mixed with the other herbicide or herbicides, or applied sequentially with the other herbicide or herbicides. Some of the herbicides that can be employed in conjunction with the compounds of the present invention include sulfonamides such as metosulam, flumetsulam, cloransulam-methyl, diclosulam, and N-2,6-dichlorophenyl-5-ethoxy-7-fluoro-
15 [1,2,4]triazolo[1,5-c]pyrimidine-2-sulfonamide, sulfonylureas such as chlorimuron, nicosulfuron and metsulfuron, imidazolinones such as imazaquin, imazapic, imazethapyr and imazamox, phenoxyalkanoic acids such as 2,4-D and MCPA, pyridinyloxyacetic acids such as triclopyr
20 and fluroxypyr, carboxylic acids such as clopyralid and dicamba, dinitroanilines such as trifluralin and pendimethalin, chloroacetanilides such as alachlor, acetochlor and metolachlor and other common herbicides including acifluorfen, bentazon, clomazone, fumiclorac,
25 fluometuron, fomesafen, lactofen, linuron, isoproturon, and metribuzin. They can, further, be used in conjunction with glyphosate and glufosinate on glyphosate-tolerant or glufosinate-tolerant crops. It is generally preferred to use the compounds of the invention in combination with
30 herbicides that are selective for the crop being treated and which complement the spectrum of weeds controlled by these compounds at the application rate employed. It is further generally preferred to apply the compounds of the invention and other complementary herbicides at the same
35 time, either as a combination formulation or as a tank mix.

The compounds of the present invention can generally be employed in combination with known herbicide safeners, such as cloquintocet, furilazole, dichlormid, benoxacor, mefenpyr-ethyl, fenclorazole-ethyl, flurazole, and fluxofenim, to enhance their selectivity. They can additionally be employed to control undesirable vegetation in many crops that have been made tolerant to or resistant to them or to other herbicides by genetic manipulation or by mutation and selection. For example, corn, wheat, rice, soybean, sugarbeet, cotton, canola, and other crops that have been made tolerant or resistant to compounds that are acetolactate synthase inhibitors in sensitive plants can be treated. Many glyphosate and glufosinate tolerant crops can be treated as well, alone or in combination with these herbicides. Some crops (e.g. cotton) have been made tolerant to auxinic herbicides such as 2,4-dichlorophenoxyacetic acid. These herbicides may be used to treat such resistant crops or other auxin tolerant crops.

While it is possible to utilize the 4-aminopicolinate compounds of Formula I directly as herbicides, it is preferable to use them in mixtures containing a herbicidally effective amount of the compound along with at least one agriculturally acceptable adjuvant or carrier. Suitable adjuvants or carriers should not be phytotoxic to valuable crops, particularly at the concentrations employed in applying the compositions for selective weed control in the presence of crops, and should not react chemically with the compounds of Formula I or other composition ingredients. Such mixtures can be designed for application directly to weeds or their locus or can be concentrates or formulations that are normally diluted with additional carriers and adjuvants before application. They can be solids, such as, for example, dusts, granules, water dispersible granules, or wettable powders, or liquids, such as, for example, emulsifiable concentrates, solutions, emulsions or suspensions.

Suitable agricultural adjuvants and carriers that are useful in preparing the herbicidal mixtures of the invention are well known to those skilled in the art.

Liquid carriers that can be employed include
5 water, toluene, xylene, petroleum naphtha, crop oil, acetone, methyl ethyl ketone, cyclohexanone, trichloroethylene, perchloroethylene, ethyl acetate, amyl acetate, butyl acetate, propylene glycol monomethyl ether and diethylene glycol monomethyl ether, methanol, ethanol,
10 isopropanol, amyl alcohol, ethylene glycol, propylene glycol, glycerine, and the like. Water is generally the carrier of choice for the dilution of concentrates.

Suitable solid carriers include talc, pyrophyllite clay, silica, attapulgius clay, kieselguhr, chalk,
15 diatomaceous earth, lime, calcium carbonate, bentonite clay, Fuller's earth, cotton seed hulls, wheat flour, soybean flour, pumice, wood flour, walnut shell flour, lignin, and the like.

It is usually desirable to incorporate one or
20 more surface-active agents into the compositions of the present invention. Such surface-active agents are advantageously employed in both solid and liquid compositions, especially those designed to be diluted with carrier before application. The surface-active agents can
25 be anionic, cationic or nonionic in character and can be employed as emulsifying agents, wetting agents, suspending agents, or for other purposes. Typical surface-active agents include salts of alkyl sulfates, such as diethanolammonium lauryl sulfate; alkylarylsulfonate salts, such as
30 calcium dodecylbenzenesulfonate; alkylphenol-alkylene oxide addition products, such as nonylphenol-C₁₆ ethoxylate; alcohol-alkylene oxide addition products, such as tridecyl alcohol-C₁₆ ethoxylate; soaps, such as sodium stearate; alkyl naphthalenesulfonate salts, such as sodium dibutyl-
35 naphthalenesulfonate; dialkyl esters of sulfosuccinate

salts, such as sodium di(2-ethylhexyl) sulfosuccinate; sorbitol esters, such as sorbitol oleate; quaternary amines, such as lauryl trimethylammonium chloride; polyethylene glycol esters of fatty acids, such as polyethylene glycol stearate; block copolymers of ethylene oxide and propylene oxide; and salts of mono and dialkyl phosphate esters.

Other adjuvants commonly used in agricultural compositions include compatibilizing agents, antifoam agents, sequestering agents, neutralizing agents and buffers, corrosion inhibitors, dyes, odorants, spreading agents, penetration aids, sticking agents, dispersing agents, thickening agents, freezing point depressants, antimicrobial agents, and the like. The compositions may also contain other compatible components, for example, other herbicides, plant growth regulants, fungicides, insecticides, and the like and can be formulated with liquid fertilizers or solid, particulate fertilizer carriers such as ammonium nitrate, urea and the like.

The concentration of the active ingredients in the herbicidal compositions of this invention is generally from about 0.001 to about 98 percent by weight. Concentrations from about 0.01 to about 90 percent by weight are often employed. In compositions designed to be employed as concentrates, the active ingredient is generally present in a concentration from about 5 to about 98 weight percent, preferably about 10 to about 90 weight percent. Such compositions are typically diluted with an inert carrier, such as water, before application. The diluted compositions usually applied to weeds or the locus of weeds generally contain about 0.0001 to about 1 weight percent active ingredient and preferably contain about 0.001 to about 0.05 weight percent.

The present compositions can be applied to weeds or their locus by the use of conventional ground or aerial

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dusters, sprayers, and granule applicators, by addition to irrigation water, and by other conventional means known to those skilled in the art.

The following Examples are presented to
5 illustrate the various aspects of this invention and should not be construed as limitations to the claims.

Examples

1. Preparation of 4-amino-3,6-dichloropyridine-2-carboxylic acid (Compound 1)

10 In a 3-liter (L) beaker was added 2000 grams (g) of hot water, 115.1 g of 50 percent by weight NaOH, and 200 g of wet 4-amino-3,5,6-trichloropyridine-2-carboxylic acid (79.4 percent). The solution was stirred for 30 minutes (min), filtered through a paper filter, and transferred to
15 a 5-L feed/recirculation tank. This solution weighed 2315 g and contained 6.8 percent 4-amino-3,5,6-trichloropyridine-2-carboxylic acid. This feed was recirculated at a rate of about 9.46 L/min and a temperature of 30 °C through an undivided electrochemical
20 cell having a Hastelloy C anode and an expanded silver mesh screen cathode. After normal anodization at +0.7 volt (v), the polarity of the cell was reversed and the electrolysis was started. The cathode working potential was controlled at -1.1 to -1.4 v relative to an Ag/AgCl (3.0 M Cl⁻)
25 reference electrode. While recirculating the feed, a solution of 50 percent NaOH is slowly pumped into the recirculation tank to maintain the NaOH concentration at a 1.5 to 2.0 percent excess. After about 15 hours (h), the electrolysis was terminated and the cell effluent was
30 filtered through a paper filter. The solution was neutralized with concentrated HCl and concentrated to about 750 g of crude concentrate. The concentrate was warmed to 85 °C with stirring and the pH was adjusted to less than 1 with concentrated HCl over 30 min. The resulting slurry
35 was cooled to ambient temperature and filtered. The filter

cake was washed with 3x200 milliliter (mL) portions of water and dried under vacuum at 80 °C. The dried product, 118.1 g assayed at 90.6 percent desired product; gas chromatography (GC) indicated about 4 percent 4-amino-3,5,6-trichloropyridine-2-carboxylic acid remaining as an impurity. A purified sample of 4-amino-3,6-dichloropyridine-2-carboxylic acid had a melting point (mp) of 185-187 °C (dec.); ¹H NMR (DMSO-d₆): δ 13.9 (br, 1H), 7.0 (br m, 2H), 6.8 (s, 1H); ¹³C NMR (DMSO-d₆): δ 165.4 (1C), 153.4 (1C), 149.5 (1C), 147.7 (1C), 111.0 (1C), 108.1 (1C).

2. Preparation of 2-ethylhexyl 4-amino-3,6-dichloropyridine-2-carboxylate (Compound 2)

To a solution of 2-ethylhexanol (10 mL) and sulfuric acid (1 mL) was added 4-amino-3,6-dichloropyridine-2-carboxylic acid (0.0097 mol, 2.0 g). After heating the reaction to reflux overnight, the reaction mixture was cooled, poured into water (75 mL), and extracted with ethyl acetate (75 mL). The organic phase was washed with sodium bicarbonate (75 mL), dried (Na₂SO₄), and concentrated. The resulting solid was recrystallized out of dichloromethane and hexane and filtered to give 2-ethylhexyl 4-amino-3,6-dichloropyridine-2-carboxylate (0.0074 mol, 2.36 g) as a crystalline solid (mp 55 °C). ¹H NMR (CDCl₃): δ 0.9 (7 H, m), 1.3 (7 H, m), 1.7 (1 H, m), 4.3 (2 H, d), 5.1 (2 H, bs), 6.7 (1 H, s).

The following esters of 4-amino-3,5,6-trichloropyridine-2-carboxylic acid were prepared according to the procedure of Example 2:

30 methyl 4-amino-3,6-dichloropyridine-2-carboxylate (Compound 3); mp 134-135 °C.

ethyl 4-amino-3,6-dichloropyridine-2-carboxylate (Compound 4); mp 98-99 °C.

n-propyl 4-amino-3,6-dichloropyridine-2-carboxylate (Compound 5); mp 94-95 °C.

i-propyl 4-amino-3,6-dichloropyridine-2-carboxylate (Compound 6); mp 114-115 °C.

5 *n*-butyl 4-amino-3,6-dichloropyridine-2-carboxylate (Compound 7); mp 78-79 °C.

n-pentyl 4-amino-3,6-dichloropyridine-2-carboxylate (Compound 8); mp 71-73 °C.

10 *n*-hexyl 4-amino-3,6-dichloropyridine-2-carboxylate (Compound 9); mp 65-66 °C.

phenyl 4-amino-3,6-dichloropyridine-2-carboxylate (Compound 10);

3. Preparation of *N*-ethyl 4-amino-3,6-dichloropyridine-2-carboxamide (Compound 11)

15 A solution of ethylamine 2.0 M in methanol (34 mL) and methyl 4-amino-3,6-dichloropyridine-2-carboxylate (0.00678 mol, 1.5 g) was stirred and heated to reflux for 60 h. The reaction mixture was cooled, concentrated, and dissolved in ethyl acetate. The resulting solution was
20 washed with water (50 mL) and brine (50 mL), dried (Na₂SO₄), and concentrated. The resulting solid was dissolved in methanol and purified by reverse phase HPLC to give ethyl 4-amino-3,6-dichloropyridine-2-carboxamide (0.0035 mol, 0.820 g); mp 136-137 °C.

25 4. Preparation of methyl *N*-acetyl 4-amino-3,6-dichloropyridine-2-carboxylate (Compound 12) and *N,N*-diacetyl 4-amino-3,6-dichloropyridine-2-carboxylate (Compound 13)

30 A solution of acetic anhydride (75 mL) and methyl 4-amino-3,6-dichloropyridine-2-carboxylate (0.00904 mol, 2.0 g) was stirred and heated to reflux overnight. The

solution was cooled, concentrated, taken up in ethyl acetate (100 mL), and washed with water (100 mL). The organic phase was washed with saturated sodium bicarbonate (100 mL), dried (Na₂SO₄), and concentrated. The solution was purified by chromatography on silica gel. The front running spot was isolated and gave a yellow oil identified as the diacylated 4-amide (0.0023 mol, 0.700 g). ¹H NMR 2.2 (6 H, s), 3.9 (3 H, s), 7.3 (1 H, s). The second spot gave a yellow solid identified as the monoacylated 4-amide (0.0035 mol, 0.920 g); mp 102-103 °C.

5. Preparation of 4-amino-6-bromo-3-chloropyridine-2-carboxylic acid (Compound 14)

15 A. Methyl 6-bromo-3-chloro-pyridine-2-carboxylate, N-oxide

To a solution of methyl 6-bromo-3-chloro-pyridine-2-carboxylate (0.13 mol, 32.1 g) in trifluoroacetic acid (75 mL) and trifluoroacetic anhydride (40 mL) was cautiously added 50% hydrogen peroxide (0.17 mol, 13 g). The reaction exothermed to reflux. After stirring for 30 min, the solution was poured into a mixture of ice and 10 percent sodium bisulfite (150 mL). The resulting solid was collected and dried *in vacuo* to give a white solid (0.08 mol, 21.4 g). ¹H NMR (CDCl₃): δ 4.1 (3H, s), 7.3 (1H, d), 7.7 (1H, d).

B. Methyl 6-bromo-3-chloro-4-nitropyridine-2-carboxylate, N-oxide

To a solution of fuming nitric acid (10 mL) and fuming sulfuric acid (10 mL) was added methyl 6-bromo-3-chloro-pyridine-2-carboxylate, N-oxide and the reaction was heated to 70° C in an oil bath for 4 h. The mixture was poured over ice water (100 mL) and extracted with ethyl acetate (3 x 75 mL) and the combined extracts were backwashed with brine, dried (Na₂SO₄) and concentrated. The

dark oil was chromatographed over silica in 4:1 EtOAc/hexane to give methyl 6-bromo-3-chloro-4-nitropyridine-2-carboxylate, N-oxide (0.007 mol, 2.2 g). ^1H NMR (CDCl_3): δ 4.1 (3H, s), 8.4 (1H, s).

5 C. Methyl 4-amino-6-bromo-3-chloropyridine-2-carboxylate (Compound 15)

To a solution of titanium tetrachloride (0.015 mol, 2.8 g) in tetrahydrofuran (50 mL) was added lithium aluminum hydride (0.0175 mol, 0.7 g). The black slurry was
10 stirred 15 minutes before adding methyl 6-bromo-3-chloro-4-nitropyridine-2-carboxylate, N-oxide (0.007 mol, 2.3 g) in THF (25 mL). The solution was stirred one hour before pouring into 1:1 $\text{H}_2\text{O}/\text{NH}_4\text{OH}$ and filtering. The filtrate was extracted with EtOAc (2 x 75 mL). The organic phase was
15 dried (Na_2SO_4), and concentrated. The red solid was chromatographed over silica in 4:1 EtOAc/hexane to give methyl 4-amino-6-bromo-3-chloropyridine-2-carboxylate (0.003 mol, 0.8 g); mp 194-5 $^\circ\text{C}$. ^1H NMR(CDCl_3): δ 3.95 (3H, s), 5.3 (2H, bs), 6.9 (1H, s).

20 D. 4-amino-6-bromo-3-chloropyridine-2-carboxylic acid (Compound 14)

To methyl 4-amino-6-bromo-3-chloropyridine-2-carboxylate (200mg; 0.8 mmol) in 10 mL of methanol was added excess 2N NaOH (10 mL). The mixture was stirred for
25 1 h at ambient temperature and then evaporated to dryness *in vacuo*. The residue was dissolved in water and diethyl ether. After separation of the phases, the aqueous layer was acidified with 1N HCl to a pH=2. The aqueous layer was evaporated to dryness and the residue was dissolved in 50
30 mL of methanol and filtered. The filtrate was evaporated under reduced pressure and the residue was triturated with 5 percent diethyl ether in petroleum ether to give 70 mg of 4-amino-6-bromo-3-chloropyridine-2-carboxylic acid, mp 182-183 $^\circ\text{C}$.

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6. Preparation of Methyl 4-amino-3-chloro-6-fluoropyridine-2-carboxylate (Compound 16)

A. Methyl 3-chloro-4,6-difluoropyridine-2-carboxylate

To a solution of methyl 3,4,6-trichloropyridine-2-carboxylate (0.010 mol, 2.4 g) in DMSO (10 mL) was added cesium fluoride (0.038 mol, 3.8 g) and the suspension was heated for 2 h at 100 °C. The reaction mixture was dissolved in dilute HCl and extracted with ethyl acetate (EtOAc). The organic layer was treated with (trimethylsilyl)diazomethane (TMSCHN₂) to re-esterify any hydrolyzed ester. The mixture was concentrated and the resultant residue was chromatographed over silica with 10 percent EtOAc/hexane to give methyl 3-chloro-4,6-difluoropyridine-2-carboxylate (0.0072 mol, 1.5 g). ¹H NMR(CDCl₃): δ 4.00 (3H, s), 6.95-6.90 (1H, m). ¹⁹F NMR {¹H}: δ -65.0 (d, J = 17 Hz), 95.8 (d, J = 17 Hz).

B. Methyl 4-amino-3-chloro-6-fluoropyridine-2-carboxylate (Compound 16)

Sodium azide (0.0086 mol, 0.60 g) was added to a solution of methyl 3-chloro-4,6-difluoropyridine-2-carboxylate (0.0072 mol, 1.5 g) in 15 mL dimethyl formamide (DMF). The solution was stirred 10 min at ambient temperature before pouring into 350 mL water and extracting the aqueous mixture with EtOAc (2 x 100 mL). The organic phase was dried (Na₂SO₄) and then treated with excess NaBH₄ for 30 min. The excess NaBH₄ was quenched with aqueous EtOH and the mixture was diluted with water (200mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 200 mL). The combined organic layers were dried (Na₂SO₄) and concentrated to an off-white powder which was purified by reversed-phase HPLC to give methyl 4-amino-3-chloro-6-fluoropyridine-2-carboxylate (0.0059 mol, 1.2 g). ¹H NMR(CDCl₃): δ 3.95 (3H, s), 5.2-5.1 (2H, bs), 6.36 (1H, s). ¹⁹F NMR {¹H}: δ -72.7.

7. Preparation of Methyl 4-amino-3,5,6-tribromopyridine-2-carboxylate (Compound 17)

Methyl 4-amino-3,5,6-tribromopyridine-2-carboxylate was prepared by amination of methyl 3,4,5,6-tetrabromopyridine-2-carboxylate following the procedure of Example 6B. ¹H NMR(CDCl₃): δ 3.95 (3H, s), 6.9-6.8 (2H, bs).

8. Preparation of 4-Amino-3,6-dichloro-5-fluoropyridine-2-carboxylic acid (Compound 18)

10 To a solution of 4-amino-3,6-dichloropyridine-2-carboxylate (1.5 g, 6.8 mmol) in 20 mL of dry acetonitrile was added 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis (tetrafluoroborate) (SelectfluorTM from Aldrich Chemical Company, Inc.; 2.9 g, 15 2.59 mmol [F⁺]/g). The resulting mixture was heated at reflux for 3 h, then allowed to cool to room temperature. This material was taken up in Et₂O and washed with H₂O. The organic layer was dried over MgSO₄, filtered and concentrated to yield a brown oil. The crude product was 20 purified via reverse phase HPLC (50% acetonitrile/water) to give 0.37 g of white solid which was stirred in 1N NaOH for 1 h then made acidic with conc. HCl. The precipitated white solid was collected with suction, washed with H₂O and dried under vacuum to give 170 mg of 4-amino-3,6-dichloro-25 5-fluoropyridine-2-carboxylic acid (11% yield); mp 214 °C dec.

9. Preparation of 4-Amino-3,6-dichloro-5-bromopyridine-2-carboxylic acid (Compound 19)

To a solution of methyl 4-amino-3,6-dichloropyridine-2-carboxylate (18 g, 81 mmol) in 100 mL, 30 fuming sulfuric acid was added bromine (15 mL, excess). The resulting mixture was heated to 70 °C for 30 min, then allowed to cool to room temperature. This material was poured into ice water (1000 mL) and extracted with EtOAc (4

x 500 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated to yield a brown solid. The crude product was purified via reverse phase HPLC (50% acetonitrile/water) to give 21 g of 4-amino-3,6-dichloro-5-bromopyridine-2-carboxylic acid as a white solid (91% yield); mp 201-202 °C.

10. Preparation of 4-amino-3,6-dichloro-5-methoxypyridine-2-carboxylate (Compound 20)

10 A. Methyl 3-chloro-5-methoxypyridine-2-carboxylate, N-oxide

In a dry 3-neck round bottom flask was added methyl 3,5-dichloropyridine-2-carboxylate, N-oxide (5.0 g, 22.5 mmol) to 25 mL of methanol to give a slurry. A 25% solution of sodium methoxide in methanol (5.40 mL, 23.62 mmol) was added and heated to reflux for 1.5 h. The reaction mixture was diluted in ethyl acetate and added to H₂O. The layers were separated and the aqueous layer was saturated with brine and extracted 2 more times in ethyl acetate. The combined organic layers were dried (MgSO₄) and concentrated to give a white solid. Purification by column chromatography (silica gel) using an eluent of 50% Et₂O/Petroleum ether (1.5 L) then 100% Et₂O to give 1.76 g of a white solid; mp 154-156 °C.

25 B. Methyl 3-chloro-5-methoxy-4-nitropyridine-2-carboxylate, N-oxide

To methyl 3-chloro-5-methoxypyridine-2-carboxylate, N-oxide (1.41 g, 5.97 mmol) in H₂SO₄ cooled to 0 °C was slowly added a 50/50 mixture of 30% oleum and fuming HNO₃. Reaction mixture stirred for 30 minutes at room temperature and then heated to 70 °C for 3 days. The reaction mixture was diluted with ethyl acetate and cooled to 0 °C. Saturated sodium bicarbonate was carefully added and the layers were separated. Aqueous layer was washed 2 more times with ethyl acetate. The combined organic layers

were dried (MgSO_4) and concentrated to dryness. Purification by column chromatography (silica gel) using an eluent of 20% ethyl acetate/hexane gave 300 mg of a yellow solid; mp 160 °C

5 C. Methyl 3,6-dichloro-5-methoxy-4-nitropyridine-2-carboxylate

To methyl 3-chloro-5-methoxy-4-nitropyridine-2-carboxylate, *N*-oxide (0.300 g, 1.12 mmol) in 5 mL of chloroform was added PCl_3 (0.664 mL, 7.62 mmol). The
10 reaction mixture was heated to reflux for 8 h and then concentrated to dryness *in vacuo* to give 300 mg of a white solid.

D. Methyl 4-amino-3,6-dichloro-5-methoxypyridine-2-carboxylate

15 To methyl 3,6-dichloro-5-methoxy-4-nitropyridine-2-carboxylate (0.300 g, 1.06 mmol) in 5 mL of ethyl acetate was added $\text{SnCl}_2 \times 2\text{H}_2\text{O}$ (1.60 g, 7.1 mmol). The reaction mixture was heated to 70 °C for 30 min and then cooled to room temperature. Saturated sodium bicarbonate and a
20 saturated solution of KHF_2 were added to reaction mixture. The mixture was extracted with ethyl acetate and the layers were separated. The aqueous layer was washed 2 more times with ethyl acetate. The combined organic layers were dried (MgSO_4) and concentrated to dryness to give 0.250 g of a
25 yellow solid.

E. 4-Amino-3,6-dichloro-5-methoxypyridine-2-carboxylate (Compound 20)

4-Amino-3,6-dichloro-5-methoxypyridine-2-carboxylate was prepared by saponification of the methyl ester
30 according to the procedure of Example 12(D); mp 154-156 °C.

11. Preparation of 4-Amino-3,6-dichloro-5-methylthiopyridine-2-carboxylic acid (Compound 21)

4-Amino-3,6-dichloro-5-methylthiopyridine-2-carboxylic acid was prepared by analogy to the preparation of 4-amino-3,6-dichloro-5-methoxypyridine-2-carboxylic acid following the procedure of Example 10; mp 160 °C dec.

5 12. Preparation of 4-N-Methylamino-3,6-Dichloropyridine-2-carboxylic acid (Compound 22)

A. Methyl 3,6-Dichloropyridine-2-carboxylate

To a 3-neck round bottom flask equipped with a reflux condenser was added 3,6-dichloropyridine-2-carboxylic acid (50.0 g, 260.42 mmol) in methanol (200 mL). HCl(g) was bubbled in until solution became saturated and stirred at room temperature for 2 h. The solution was concentrated to dryness *in vacuo*. Diethyl ether was added to make a slurry that was subsequently added to a flask filled with a 1:1 mixture of saturated sodium bicarbonate/diethyl ether and stirred for 10 min. The aqueous phase was extracted with diethyl ether (3 X 300 mL). The combined extracts were dried (MgSO₄) and concentrated to give 46.6 g of a light yellow solid. 1H NMR(CDCl₃): δ 4.00 (s, 3H); 7.41 (d, 1H); 7.80 (d, 1H).

B. Methyl 3,6-Dichloropyridine-2-carboxylate, N-oxide

Methyl 3,6-dichloropicolinate (20.0 g, 97.07 mmol) was dissolved in a minimum amount of trifluoroacetic acid (TFA). In a separate flask was stirred trifluoroacetic anhydride (TFAA, 38 mL) and 50% H₂O₂ (9.9 g, 145.61 mmol) which was added to the TFA solution. The reaction mixture was stirred at reflux for 1 h and concentrated to dryness. The orange oil was dissolved in ethyl acetate and saturated sodium bicarbonate. The phases were separated and the aqueous phase was extracted with ethyl acetate (2 X 200mL). The combined extracts were dried (MgSO₄) and concentrated to a yellow solid. Purification by column chromatography (silica gel) using an eluent of 50% ethyl acetate/hexane gave 12.13 g of a yellow

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solid. ^1H NMR(CDCl_3): δ 4.00 (s, 3H); 7.25 (d, 1H); 7.50 (d, 1H).

C. Methyl 3,4,6-Trichloropyridine-2-carboxylate

To methyl 3,6-dichloropicolinate N-oxide (5.0 g, 22.52 mmol) dissolved in 15 mL of acetonitrile was added POCl_3 (4.20 mL, 45.04 mmol). The reaction mixture was stirred at reflux for 5 h, cooled to room temperature and concentrated to dryness in vacuo. The resultant orange oil was dissolved in diethyl ether. Carefully, saturated sodium bicarbonate was added and the aqueous phase was extracted with diethyl ether (2 X 100mL). The combined extracts were dried (MgSO_4) and concentrated to dryness. Purification by column chromatography (silica gel) using an eluent of 20% ethyl acetate/hexane gave 5.89 g of a light yellow solid. ^1H NMR(CDCl_3): δ 4.00 (s, 3H); 7.55 (s, 1H).

D. 3,4,6-Trichloropyridine-2-carboxylic acid

To methyl 3,4,6-Trichloropicolinate (3.57 g, 14.85 mmol) in 20 mL of methanol was added 1N NaOH (14.85 mL, 14.85 mmol). The reaction mixture was stirred at room temperature for 1 h and then concentrated to dryness in vacuo. 100 mL each of diethyl ether and H_2O were added. Aqueous layer was acidified with 1N HCl until pH=2. CH_2Cl_2 was added and the aqueous phase was extracted with CH_2Cl_2 (2 X 100 mL). The combined extracts were dried (MgSO_4) and concentrated to give 3.13 g of a white solid. ^1H NMR(CDCl_3): δ 7.50 (s, 1H).

E. 4-N-Methylamino-3,6-Dichloropyridine-2-carboxylic acid (Compound 22)

3,4,6-Trichloropyridine-2-carboxylic acid (1.56 g, 6.89 mmol) was dissolved in methylamine and placed in a Parr bomb at 80° for 2 days. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. 1N HCl was added until pH=2. The aqueous phase was

extracted with ethyl acetate (2 X 50 mL) and the combined extracts were dried (MgSO₄) and concentrated to dryness. Desired product was triturated from 5% diethyl ether/pet ether; the solid was filtered and dried to give 0.600 g of a light yellow solid. ¹H NMR(CDCl₃): δ 2.75 (s, 3H); 5.70 (s, 1H); 6.30 (s, 1H); mp 170-172 °C.

The following N-alkyl analogs of 4-amino-3,6-dichloropyridine-2-carboxylic acid were prepared according to the procedure of Example 12:

10 4-N-Ethylamino-3,6-Dichloropyridine-2-carboxylic acid (Compound 23); mp 136-137 °C.

4-N-isopropylamino-3,6-Dichloropyridine-2-carboxylic acid (Compound 24); mp 146-147 °C.

15 4-N-Methoxyethylamino-3,6-Dichloropyridine-2-carboxylic acid (Compound 25); mp 97-99 °C.

4-N-Butylamino-3,6-Dichloropyridine-2-carboxylic acid (Compound 26); mp 96-97 °C.

4-N,N-Dimethylamino-3,6-Dichloropyridine-2-carboxylic acid (Compound 27); mp 110 °C.

20 4-pyrrolidino-3,6-Dichloropyridine-2-carboxylic acid (Compound 28); mp 153-5 °C.

4-Morpholino-3,6-Dichloropyridine-2-carboxylic acid (Compound 29); mp 183-4 °C.

25 13. Preparation of 4-amino-6-bromo-3-methoxypyridine-2-carboxylic acid (Compound 30)

A. Methyl 4,6-dibromo-3-methoxypyridine-2-carboxylate

30 To methyl 4,6-dibromo-3-hydroxypyridine-2-carboxylate 3.98 g (3.98 g, 12.81 mmol) in 40 mL of acetone was added K₂CO₃ (2.0 g, 14.47 mmol) and dimethyl sulfate (1.20 mL, 12.37 mmol). The reaction mixture was refluxed

overnight and concentrated to dryness. The residue was dissolved in ethyl acetate and saturated sodium bicarbonate. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 X 100 mL). The combined extracts were dried (MgSO₄) and concentrated to dryness. The residue was purified by chromatography (silica gel). Elution with 15% ethyl acetate/hexane gave 0.980 g, of a white solid. ¹H NMR(CDCl₃): δ 3.95 (s, 3H); 3.90 (s, 3H); 7.80 (s, 1H).

10 B. Methyl 4-azido-6-bromo-3-methoxypyridine-2-carboxylate

Methyl-4,6-dibromo-3-methoxypyridine-2-carboxylate (0.980 g, 3.02 mmol) was dissolved in a minimum amount of DMF. Slowly sodium azide (0.216 g, 3.32 mmol) was added followed by H₂O to form a homogeneous solution. The reaction mixture was heated to 60° and stirred for 2 days. Reaction mixture added to a flask filled with ice water and extracted with ethyl acetate (3 X 50 mL). Extracts were combined and back washed with H₂O, dried (MgSO₄) and concentrated to give 0.500 g of an orange oil. ¹H NMR(CDCl₃): δ 3.90 (s, 3H); 3.95 (s, 3H); 7.20 (s, 1H).

C. Methyl 4-amino-6-bromo-3-methoxypyridine-2-carboxylate

To methyl 4-azido-6-bromo-3-methoxypyridine-2-carboxylate (0.500 g, 1.74 mmol) in 10 mL of methanol was added NaBH₄ (0.046 g, 1.22 mmol). The reaction mixture was stirred at room temperature for 10 min. Ethyl acetate and water were added and the phases were separated. The organic phase was washed with H₂O, dried (MgSO₄) and concentrated to dryness *in vacuo*. The residue was purified by chromatography (silica gel). Elution with 100% ethyl acetate gave 0.300 g of a white solid. ¹H NMR(CDCl₃): δ 3.90 (s, 1H); 3.95 (s, 1H); 4.60 (s, 2H); 6.85 (s, 1H).

D. 4-amino-6-bromo-3-methoxypyridine-2-carboxylic acid (Compound 30)

To methyl 4-amino-6-bromo-3-methoxypyridine-2-carboxylate (0.300 g, 1.15 mmol) in 10 mL of methanol was
5 added 1N NaOH (1.15 mL, 1.15 mmol). The reaction mixture was stirred at room temperature for 1 h and concentrated to dryness in vacuo. Diethyl ether and H₂O were added. The aqueous layer was acidified with 1N HCl until pH=2 and concentrated to dryness. Methanol (50 mL) was added to the
10 white solid. The mixture was filtered and the filtrate concentrated to dryness. Triturating with 5% diethyl ether/pet ether gave 0.180 g of a light pink solid. ¹H NMR(DMSO): δ 3.60 (s, 3H); 6.80 (s, 1H).

14. Preparation of 4-amino-6-bromo-5-chloro-3-methoxypyridine-2-carboxylic acid (Compound 31)

A. Methyl 4-amino-6-bromo-5-chloro-3-methoxypyridine-2-carboxylate

To methyl 4-amino-6-bromo-3-methoxypyridine-2-carboxylate (1.45 g, 5.56 mmol) in 10 mL of acetonitrile
20 was added sulfuryl chloride, in excess, via pipette until the solution remained yellow. The solution was heated to reflux for 5 min. The reaction mixture was added to saturated sodium bicarbonate and aqueous phase was extracted with diethyl ether (3 x). The combined organic
25 extracts were dried (MgSO₄), filtered and concentrated in vacuo to give a yellow solid. Solid was washed in 10% diethyl ether/petroleum ether and solid filtered to give 0.580 g of a white solid.

B. 4-amino-6-bromo-5-chloro-3-methoxypyridine-2-carboxylic acid (Compound 31)

To methyl-4-amino-6-bromo-5-chloro-3-methoxypyridine-2-carboxylate (0.300 g, 1.02 mmol) in 10 mL of methanol was added 1 N NaOH (1.10 mL, 1.10 mmol). The

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reaction mixture was stirred at room temperature for 4 h and was then concentrated to dryness in vacuo. The resulting aqueous layer was acidified with concentrated HCl. The white solid was collected by filtration and was
5 rinsed with H₂O. The solid was dried at 50 °C under vacuum to give 0.230 g of a white fluffy solid; mp 154-156 °C.

15. Preparation of 4-Amino-5,6-dichloro-3-fluoropyridine-2-carboxylic acid (Compound 32)

A. 4-Amino-5,6-dichloro-2-trichloromethylpyridine

10 To a solution of 4,5,6-trichloro-2-trichloromethylpyridine (2 g, 6.7 mmol) in aqueous DMF was added NaN₃ (0.5 g, 7.7 mmol). The resulting mixture was heated at 70°C for 2 h, added to H₂O and extracted (3x) with Et₂O. Organic layer was concentrated to yield a white
15 solid, which was dissolved in 10 mL of MeOH. Excess NaBH₄ was added and the reaction mixture was stirred at room temperature for 0.5 h. This material was added to H₂O, extracted (3x) with Et₂O, dried over MgSO₄ and concentrated in vacuo. The resulting solid was washed several times
20 with hexane to give 1.3 g of 4-amino-5,6-dichloro-2-trichloromethylpyridine.

B. 4-Amino-5,6-dichloro-3-fluoropyridine-2-carboxylic acid (Compound 32)

25 To a solution of 4-amino-5,6-dichloro-2-trichloromethylpyridine (1.25 g, 4.46 mmol) in 20 mL of dry acetonitrile was added Selectfluor™ (1.9 g, 2.59 mmol [F⁺]/g). The resulting mixture was heated at reflux for 72 h, then allowed to cool to room temperature. This material was taken up in Et₂O and washed with H₂O. The organic layer
30 was dried over MgSO₄, filtered and concentrated to yield a dark oil. The crude product was purified via reverse phase HPLC (75% acetonitrile/water) to give 0.2 g of white solid which was stirred in 80% H₂SO₄ at 155°C for 0.5 h. Reaction mixture was allowed to cool and extracted several times

with 10% MeOH/CH₂Cl₂. Organic layer was dried over MgSO₄, filtered and concentrated to give a white solid which was washed several times with hexane-diethyl ether to give 60 mg of 4-amino-5,6-dichloro-3-fluoropyridine-2-carboxylic acid; mp 208°C dec.

16. Preparation of 4-Amino-3-bromo-6-chloropyridine-2-carboxylic acid (Compound 33)

A. Methyl 3-Bromo-4-chloropyridine-2-carboxylate

To a solution of 3-bromo-4-chloropyridine-2-carboxylic acid (1.75 g, 7.4 mmol) in MeOH was added anhydrous HCl. The resulting mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated to give a solid, which was partitioned between Et₂O and saturated NaHCO₃. Organic layer was dried over MgSO₄, filtered and concentrated to give a brown residue. This material was purified via flash column chromatography to yield 1.35 g of product as a pale yellow oil.

B. Methyl 3-Bromo-4,6-dichloropyridine-2-carboxylate

To a solution of methyl 3-bromo-4-chloropyridine-2-carboxylate (1.35 g, 5.4 mmol) in 5 mL of TFA was added 30% H₂O₂ (1 g, 9.8 mmol). The resulting mixture was stirred at 75°C for 0.5 h and allowed to cool to room temperature. Et₂O was added and the organic layer was washed carefully with saturated NaHCO₃, dried over MgSO₄, filtered and concentrated to give the corresponding N-Oxide intermediate as a white solid. This material was taken up in acetonitrile (5 mL), POCl₃ (2-3 mL) and heated at reflux for 2 h. The reaction mixture was allowed to cool, added to Et₂O and washed carefully with saturated NaHCO₃, dried over MgSO₄, filtered and concentrated to give 0.9 g of product as a light brown oil. This material was sufficiently pure to carry on to the next step.

C. 4-Amino-3-bromo-6-chloropyridine-2-carboxylic acid
(Compound 33)

To a solution of methyl 3-bromo-4,6-dichloropyridine-2-carboxylate (0.9 g, 3.2 mmol) in aqueous
5 DMF was added NaN_3 (0.25 g, 3.8 mmol). The resulting
mixture was heated at 60 °C for 1 h, added to H_2O and
extracted (3x) with Et_2O . Organic layer was concentrated
to yield a white solid, which was dissolved in 10 mL of
MeOH. Excess NaBH_4 was added and the reaction mixture
10 stirred at room temperature for 0.5 h. This material was
added to H_2O , extracted (3x) with Et_2O , dried over MgSO_4 and
concentrated. The resulting solid was stirred in 1N NaOH
for 1 h, made acidic with conc. HCl and concentrated to
dryness. This material was extracted with MeOH,
15 concentrated to give 220 mg of 4-amino-3-bromo-6-
chloropyridine-2-carboxylic acid; mp 175 °C dec.

17. Preparation of 4-Amino-3,5-dichloro-6-
trifluoromethylpyridine-2-carboxylic acid (Compound 34)

20 A. Methyl 4-chloro-6-trifluoromethylpyridine-2-
carboxylate

To a solution of 6-trifluoromethylpicolinic acid
(8.6 g, 45 mmol; prepared from the corresponding 6-
25 trifluoromethyl-2-cyanopyridine) in 25 mL of TFA was added
30% H_2O_2 (7.8 g, 67.5 mmol). Reaction mixture was stirred
at 70°C for 18 h and concentrated to give 8.0 g of the N-
oxide. This material was stirred in HCl/MeOH solution for
18 h. The reaction mixture was concentrated to give an
30 oily residue which was partitioned between Et_2O and
saturated NaHCO_3 . The organic layer was dried over MgSO_4 ,
filtered and concentrated to give 5.0 g of a yellow oil.
Neat POCl_3 was added and stirred at reflux for 2 h. The
mixture was allowed to cool, added carefully to saturated
35 NaHCO_3 , and extracted (3x) with Et_2O . The organic layer was

dried over MgSO_4 , filtered and concentrated to give a brown solid. This material was purified via flash column chromatograph to give 2.64 g of product as a white solid (mp $62-3^\circ\text{C}$).

5

B. Methyl 4-Amino-6-trifluoromethylpyridine-2-carboxylate

To a solution of methyl 4-chloro-6-trifluoromethylpyridine-2-carboxylate (2.44 g, 10.2 mmol) in aqueous DMF was added NaN_3 (0.7 g, 10.8 mmol). The resulting mixture was heated at 70°C for 18 h, added to H_2O and extracted (3x) with Et_2O . The organic layer was concentrated to yield a white solid that was dissolved in 10 mL of MeOH. Excess NaBH_4 was added and the reaction mixture stirred at RT for 0.5 h. This material was added to H_2O , extracted (3x) with Et_2O . The extract was dried over MgSO_4 and concentrated. The resulting residue was purified via flash column chromatography to give 0.95 of product as a white solid (mp 114°C).

C. Methyl 4-Amino-3,5-dichloro-6-trifluoromethylpyridine-2-carboxylate

To a solution of methyl 4-amino-6-trifluoromethylpyridine-2-carboxylate (0.75 g, 3.4 mmol) in 5 mL of dry acetonitrile was added SO_2Cl_2 (0.55 mL, 6.8 mmol). The resulting mixture was heated at reflux for 0.5 h, then allowed to cool to room temperature. This material was taken up in Et_2O and washed with saturated NaHCO_3 . The organic layer was dried over MgSO_4 , filtered and concentrated to give solid. The crude material was purified via flash column chromatography to yield 0.28 g of product as a white solid (mp $135-6^\circ\text{C}$).

35

D. Preparation of 4-Amino-3,5-dichloro-6-trifluoromethylpyridine-2-carboxylate (Compound 34)

To a solution of methyl 4-amino-3-5-dichloro-6-trifluoromethylpyridine-2-carboxylate (0.16 g, 0.56 mmol) in 5 mL of MeOH was added excess 1N NaOH. The resulting reaction mixture was stirred at room temperature for 1 h, then made acidic with conc. HCl. The precipitated white solid was collected with suction, washed with H₂O and dried under vacuum to give 80 mg of compound 34; mp 178°C dec.

18. Preparation of 4-Amino-3-chloro-6-trifluoromethylpyridine-2-carboxylic acid (Compound 35)

4-Amino-3-chloro-6-trifluoromethylpyridine-2-carboxylic acid was prepared by analogy to the preparation of 4-Amino-3,5-dichloro-6-trifluoromethylpyridine-2-carboxylic acid but using only one equivalent of SO₂Cl₂ to perform mono-chlorination rather than bis-chlorination in procedure 17C

Preparation of Herbicidal Compositions

19. Preparation of Herbicidal Compositions

In the following illustrative compositions, parts and percentages are by weight.

EMULSIFIABLE CONCENTRATES

<u>Formulation A</u>	
	<u>WT%</u>
4-Amino-3,6-dichloropicolinic acid	26.2
Polyglycol 26-3	5.2
Nonionic emulsifier-(di-sec-butyl)-phenyl-poly(oxypropylene)block polymer with (oxyethylene). The polyoxyethelene content is about 12 moles.	
Witconate P12-20 (Anionic emulsifier-calcium dodecylbenzene	5.2

sulfonate-
60 wt. % active)
Aromatic 100 (Xylene range
aromatic
solvent) 63.4

Formulation B

	<u>WT%</u>
4-Amino-3,6-dichloropicolinic acid	3.
Sunspray 11N (paraffin oil)	40.0
Polyglycol 26-3	19.0
Oleic acid	1.
Xylene range aromatic solvent	36.5

Formulation C

	<u>WT%</u>
4-Amino-3,6-dichloropicolinic acid	13.2
Stepon C-65	25.7
Ethomeen T/25	7.7
Ethomeen T/15	18.0
Xylene range aromatic solvent	35.4

- 5 These concentrates can be diluted with water to give emulsions of suitable concentrations for controlling weeds.

WETTABLE POWDERS

10

Formulation D

	<u>WT%</u>
4-Amino-3,6-dichloropicolinic acid	26.0
Polyglycol 26-3	2.0
Polyfon H	4.0
Zeosyl 100 (Precipitated hydrated SiO ₂)	17.0
Barden clay + inerts	51.0

Formulation E

	<u>WT%</u>
4-Amino-3,6-dichloropicolinic acid	62.4
Polyfon H (sodium salt of lignin)	6.0

sulfonate)
Sellogen HR (sodium naphthalene
4.0
sulfonate)
Zeosyl 100 27.6

The active ingredient is applied to the corresponding
carriers and then these are mixed and ground to yield
wetable powders of excellent wettability and suspension
5 power. By diluting these wettable powders with water it is
possible to obtain suspensions of suitable concentrations
for controlling weeds.

WATER DISPERSIBLE GRANULES

10

Formulation F

	<u>WT%</u>
4-Amino-3,6-dichloropicolinic acid	26.0
Sellogen HR	
	4.0
Polyfon H	
	5.0
Zeosyl 100	17.0
Kaolinite clay	48.0

The active ingredient is applied in a liquid state to the
15 hydrated silica, which is then mixed with the other
ingredients and ground to a powder. The powder is
agglomerated with water and sieved to provide granules in
the range of -10 to +60 mesh. By dispersing these granules
in water it is possible to obtain suspensions of suitable
20 concentrations for controlling weeds.

GRANULES

25

Formulation G

	<u>WT%</u>
4-Amino-3,6-dichloropicolinic acid	5.0
Celetom MP-88	95.0

The active ingredient is applied in a liquid state to the Celetom MP 88 carrier or to other suitable carriers. The resulting granules can be applied by hand, granule applicator, airplane, etc. in order to control weeds.

5

<u>Formulation H</u>	
	<u>WT%</u>
4-Amino-3,6-dichloropicolinic acid	1.0
Polyfon H	8.0
Nekal BA 77	2.0
Zinc Stearate	2.0
Barden Clay	87.0

10 All materials are blended and ground to a powder then water is added and the clay mixture is stirred until a paste is formed. The mixture is extruded through a die to provide granules of proper size.

20. Evaluation of Postemergence Herbicidal Activity

15 Seeds of the desired test plant species were planted in Grace-Sierra MetroMix® 306 planting mixture, which typically has a pH of 6.0 to 6.8 and an organic matter content of about 30 percent, in plastic pots with a surface area of 64 square centimeters. When required to ensure good germination and healthy plants, a fungicide treatment and/or other chemical or physical treatment was applied. The plants were grown for 7-21 days in a
20 greenhouse with an approximate 15 hr photoperiod which was maintained at about 23-29°C during the day and 22-28°C during the night. Nutrients and water were added on a regular basis and supplemental lighting was provided with overhead metal halide 1000-Watt lamps as necessary. The
25 plants were employed for testing when they reached the first or second true leaf stage.

A weighed amount, determined by the highest rate to be tested, of each test compound was placed in a 20 mL

glass vial and was dissolved in 4 mL of a 97:3 v/v (volume/volume) mixture of acetone and dimethyl sulfoxide (DMSO) to obtain concentrated stock solutions. If the test compound did not dissolve readily, the mixture was warmed and/or sonicated. The concentrated stock solutions obtained were diluted with an aqueous mixture containing acetone, water, isopropyl alcohol, DMSO, Atplus 411F crop oil concentrate, and Triton X-155 surfactant in a 48.5:39:10:1.5:1.0:0.02 v/v ratio to obtain spray solutions of known concentration. The solutions containing the highest concentration to be tested were prepared by diluting 2 mL aliquots of the stock solution with 13 mL of the mixture and lower concentrations were prepared by serial dilution of the stock solution. Approximately 1.5 mL aliquots of each solution of known concentration were sprayed evenly onto each of the test plant pots using a DeVilbiss atomizer driven by compressed air pressure of 2 to 4 psi (140 to 280 kiloPascals) to obtain thorough coverage of each plant. Control plants were sprayed in the same manner with the aqueous mixture. In this test an application rate of 1 ppm results in the application of approximately 1 g/ha.

The treated plants and control plants were placed in a greenhouse as described above and watered by sub-irrigation to prevent wash-off of the test compounds. After 2 weeks the condition of the test plants as compared with that of the untreated plants was determined visually and scored on a scale of 0 to 100 percent where 0 corresponds to no injury and 100 corresponds to complete kill.

By applying the well-accepted probit analysis as described by J. Berkson in *Journal of the American Statistical Society*, 48, 565 (1953) and by D. Finney in "Probit Analysis" Cambridge University Press (1952), the above data can be used to calculate GR_{50} and GR_{80} values, which are defined as growth reduction factors that

correspond to the effective dose of herbicide required to kill or control 50 percent or 80 percent, respectively, of a target plant.

Some of the compounds tested, application rates
5 employed, plant species tested, and results are given in Tables 1-2. Selectivity to rice, corn and wheat are illustrated in Tables 3-5.

55

Table 1
Post-emergent % Control

#	M	R1	R2	X	Y	Z	% Control			Rate (ppm)
							XANST	STEME	POLCO	
1	OH	H	H	H	Cl	Cl	95	100	100	125
2	Oethylhexyl	H	H	H	Cl	Cl	95	80	100	250
3	OMe	H	H	H	Cl	Cl	100	100	100	125
4	OEt	H	H	H	Cl	Cl	100	100	100	125
5	On-Pr	H	H	H	Cl	Cl	100	100	100	125
6	Oi-Pr	H	H	H	Cl	Cl	100	100	100	125
7	On-Bu	H	H	H	Cl	Cl	100	100	100	250
8	On-pentyl	H	H	H	Cl	Cl	100	90	100	250
9	On-hexyl	H	H	H	Cl	Cl	100	100	100	250
10	OPh	H	H	H	Cl	Cl				
11	NHEt	H	H	H	Cl	Cl	0	0	0	125
12	OMe	H	C(O)Me	H	Cl	Cl	90	30	100	125
13	OMe	C(O)Me	C(O)Me	H	Cl	Cl	95	100	80	250
14	OH	H	H	H	Br	Cl	85	90	50	250
15	OMe	H	H	H	Br	Cl	95	95	100	250
16	OMe	H	H	H	F	Cl	90	80	95	250
17	OMe	H	H	Br	Br	Br	85	90	75	250
18	OH	H	H	F	Cl	Cl	95	95	100	125
19	OH	H	H	Br	Cl	Cl	85	90	50	250
20	OH	H	H	OMe	Cl	Cl	80	70	100	250
21	OH	H	H	SMe	Cl	Cl	90	90	98	125
22	OH	H	Me	H	Cl	Cl	90	90	95	125
23	OH	H	Et	H	Cl	Cl	85	100	90	125
24	OH	H	i-Pr	H	Cl	Cl	95	90	95	250
25	OH	H	EtOMe	Cl	Cl	Cl	80	90	100	250
26	OH	H	n-Bu	H	Cl	Cl	95	90	90	250
27	OH	Me	Me	H	Cl	Cl	100	100	100	250
28	OH	pyrrolidine		H	Cl	Cl	30	50	100	250
29	OH	morpholine		H	Cl	Cl	0	0	0	250
30	OH	H	H	H	Br	OMe	80	90	100	125
31	OH	H	H	Cl	Br	OMe	85	90	90	250
32	OH	H	H	Cl	Cl	F	90	85	60	125
33	OH	H	H	H	Cl	Br	90	90	95	125
34	OH	H	H	Cl	CF3	Cl	90	0	80	250
35	OH	H	H	H	CF3	Cl	90	60	100	250

XANST = cocklebur (*Xanthium strumarium*)

STEME = chickweed (*Stellaria media*)

POLCO = wild buckwheat (*Polygonum convolvulus*)

TABLE 2
POSTMERGENCE HERBICIDAL ACTIVITY & CONTROL

Qpd. No.	Rate, ppm	STEME	XANST	CHEAL	AMARE	ABUTH	VIOTR	POLCO	ALOMY	ECHCG	DIGSA	SETFA	SORBI	AVEFA
1	125	90	100	100	95	70	80	100	50	45	60	75	50	50
4	125	70	100	100	100	70	70	100	40	50	70	75	40	40
14	125	65	100	95	90	85	75	100	50	65	65	65	60	40
18	125	60	95	95	60	50	50	100	20	10	30	20	10	20

STEME=chickweed(*Stellaria media*)
CHEAL=lambsquarters(*Chenopodium album*)
ABUTH=velvetleaf(*Abutilion theophrasti*)
POLCO=wild buckwheat(*Polygonum convolvulus*)
ECHCG=barnyardgrass(*Echinochloa crus-galli*)
SETFA=giant foxtail(*Setaria faberi*)
AVEFA=wild oats(*Avena fatua*)

XANST=cocklebur(*Xanthium strumarium*)
AMARE=pigweed(*Amaranthus retroflexus*)
VIOTR=viola(*Viola tricolor*)
ALOMY=blackgrass(*Alopecurus myosuroides*)
DIGSA=crabgrass(*Digitaria sanguinalis*)
SORBI=Rox orange sorghum(*Sorghum bicolor*)

Table 3

Control of Several Key Weeds in Rice

post emergent evaluation - % control			
ORYZA	ECHCG	CYPES	Rate (ppm)
10	75	75	250
10	65	75	250
40	70	50	250

ORYZA = rice (*Oryza sativa*)
ECHCG = Barnyardgrass (*Echinochloa crus-galli*)
CYPES = yellow nutsedge (*Cyperus esculentus*)

Table 4

Control of Several Key Weeds in Corn

Post-emergent Evaluation - % control					
compd #	ZEAMX	ABUTH	AMARE	XANST	Rate (ppm)
16	0	40	75	90	250
19	10	70	90	85	250
27	20	80	50	100	125
32	0	70	90	85	250

ZEAMX = corn (*Zea mays*)
ABUTH = velvetleaf (*Abutilon theophrasti*)
AMARE = pigweed (*Amaranthus retroflexus*)
XANST = cocklebur (*Xanthium strumarium*)

Table 5

Control of Several Key Weeds in Wheat

Post-emergent Evaluation - % control					
cmpd #	TRZAS	STEME	CHEAL	POLCO	Rate (ppm)
15	0	50	80	95	250
21	20	30	90	98	125
30	10	20	90	100	250
35	10	50	100	100	31

TRZAS = wheat (*Triticum aestivum*)
STEME = chickweed (*Stellaria media*)
CHEAL = lambsquarters (*Chenopodium album*)
POLCO = wild buckwheat (*Polygonum convolvulus*)

21. Evaluation of Preemergence Herbicidal Activity

Seeds of the desired test plant species were
5 planted in a soil matrix prepared by mixing a loam soil (43 percent silt, 19 percent clay, and 38 percent sand, with a pH of about 8.1 and an organic matter content of about 1.5 percent) and sand in a 70 to 30 ratio. The soil matrix was contained in plastic pots with a surface area of 113 square
10 centimeters. When required to ensure good germination and healthy plants, a fungicide treatment and/or other chemical or physical treatment was applied.

A weighed amount, determined by the highest rate to be tested, of each test compound was placed in a 20 mL
15 glass vial and was dissolved in 4 mL of a 97:3 v/v (volume/volume) mixture of acetone and dimethyl sulfoxide to obtain concentrated stock solutions. If the test compound did not dissolve readily, the mixture was warmed and/or sonicated. The stock solutions obtained were
20 diluted with a 99.9:0.1 mixture of water and Tween® 155 surfactant to obtain application solutions of known

concentration. The solutions containing the highest concentration to be tested were prepared by diluting 2 mL aliquots of the stock solution with 15 mL of the mixture and lower concentrations were prepared by serial dilution of the stock solution. A 2.5 mL aliquot of each solution of known concentration was sprayed evenly onto the soil surface (113 sq. cm) of each seeded pot using a Cornwall 5.0 mL glass syringe fitted with a TeeJet TN-3 hollow cone nozzle to obtain thorough coverage of the soil in each pot. Control pots were sprayed in the same manner with the aqueous mixture.

The treated pots and control pots were placed in a greenhouse maintained with an approximate 15 hr photoperiod and temperatures of about 23-29°C during the day and 22-28°C during the night. Nutrients and water were added on a regular basis and supplemental lighting was provided with overhead metal halide 1000-Watt lamps as necessary. The water was added by top-irrigation. After 3 weeks the condition of the test plants that germinated and grew as compared with that of the untreated plants that germinated and grew was determined visually and scored on a scale of 0 to 100 percent where 0 corresponds to no injury and 100 corresponds to complete kill or no germination. Some of the compounds tested, application rates employed, plant species tested, and results are given in Tables 6-7.

Table 6
Pre-emergent % Control

#	M	R1	R2	X	Y	Z	IPOHE	% Control		Rate (g/ha)
								AMARE	ABUTH	
1	OH	H	H	H	Cl	Cl	100	100	100	280
2	Oethylhexyl	H	H	H	Cl	Cl	100	100	100	280
3	OMe	H	H	H	Cl	Cl	100	100	100	280
4	OEt	H	H	H	Cl	Cl	100	100	100	560
5	On-Pr	H	H	H	Cl	Cl	100	100	100	560
6	Oi-Pr	H	H	H	Cl	Cl	100	100	100	280
7	On-Bu	H	H	H	Cl	Cl	100	100	100	280
8	On-pentyl	H	H	H	Cl	Cl	100	100	100	280
9	On-hexyl	H	H	H	Cl	Cl	98	100	100	560
10	OPh	H	H	H	Cl	Cl				
11	NHEt	H	H	H	Cl	Cl	0	0	0	280
12	OMe	H	C(O)Me	H	Cl	Cl	95	100	95	280
13	OMe	C(O)Me	C(O)Me	H	Cl	Cl	95	100	95	280
14	OH	H	H	H	Br	Cl	100	100	100	280
15	OMe	H	H	H	Br	Cl	100	100	100	280
16	OMe	H	H	H	F	Cl	100	100	100	560
17	OMe	H	H	Br	Br	Br	60	100	100	560
18	OH	H	H	F	Cl	Cl	100	100	100	560
19	OH	H	H	Br	Cl	Cl	100	100	100	560
20	OH	H	H	OMe	Cl	Cl	100	100	100	560
21	OH	H	H	SMe	Cl	Cl	90	95	70	560
22	OH	H	Me	H	Cl	Cl	100	100	100	560
23	OH	H	Et	H	Cl	Cl	100	100	100	560
24	OH	H	i-Pr	H	Cl	Cl	100	100	100	560
25	OH	H	EtOMe	Cl	Cl	Cl	90	100	90	560
26	OH	H	n-Bu	H	Cl	Cl	100	100	100	560
27	OH	Me	Me	H	Cl	Cl	100	100	98	560
28	OH	pyrrolidine		H	Cl	Cl	80	95	100	560
29	OH	morpholine		H	Cl	Cl	0	0	60	560
30	OH	H	H	H	Br	OMe	100	90	98	560
31	OH	H	H	Cl	Br	OMe	100	100	100	560
32	OH	H	H	Cl	Cl	F	90	70	70	280
33	OH	H	H	H	Cl	Br	100	100	100	560
34	OH	H	H	Cl	CF3	Cl	100	100	90	560
35	OH	H	H	H	CF3	Cl	100	100	95	560

IPOHE = morningglory (*Ipomoea hederacea*)

AMARE = pigweed (*Amaranthus retroflexus*)

ABUTH = velvetleaf (*Abutilon theophrasti*)

TABLE 7
PREEMERGENCE HERBICIDAL ACTIVITY & CONTROL

Cpd. No.	Rate, g/Ha	XANST	CHEAL	AMARE	ABUTH	EPHHL	ALOMY	ECHCG	DIGSA	SETFA	SORBI	AVEFA
1	35	99	99	88	95	62	36	17	20	40	60	37
3	35	90	100	90	95	20	nt	20	40	40	30	10
14	35	100	100	100	100	70	60	40	80	98	50	40
31	35	98	90	60	80	40	30	30	30	30	20	30

nt=no test
XANST=cocklebur (*Xanthium strumarium*)
ABUTH=velvetleaf (*Abutilon theophrasti*)
ALOMY=blackgrass (*Alopecurus myosuroides*)
DIGSA=crabgrass (*Digitaria sanguinalis*)
SORBI=Rox orange sorghum (*Sorghum bicolor*)
CHEAL=lambquarters (*Chenopodium album*)
AMARE=pigweed (*Amaranthus retroflexus*)
EPHHL=wild poinsettia (*Euphorbia heterophylla*)
ECHCG=barnyardgrass (*Echinochloa crus-galli*)
SETFA=giant foxtail (*Setaria faberi*)
AVEFA=wild oats (*Avena fatua*)

22. Range & Pasture Crop Testing

5 Rates are calculated based upon 5 doses being applied. The high rate (X), followed by serial dilutions of 1/2X, 1/4X, 1/8X and 1/16X. Compound requirements are based upon the 187 l/ha carrier volume, specifications of the delivery system (Mandel track sprayer) and generating 24 mL of technical spray material to allow for the dilutions and overage in the sprayer.

10
$$\frac{\text{Rate g/ha}}{187 \text{ L/ha}} = \frac{\text{X mg}}{24 \text{ mL}}$$

	Example:	<u>Starting X rate (g/ha)</u>	<u>mgs required</u>
		560	71.9
15		280	35.9
		140	17.95
		70	8.9

20 All technical materials were formulated in 97:3 (acetone:DMSO) with 0.25% X-77. The total volume of solvent is maintained at less than 7%. An overhead Mandel track sprayer calibrated to deliver 187 l/ha was used for all treatment applications (post-emergence). Picloram was included as a comparison treatment.

25 Solutions were applied with a mechanized track-sprayer at the following settings:

Nozzle: 8002E

Speed: 2 mph

Spray Pressure: 40 psi

30 Spray height: 17 inches above top of plants

This provides an application volume of 187 l/ha

Percent weed control (burn down) was evaluated 3 weeks after treatment. Visual control on a 0-100 linear scale was used, with 0 representing no control and 100 representing total control. Burn down ratings were taken for annual and perennial weed species. Some of the compounds tested, application rates employed, plant species tested, and results are given in Tables 8-10.

Table 8

Salts of Compound 1

salt	Post-emergent GR ₈₀ g/Ha		
	CASOB	CONAR	CIRAR
free acid	11	59	47
potassium salt	<8.8	36	27
amine salt	<8.8	34	37
dimethylamine salt	11.8	>140	43
monoethanolamine salt	11	20	18
triethylamine salt	<8.8	16	<8.8
triisopropanolamine salt	11	20	43

CASOB=sicklepod (*Cassia obtusifolia*)
 CONAR=field bindweed (*Convolvulus arvensis*)
 CIRAR=Canada thistle (*Cirsium arvense*),
 3 week evaluation

Table 9

Control of Several Key Weeds in Pasture

Cmpd #	Post-emergent Evaluation - % control				Rate (g/Ha)
	AGRCR	CIRAR	RUMOB	AMBEL	
3	30	90	100	100	70
6	30	95	100	93	70
22	10	90	100	nt	70
27	30	80	100	85	70

AGRCR = crested wheatgrass (*Agropyron cristatum*)
 CIRAR = Canada thistle (*Cirsium arvense*)
 RUMOB = broadleaf dock (*Rumex obtusifolia*)
 AMBEL = common ragweed (*Ambrosia artemisiifolia*)
 3 week evaluation
 nt = not tested

Table 10

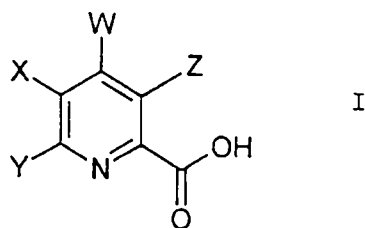
Control of Several Key Weeds in Clover
Pasture

Cmpd	GR ₂₀ TRFRE	g/ha	
		GR ₈₀ CONAR	GR ₈₀ CIRAR
3	<17.5	127.7	<17.5
4	<17.5	59	<17.5
5	<17.5	140.1	<17.5
6	98.8	98.8	<17.5
7	15.3	116.6	17.3
9	20.7	66	20.7

TRFRE=White Clover (*Trifolium repens*)CONAR=Field Bindweed (*Convolvulus arvensis*)CIRAR=Canada thistle (*Cirsium arvense*)

WHAT IS CLAIMED IS:

1. A compound of Formula I:



wherein

- 5 X represents H, halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, cyano or trifluoromethyl;

Y represents halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, cyano or trifluoromethyl;

- 10 Z represents halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, cyano or trifluoromethyl;

W represents -NR₁R₂, -N=CR₃R₄ or -NHN=CR₃R₄

where

- 15 R₁ and R₂ independently represent H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl, heteroaryl, hydroxy, C₁-C₆ alkoxy, amino, C₁-C₆ acyl, C₁-C₆ carboalkoxy, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylsulfonyl, C₁-C₆ trialkylsilyl or C₁-C₆ dialkyl phosphonyl or R₁ and R₂ taken together with N represent a 5- or 6-membered saturated or unsaturated ring which may contain additional O or N heteroatoms; and

- 20 R₃ and R₄ independently represent H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl or heteroaryl or R₃ and R₄ taken together with =C represent a 5- or 6-membered saturated ring; and

bb

agriculturally acceptable derivatives of the carboxylic acid, with the proviso that when X represents H or Cl, then Y and Z are not both Cl.

2. A compound of claim 1 wherein:

5 X represents H, halogen, cyano or trifluoromethyl;

Y represents halogen, cyano or trifluoromethyl;

Z represents halogen, cyano or trifluoromethyl;

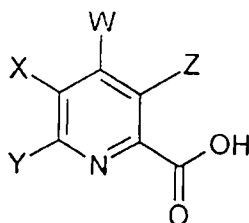
W represents $-NR_1R_2$

10 where

R_1 and R_2 independently represent H, C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl or R_1 and R_2 taken together with N represent a 5- or 6-membered saturated ring which may contain additional O or N heteroatoms; and

15 agriculturally acceptable salts, esters or amides of the carboxylic acid.

3. A composition comprising an herbicidally effective amount of a 4-aminopicolinate of Formula I:



20

wherein

X represents H, halogen, C_1-C_6 alkoxy, C_1-C_6 alkylthio, aryloxy, cyano or trifluoromethyl;

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Y represents halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, cyano or trifluoromethyl;

Z represents halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, cyano or trifluoromethyl;

5 W represents -NR₁R₂, -N=CR₃R₄ or -NHN=CR₃R₄

where

R₁ and R₂ independently represent H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl, heteroaryl, hydroxy, C₁-C₆ alkoxy, amino, C₁-C₆ acyl, C₁-C₆ carboalkoxy, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylsulfonyl, C₁-C₆ trialkylsilyl or C₁-C₆ dialkyl phosphonyl or R₁ and R₂ taken together with N represent a 5- or 6-membered saturated or unsaturated ring which may contain additional O or N heteroatoms; and

R₃ and R₄ independently represent H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl or heteroaryl or R₃ and R₄ taken together with =C represent a 5- or 6-membered saturated ring; and

agriculturally acceptable derivatives of the carboxylic acid, with the proviso that when X represents Cl, then Y and Z are not both Cl, in admixture with an agriculturally acceptable adjuvant or carrier.

4. A composition of claim 3 wherein:

X represents H, halogen, cyano or trifluoromethyl;

25 Y represents halogen, cyano or trifluoromethyl;

Z represents halogen, cyano or trifluoromethyl;

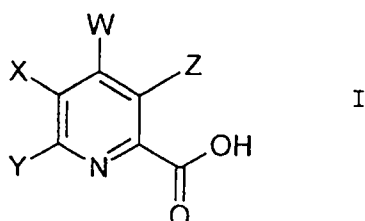
W represents -NR₁R₂

where

R_1 and R_2 independently represent H, C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl or R_1 and R_2 taken together with N represent a 5- or 6-membered saturated ring which may contain additional O or N heteroatoms; and

- 5 agriculturally acceptable salts, esters or amides of the carboxylic acid.

5. A method of controlling undesirable vegetation which comprises contacting the vegetation or the locus thereof or applying to the soil to prevent the emergence of vegetation with an herbicidally effective amount of a 4-aminopicolinate of Formula I:



- 15 wherein

X represents H, halogen, C_1-C_6 alkoxy, C_1-C_6 alkylthio, aryloxy, cyano or trifluoromethyl;

Y represents halogen, C_1-C_6 alkoxy, C_1-C_6 alkylthio, aryloxy, cyano or trifluoromethyl;

- 20 Z represents halogen, C_1-C_6 alkoxy, C_1-C_6 alkylthio, aryloxy, cyano or trifluoromethyl;

W represents $-NR_1R_2$, $-N=CR_3R_4$ or $-NHN=CR_3R_4$

where

- 25 R_1 and R_2 independently represent H, C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, aryl, heteroaryl, hydroxy, C_1-

C₃ alkoxy, amino, C₁-C₅ acyl, C₁-C₅ carboalkoxy, C₁-C₅ alkylcarbonyl, C₁-C₅ alkylsulfonyl, C₁-C₆ trialkylsilyl or C₁-C₅ dialkyl phosphonyl or R₁ and R₂ taken together with N represent a 5- or 6-membered saturated or unsaturated ring which may contain additional O or N heteroatoms; and

R₃ and R₄ independently represent H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl or heteroaryl or R₃ and R₄ taken together with =C represent a 5- or 6-membered saturated ring; and

10 agriculturally acceptable derivatives of the carboxylic acid, with the proviso that when X represents Cl, then Y and Z are not both Cl.

6. A method of claim 5 wherein:

15 X represents H, halogen, cyano or trifluoromethyl;

Y represents halogen, cyano or trifluoromethyl;

Z represents halogen, cyano or trifluoromethyl;

W represents -NR₁R₂

where

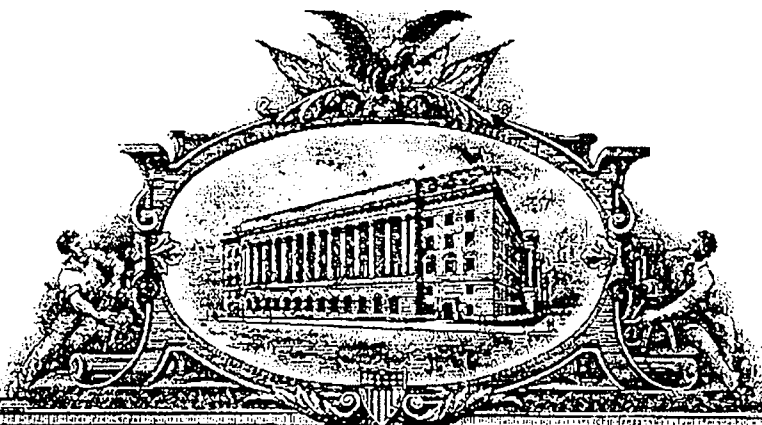
20 R₁ and R₂ independently represent H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl or R₁ and R₂ taken together with N represent a 5- or 6-membered saturated ring which may contain additional O or N heteroatoms; and

25 agriculturally acceptable salts, esters or amides of the carboxylic acid.

ABSTRACT

- 5 4-Aminopicolinic acids, having halogen, alkoxy, alkylthio, aryloxy, cyano or trifluoromethyl substituents in the 3-, 5- and 6-positions, and their amine and acid derivatives are potent herbicides demonstrating a broad spectrum of weed control.

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NÚMERO DE SOLICITUD: 60/176,720
FECHA DE PRESENTACIÓN: 14 de enero de 2000

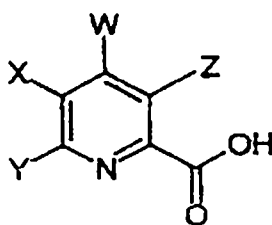


Por la Autoridad del
COMISARIO DE PATENTES Y MARCAS

Oficial certificador

REIVINDICACIONES

1. Un compuesto de fórmula I:



I

En donde

X representa H, halógeno, alcoxi C₁-C₆, alquiltio C₁-C₆, ariloxi, nitro o trifluorometilo;

Y representa halógeno, alcoxi C₁-C₆ alquiltio, ariloxi, heteroariloxi, o trifluorometilo;

Z representa halógeno, alcoxi C₁-C₆, alquiltio, C₁-C₆ ariloxi o nitro;

W representa $-\text{NO}_2$, $-\text{N}_3$, $-\text{NR}_1\text{R}_2$, $-\text{N}=\text{CR}_3\text{R}_4$ o $-\text{NHN}=\text{CR}_3\text{R}_4$

Donde

R_1 y R_2 independientemente representan H, alquilo, $\text{C}_1\text{-C}_6$ alquenilo $\text{C}_3\text{-C}_6$, alquinilo $\text{C}_3\text{-C}_6$, arilo, heteroarilo, hidroxilo, alcoxi $\text{C}_1\text{-C}_6$, amino, acilo $\text{C}_1\text{-C}_6$, carboalcoxi $\text{C}_1\text{-C}_6$, alquilcarbamilo $\text{C}_1\text{-C}_6$, alquilsulfonilo $\text{C}_1\text{-C}_6$, trialquisililo $\text{C}_1\text{-C}_6$ o dialquilsulfonilo $\text{C}_1\text{-C}_6$ o R_1 y R_2 tomados juntos con N representan un anillo saturado o insaturado de 5 o 6 miembros que puede contener heteroátomos O, S o N adicionales;

R_3 y R_4 independientemente representan H, alquilo $\text{C}_1\text{-C}_6$, alquenilo $\text{C}_3\text{-C}_6$, alquinilo $\text{C}_3\text{-C}_6$, arilo o heteroarilo o R_3 o R_4 tomados juntos con $=\text{C}$ representan un anillo saturado de 5 o 6 miembros; y

Los derivados agrícolamente aceptables del ácido carboxílico, con la condición de que cuando X representa CL, entonces Y y Z no son ambos CL.

2. Un compuesto de la fórmula 1 en donde:

X representa H, halógeno, o trifluorometilo;

Y representa halógeno, ariloxi, heteroariloxi, o trifluorometilo;

Z representa halógeno;

W representa $-NR_1R_2$

En donde R_1 y R_2 independientemente representan H, alquilo C_1-C_6 , alquenilo C_3-C_6 , alquinilo C_3-C_6 , o R_1 y R_2 tomados juntos con N representan un anillo saturado o insaturado de 5 o 6 miembros que puede contener heteroátomos O, S o N adicionales; y

Sales agriculturalmente aceptables, ésteres o amidas del ácido carboxílico.

3. Un compuesto según la reivindicación 1 o la reivindicación 2 en donde:

X representa H o F;

Y representa F, CL, Br o ariloxi;

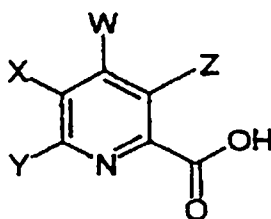
Z representa Cl; y

W representa $-NH_2$.

4. Un compuesto según una cualquiera de las reivindicaciones 1 a 3 en donde:

Y representa un grupo fenoxi sustituido con halógeno o grupos alquilo con 1 a 4 átomos de carbono en la posición 3.

5. Una composición herbicida que comprende una cantidad herbicidamente efectiva de un 4-aminopicolinato de fórmula I:



I

En donde

X representa H, halógeno, alcoxi C_1-C_6 , alquiltio C_1-C_6 , ariloxi, nitro o trifluorometilo;

Y representa halógeno, alcoxi C_1-C_6 alquiltio C_1-C_6 , ariloxi, heteroariloxi, o trifluorometilo;

Z representa halógeno, alcoxi C_1-C_6 , alquiltio C_1-C_6 , ariloxi o nitro; y

W representa $-NO_2$, $-N_3$, $-NR_1R_2$, $-N=CR_3R_4$ o $-NHN=CR_3R_4$

Donde

R_1 y R_2 independientemente representan H, alquilo C_1-C_6 , alquenilo C_3-C_6 , alquinilo C_3-C_6 , arilo, heteroarilo, hidroxilo, alcoxi C_1-C_6 , amino, acilo C_1-C_6 , carboalcoxi C_1-C_6 , alquilcarbamilo C_1-C_6 , alquilsulfonilo C_1-C_6 , trialquilsililo C_1-C_6 o dialquilsulfonilo C_1-C_6 o R_1 y R_2 tomados juntos con N representan un anillo saturado o insaturado de 5 o 6 miembros que puede contener heteroátomos O, S o N adicionales; y

R_3 y R_4 independientemente representa H, alquilo C_1-C_6 , alquenilo C_3-C_6 , alquinilo C_3-C_6 , arilo o heteroarilo o R_3 o R_4 tomados juntos con $=C$ representan un anillo saturado de 5 o 6 miembros; y

Los derivados agrícolamente aceptables del ácido carboxílico, con la condición de que cuando X representa Cl, entonces Y y Z no son ambos Cl, en mezcla con un adyuvante o portador agrícolamente aceptable.

6. Una composición herbicida de la reivindicación 5 en donde:

X representa H, halógeno o trifluorometilo;

Y representa halógeno, ariloxi, heteroariloxi o trifluorometilo;

Z representa halógeno; y

W representa $-NR_1R_2$

En donde

R_1 y R_2 independientemente representan H, alquilo C_1-C_6 , alquenilo C_3-C_6 , alquinilo C_3-C_6 , o R_1 y R_2 tomados juntos con N representan un anillo saturado o insaturado de 5 o 6 miembros que puede contener heteroátomos O, S o N adicionales; y

Sales agrícolas aceptables, ésteres o amidas del ácido carboxílico.

4-AMINOPICOLINATES AND THEIR USE AS HERBICIDES

This invention relates to certain novel 4-aminopicolinates and their derivatives and to the use of these compounds as herbicides.

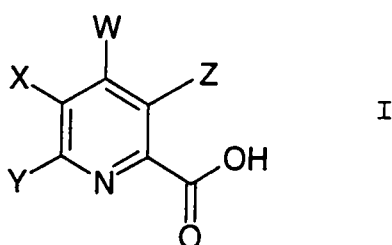
A number of picolinic acids and their pesticidal properties have been described in the art. For example, U.S. Patent 3,285,925 discloses 4-amino-3,5,6-trichloropicolinic acid derivatives and their use as plant growth control agents and herbicides. U.S. Patent 3,325,272 discloses 4-amino-3,5-dichloropicolinic acid derivatives and their use for the control of plant growth. U.S. Patent 3,317,549 discloses 3,6-dichloropicolinic acid derivatives and their use as plant growth control agents. U.S. Patent 3,334,108 discloses chlorinated dithiopicolinic acid derivatives and their use as parasiticides. U.S. Patent 3,234,229 discloses 4-amino-polychloro-2-trichloromethylpyridines and their use as herbicides. In *Applied and Environmental Microbiology*, Vol. 59, No. 7, July 1993, pp. 2251-2256, 4-amino-3,6-dichloropicolinic acid is identified as a product of the anaerobic degradation of 4-amino-3,5,6-trichloropicolinic acid, the commercially available herbicide picloram.

While picloram is recommended for the control of woody plants and broadleaf weeds in certain applications, its properties are not ideal. It would be highly desirable to discover related compounds that

are more potent, more selective or of broader spectrum in their herbicidal activity and/or that have improved toxicological or environmental properties.

It has now been found that certain 4-amino-
5 picolinic acids and their derivatives having selected substituents in the 3-, 5-, and 6-positions are potent herbicides with a broad spectrum of weed control and excellent crop selectivity. The compounds further possess excellent toxicological or environmental
10 profiles.

The invention includes compounds of Formula I:



15 wherein

X represents H, halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, nitro or trifluoromethyl;

Y represents halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, heteroaryloxy or trifluoromethyl;

20 Z represents halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy or nitro; and

W represents $-\text{NO}_2$, $-\text{N}_3$, $-\text{NR}_1\text{R}_2$, $-\text{N}=\text{CR}_3\text{R}_4$ or $-\text{NHN}=\text{CR}_3\text{R}_4$

where

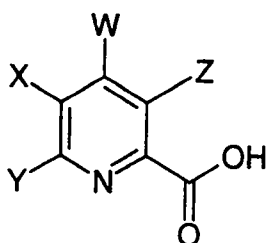
R_1 and R_2 independently represent H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ alkenyl, $\text{C}_3\text{-C}_6$ alkynyl, aryl, heteroaryl, hydroxy, $\text{C}_1\text{-C}_6$ alkoxy, amino, $\text{C}_1\text{-C}_6$ acyl, $\text{C}_1\text{-C}_6$ carboalkoxy, $\text{C}_1\text{-C}_6$ alkylcarbonyl, $\text{C}_1\text{-C}_6$ alkylsulfonyl, $\text{C}_1\text{-C}_6$ trialkylsilyl or $\text{C}_1\text{-C}_6$ dialkyl phosphonyl or R_1 and R_2 taken together with N represent a 5- or 6-membered saturated or unsaturated ring which may contain additional O, S or N heteroatoms; and

R_3 and R_4 independently represent H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ alkenyl, $\text{C}_3\text{-C}_6$ alkynyl, aryl or heteroaryl or R_3 and R_4 taken together with $=\text{C}$ represent a 5- or 6-membered saturated ring; and

agriculturally acceptable derivatives of the carboxylic acid, with the proviso that when X represents H or Cl, then Y and Z are not both Cl.

Compounds of Formula I wherein X represents H or F, wherein Y represents F, Cl, Br or aryloxy, wherein Z represents Cl and wherein R_1 and R_2 represent H are independently preferred.

The invention includes herbicidal compositions comprising a herbicidally effective amount of a 4-amino-picolinate of Formula I:



I

wherein

X represents H, halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, nitro or trifluoromethyl;

5 Y represents halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, heteroaryloxy or trifluoromethyl;

Z represents halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy or nitro; and

10 W represents -NO₂, -N₃, -NR₁R₂, -N=CR₃R₄ or -NHN=CR₃R₄

where

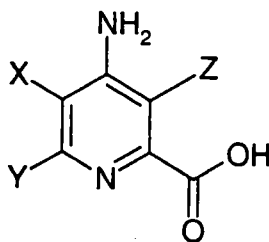
R₁ and R₂ independently represent H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl, heteroaryl, hydroxy, C₁-C₆ alkoxy, amino, C₁-C₆ acyl, C₁-C₆ carboalkoxy, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylsulfonyl, C₁-C₆ trialkylsilyl or C₁-C₆ dialkyl phosphonyl or R₁ and R₂ taken together with N represent a 5- or 6-membered saturated or unsaturated ring which may contain additional O, S or N heteroatoms; and

20 R₃ and R₄ independently represent H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl or heteroaryl or R₃ and R₄ taken together with =C represent a 5- or 6-membered saturated ring; and

agriculturally acceptable derivatives of the carboxylic acid, with the proviso that when X represents Cl, then Y and Z are not both Cl

in admixture with an agriculturally acceptable
5 adjuvant or carrier. The invention also includes a method of use of the compounds and compositions of the present invention to kill or control undesirable vegetation by application of an herbicidal amount of the compound to the vegetation or to the locus of the
10 vegetation as well as to the soil prior to emergence of the vegetation. The use of the compounds to kill or control woody plants and broadleaf weeds in grass crops is a preferred utility and post-emergent application of the compounds to the undesirable
15 vegetation is a preferred method of application.

The herbicidal compounds of the present invention are derivatives of 4-aminopicolinic acids:



These compounds are characterized by possessing
20 halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy or nitro substituents in the 3-position with halogen being preferred and chlorine being most preferred; by possessing hydrogen, halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, nitro or trifluoromethyl
25 substituents in the 5-position with hydrogen and fluorine being preferred; and by possessing halogen,

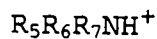
C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, heteroaryloxy or trifluoromethyl substituents in the 6-position with fluorine, chlorine, bromine or aryloxy being preferred. Preferred aryloxy groups in the 6-position are 3-substituted phenoxy groups, most preferably phenoxy groups substituted with halogen or C₁-C₄ alkyl groups in the 3-position.

The amino group at the 4-position can be unsubstituted or substituted with one or more C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl, heteroaryl, hydroxy, C₁-C₆ alkoxy or amino substituents. The amino group can be further derivatized as an amide, a carbamate, a urea, a sulfonamide, a silylamine, a phosphoramidate, an imine or a hydrazone. Such derivatives are capable of breaking down into the amine. An unsubstituted amino group or one substituted with one or more alkyl substituents is preferred.

The carboxylic acids of Formula I are believed to be the compounds that actually kill or control undesirable vegetation and are typically preferred. Analogs of these compounds in which the acid or amine group of the picolinic acid is derivatized to form a related substituent that can be transformed within plants or the environment to a acid group possess essentially the same herbicidal effect and are within the scope of the invention. Therefore, an "agriculturally acceptable derivative", when used to describe the carboxylic acid functionality at the 2-position, is defined as any salt, ester, acylhydrazide, imidate, thioimidate, amidine, amide, orthoester, acylcyanide, acyl halide, thioester,

thionoester, dithiolester, nitrile or any other acid derivative well known in the art which (a) does not substantially affect the herbicidal activity of the active ingredient, i.e., the 4-aminopicolinic acid, and (b) is or can be hydrolyzed in plants or soil to the picolinic acid of Formula I that, depending upon the pH, is in the dissociated or the undissociated form. Likewise, an "agriculturally acceptable derivative", when used to describe the amine functionality at the 4-position, is defined as any salt, silylamine, phosphorylamine, phosphinimine, phosphoramidate, sulfonamide, sulfinimine, sulfoximine, aminal, hemiaminal, amide, thioamide, carbamate, thiocarbamate, amidine, urea, imine, nitro, nitroso, azide, or any other nitrogen containing derivative well known in the art which (a) does not substantially affect the herbicidal activity of the active ingredient, i.e., the 4-aminopicolinic acid, and (b) is or can be hydrolyzed in plants or soil to a free amine of Formula I. N-Oxides which are also capable of breaking into the parent pyridine of Formula I are also covered by the scope of this invention.

Suitable salts include those derived from alkali or alkaline earth metals and those derived from ammonia and amines. Preferred cations include sodium, potassium, magnesium, and aminium cations of the formula:



wherein R_5 , R_6 , and R_7 each, independently represents hydrogen or C_1 - C_{12} alkyl, C_3 - C_{12} alkenyl or C_3 - C_{12}

alkynyl, each of which is optionally substituted by one or more hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkylthio or phenyl groups, provided that R₅, R₆, and R₇ are sterically compatible. Additionally, any two of R₅,
5 R₆, and R₇ together may represent an aliphatic difunctional moiety containing 1 to 12 carbon atoms and up to two oxygen or sulfur atoms. Salts of the compounds of Formula I can be prepared by treatment of
10 compounds of Formula I with a metal hydroxide, such as sodium hydroxide, or an amine, such as ammonia, trimethylamine, diethanolamine, 2-methylthiopropylamine, bisallylamine, 2-butoxyethylamine, morpholine, cyclododecylamine, or benzylamine. Amine salts are often preferred forms of the compounds of
15 Formula I because they are water-soluble and lend themselves to the preparation of desirable aqueous based herbicidal compositions.

Suitable esters include those derived from C₁-C₁₂ alkyl, C₃-C₁₂ alkenyl or C₃-C₁₂ alkynyl alcohols,
20 such as methanol, *iso*-propanol, butanol, 2-ethylhexanol, butoxyethanol, methoxypropanol, allyl alcohol, propargyl alcohol or cyclohexanol. Esters can be prepared by coupling of the picolinic acid with the alcohol using any number of suitable activating
25 agents such as those used for peptide couplings such as dicyclohexylcarbodiimide (DCC) or carbonyl diimidazole (CDI), by reacting the corresponding acid chloride of a picolinic acid of Formula I with an appropriate alcohol or by reacting the corresponding
30 picolinic acid of Formula I with an appropriate alcohol in the presence of an acid catalyst. Suitable amides include those derived from ammonia or from

C₁-C₁₂ alkyl, C₃-C₁₂ alkenyl or C₃-C₁₂ alkynyl mono- or di-substituted amines, such as but not limited to dimethylamine, diethanolamine, 2-methylthiopropylamine, bisallylamine, 2-butoxyethylamine, cyclo-
5 dodecylamine, benzylamine or cyclic or aromatic amines with or without additional heteroatoms such as but not limited to aziridine, azetidine, pyrrolidine, pyrrole, imidazole, tetrazole or morpholine. Amides can be prepared by reacting the corresponding
10 picolinic acid chloride, mixed anhydride, or carboxylic ester of Formula I with ammonia or an appropriate amine.

The terms "alkyl", "alkenyl" and "alkynyl", as well as derivative terms such as "alkoxy", "acyl",
15 "alkylthio" and "alkylsulfonyl", as used herein, include within their scope straight chain, branched chain and cyclic moieties. Unless specifically stated otherwise, each may be unsubstituted or substituted with one or more substituents selected from but not
20 limited to halogen, hydroxy, alkoxy, alkylthio, C₁-C₆ acyl, formyl, cyano, aryloxy or aryl, provided that the substituents are sterically compatible and the rules of chemical bonding and strain energy are satisfied. The terms "alkenyl" and "alkynyl" are
25 intended to include one or more unsaturated bonds.

The term "aryl", as well as derivative terms such as "aryloxy", refers to a phenyl or naphthyl group. The term "heteroaryl", as well as derivative terms such as "heteroaryloxy", refers to a 5- or 6-
30 membered aromatic ring containing one or more heteroatoms, viz., N, O or S; these heteroaromatic

rings may be fused to other aromatic systems. The aryl or heteroaryl substituents may be unsubstituted or substituted with one or more substituents selected from halogen, hydroxy, nitro, cyano, aryloxy, formyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, halogenated C₁-C₆ alkyl, halogenated C₁-C₆ alkoxy, C₁-C₆ acyl, C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonyl, aryl, C₁-C₆ OC(O)alkyl, C₁-C₆ NHC(O)alkyl, C(O)OH, C₁-C₆ C(O)Oalkyl, C(O)NH₂, C₁-C₆ C(O)NHalkyl, or C₁-C₆ C(O)N(alkyl)₂, provided that the substituents are sterically compatible and the rules of chemical bonding and strain energy are satisfied.

Unless specifically limited otherwise, the term halogen includes fluorine, chlorine, bromine, and iodine.

The compounds of Formula I can be made using well-known chemical procedures. The required starting materials are commercially available or readily synthesized utilizing standard procedures.

In general, reduction of picolinate N-oxides can be used to prepare the corresponding picolines. Electrolytic dehalogenation of 5-halogenated picolines can be used to prepare the 5-H (unsubstituted) picolines, and hydrolysis of pyridines substituted at the 2 position by nitriles, amides, esters and other hydrolyzable functionalities can be used to prepare the desired picolines.

4-N-amide, carbamate, urea, sulfonamide, silylamine and phosphoramidate amino derivatives can be prepared by the reaction of the free amino compound

with, for example, a suitable acid halide, chloroformate, carbamyl chloride, sulfonyl chloride, silyl chloride or chlorophosphate. The imine or hydrazone can be prepared by reaction of the free
5 amine or hydrazine with a suitable aldehyde or ketone.

6-Bromo analogs can be prepared by the reduction of several key intermediates, e.g., the corresponding 6-bromo-4-azido, 6-bromo-4-nitro, and 6-bromo-4-nitro pyridine *N*-oxide analogs. These
10 intermediates, in turn, can be prepared either by nucleophilic displacement of 6-bromo-4-halo analogs with NaN_3 or by electrophilic nitration of the corresponding 6-bromopyridine-*N*-oxides. Alternatively, such analogs can be prepared by direct
15 amination of the corresponding 4,6-dibromo analogs.

6-Fluoro analogs can be prepared by direct amination of the corresponding 4,6-difluoro analog.

3- and 5-Alkoxy and aryloxy analogs can be prepared by reduction of the corresponding 4-azido derivatives, which in turn can be prepared by
20 nucleophilic displacement of the corresponding 4-bromopyridines with NaN_3 . The required 3- and 5-alkoxy-4-bromopyridines can be prepared according to literature procedures.

25 6-Alkoxy, alkylthio, aryloxy and heteroaryloxy analogs can be prepared by nucleophilic displacement with alkoxide, thioalkoxide, aryloxide or heteroaryloxide on the appropriate 6-halopyridine.

3- and 5-Alkylthio analogs can be prepared by lithiation of the appropriate chloropyridines at low temperature and sequential treatment with alkyl disulfides and carbon dioxide. Reaction of the
5 resulting picolinic acids with ammonium hydroxide gave the desired products.

6-Cyano analogs can be prepared by amination of the appropriate 4-halo-6-cyanopicolinate. 4-Halo-6-cyanopicolines can be prepared by action of
10 trimethylsilyl cyanide (TMSCN) on the appropriate pyridine *N*-oxide, which can be prepared by hydrogen peroxide mediated oxidation of the corresponding pyridine.

3- and 5-Cyano analogs can be prepared by
15 action of KCN on the appropriate fluoropyridine at high temperature. 3- and 5-Fluoro, bromo, iodo and nitro analogs can be prepared by electrophilic reaction of the unsubstituted precursor with positive halogen or nitro sources such as fluorine gas,
20 bromine, iodine and fuming nitric acid respectively.

6-Trifluoromethyl analogs can be prepared by amination of readily available methyl trifluoromethylpicolinate (oxidative halogenation of the 4-position followed by displacement with ammonia or an amine
25 equivalent) followed by chlorination of the 3- and 5-positions.

3- and 5-Trifluoromethyl analogs can be prepared by standard manipulations known to those skilled in the art starting from the known compounds

2-fluoro-3-chloro-5-trifluoromethylpyridine and 2,5-dichloro-3-trifluoromethylpyridine.

Substituted 4-amino analogs can be prepared by reacting the corresponding 4-halopyridine-2-carboxylate or any other displaceable 4-substituent with the substituted amine.

The compounds of Formula I, obtained by any of these processes, can be recovered by conventional means. Typically, the reaction mixture is acidified with an aqueous acid, such as hydrochloric acid, and extracted with an organic solvent, such as ethyl acetate or dichloromethane. The organic solvent and other volatiles can be removed by distillation or evaporation to obtain the desired compound of Formula I, which can be purified by standard procedures, such as by recrystallization or chromatography.

The compounds of Formula I have been found to be useful pre-emergence and post-emergence herbicides. They can be employed at non-selective (higher) rates of application to control a broad spectrum of the vegetation in an area or at lower rates of application for the selective control of undesirable vegetation. Areas of application include pasture and rangelands, roadsides and rights of ways, and crops such as corn, rice and cereals. It is usually preferred to employ the compounds post-emergence. It is further usually preferred to use the compounds to control a wide spectrum of broadleaf weeds, including Dock species (*Rumex* spp), Canada thistle (*Cirsium arvense*), pigweed species (*Amaranthus* spp.), Senna species (*Cassia* spp.), spurge species

(Euphorbia spp), ragweed species (Ambrosia spp.), Sida species (Sida spp.), field bindweed (Convolvulus arvensis), and knapweed species (Centaurea spp.), among others. Use of the compounds to control undesirable vegetation in grassy areas is especially indicated. While each of the 4-aminopicolinate compounds encompassed by Formula I is within the scope of the invention, the degree of herbicidal activity, the crop selectivity, and the spectrum of weed control obtained varies depending upon the substituents present. An appropriate compound for any specific herbicidal utility can be identified by using the information presented herein and routine testing.

The term herbicide is used herein to mean an active ingredient that kills, controls or otherwise adversely modifies the growth of plants. An herbicidally effective or vegetation controlling amount is an amount of active ingredient which causes an adversely modifying effect and includes deviations from natural development, killing, regulation, desiccation, retardation, and the like. The terms plants and vegetation include germinant seeds, emerging seedlings and established vegetation.

Herbicidal activity is exhibited by the compounds of the present invention when they are applied directly to the plant or to the locus of the plant at any stage of growth or before planting or emergence. The effect observed depends upon the plant species to be controlled, the stage of growth of the plant, the application parameters of dilution and spray drop size, the particle size of solid

components, the environmental conditions at the time of use, the specific compound employed, the specific adjuvants and carriers employed, the soil type, and the like, as well as the amount of chemical applied.

5 These and other factors can be adjusted as is known in the art to promote non-selective or selective herbicidal action. Generally, it is preferred to apply the compounds of Formula I postemergence to relatively immature undesirable vegetation to achieve

10 the maximum control of weeds.

Application rates of 1 to 500 g/Ha are generally employed in postemergence operations; for preemergence applications, rates of 10 to 1000 g/Ha are generally employed. The higher rates designated

15 generally give non-selective control of a broad variety of undesirable vegetation. The lower rates typically give selective control and can be employed in the locus of crops.

The herbicidal compounds of the present

20 invention are often best applied in conjunction with one or more other herbicides to obtain control of a wider variety of undesirable vegetation. When used in conjunction with other herbicides, the presently claimed compounds can be formulated with the other

25 herbicide or herbicides, tank mixed with the other herbicide or herbicides, or applied sequentially with the other herbicide or herbicides. Some of the herbicides that can be employed in conjunction with the compounds of the present invention include

30 sulfonamides such as metosulam, flumetsulam, cloransulam-methyl, diclosulam and florasulam,

sulfonylureas such as chlorimuron, nicosulfuron and metsulfuron, imidazolinones such as imazaquin, imazapic, imazethapyr and imazamox, phenoxyalkanoic acids such as 2,4-D and MCPA, pyridinyloxyacetic acids
5 such as triclopyr and fluroxypyr, carboxylic acids such as clopyralid and dicamba, dinitroanilines such as trifluralin and pendimethalin, chloroacetanilides such as alachlor, acetochlor and metolachlor and other common herbicides including acifluorfen, bentazon,
10 clomazone, fumiclorac, fluometuron, fomesafen, lactofen, linuron, isoproturon, and metribuzin. Particularly preferred combinations are those with florasulam, 2,4-D and fluroxypyr, which, against some weed species, may actually exhibit synergy. A
15 synergistic response may also be obtained with compounds of the present invention when mixed with auxin transport inhibitors such as diflufenzopyr and chlorflurenol. The herbicidal compounds of the present invention can, further, be used in conjunction
20 with glyphosate and glufosinate on glyphosate-tolerant or glufosinate-tolerant crops. It is generally preferred to use the compounds of the invention in combination with herbicides that are selective for the crop being treated and which complement the spectrum
25 of weeds controlled by these compounds at the application rate employed. It is further generally preferred to apply the compounds of the invention and other complementary herbicides at the same time, either as a combination formulation or as a tank mix.

30 The compounds of the present invention can generally be employed in combination with known herbicide safeners, such as cloquintocet, furilazole,

dichlormid, benoxacor, mefenpyr-ethyl, fenclozazole-ethyl, flurazole, and fluxofenim, to enhance their selectivity. They can additionally be employed to control undesirable vegetation in many crops that have been made tolerant to or resistant to them or to other herbicides by genetic manipulation or by mutation and selection. For example, corn, wheat, rice, soybean, sugarbeet, cotton, canola, and other crops that have been made tolerant or resistant to compounds that are acetolactate synthase inhibitors in sensitive plants can be treated. Many glyphosate and glufosinate tolerant crops can be treated as well, alone or in combination with these herbicides. Some crops (e.g. cotton) have been made tolerant to auxinic herbicides such as 2,4-dichlorophenoxyacetic acid. These herbicides may be used to treat such resistant crops or other auxin tolerant crops.

While it is possible to utilize the 4-amino-picolinate compounds of Formula I directly as herbicides, it is preferable to use them in mixtures containing a herbicidally effective amount of the compound along with at least one agriculturally acceptable adjuvant or carrier. Suitable adjuvants or carriers should not be phytotoxic to valuable crops, particularly at the concentrations employed in applying the compositions for selective weed control in the presence of crops, and should not react chemically with the compounds of Formula I or other composition ingredients. Such mixtures can be designed for application directly to weeds or their locus or can be concentrates or formulations that are normally diluted with additional carriers and

adjuvants before application. They can be solids, such as, for example, dusts, granules, water dispersible granules, or wettable powders, or liquids, such as, for example, emulsifiable concentrates,
5 solutions, emulsions or suspensions.

Suitable agricultural adjuvants and carriers that are useful in preparing the herbicidal mixtures of the invention are well known to those skilled in the art.

10 Liquid carriers that can be employed include water, toluene, xylene, petroleum naphtha, crop oil, acetone, methyl ethyl ketone, cyclohexanone, trichloroethylene, perchloroethylene, ethyl acetate, amyl acetate, butyl acetate, propylene glycol
15 monomethyl ether and diethylene glycol monomethyl ether, methanol, ethanol, isopropanol, amyl alcohol, ethylene glycol, propylene glycol, glycerine, and the like. Water is generally the carrier of choice for the dilution of concentrates.

20 Suitable solid carriers include talc, pyrophyllite clay, silica, attapulgus clay, kaolin clay, kieselguhr, chalk, diatomaceous earth, lime, calcium carbonate, bentonite clay, Fuller's earth, cotton seed hulls, wheat flour, soybean flour, pumice, wood flour,
25 walnut shell flour, lignin, and the like.

It is usually desirable to incorporate one or more surface-active agents into the compositions of the present invention. Such surface-active agents are advantageously employed in both solid and liquid
30 compositions, especially those designed to be diluted

with carrier before application. The surface-active agents can be anionic, cationic or nonionic in character and can be employed as emulsifying agents, wetting agents, suspending agents, or for other purposes. Typical surface-active agents include salts of alkyl sulfates, such as diethanolammonium lauryl sulfate; alkylarylsulfonate salts, such as calcium dodecylbenzenesulfonate; alkylphenol-alkylene oxide addition products, such as nonylphenol-C₁₈ ethoxylate; alcohol-alkylene oxide addition products, such as tridecyl alcohol-C₁₆ ethoxylate; soaps, such as sodium stearate; alkyl naphthalenesulfonate salts, such as sodium dibutyl naphthalenesulfonate; dialkyl esters of sulfosuccinate salts, such as sodium di(2-ethylhexyl) sulfosuccinate; sorbitol esters, such as sorbitol oleate; quaternary amines, such as lauryl trimethylammonium chloride; polyethylene glycol esters of fatty acids, such as polyethylene glycol stearate; block copolymers of ethylene oxide and propylene oxide; and salts of mono and dialkyl phosphate esters.

Other adjuvants commonly used in agricultural compositions include compatibilizing agents, antifoam agents, sequestering agents, neutralizing agents and buffers, corrosion inhibitors, dyes, odorants, spreading agents, penetration aids, sticking agents, dispersing agents, thickening agents, freezing point depressants, antimicrobial agents, and the like. The compositions may also contain other compatible components, for example, other herbicides, plant growth regulants, fungicides, insecticides, and the like and can be formulated with liquid fertilizers or

solid, particulate fertilizer carriers such as ammonium nitrate, urea and the like.

The concentration of the active ingredients in the herbicidal compositions of this invention is generally from 0.001 to 98 percent by weight. Concentrations from 0.01 to 90 percent by weight are often employed. In compositions designed to be employed as concentrates, the active ingredient is generally present in a concentration from 5 to 98 weight percent, preferably 10 to 90 weight percent. Such compositions are typically diluted with an inert carrier, such as water, before application. The diluted compositions usually applied to weeds or the locus of weeds generally contain 0.0001 to 1 weight percent active ingredient and preferably contain 0.001 to 0.05 weight percent.

The present compositions can be applied to weeds or their locus by the use of conventional ground or aerial dusters, sprayers, and granule applicators, by addition to irrigation water, and by other conventional means known to those skilled in the art.

The following Examples are presented to illustrate the various aspects of this invention and should not be construed as limitations to the claims.

Examples1. Preparation of 4-Amino-3,6-dichloropyridine-2-carboxylic acid (Compound 1)

In a 3-liter (L) beaker was added 2000 grams
5 (g) of hot water, 115.1 g of 50 percent by weight
NaOH, and 200 g of wet 4-amino-3,5,6-trichloro-
pyridine-2-carboxylic acid (79.4 percent). The
solution was stirred for 30 minutes (min), filtered
through a paper filter, and transferred to a 5-L
10 feed/recirculation tank. This solution weighed 2315 g
and contained 6.8 percent 4-amino-3,5,6-trichloro-
pyridine-2-carboxylic acid. This feed was
recirculated at a rate of about 9.46 L/min and a
temperature of 30°C through an undivided
15 electrochemical cell having a Hastelloy C anode and an
expanded silver mesh screen cathode. After normal
anodization at +0.7 volt (v), the polarity of the cell
was reversed and the electrolysis was started. The
cathode working potential was controlled at -1.1 to
20 -1.4 v relative to an Ag/AgCl (3.0 M Cl⁻) reference
electrode. While recirculating the feed, a solution of
50 percent NaOH is slowly pumped into the
recirculation tank to maintain the NaOH concentration
at a 1.5 to 2.0 percent excess. After about 15 hours
25 (hr), the electrolysis was terminated and the cell
effluent was filtered through a paper filter. The
solution was neutralized with concentrated HCl and
concentrated to about 750 g of crude concentrate. The
concentrate was warmed to 85°C with stirring and the
30 pH was adjusted to less than 1 with concentrated HCl
over 30 min. The resulting slurry was cooled to

ambient temperature and filtered. The filter cake was washed with 3x200 milliliter (mL) portions of water and dried under vacuum at 80°C. The dried product, 118.1 g assayed at 90.6 percent desired product; gas chromatography (GC) indicated about 4 percent 4-amino-3,5,6-trichloropyridine-2-carboxylic acid remaining as an impurity. A purified sample of 4-amino-3,6-dichloropyridine-2-carboxylic acid had a melting point (mp) of 185-187°C (dec.); ¹H NMR (DMSO-d₆): δ 13.9 (br, 1H), 7.0 (br m, 2H), 6.8 (s, 1H); ¹³C NMR {¹H} (DMSO-d₆): δ 165.4 (1C), 153.4 (1C), 149.5 (1C), 147.7 (1C), 111.0 (1C), 108.1 (1C).

2. Preparation of 2-Ethylhexyl 4-amino-3,6-dichloropyridine-2-carboxylate (Compound 2)

To a solution of 2-ethylhexanol (10 mL) and sulfuric acid (1 mL) was added 4-amino-3,6-dichloropyridine-2-carboxylic acid (0.0097 mol, 2.0 g). After heating the reaction to reflux overnight, the reaction mixture was cooled, poured into water (75 mL), and extracted with ethyl acetate (75 mL). The organic phase was washed with sodium bicarbonate (75 mL), dried (Na₂SO₄), and concentrated. The resulting solid was recrystallized out of dichloromethane and hexane and filtered to give 2-ethylhexyl 4-amino-3,6-dichloropyridine-2-carboxylate (0.0074 mol, 2.36 g) as a crystalline solid (mp 55°C). ¹H NMR (CDCl₃): δ 0.9 (7 H, m), 1.3 (7 H, m), 1.7 (1 H, m), 4.3 (2 H, d), 5.1 (2 H, bs), 6.7 (1 H, s).

The following esters of 4-amino-3,5,6-trichloro-pyridine-2-carboxylic acid were prepared according to the procedure of Example 2:

methyl 4-amino-3,6-dichloropyridine-2-carboxylate(Compound 3); mp 134-135°C.

ethyl 4-amino-3,6-dichloropyridine-2-carboxylate(Compound 4); mp 98-99°C.

5 *n*-propyl 4-amino-3,6-dichloropyridine-2-carboxylate(Compound 5); mp 94-95°C.

i-propyl 4-amino-3,6-dichloropyridine-2-carboxylate(Compound 6); mp 114-115°C.

10 *n*-butyl 4-amino-3,6-dichloropyridine-2-carboxylate(Compound 7); mp 78-79°C.

n-pentyl 4-amino-3,6-dichloropyridine-2-carboxylate (Compound 8); mp 71-73°C.

n-hexyl 4-amino-3,6-dichloropyridine-2-carboxylate (Compound 9); mp 65-66°C.

15 butoxyethyl 4-amino-3,6-dichloropyridine-2-carboxylate (Compound 10); mp 64-7°C as the monohydrate.

20 3. Preparation of 4-Amino-3,6-dichloropyridine-2-carboxamide (Compound 11)

To a 250 mL three neck roundbottom flask fitted with a mechanical stirrer were added methyl 750 (10.0 g, 45 mmol) and 28% aq. NH₄OH (35 mL) at 0°C.
25 The suspension was stirred vigorously for 24 hr while warming gradually to 25°C. The suspension was suction filtered, and the filter cake was washed on the filter

with cold water (2 x 100 mL). After air drying on the filter, the analytically pure white solid product was collected to give 4-amino-3,6-dichloropyridine-2-carboxamide 11 (8.58 g, 92% yield); mp 240-241°C.

5 4. Preparation of Methyl N-acetyl 4-amino-3,6-
dichloropyridine-2-carboxylate (Compound 12) and N,N-
diacetyl 4-amino-3,6-dichloropyridine-2-carboxylate
(Compound 13)

10 A solution of acetic anhydride (75 mL) and
methyl 4-amino-3,6-dichloropyridine-2-carboxylate
(0.00904 mol, 2.0 g) was stirred and heated to reflux
overnight. The solution was cooled, concentrated,
taken up in ethyl acetate (100 mL), and washed with
water (100 mL). The organic phase was washed with
15 saturated sodium bicarbonate (100 mL), dried (Na_2SO_4),
and concentrated. The solution was purified by
chromatography on silica gel. The front running spot
was isolated and gave a yellow oil identified as the
diacylated 4-amide Compound 13 (0.0023 mol, 0.700 g).
20 ^1H NMR 2.2 (6 H, s), 3.9 (3 H, s), 7.3 (1 H, s). The
second spot gave a yellow solid identified as the
monoacylated 4-amide compound 12 (0.0035 mol, 0.920 g);
mp 102-103°C.

C. Methyl 4-amino-6-bromo-3-chloropyridine-2-carboxylate

To a solution of titanium tetrachloride (0.015 mol, 2.8 g) in tetrahydrofuran (50 mL) was added lithium aluminum hydride (0.0175 mol, 0.7 g). The black slurry was stirred 15 min before adding methyl 6-bromo-3-chloro-4-nitropyridine-2-carboxylate, N-oxide (0.007 mol, 2.3 g) in THF (25 mL). The solution was stirred 1 hr before pouring into 1:1 H₂O/NH₄OH and filtering. The filtrate was extracted with EtOAc (2 x 75 mL). The organic phase was dried (Na₂SO₄), and concentrated. The red solid was chromatographed over silica in 4:1 EtOAc/hexane to give methyl 4-amino-6-bromo-3-chloropyridine-2-carboxylate (0.003 mol, 0.8 g); mp 194-5°C. ¹H NMR(CDCl₃): δ 3.95 (3H, s), 5.3 (2H, bs), 6.9 (1H, s).

D. 4-Amino-6-bromo-3-chloropyridine-2-carboxylic acid (Compound 14)

To methyl 4-amino-6-bromo-3-chloropyridine-2-carboxylate (200mg; 0.8 mmol) in 10 mL of methanol was added excess 2N NaOH (10 mL). The mixture was stirred for 1 hr at ambient temperature and then evaporated to dryness *in vacuo*. The residue was dissolved in water and diethyl ether. After separation of the phases, the aqueous layer was acidified with 1N HCl to a pH=2. The aqueous layer was evaporated to dryness and the residue was dissolved in 50 mL of methanol and filtered. The filtrate was evaporated under reduced pressure and the residue was triturated with 5 percent diethyl ether in

petroleum ether to give 70 mg of 4-amino-6-bromo-3-chloropyridine-2-carboxylic acid, mp 182-183°C.

6. Preparation of Methyl 4-amino-3-chloro-6-fluoropyridine-2-carboxylate (Compound 15)

5 A. Methyl 3-chloro-4,6-difluoropyridine-2-carboxylate

To a solution of methyl 3,4,6-trichloropyridine-2-carboxylate (0.010 mol, 2.4 g) in DMSO (10 mL) was added cesium fluoride (0.038 mol, 3.8 g) and the suspension was heated for 2 hr at 100°C. The reaction mixture was dissolved in dilute HCl and extracted with ethyl acetate (EtOAc). The organic layer was treated with (trimethylsilyl)diazomethane (TMSCHN₂) to re-esterify any hydrolyzed ester. The mixture was concentrated and the resultant residue was chromatographed over silica with 10 percent EtOAc/hexane to give methyl 3-chloro-4,6-difluoropyridine-2-carboxylate (0.0072 mol, 1.5 g). ¹H NMR (CDCl₃): δ 4.00 (3H, s), 6.95-6.90 (1H, m). ¹⁹F NMR {¹H}: δ -65.0 (d, J = 17 Hz), 95.8 (d, J = 17 Hz).

B. Methyl 4-amino-3-chloro-6-fluoropyridine-2-carboxylate (Compound 15)

Sodium azide (0.0086 mol, 0.60 g) was added to a solution of methyl 3-chloro-4,6-difluoropyridine-2-carboxylate (0.0072 mol, 1.5 g) in 15 mL dimethyl formamide (DMF). The solution was stirred 10 min at ambient temperature before pouring into 350 mL water and extracting the aqueous mixture with EtOAc (2 x 100 mL). The organic phase was dried (Na₂SO₄) and then

treated with excess NaBH_4 for 30 min. The excess NaBH_4 was quenched with aqueous EtOH and the mixture was diluted with water (200 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to an off-white powder which was purified by reversed-phase HPLC to give methyl 4-amino-3-chloro-6-fluoropyridine-2-carboxylate (0.0059 mol, 1.2 g). ^1H NMR(CDCl_3): δ 3.95 (3H, s), 5.2-5.1 (2H, bs), 6.36 (1H, s). ^{19}F NMR (^1H): δ -72.7.

7. Preparation of 4-Amino-3,5-difluoro-6-bromopyridine-2-carboxylic acid (Compound 16)

15 A. Preparation of 4-Amino-3,5,6-trifluoro-2-cyanopyridine

To a solution of 3,4,5,6-tetrafluoro-2-cyanopyridine in DMF (75 mL) at 0°C was slowly added concentrated ammonium hydroxide (15 mL). The reaction was stirred and additional 15 min and the solution was diluted with water (150 mL). The solid was collected and air dried to give 4-amino-3,5,6-trifluoro-2-cyanopyridine (25.5 g, 0.16 mol, 92%); mp $291-3^\circ\text{C}$.

25 B. Preparation of Methyl, 4-amino-6-bromo-3,5-difluoropyridine-2-carboxylate (Compound 16)

A solution of 4-amino-3,5,6-trifluoro-2-cyanopyridine (19 g, 0.12 mol) in thirty percent hydrogen bromide in acetic acid (150 mL) was placed in a Paar bomb and heated to 110°C for 3 hr. The

reaction was diluted with water (300 ml) and the solid (4-amino-6-chloro-3,5-difluoropyridine-2-carboxamide) was collected. This material, without further purification, was slurried in methanol (500 ml) and concentrated hydrochloric acid added. The slurry was heated under reflux for 4 hr and, after cooling to room temperature, diluted with water (1,000 mL) and the solid collected and dried to give methyl 4-amino-6-bromo-3,5-difluoropyridine-2-carboxylate (9.6 g, 0.04 mol, 25%); mp 110-111°C.

8. Preparation of 4-Amino-3,6-dibromopyridine-2-carboxylic acid (Compound 17)

3,4,5,6-Tetrabromopyridine-2-carboxamide (5.0 g) was selectively aminated with ammonia gas at RT in 100 mL methanol. The resultant solution was concentrated to an off-white solid and hydrolyzed with conc. sulfuric acid (25 mL) at 140°C for 3 hr. the mixture was made basic with NaOH, extracted with EtOAc (2 x 100 mL), acidified and filtered to give 1.4 g of pure 4-amino-3,6-dibromopyridine-2-carboxylic acid; mp 205°C dec.

9. Preparation of Methyl 4-amino-3,5,6-tribromopyridine-2-carboxylate (Compound 18)

Methyl 4-amino-3,5,6-tribromopyridine-2-carboxylate was prepared by amination of methyl 3,4,5,6-tetrabromopyridine-2-carboxylate following the procedure of Example 6B. ¹H NMR(CDCl₃): δ 3.95 (3H, s), 6.9-6.8 (2H, bs).

10. Preparation of 4-Amino-3,6-dichloro-5-fluoropyridine-2-carboxylic acid (Compound 19)

To a solution of 4-amino-3,6-dichloro-pyridine-2-carboxylate (1.5 g, 6.8 mmol) in 20 mL of
5 dry acetonitrile was added 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis
(tetrafluoroborate) (Selectfluor™ from Aldrich
Chemical Company, Inc.; 2.9 g, 2.59 mmol [F⁺]/g). The
10 resulting mixture was heated at reflux for 3 hr, then allowed to cool to room temperature. This material
was taken up in Et₂O and washed with H₂O. The organic
layer was dried over MgSO₄, filtered and concentrated
to yield a brown oil. The crude product was purified
15 via reverse phase HPLC (50% acetonitrile/water) to
give 0.37 g of white solid which was stirred in 1N
NaOH for 1 hr then made acidic with conc. HCl. The
precipitated white solid was collected with suction,
washed with H₂O and dried under vacuum to give 170 mg
20 of 4-amino-3,6-dichloro-5-fluoropyridine-2-carboxylic
acid (11% yield); mp 214°C dec.

11. Preparation of 4-Amino-3,6-dichloro-5-bromopyridine-2-carboxylic acid (Compound 20)

To a solution of methyl 4-amino-3,6-dichloropyridine-2-carboxylate (18 g, 81 mmol) in 100
25 mL fuming sulfuric acid was added bromine (15 mL,
excess). The resulting mixture was heated to 70°C for
30 min, then allowed to cool to room temperature.
This material was poured into ice water (1000 mL) and
extracted with EtOAc (4 x 500 mL). The combined
30 organic extracts were dried (MgSO₄), filtered and
concentrated to yield a brown solid. The crude

product was purified via reverse phase HPLC (50% acetonitrile/water) to give 21 g of 4-amino-3,6-dichloro-5-bromopyridine-2-carboxylic acid as a white solid (91% yield); mp 201-202°C.

5 12. Preparation of 4-Amino-3,6-dichloro-5-trifluoromethylpyridine-2-carboxylic acid (Compound 21)

6 A solution of 4-amino-3,6-dichloro-5-trifluoromethyl-2-cyanopyridine (0.5 g, 1.96 mmol) in
10 10 mL of 85% H₂SO₄ was stirred at 140°C for 0.5 hr. The reaction mixture was allowed to cool and added to ice. The precipitated white solid was collected with suction, rinsed several more times with water and allowed to air dry to give 0.33 g of product as a
15 white solid (61.4% yield); mp 173°C.

13. Preparation of 4-Amino-3,6-dichloro-5-methoxypyridine-2-carboxylic acid (Compound 22)

A. Methyl 3-chloro-5-methoxypyridine-2-carboxylate, N-oxide

20 In a dry 3-neck round bottom flask was added methyl 3,5-dichloropyridine-2-carboxylate, N-oxide (5.0 g, 22.5 mmol) to 25 mL of methanol to give a slurry. A 25% solution of sodium methoxide in methanol (5.40 mL, 23.62 mmol) was added and heated to reflux
25 for 1.5 h. The reaction mixture was diluted in ethyl acetate and added to H₂O. The layers were separated and the aqueous layer was saturated with brine and extracted 2 more times in ethyl acetate. The combined organic layers were dried (MgSO₄) and concentrated to

give a white solid. Purification by column chromatography (silica gel) using an eluent of 50% Et₂O/Petroleum ether (1.5 L) then 100% Et₂O to give 1.76 g of a white solid; mp 154-156°C.

5 B. Methyl 3-chloro-5-methoxy-4-nitropyridine-2-carboxylate, N-oxide

To methyl 3-chloro-5-methoxypyridine-2-carboxylate, N-oxide (1.41 g, 5.97 mmol) in H₂SO₄ cooled to 0°C was slowly added a 50/50 mixture of 30% oleum and fuming HNO₃. Reaction mixture stirred for 30 min at room temperature and then heated to 70°C for 3 days. The reaction mixture was diluted with ethyl acetate and cooled to 0°C. Saturated sodium bicarbonate was carefully added and the layers were separated. Aqueous layer was washed 2 more times with ethyl acetate. The combined organic layers were dried (MgSO₄) and concentrated to dryness. Purification by column chromatography (silica gel) using an eluent of 20% ethyl acetate/hexane gave 300 mg of a yellow solid; mp 160°C.

C. Methyl 3,6-dichloro-5-methoxy-4-nitropyridine-2-carboxylate

To methyl 3-chloro-5-methoxy-4-nitropyridine-2-carboxylate, N-oxide (0.300 g, 1.12 mmol) in 5 mL of chloroform was added PCl₃ (0.664 mL, 7.62 mmol). The reaction mixture was heated to reflux for 8 hr and then concentrated to dryness in vacuo to give 300 mg of a white solid.

(12)

D. Methyl 4-amino-3,6-dichloro-5-methoxypyridine-2-carboxylate

To methyl 3,6-dichloro-5-methoxy-4-nitropyridine-2-carboxylate (0.300 g, 1.06 mmol) in 5 mL of ethyl acetate was added $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (1.60 g, 7.1 mmol). The reaction mixture was heated to 70°C for 30 min and then cooled to room temperature. Saturated sodium bicarbonate and a saturated solution of KHF_2 were added to reaction mixture. The mixture was extracted with ethyl acetate and the layers were separated. The aqueous layer was washed 2 more times with ethyl acetate. The combined organic layers were dried (MgSO_4) and concentrated to dryness to give 0.250 g of a yellow solid.

15 E. 4-Amino-3,6-dichloro-5-methoxypyridine-2-carboxylic acid (Compound 22)

4-Amino-3,6-dichloro-5-methoxypyridine-2-carboxylic acid was prepared by saponification of the methyl ester according to the procedure of Example 17(D); mp 154-156°C.

14. Preparation of 4-Amino-3,6-dichloro-5-methylthiopyridine-2-carboxylic acid (Compound 23)

4-Amino-3,6-dichloro-5-methylthiopyridine-2-carboxylic acid was prepared by analogy to the preparation of 4-amino-3,6-dichloro-5-methoxypyridine-2-carboxylic acid following the procedure of Example 13 using sodium thiomethoxide instead of sodium methoxide; mp 160°C dec.

15. Preparation of 4-Amino-3,6-dichloro-5-phenylthio-
pyridine-2-carboxylate (Compound 24)

4-Amino-3,6-dichloro-5-phenylthiopyridine-2-
carboxylic acid was prepared by analogy to the
5 preparation of 4-amino-3,6-dichloro-5-methoxypyridine-
2-carboxylic acid following the procedure of Example
13 using sodium thiophenoxide instead of sodium
methoxide; mp 160°C dec.

10 16. Preparation of Methyl 4-amino-3,6-dichloro-5-
nitropyridine-2-carboxylate (Compound 25)

To a solution containing 4-amino-3,6-
dichloropyridine-2-carboxylic acid (0.5 g, 2.43 mmol)
and 10 mL of conc. H_2SO_4 was added dropwise a mixture
15 of conc. HNO_3/H_2SO_4 (1 mL/ 1 mL) at RT. After stirring
for 5 min, the reaction mixture was added to ice and
the solid was collected by vacuum filtration. The
resulting solid was dissolved in 20% MeOH/EtOAc and
trimethylsilyl diazomethane ($TMSCHN_2$) was then added
20 until reaction was complete. Reaction mixture was
concentrated under reduced pressure, taken up in Et_2O
and washed with aqueous $NaHCO_3$, dried over $MgSO_4$,
filtered and concentrated to give a brown oil. The
crude product was purified by chromatography, eluting
25 with 10% ethyl acetate-hexane to give 80 mg of the
methyl ester as a yellow solid; mp 127-8°C.

17. Preparation of 4-N-Methylamino-3,6-
dichloropyridine-2-carboxylic acid (Compound 26)

A. Methyl 3,6-dichloropyridine-2-carboxylate

To a 3-neck round bottom flask equipped with
5 a reflux condenser was added 3,6-dichloropyridine-2-
carboxylic acid (50.0 g, 260.42 mmol) in methanol (200
mL). HCl_(g) was bubbled in until solution became
saturated and stirred at room temperature for 2 hr.
The solution was concentrated to dryness *in vacuo*.
10 Diethyl ether was added to make a slurry that was
subsequently added to a flask filled with a 1:1
mixture of saturated sodium bicarbonate/diethyl ether
and stirred for 10 min. The aqueous phase was
extracted with diethyl ether (3 X 300 mL). The
15 combined extracts were dried (MgSO₄) and concentrated
to give 46.6 g of a light yellow solid. ¹H NMR(CDCl₃):
δ 4.00 (s, 3H); 7.41 (d, 1H); 7.80 (d, 1H).

B. Methyl 3,6-dichloropyridine-2-carboxylate, N-
oxide

20 Methyl 3,6-dichloropicolinate (20.0 g, 97.07
mmol) was dissolved in a minimum amount of
trifluoroacetic acid (TFA). In a separate flask was
stirred trifluoroacetic anhydride (TFAA, 38 mL) and
50% H₂O₂ (9.9 g, 145.61 mmol) which was added to the
25 TFA solution. The reaction mixture was stirred at
reflux for 1 hr and concentrated to dryness. The
orange oil was dissolved in ethyl acetate and
saturated sodium bicarbonate. The phases were
separated and the aqueous phase was extracted with
30 ethyl acetate (2 X 200mL). The combined extracts were

dried (MgSO_4) and concentrated to a yellow solid. Purification by column chromatography (silica gel) using an eluent of 50% ethyl acetate/hexane gave 12.13 g of a yellow solid. ^1H NMR (CDCl_3): δ 4.00 (s, 3H);
5 7.25 (d, 1H); 7.50 (d, 1H).

C. Methyl 3,4,6-Trichloropyridine-2-carboxylate

To methyl 3,6-dichloropicolinate *N*-oxide (5.0 g, 22.52 mmol) dissolved in 15 mL of acetonitrile was added POCl_3 (4.20 mL, 45.04 mmol). The reaction
10 mixture was stirred at reflux for 5 hr, cooled to room temperature and concentrated to dryness *in vacuo*. The resultant orange oil was dissolved in diethyl ether. Carefully, saturated sodium bicarbonate was added and the aqueous phase was extracted with diethyl ether (2
15 X 100 mL). The combined extracts were dried (MgSO_4) and concentrated to dryness. Purification by column chromatography (silica gel) using an eluent of 20% ethyl acetate/hexane gave 5.89 g of a light yellow solid. ^1H NMR(CDCl_3): δ 4.00 (s, 3H); 7.55 (s, 1H).

20 D. 3,4,6-Trichloropyridine-2-carboxylic acid

To methyl 3,4,6-Trichloropicolinate (3.57 g, 14.85 mmol) in 20 mL of methanol was added 1N NaOH (14.85 mL, 14.85 mmol). The reaction mixture was stirred at room temperature for 1 hr and then
25 concentrated to dryness *in vacuo*. 100 mL each of diethyl ether and H_2O were added. Aqueous layer was acidified with 1N HCl until pH=2. Methylene chloride was added and the aqueous phase was extracted with additional CH_2Cl_2 (2 X 100 mL). The combined extracts

were dried (MgSO_4) and concentrated to give 3.13 g of a white solid. $^1\text{H NMR}(\text{CDCl}_3)$: δ 7.50 (s, 1H).

E. 4-N-Methylamino-3,6-dichloropyridine-2-carboxylic acid (Compound 26)

5 3,4,6-Trichloropyridine-2-carboxylic acid
(1.56 g, 6.89 mmol) was dissolved in methylamine and
placed in a Parr bomb at 80°C for 2 days. The
reaction mixture was cooled to room temperature and
diluted with ethyl acetate. 1N HCl was added until
10 pH=2. The aqueous phase was extracted with ethyl
acetate (2 X 50 mL) and the combined extracts were
dried (MgSO_4) and concentrated to dryness. Desired
product was triturated from 5% diethyl ether/pet
ether; the solid was filtered and dried to give 0.600
15 g of a light yellow solid. $^1\text{H NMR}(\text{CDCl}_3)$: δ 2.75 (s,
3H); 5.70 (s, 1H); 6.30 (s, 1H); mp $170-172^\circ\text{C}$.

The following *N*-alkyl analogs of 4-amino-
3,6-dichloropyridine-2-carboxylic acid were prepared
according to the procedure of Example 17:

20 4-N-ethylamino-3,6-dichloropyridine-2-
carboxylic acid (Compound 27); mp $136-137^\circ\text{C}$.

4-N-isopropylamino-3,6-dichloropyridine-2-
carboxylic acid (Compound 28); mp $146-147^\circ\text{C}$.

25 4-N-butylamino-3,6-dichloropyridine-2-
carboxylic acid (Compound 29); mp $96-97^\circ\text{C}$.

4-N-allylamino-3,6-dichloropyridine-2-
carboxylic acid (Compound 30); mp $128-131^\circ\text{C}$.

4-*N*-hydroxyethylamino-3,6-dichloropyridine-2-carboxylic acid (Compound 31); mp 140-141°C.

4-*N*-methoxyethylamino-3,6-dichloropyridine-2-carboxylic acid (Compound 32); mp 97-99°C.

5 4-*N,N*-dimethylamino-3,6-dichloropyridine-2-carboxylic acid (Compound 33); mp 110°C.

4-*N*-hydroxy-*N*-methyl-amino-3,6-dichloropyridine-2-carboxylic acid (Compound 34); mp 140-1°C.

10 4-*N*-methoxy-*N*-methyl-3,6-dichloropyridine-2-carboxylic acid (Compound 35); mp 98-99°C.

4-pyrrolidino-3,6-dichloropyridine-2-carboxylic acid (Compound 36); mp 153-5°C.

15 4-pyrrolo-3,6-Dichloropyridine-2-carboxylic acid (Compound 37); mp 155-156°C.

18. Preparation of Methyl 4-azido-6-bromo-3-chloropyridine-2-carboxylic acid (Compound 38)

20 To a solution of methyl 4,6-dibromo-3-chloropyridine-2-carboxylate (6.0 g 0.018 mol) in DMF (50 mL) was added sodium azide (2.0 g 0.03 mol) and the solution warmed to 50°C for 1 hr. The reaction was diluted with water (200 mL) and cooled to 0°C for
25 1 hr. The solid was collected to give methyl 4-azido-6-bromo-3-chloropyridine-2-carboxylate (4.4 g, 0.012 mol, 66%); mp 84-86°C

19. Preparation of 4-Nitro-3,6-dichloropyridine-2-
5 carboxylic acid (Compound 39)

Methyl 3,6-dichloropyridine-2-carboxylate *N*-oxide (5.0 g, 22.52 mmol) was dissolved in a minimum amount of H₂SO₄. The mixture was cooled in an ice/water
10 bath and to it was slowly added 30% oleum (9.6 mL) and fuming HNO₃ (9.6 mL), gradually heated to 65°C and stirred for 48 hr. The cooled reaction mixture was diluted with ethyl acetate (200 mL) and to it was carefully added saturated sodium bicarbonate. The
15 product was extracted with ethyl acetate (2 X 150 mL) and the combined extracts were dried (MgSO₄) and concentrated to give 0.10 g of a yellow solid; mp 192-193°C

20. Preparation of 4-*N,N*-Dimethylformamidino-3,6-
20 dichloropyridine-2-carboxylic acid (Compound 40)

To a suspension of methyl 4-amino-3,6-dichloro-pyridine-2-carboxylic acid (2.07 g, 10.0
25 mmol) in THF (50 mL) was added 5.0 eq *N,N*-dimethylformamide dimethyl acetal (50 mmol). The mixture was heated to 50°C for 1 hr during which time the suspension became a homogeneous solution. The cooled reaction mixture was concentrated *in vacuo*,
30 triturated with hexanes to a white amorphous solid and dried under high vacuum to give 2.5 g of a highly

hygroscopic white powder (95% yield); ^1H NMR (DMSO) δ 8.21 (1H, s), 7.95 (1H, s), 3.25 (3H, s), 3.17 (3H, s).

5 21. Preparation of 4-Amino-6-bromo-3-methoxypyridine-2-carboxylic acid (Compound 41)

10 A. Methyl 4,6-dibromo-3-methoxypyridine-2-carboxylate

To methyl 4,6-dibromo-3-hydroxypyridine-2-carboxylate 3.98 g (3.98 g, 12.81 mmol) in 40 mL of acetone was added K_2CO_3 (2.0 g, 14.47 mmol) and dimethyl sulfate (1.20 mL, 12.37 mmol). The reaction mixture was refluxed overnight and concentrated to dryness. The residue was dissolved in ethyl acetate and saturated sodium bicarbonate. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 X 100 mL). The combined extracts were dried (MgSO_4) and concentrated to dryness. The residue was purified by chromatography (silica gel). Elution with 15% ethyl acetate/hexane gave 0.980 g, of a white solid. ^1H NMR(CDCl_3): δ 3.95 (s, 3H); 3.90 (s, 3H); 7.80 (s, 1H).

25 B. Methyl 4-azido-6-bromo-3-methoxypyridine-2-carboxylate

Methyl 4,6-dibromo-3-methoxypyridine-2-carboxylate (0.980 g, 3.02 mmol) was dissolved in a minimum amount of DMF. Slowly sodium azide (0.216 g, 3.32 mmol) was added followed by H_2O to form a

30

homogeneous solution. The reaction mixture was heated to 60°C and stirred for 2 days. Reaction mixture added to a flask filled with ice water and extracted with ethyl acetate (3 X 50 mL). Extracts were
5 combined and back washed with H₂O, dried (MgSO₄) and concentrated to give 0.500 g of an orange oil. ¹H NMR(CDCl₃): δ 3.90 (s, 3H); 3.95 (s, 3H); 7.20 (s, 1H).

10 C. Methyl 4-amino-6-bromo-3-methoxypyridine-2-carboxylate

To methyl 4-azido-6-bromo-3-methoxypyridine-2-carboxylate (0.500 g, 1.74 mmol) in 10 mL of methanol was added NaBH₄ (0.046 g, 1.22 mmol). The reaction mixture was stirred at room temperature for
15 10 min. Ethyl acetate and water were added and the phases were separated. The organic phase was washed with H₂O, dried (MgSO₄) and concentrated to dryness in vacuo. The residue was purified by chromatography (silica gel). Elution with 100% ethyl acetate gave
20 0.300 g of a white solid. ¹H NMR(CDCl₃): δ 3.90 (s, 1H); 3.95 (s, 1H); 4.60 (s, 2H); 6.85 (s, 1H).

D. 4-Amino-6-bromo-3-methoxypyridine-2-carboxylic acid (Compound 41)

To methyl 4-amino-6-bromo-3-methoxypyridine-2-carboxylate (0.300 g, 1.15 mmol) in 10 mL of
25 methanol was added 1N NaOH (1.15 mL, 1.15 mmol). The reaction mixture was stirred at room temperature for 1 hr and concentrated to dryness in vacuo. Diethyl ether and H₂O were added. The aqueous layer was
30 acidified with 1N HCl until pH=2 and concentrated to

dryness. Methanol (50 mL) was added to the white solid. The mixture was filtered and the filtrate concentrated to dryness. Triturating with 5% diethyl ether/pet ether gave 0.180 g of a light pink solid. ¹H NMR(DMSO): δ 3.60 (s, 3H); 6.80 (s, 1H).

22. Preparation of 4-Amino-6-bromo-5-chloro-3-methoxypyridine-2-carboxylic acid (Compound 42)

A. Methyl 4-amino-6-bromo-5-chloro-3-methoxypyridine-2-carboxylate

10 To methyl 4-amino-6-bromo-3-methoxypyridine-2-carboxylate (1.45 g, 5.56 mmol) in 10 mL of acetonitrile was added sulfuryl chloride, in excess, via pipette until the solution remained yellow. The solution was heated to reflux for 5 min. The reaction mixture was added to saturated sodium bicarbonate and aqueous phase was extracted with diethyl ether (3 x). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo to give a yellow solid. Solid was washed in 10% diethyl
15 ether/petroleum ether and solid filtered to give 0.580 g of a white solid.

B. 4-Amino-6-bromo-5-chloro-3-methoxypyridine-2-carboxylic acid (Compound 42)

25 To methyl-4-amino-6-bromo-5-chloro-3-methoxypyridine-2-carboxylate (0.300 g, 1.02 mmol) in 10 mL of methanol was added 1 N NaOH (1.10 mL, 1.10 mmol). The reaction mixture was stirred at room temperature for 4 hr and was then concentrated to dryness in vacuo. The resulting aqueous layer was

acidified with concentrated HCl. The white solid was collected by filtration and was rinsed with H₂O. The solid was dried at 50°C under vacuum to give 0.230 g of a white fluffy solid; mp 154-156°C.

5 23. Preparation of 4-Amino-5,6-dichloro-3-fluoropyridine-2-carboxylic acid (Compound 43)

A. 4-Amino-5,6-dichloro-2-trichloromethylpyridine

To a solution of 4,5,6-trichloro-2-trichloromethylpyridine (2 g, 6.7 mmol) in aqueous DMF was added NaN₃ (0.5 g, 7.7 mmol). The resulting mixture was heated at 70°C for 2 hr, added to H₂O and extracted (3x) with Et₂O. Organic layer was concentrated to yield a white solid, which was dissolved in 10 mL of MeOH. Excess NaBH₄ was added and the reaction mixture was stirred at room temperature for 0.5 hr. This material was added to H₂O, extracted (3x) with Et₂O, dried over MgSO₄ and concentrated in vacuo. The resulting solid was washed several times with hexane to give 1.3 g of 4-amino-5,6-dichloro-2-trichloromethylpyridine.

B. 4-Amino-5,6-dichloro-3-fluoropyridine-2-carboxylic acid (Compound 43)

To a solution of 4-amino-5,6-dichloro-2-trichloromethylpyridine (1.25 g, 4.46 mmol) in 20 mL of dry acetonitrile was added Selectfluor™ (1.9 g, 2.59 mmol [F⁺]/g). The resulting mixture was heated at reflux for 72 hr, then allowed to cool to room temperature. This material was taken up in Et₂O and

washed with H₂O. The organic layer was dried over MgSO₄, filtered and concentrated to yield a dark oil. The crude product was purified via reverse phase HPLC (75% acetonitrile/water) to give 0.2 g of white solid which was stirred in 80% H₂SO₄ at 155°C for 0.5 hr. Reaction mixture was allowed to cool and extracted several times with 10% MeOH/CH₂Cl₂. Organic layer was dried over MgSO₄, filtered and concentrated to give a white solid which was washed several times with hexane-diethyl ether to give 60 mg of 4-amino-5,6-dichloro-3-fluoropyridine-2-carboxylic acid; mp 208°C dec.

24. Preparation of 4-Amino-3-bromo-6-chloropyridine-2-carboxylic acid (Compound 44)

15 A. Methyl 3-bromo-4-chloropyridine-2-carboxylate

To a solution of 3-bromo-4-chloropyridine-2-carboxylic acid (1.75 g, 7.4 mmol) in MeOH was added anhydrous HCl. The resulting mixture was stirred at room temperature for 18 hr. The reaction mixture was concentrated to give a solid, which was partitioned between Et₂O and saturated NaHCO₃. Organic layer was dried over MgSO₄, filtered and concentrated to give a brown residue. This material was purified via flash column chromatography to yield 1.35 g of product as a pale yellow oil.

B. Methyl 3-bromo-4,6-dichloropyridine-2-carboxylate

To a solution of methyl 3-bromo-4-chloropyridine-2-carboxylate (1.35 g, 5.4 mmol) in 5

mL of TFA was added 30% H₂O₂ (1 g, 9.8 mmol). The resulting mixture was stirred at 75°C for 0.5 hr and allowed to cool to room temperature. Et₂O was added and the organic layer was washed carefully with
5 saturated NaHCO₃, dried over MgSO₄, filtered and concentrated to give the corresponding N-Oxide intermediate as a white solid. This material was taken up in acetonitrile (5 mL), POCl₃ (2-3 mL) and heated at reflux for 2 hr. The reaction mixture was
10 allowed to cool, added to Et₂O and washed carefully with saturated NaHCO₃, dried over MgSO₄, filtered and concentrated to give 0.9 g of product as a light brown oil. This material was sufficiently pure to carry on to the next step.

15 C. 4-Amino-3-bromo-6-chloropyridine-2-carboxylic acid (Compound 44)

To a solution of methyl 3-bromo-4,6-dichloropyridine-2-carboxylate (0.9 g, 3.2 mmol) in aqueous DMF was added NaN₃ (0.25 g, 3.8 mmol). The
20 resulting mixture was heated at 60°C for 1 hr, added to H₂O and extracted (3x) with Et₂O. Organic layer was concentrated to yield a white solid, which was dissolved in 10 mL of MeOH. Excess NaBH₄ was added and the reaction mixture stirred at room temperature for
25 0.5 hr. This material was added to H₂O, extracted (3x) with Et₂O, dried over MgSO₄ and concentrated. The resulting solid was stirred in 1N NaOH for 1 hr, made acidic with conc. HCl and concentrated to dryness. This material was extracted with MeOH, concentrated to
30 give 220 mg of 4-amino-3-bromo-6-chloropyridine-2-carboxylic acid; mp 175°C dec.

25. Preparation of 4-Amino-3,5-dichloro-6-trifluoro-
methylpyridine-2-carboxylic acid (Compound 45)

5 A. Methyl 4-chloro-6-trifluoromethylpyridine-2-
carboxylate

To a solution of 6-trifluoromethylpicolinic acid (8.6 g, 45 mmol; prepared from the corresponding 6-trifluoromethyl-2-cyanopyridine) in 25 mL of TFA was
10 added 30% H₂O₂ (7.8 g, 67.5 mmol). Reaction mixture was stirred at 70°C for 18 h and concentrated to give 8.0 g of the N-oxide. This material was stirred in HCl/MeOH solution for 18 hr. The reaction mixture was concentrated to give an oily residue which was
15 partitioned between Et₂O and saturated NaHCO₃. The organic layer was dried over MgSO₄, filtered and concentrated to give 5.0 g of a yellow oil. Neat POCl₃ was added and stirred at reflux for 2 hr. The mixture was allowed to cool, added carefully to saturated
20 NaHCO₃ and extracted (3x) with Et₂O. The organic layer was dried over MgSO₄, filtered and concentrated to give a brown solid. This material was purified via flash column chromatograph to give 2.64 g of product as a white solid; mp 62-3°C.

25

B. Methyl 4-amino-6-trifluoromethylpyridine-2-
carboxylate

To a solution of methyl 4-chloro-6-
30 trifluoromethylpyridine-2-carboxylate (2.44 g, 10.2 mmol) in aqueous DMF was added NaN₃ (0.7 g, 10.8 mmol).

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The resulting mixture was heated at 70°C for 18 hr, added to H₂O and extracted (3x) with Et₂O. The organic layer was concentrated to yield a white solid that was dissolved in 10 mL of MeOH. Excess NaBH₄ was added and the reaction mixture stirred at RT for 0.5 hr. This material was added to H₂O, extracted (3x) with Et₂O. The extract was dried over MgSO₄ and concentrated. The resulting residue was purified via flash column chromatography to give 0.95 of product as a white solid; mp 114°C.

C. Methyl 4-amino-3-5-dichloro-6-trifluoro-methylpyridine-2-carboxylate

To a solution of methyl 4-amino-6-trifluoro-methylpyridine-2-carboxylate (0.75 g, 3.4 mmol) in 5 mL of dry acetonitrile was added SO₂Cl₂ (0.55 ml, 6.8 mmol). The resulting mixture was heated at reflux for 0.5 hr, then allowed to cool to room temperature. This material was taken up in Et₂O and washed with saturated NaHCO₃. The organic layer was dried over MgSO₄, filtered and concentrated to give solid. The crude material was purified via flash column chromatography to yield 0.28 g of product as a white solid; mp 135-6°C.

D. Preparation of 4-Amino-3,5-dichloro-6-trifluoromethylpyridine-2-carboxylate (Compound 45)

To a solution of methyl 4-amino-3-5-dichloro-6-trifluoromethylpyridine-2-carboxylate (0.16

g, 0.56 mmol) in 5 mL of MeOH was added excess 1N NaOH. The resulting reaction mixture was stirred at room temperature for 1 hr, then made acidic with conc. HCl. The precipitated white solid was collected with suction, washed with H₂O and dried under vacuum to give 80 mg of compound 45; mp 178°C dec.

26. Preparation of 4-Amino-3-chloro-6-trifluoromethylpyridine-2-carboxylic acid (Compound 46)

To a solution containing 4-amino-6-trifluoromethylpyridine-2-carboxylic acid methyl ester (0.75 g, 3.4 mmol) in 5 mL of CH₃CN was added dropwise a solution of sulfuryl chloride (0.27 mL, 3.4 mmol) in 1 mL of CH₃CN. After stirring at RT for 1hr, reaction mixture was added to 50 mL of Et₂O and washed with aqueous NaHCO₃, dried over MgSO₄, filtered and concentrated to give a solid. The crude product was purified by chromatography, eluting with 10% ethyl acetate-hexane to give 200 mg of product as a white solid; mp 131-3°C.

27. Preparation of 4-Amino-3-chloro-6-(3,5-dichlorophenoxy)pyridine-2-carboxylic acid (Compound 47)

A. Preparation of Methyl 3-chloro-6-(3,5-dichlorophenoxy)pyridine-2-carboxylate N-oxide

To a dry 3-neck round bottom flask was added 60% NaH (0.432 g, 10.81 mmol), dry THF (30 mL) and 3,5-dichlorophenol (1.76 g, 10.81 mmol). The mixture was stirred until evolution of H₂ (g) ceased. Methyl

3,6-dichloropyridine-2-carboxylate *N*-oxide (2.0 g, 9.00 mmol) was added in one portion and stirred at RT for 3 hr, diluted with ethyl acetate and 100 mL of water. The aqueous phase was extracted with ethyl acetate (2 X 200 mL). The combined extracts were dried (MgSO₄) and concentrated to give 2.40 g of white solid.

B. Preparation of Methyl 3,4-dichloro-6-(3,5-dichlorophenoxy)pyridine-2-carboxylate

To Methyl 3-chloro-6-(3,5-dichlorophenoxy)pyridine-2-carboxylic acid *N*-oxide (2.40 g, 6.89 mmol) dissolved in 50 mL of acetonitrile was added POCl₃ (1.28 mL, 13.77 mmol). The mixture was stirred at reflux overnight after which it was cooled to RT and concentrated to dryness in vacuo. The resultant orange oil was dissolved in diethyl ether and saturated sodium bicarbonate was added carefully. The aqueous phase was extracted with diethyl ether (2 X 100 mL). The combined organic extracts were dried (MgSO₄) and concentrated to dryness. Purification by column chromatography (silica gel) using an eluent of 20% diethyl ether/hexane gave 1.93 g of white solid.

C. Preparation of Methyl 4-amino-3-chloro-6-(3,5-dichlorophenoxy)pyridine-2-carboxylate

Methyl 3,4-dichloro-6-(3,5-dichlorophenoxy)pyridine-2-carboxylic acid (1.93 g, 5.26 mmol) was dissolved in a minimum amount of DMF and to it was

V2A

carefully added NaN_3 (0.444 g, 6.84 mmol) and water to form a homogeneous mixture which was heated to 70°C and stirred overnight. The reaction mixture was poured into a water-ice mixture and the product was
5 extracted with ethyl acetate (3 X 100 mL). The combined extracts were washed with pet ether/water (200 mL), dried (MgSO_4) and concentrated to dryness in vacuo. The resulting oil was dissolved in methanol and to it was added NaBH_4 (0.200 g, 5.26 mmol) and
10 stirred at RT for 1.5 hr. Ethyl acetate and water was added and the aqueous phase was extracted with ethyl acetate (2 X 100 mL). The combined extracts were dried (MgSO_4) and concentrated to dryness. Purification by column chromatography (silica gel)
15 using an eluent of 20% diethyl ether/hexane-50% diethyl ether/hexane to give 0.900 g of clear solid.

D. Preparation of 4-Amino-3-chloro-6-(3,5-dichlorophenoxy)pyridine-2-carboxylic acid (Compound
20 47)

To Methyl 4-amino-3-chloro-6-(3,5-dichlorophenoxy)pyridine-2-carboxylic acid (0.0.720 g, 2.07 mmol) in 20 mL of methanol was added 1N NaOH
25 (2.07 mL) and stirred at RT for 1 hr. The reaction mixture was concentrated to dryness in vacuo and 100 mL each of diethyl ether and H_2O added. The aqueous layer acidified with 1N HCl until pH=2. Methylene chloride was added and the aqueous phase was extracted
30 with additional CH_2Cl_2 (2 X 100 mL). The combined extracts were dried (MgSO_4) and concentrated to dryness.

in vacuo to give 0.390 g of white solid 4-amino-3-chloro-6-(3,5-dichlorophenoxy)pyridine-2-carboxylic acid (Compound 47); mp 196°C.

- 5 The following 6-phenoxy analogs of 4-amino-3-chloropyridine-2-carboxylic acid were prepared according to the procedure of Example 27:

10 4-amino-3-chloro-6-phenoxy pyridine-2-carboxylic acid (Compound 48); mp 178°C.

 4-amino-3-chloro-6-(4-methoxyphenoxy) -
pyridine-2-carboxylic acid (Compound 49); mp
174°C.

15 4-amino-3-chloro-6-(4-methylphenoxy) -
pyridine-2-carboxylic acid (Compound 50); mp
173°C.

20 4-amino-3-chloro-6-(3,4-dichlorophenoxy) -
pyridine-2-carboxylic acid (Compound 51); mp 186-
187°C.

25 4-amino-3-chloro-6-(3-methylphenoxy) -
pyridine-2-carboxylic acid (Compound 52); mp
169°C.

30 4-amino-3-chloro-6-(3-chlorophenoxy) -
pyridine-2-carboxylic acid (Compound 53); mp
176°C.

28. Preparation of 4-Amino-3,5-dichloro-6-phenoxypyridine-2-carboxylic acid (Compound 54)

5 A. Preparation of Methyl 4-amino-3,5-dichloro-6-phenoxypyridine-2-carboxylate

A solution of 4-amino-3,5,6-trichloro-pyridine-2-carboxylic acid (7.2 g, 0.03 mol), phenol (3.0 g, 0.036 mol) and sodium hydroxide (2.7 g 0.068 mol) in DMSO (60 mL) and water (9 mL) was heated to 130°C for 18 hr. The reaction was diluted with water (250 mL) and a tacky solid collected. This material was dissolved in methanol (100 mL) and treated with TMSCHN₂ (25 mL 2M in hexanes). The reaction was stirred 30 min and concentrated. The resulting oil was chromatographed over silica gel (80% hexane and 20% ethyl acetate) to give methyl 4-amino-3,5-dichloro-6-phenoxypyridine-2-carboxylate (1.2, g, 14%); mp 88-90°C.

20

B. Preparation of 4-Amino-3,5-dichloro-6-phenoxypyridine-2-carboxylic acid (Compound 54)

To a solution of methyl 4-amino-3,5-dichloro-6-phenoxypyridine-2-carboxylate in methanol (10 mL) and water (100 mL) was added sodium hydroxide (0.5 g excess) and the solution heated under reflux for 3 hr. The solution was cooled and concentrated hydrochloric acid (2 mL) added. The solid was collected to give 4-amino-3,5-dichloro-6-

30

phenoxy pyridine-2-carboxylic acid (1.1 g, 90%); mp 158-60°C.

29. Preparation of 4-Amino-3-chloro-5-fluoro-6-(3,4-dichlorophenoxy)pyridine-2-carboxylic acid (Compound 55)

4-Amino-3-chloro-6-(3,4-dichlorophenoxy)-pyridine-2-carboxylic acid was fluorinated with [1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate)] (F-TEDA) in refluxing acetonitrile; mp 156-160°C.

30. Preparation of 4-Amino-3,5-dichloro-6-(2-methylpropoxy)pyridine-2-carboxylic acid (Compound 56)

4-amino-3,5-dichloro-6-(2-methylpropoxy)-pyridine-2-carboxylic acid (Compound 56) was prepared following the procedure of Example 27 using 2-methylpropanol instead of phenol; mp 104-6°C.

31. Preparation of Herbicidal Compositions

In the following illustrative compositions, parts and percentages are by weight.

EMULSIFIABLE CONCENTRATES

Formulation A

	<u>WT%</u>
4-Amino-3,6-dichloropicolinate, 2-butoxyethyl ester	26.2
Polyglycol 26-3	5.2
Nonionic emulsifier-(di-sec- butyl)phenylpoly(oxypropylene)b lock polymer with oxyethylene). The polyoxyethelene content is about 12 moles.	
Witconate P12-20 (Anionic emulsifier-calcium dodecylbenzene sulfonate- 60 wt. % active)	5.2
Aromatic 100 (Xylene range aromatic solvent)	63.4

5

Formulation B

	<u>WT%</u>
4-Amino-3,6-dichloropicolinate, 2-ethylhexyl ester	3.5
Sunspray 11N (paraffin oil)	40.0
Polyglycol 26-3	19.0
Oleic acid	1.0
Xylene range aromatic solvent	36.5

Formulation C

	<u>WT%</u>
4-Amino-3,6-dichloropicolinate, n-butyl ester	13.2
Stepon C-65	25.7
Ethomeen T/25	7.7
Ethomeen T/15	18.0
Xylene range aromatic solvent	35.4

These concentrates can be diluted with water to give emulsions of suitable concentrations for controlling weeds.

5

WETTABLE POWDERS

Formulation D

	<u>WT%</u>
4-Amino-3,6-dichloropicolinic acid	26.0
Polyglycol 26-3	2.0
Polyfon H	4.0
Zeosyl 100 (Precipitated hydrated SiO ₂)	17.0
Barden clay + inerts	51.0

10

Formulation E

	<u>WT%</u>
4-Amino-3,6-dichloropicolinic acid	62.4
Polyfon H (sodium salt of lignin sulfonate)	6.0
Sellogen HR (sodium naphthalene sulfonate)	4.0
Zeosyl 100	27.6

5 The active ingredient is applied to the corresponding carriers and then these are mixed and ground to yield wettable powders of excellent wettability and suspension power. By diluting these wettable powders with water it is possible to obtain suspensions of suitable concentrations for controlling weeds.

10

WATER DISPERSIBLE GRANULES

Formulation F

	<u>WT%</u>
4-Amino-3,6-dichloropicolinic acid	26.0
Sellogen HR	4.0
Polyfon H	5.0
Zeosyl 100	17.0
Kaolinite clay	48.0

15

The active ingredient is added to the hydrated silica, which is then mixed with the other ingredients and ground to a powder. The powder is agglomerated with water and sieved to provide granules in the range of

-10 to +60 mesh. By dispersing these granules in water it is possible to obtain suspensions of suitable concentrations for controlling weeds.

5

GRANULES

Formulation G

	<u>WT%</u>
4-Amino-3,6-dichloropicolinic acid	5.0
Celetom MP-88	95.0

10 The active ingredient is applied in a polar solvent such as N-methyl-pyrrolidinone, cyclohexanone, gamma-butyrolactone, etc. to the Celetom MP 88 carrier or to other suitable carriers. The resulting granules can be applied by hand, granule applicator, airplane, etc. in order to control weeds.

15

Formulation H

	<u>WT%</u>
4-Amino-3,6-dichloropicolinic acid	1.0
Polyfon H	8.0
Nekal BA 77	2.0
Zinc Stearate	2.0
Barden Clay	87.0

20 All materials are blended and ground to a powder then water is added and the clay mixture is stirred until a paste is formed. The mixture is extruded through a die to provide granules of proper size.

Water Soluble Liquids

Formulation I

	<u>Wt%</u>
4-Amino-3,6-dichloropicolinic acid	11.2
KOH	3.7
Water	85.1

4-Amino-3,6-dichloropicolinic acid is dispersed in water. KOH is slowly added to neutralize the acid to a pH of between 9-12. A water-soluble surfactant may be added. Other aids may be incorporated to improve physical, chemical and/or formulation properties.

32. Evaluation of Postemergence Herbicidal Activity

- Seeds of the desired test plant species were planted in Grace-Sierra MetroMix® 306 planting mixture, which typically has a pH of 6.0 to 6.8 and an organic matter content of about 30 percent, in plastic pots with a surface area of 64 square centimeters. When required to ensure good germination and healthy plants, a fungicide treatment and/or other chemical or physical treatment was applied. The plants were grown for 7-21 days in a greenhouse with an approximate 15 hr photoperiod which was maintained at about 23-29°C during the day and 22-28°C during the night.
- Nutrients and water were added on a regular basis and supplemental lighting was provided with overhead metal halide 1000-Watt lamps as necessary. The plants were

employed for testing when they reached the first or second true leaf stage.

A weighed amount, determined by the highest rate to be tested, of each test compound was placed in a 20 mL glass vial and was dissolved in 4 mL of a 97:3 v/v (volume/volume) mixture of acetone and dimethyl sulfoxide (DMSO) to obtain concentrated stock solutions. If the test compound did not dissolve readily, the mixture was warmed and/or sonicated. The concentrated stock solutions obtained were diluted with an aqueous mixture containing acetone, water, isopropyl alcohol, DMSO, Atplus 411F crop oil concentrate, and Triton X-155 surfactant in a 48.5:39:10:1.5:1.0:0.02 v/v ratio to obtain spray solutions of known concentration. The solutions containing the highest concentration to be tested were prepared by diluting 2 mL aliquots of the stock solution with 13 mL of the mixture and lower concentrations were prepared by serial dilution of the stock solution. Approximately 1.5 mL aliquots of each solution of known concentration were sprayed evenly onto each of the test plant pots using a DeVilbiss atomizer driven by compressed air pressure of 2 to 4 psi (140 to 280 kiloPascals) to obtain thorough coverage of each plant. Control plants were sprayed in the same manner with the aqueous mixture. In this test an application rate of 1 ppm results in the application of approximately 1 g/Ha.

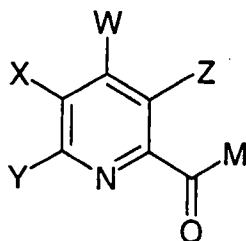
The treated plants and control plants were placed in a greenhouse as described above and watered by sub-irrigation to prevent wash-off of the test

compounds. After 2 weeks the condition of the test plants as compared with that of the untreated plants was determined visually and scored on a scale of 0 to 100 percent where 0 corresponds to no injury and 100 corresponds to complete kill.

By applying the well-accepted probit analysis as described by J. Berkson in *Journal of the American Statistical Society*, **48**, 565 (1953) and by D. Finney in "*Probit Analysis*" Cambridge University Press (1952), the above data can be used to calculate GR_{50} and GR_{80} values, which are defined as growth reduction factors that correspond to the effective dose of herbicide required to kill or control 50 percent or 80 percent, respectively, of a target plant.

Some of the compounds tested, application rates employed, plant species tested, and results are given in Tables 1-2. Selectivity to rice, corn and wheat are illustrated in Tables 3-5.

Table 1

Post-emergent % Control

#	M	W	X	Y	Z	% Control			Rate (ppm)
						XANST	STEME	POLCO	
1	OH	NH ₂	H	Cl	Cl	95	100	100	125
2	O-2-EH ²	NH ₂	H	Cl	Cl	95	80	100	250
3	O-Me	NH ₂	H	Cl	Cl	100	100	100	125
4	O-Et	NH ₂	H	Cl	Cl	100	100	100	125
5	O-Pr	NH ₂	H	Cl	Cl	100	100	100	125
6	O- <i>i</i> -Pr	NH ₂	H	Cl	Cl	100	100	100	125
7	O-Bu	NH ₂	H	Cl	Cl	100	100	100	250
8	O-pentyl	NH ₂	H	Cl	Cl	100	90	100	250
9	O-hexyl	NH ₂	H	Cl	Cl	100	100	100	250
10	O-BE ³	NH ₂	H	Cl	Cl	90	50	100	125
11	NH ₂	NH ₂	H	Cl	Cl	80	85	95	125
12	O-Me	NHC(O)Me	H	Cl	Cl	90	30	100	125
13	O-Me	N(C(O)Me) ₂	H	Cl	Cl	95	100	80	250
14	OH	NH ₂	H	Br	Cl	85	90	50	250
15	OH	NH ₂	H	F	Cl	100	70	90	250
16	OH	NH ₂	F	Br	F	60	30	70	250
17	OH	NH ₂	H	Br	Br	100	80	100	250
18	O-Me	NH ₂	Br	Br	Br	85	90	75	250
19	OH	NH ₂	F	Cl	Cl	95	95	100	125
20	OH	NH ₂	Br	Cl	Cl	85	90	50	250
21	OH	NH ₂	CF ₃	Cl	Cl	70	20	20	250

22	OH	NH ₂	O-Me	Cl	Cl	80	90	100	250
23	OH	NH ₂	S-Et	Cl	Cl	90	90	98	125
24	OH	NH ₂	S-Ph	Cl	Cl	60	50	50	250
25	O-Me	NH ₂	NO ₂	Cl	Cl	60	50	50	250
26	OH	NHMe	H	Cl	Cl	90	90	95	125
27	OH	NHEt	H	Cl	Cl	85	100	90	125
28	OH	NH- <i>i</i> -Pr	H	Cl	Cl	95	90	95	250
29	OH	NHBu	H	Cl	Cl	95	90	90	250
30	OH	NH(allyl)	H	Cl	Cl	100	80	100	250
31	OH	NH(CH ₂) ₂ OH	Cl	Cl	Cl	40	30	70	250
32	OH	NH(CH ₂) ₂ OMe	H	Cl	Cl	80	20	100	250
33	OH	NMe ₂	H	Cl	Cl	100	100	100	250
34	OH	NMe(OH)	H	Cl	Cl	100	70	100	125
35	OH	NMe(OMe)	H	Cl	Cl	90	60	100	125
36	OH	pyrrolidine	H	Cl	Cl	50	40	80	125
37	OH	pyrrole	H	Cl	Cl	90	70	90	125
38	O-Me	N ₃	H	Br	Cl	90	50	90	125
39 ¹	OH	NO ₂	H	Cl	Cl	85	30	90	125
40	OH	N=CH(NMe ₂)	H	Cl	Cl	100	90	100	250
41	OH	NH ₂	H	Br	O-Me	80	90	100	125
42	OH	NH ₂	Cl	Br	O-Me	85	90	90	250
43	OH	NH ₂	Cl	Cl	F	90	85	60	125
44	OH	NH ₂	H	Cl	Br	90	90	95	125
45	O-Me	NH ₂	Cl	CF ₃	Cl	90	0	80	250
46	O-Me	NH ₂	H	CF ₃	Cl	90	60	100	250
47	OH	NH ₂	H	O-3,5-DCPh ⁴	Cl	100	100	100	250
48	OH	NH ₂	H	O-Ph	Cl	100	60	100	250
49	OH	NH ₂	H	O-4-MeOPh ⁵	Cl	60	0	70	250
50	OH	NH ₂	H	O-4-MePh ⁶	Cl	60	0	70	250
51	OH	NH ₂	H	O-3,4-DCPh ⁷	Cl	100	70	100	250
52	OH	NH ₂	H	O-3-MePh ⁸	Cl	70	20	90	250
53	OH	NH ₂	H	O-3-CPh ⁹	Cl	100	100	100	250
54	OH	NH ₂	Cl	O-Ph	Cl	100	0	40	250

55	OH	NH ₂	F	O-3,4-DCPh ⁷	Cl	100	95	100	250
56	OH	NH ₂	Cl	O-2-MP ¹⁰	Cl	85	30	20	250

¹Compound 39 is the pyridine N-oxide

²O-2-EH = O-2-ethylhexyl

³O-BE = O-(CH₂)₂OBu

⁴O-3,5-DCPh = O-3,5-DichloroC₆H₃

5 ⁵O-4-MeOPh = O-4-MethoxyC₆H₄

⁶O-4-MePh = O-4-MethylC₆H₄

⁷O-3,4-DCPh = O-3,4-DichloroC₆H₃

⁸O-3-MePh = O-3-MethylC₆H₄

⁹O-3-CPh = O-3-ChloroC₆H₄

10 ¹⁰O-2-MP = O-2-Methylpropyl

NT = not tested

XANST = cocklebur (*Xanthium strumarium*)

STEME = chickweed (*Stellaria media*)

POLCO = wild buckwheat (*Polygonum convolvulus*)

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TABLE 2
POSTMERGENCE HERBICIDAL ACTIVITY & CONTROL

Cpd. No.	Rate, ppm	STEME	XANST	CHEAL	AMARE	ABUTH	VIOTR	POLCO	ALOMY	ECHCG	DIGSA	SETFA	SORBI	AVEFA
1	125	90	100	100	95	70	80	100	50	45	60	75	50	50
4	125	70	100	100	100	70	70	100	40	50	70	75	40	40
14	125	65	100	95	90	85	75	100	50	65	65	65	60	40
19	125	60	95	95	60	50	50	100	20	10	30	20	10	20

STEME=chickweed (*Stellaria media*)

CHEAL=lambsquarters (*Chenopodium album*)

ABUTH=velvetleaf (*Abutilon theophrasti*)

POLCO=wild buckwheat (*Polygonum convolvulus*)

ECHCG=barnyardgrass (*Echinochloa crus-galli*)

SETFA=giant foxtail (*Setaria faberi*)

AVEFA=wild oats (*Avena fatua*)

XANST=cocklebur (*Xanthium strumarium*)

AMARE=pigweed (*Amaranthus retroflexus*)

VIOTR=viola (*Viola tricolor*)

ALOMY=blackgrass (*Alopecurus myosuroides*)

DIGSA=crabgrass (*Digitaria sanguinalis*)

SORBI=Rox orange sorghum (*Sorghum bicolor*)

Table 3

Control of Several Key Weeds in Rice

post emergent evaluation - % control				
cmpd#	ORYZA	ECHCG	CYPES	Rate (ppm)
1	10	75	75	250
14	10	65	75	250
27	40	70	50	250

ORYZA = rice (*Oryza sativa*)

ECHCG = Barnyardgrass (*Echinochloa crus-galli*)

CYPES = yellow nutsedge (*Cyperus esculentus*)

Table 4

Control of Several Key Weeds in Corn

Post-emergent Evaluation - % control					
cmpd #	ZEAMX	ABUTH	AMARE	XANST	Rate (ppm)
15	0	40	75	90	250
20	10	70	90	85	250
33	20	80	50	100	125
43	0	70	90	85	250

ZEAMX = corn (*Zea mays*)

ABUTH = velvetleaf (*Abutilon theophrasti*)

AMARE = pigweed (*Amaranthus retroflexus*)

XANST = cocklebur (*Xanthium strumarium*)

Table 5

Control of Several Key Weeds in Wheat

Post-emergent Evaluation - % control					
cmpd #	TRZAS	STEME	CHEAL	POLCO	Rate (ppm)
14	0	70	70	90	250
23	20	30	90	98	125
41	10	20	90	100	250
46	10	50	100	100	31

TRZAS = wheat (*Triticum aestivum*)STEME = chickweed (*Stellaria media*)CHEAL = lambsquarters (*Chenopodium album*)POLCO = wild buckwheat (*Polygonum convolvulus*)

33. Evaluation of Preemergence Herbicidal Activity

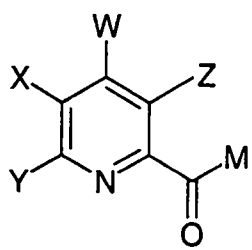
- 5 Seeds of the desired test plant species were planted in a soil matrix prepared by mixing a loam soil (43 percent silt, 19 percent clay, and 38 percent sand, with a pH of about 8.1 and an organic matter content of about 1.5 percent) and sand in a 70 to 30
- 10 ratio. The soil matrix was contained in plastic pots with a surface area of 113 square centimeters. When required to ensure good germination and healthy plants, a fungicide treatment and/or other chemical or physical treatment was applied.
- 15 A weighed amount, determined by the highest rate to be tested, of each test compound was placed in a 20 mL glass vial and was dissolved in 4 mL of a 97:3

v/v (volume/volume) mixture of acetone and dimethyl sulfoxide to obtain concentrated stock solutions. If the test compound did not dissolve readily, the mixture was warmed and/or sonicated. The stock solutions obtained were diluted with a 99.9:0.1 mixture of water and Tween® 155 surfactant to obtain application solutions of known concentration. The solutions containing the highest concentration to be tested were prepared by diluting 2 mL aliquots of the stock solution with 15 mL of the mixture and lower concentrations were prepared by serial dilution of the stock solution. A 2.5 mL aliquot of each solution of known concentration was sprayed evenly onto the soil surface (113 sq. cm) of each seeded pot using a Cornwall 5.0 mL glass syringe fitted with a TeeJet TN-3 hollow cone nozzle to obtain thorough coverage of the soil in each pot. Control pots were sprayed in the same manner with the aqueous mixture.

The treated pots and control pots were placed in a greenhouse maintained with an approximate 15 hr photoperiod and temperatures of about 23-29°C during the day and 22-28°C during the night. Nutrients and water were added on a regular basis and supplemental lighting was provided with overhead metal halide 1000-Watt lamps as necessary. The water was added by top-irrigation. After 3 weeks the condition of the test plants that germinated and grew as compared with that of the untreated plants that germinated and grew was determined visually and scored on a scale of 0 to 100 percent where 0 corresponds to no injury and 100 corresponds to complete kill or no

germination. Some of the compounds tested, application rates employed, plant species tested, and results are given in Tables 6-7.

Table 6
Pre-emergent % Control



#	M	W	X	Y	Z	% Control			Rate (ppm)
						IPOHE	AMARE	ABUTH	
1	OH	NH ₂	H	Cl	Cl	100	100	100	280
2	O-2-EH ²	NH ₂	H	Cl	Cl	100	100	100	280
3	O-Me	NH ₂	H	Cl	Cl	100	100	100	280
4	O-Et	NH ₂	H	Cl	Cl	100	100	100	280
5	O-Pr	NH ₂	H	Cl	Cl	100	100	100	280
6	O- <i>i</i> -Pr	NH ₂	H	Cl	Cl	100	100	100	280
7	O-Bu	NH ₂	H	Cl	Cl	100	100	100	280
8	O-pentyl	NH ₂	H	Cl	Cl	100	100	100	280
9	O-hexyl	NH ₂	H	Cl	Cl	100	98	100	280
10	O-BE ³	NH ₂	H	Cl	Cl	100	100	100	280
11	NH ₂	NH ₂	H	Cl	Cl	85	0	85	560
12	O-Me	NHC(O)Me	H	Cl	Cl	100	100	95	560
13	O-Me	N(C(O)Me) ₂	H	Cl	Cl	95	100	95	560
14	OH	NH ₂	H	Br	Cl	100	90	100	560
15	OH	NH ₂	H	F	Cl	100	100	100	560
16	OH	NH ₂	F	Br	F	80	70	0	560
17	OH	NH ₂	H	Br	Br	100	100	100	560
18	O-Me	NH ₂	Br	Br	Br	30	80	98	280
19	OH	NH ₂	F	Cl	Cl	100	100	100	560
20	OH	NH ₂	Br	Cl	Cl	100	100	100	560
21	OH	NH ₂	CF ₃	Cl	Cl	90	80	80	560

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22	OH	NH ₂	O-Me	Cl	Cl	100	100	100	560
23	OH	NH ₂	S-Et	Cl	Cl	0	40	40	560
24	OH	NH ₂	S-Ph	Cl	Cl	30	20	50	560
25	O-Me	NH ₂	NO ₂	Cl	Cl	nt	nt	nt	250
26	OH	NHMe	H	Cl	Cl	100	100	100	560
27	OH	NHEt	H	Cl	Cl	100	100	100	560
28	OH	NH- <i>i</i> -Pr	H	Cl	Cl	100	100	100	560
29	OH	NHBu	H	Cl	Cl	100	100	100	560
30	OH	NH(allyl)	H	Cl	Cl	85	90	95	560
31	OH	NH(CH ₂) ₂ OH	Cl	Cl	Cl	100	95	95	560
32	OH	NH(CH ₂) ₂ OMe	H	Cl	Cl	90	70	90	560
33	OH	NMe ₂	H	Cl	Cl	100	100	98	560
34	OH	NMe(OH)	H	Cl	Cl	95	100	100	560
35	OH	NMe(OMe)	H	Cl	Cl	85	95	90	560
36	OH	pyrrolidine	H	Cl	Cl	80	80	95	560
37	OH	pyrrole	H	Cl	Cl	95	100	100	560
38	O-Me	N ₃	H	Br	Cl	100	100	100	560
39 ¹	OH	NO ₂	H	Cl	Cl	100	100	100	560
40	OH	N=CH(NMe ₂)	H	Cl	Cl	100	100	100	560
41	OH	NH ₂	H	Br	O-Me	85	40	90	280
42	OH	NH ₂	Cl	Br	O-Me	100	100	100	560
43	OH	NH ₂	Cl	Cl	F	70	30	80	140
44	OH	NH ₂	H	Cl	Br	100	100	100	560
45	O-Me	NH ₂	Cl	CF ₃	Cl	100	100	90	125
46	O-Me	NH ₂	H	CF ₃	Cl	100	95	95	140
47	OH	NH ₂	H	O-3,5-DCPh ⁴	Cl	0	100	95	280
48	OH	NH ₂	H	O-Ph	Cl	100	30	100	280
49	OH	NH ₂	H	O-4-MeOPh ⁵	Cl	0	0	0	70
50	OH	NH ₂	H	O-4-MePh ⁶	Cl	0	0	0	70
51	OH	NH ₂	H	O-3,4-DCPh ⁷	Cl	0	98	80	280
52	OH	NH ₂	H	O-3-MePh ⁸	Cl	70	20	50	560
53	OH	NH ₂	H	O-3-CPh ⁹	Cl	100	0	100	560

54	OH	NH ₂	Cl	O-Ph	Cl	41	10	50	280
55	OH	NH ₂	F	O-3,4-DCPh ⁷	Cl	100	95	100	250
56	OH	NH ₂	Cl	O-2-MP ¹⁰	Cl	0	0	40	560

¹Compound 39 is the pyridine *N*-oxide

²O-2-EH = O-2-ethylhexyl

³O-BE = O-(CH₂)₂OBu

⁴O-3,5-DCPh = O-3,5-DichloroC₆H₃

5 ⁵O-4-MeOPh = O-4-MethoxyC₆H₄

⁶O-4-MePh = O-4-MethylC₆H₄

⁷O-3,4-DCPh = O-3,4-DichloroC₆H₃

⁸O-3-MePh = O-3-MethylC₆H₄

⁹O-3-CPh = O-3-ChloroC₆H₄

10 ¹⁰O-2-MP = O-2-Methylpropyl

NT = not tested

IPOHE = morningglory (*Ipomoea hederacea*)

AMARE = pigweed (*Amaranthus retroflexus*)

ABUTH = velvetleaf (*Abutilon theophrasti*)

TABLE 7
PREEMERGENCE HERBICIDAL ACTIVITY & CONTROL

Cpd. No.	Rate, g/Ha	XANST	CHEAL	AMARE	ABUTH	EPHHL	ALOMY	ECHCG	DIGSA	SETFA	SORBI	AVEFA
1	35	99	99	88	95	62	36	17	20	40	60	37
3	35	90	100	90	95	20	nt	20	40	40	30	10
14	35	100	100	100	100	70	60	40	80	98	50	40
42	35	98	90	60	80	40	30	30	30	30	20	30

nt=no test
XANST=cocklebur(*Xanthium strumarium*)
ABUTH=velvetleaf(*Abutilon theophrasti*)
ALOMY=blackgrass(*Alopecurus myosuroides*)
DIGSA=crabgrass(*Digitaria sanguinalis*)
SORBI=Rox orange sorghum(*Sorghum bicolor*)
CHEAL=lambsquarters(*Chenopodium album*)
AMARE=pigweed(*Amaranthus retroflexus*)
EPHHL=wild poinsettia(*Euphorbia heterophylla*)
ECHCG=barnyardgrass(*Echinochloa crus-galli*)
SETFA=giant foxtail(*Setaria faberi*)
AVEFA=wild oats(*Avena fatua*)

34. Range & Pasture Crop Testing

Rates are calculated based upon 5 doses being applied. The high rate (X), followed by serial dilutions of 1/2X, 1/4X, 1/8X and 1/16X. Compound requirements are based upon the 187 L/ha carrier volume, specifications of the delivery system (Mandel track sprayer) and generating 24 mL of technical spray material to allow for the dilutions and overage in the sprayer.

$$\begin{array}{lcl} \text{Rate g/ha} & = & \text{X mg} \\ 187 \text{ L/ha} & & 24 \text{ mL} \end{array}$$

Example:	<u>Starting X rate (g/ha)</u>	<u>mgs required</u>
	560	71.9
	280	35.9
	140	17.95
	70	8.9

- 20 All technical materials were formulated in 97:3 (acetone:DMSO) with 0.25% X-77. The total volume of solvent is maintained at less than 7%. An overhead Mandel track sprayer calibrated to deliver 187 L/ha was used for all treatment applications (post-emergence). Picloram was included as a comparison treatment.

Solutions were applied with a mechanized track-sprayer at the following settings:

Nozzle: 8002E

- 30 Speed: 2 mph (3.2 km/hr)

Spray Pressure: 40 psi (276 kPa)

Spray height: 17 inches (43 cm) above top of plants

This provides an application volume of 187 L/ha

Percent weed control (burn down) was
5 evaluated 3 weeks after treatment. Visual control on
a 0-100 linear scale was used, with 0 representing no
control and 100 representing total control. Burn down
ratings were taken for annual and perennial weed
species. Some of the compounds tested, application
10 rates employed, plant species tested, and results are
given in Tables 8-10.

Table 8

Salts of Compound 1

<u>salt</u>	Post-emergent GR ₈₀ g/Ha		
	CASOB	CONAR	CIRAR
free acid	11	59	47
potassium salt	<8.8	36	27
amine salt	<8.8	34	37
dimethylamine salt	11.8	>140	43
monoethanolamine salt	11	20	18
triethylamine salt	<8.8	16	<8.8
triisopropanolam ine salt	11	20	43

15 CASOB=sicklepod (*Cassia obtusifolia*)
CONAR=field bindweed (*Convolvulus arvensis*)
CIRAR=Canada thistle (*Cirsium arvense*),
3 week evaluation

Table 9

Control of Several Key Weeds in Pasture

Post-emergent Evaluation - % control

Cmpd #	AGRCR	CIRAR	RUMOB	AMBEL	Rate (g/Ha)
3	30	90	100	100	70
6	30	95	100	93	70
26	10	90	100	nt	70
23	30	80	100	85	70

AGRCR = crested wheatgrass (*Agropyron cristatum*) (grass crop)

CIRAR = Canada thistle (*Cirsium arvense*)

RUMOB = broadleaf dock (*Rumex obtusifolia*)

AMBEL = common ragweed (*Ambrosia artemisiifolia*)

3 week evaluation

nt = not tested

Table 10

Control of Several Key Weeds in Clover Pasture

Cmpd	g/ha		
	GR₂₀	GR₈₀	GR₈₀
	TRFRE	CONAR	CIRAR
3	<17.5	127.7	<17.5
4	<17.5	59	<17.5
5	<17.5	140.1	<17.5
6	98.8	98.8	<17.5
7	15.3	116.6	17.3
9	20.7	66	20.7

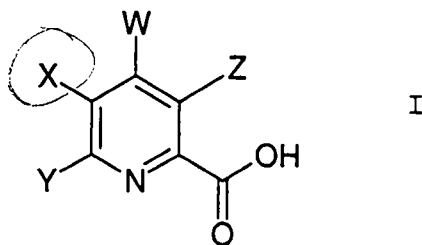
TRFRE=White Clover (*Trifolium repens*)

CONAR=Field Bindweed (*Convolvulus arvensis*)

CIRAR=Canada thistle (*Cirsium arvense*)

WHAT IS CLAIMED IS:

1. A compound of Formula I:



wherein

- 5 X represents H, halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, nitro, or trifluoromethyl;

Y represents halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy, heteroaryloxy or trifluoromethyl;

- 10 Z represents halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy or nitro; and

W represents -NO₂, -N₃, -NR₁R₂, -N=CR₃R₄ or -NHN=CR₃R₄

where

- 15 R₁ and R₂ independently represent H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl, heteroaryl, hydroxy, C₁-C₆ alkoxy, amino, C₁-C₆ acyl, C₁-C₆ carboalkoxy, C₁-C₆ alkylcarbamyl, C₁-C₆ alkylsulfonyl, C₁-C₆ trialkylsilyl or C₁-C₆ dialkyl phosphonyl or R₁ and R₂ taken together with N represent a 5- or 6-
- 20 membered saturated or unsaturated ring which may contain additional O, S or N heteroatoms; and

R₃ and R₄ independently represent H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl or heteroaryl or R₃ and R₄ taken together with =C represent a 5- or 6-membered saturated ring; and

- 5 agriculturally acceptable derivatives of the carboxylic acid, with the proviso that when X represents H or Cl, then Y and Z are not both Cl.

} E B1

2. A compound of claim 1 wherein:

X represents H, halogen, or trifluoromethyl;

- 10 Y represents halogen, aryloxy, heteroaryloxy, or trifluoromethyl;

Z represents halogen; and

W represents -NR₁R₂

where

- 15 R₁ and R₂ independently represent H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl or R₁ and R₂ taken together with N represent a 5- or 6-membered saturated ring which may contain additional O or N heteroatoms; and

- 20 agriculturally acceptable salts, esters or amides of the carboxylic acid.

3. A compound of claim 1 or claim 2

wherein:

X represents H or F;

Y represents F, Cl, Br or aryloxy;

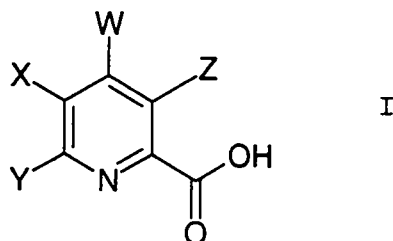
Z represents Cl; and

W represents -NH_2 .

- 5 4. A compound of any one of claims 1-3
wherein:

Y represents a phenoxy group substituted
with halogen or $\text{C}_1\text{-C}_4$ alkyl groups in the 3-position.

- 10 5. An herbicidal composition comprising an
herbicidally effective amount of a 4-aminopicolinate
of Formula I:



- 15 wherein

X represents H, halogen, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$
alkylthio, aryloxy, nitro or trifluoromethyl;

Y represents halogen, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$
alkylthio, aryloxy, heteroaryloxy or trifluoromethyl;

Z represents halogen, C₁-C₆ alkoxy, C₁-C₆ alkylthio, aryloxy or nitro; and

W represents -NO₂, -N₃, -NR₁R₂, -N=CR₃R₄ or -NHN=CR₃R₄

5 where

R₁ and R₂ independently represent H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl, heteroaryl, hydroxy, C₁-C₆ alkoxy, amino, C₁-C₆ acyl, C₁-C₆ carboalkoxy, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylsulfonyl, 10 C₁-C₆ trialkylsilyl or C₁-C₆ dialkyl phosphonyl or R₁ and R₂ taken together with N represent a 5- or 6-membered saturated or unsaturated ring which may contain additional O, S or N heteroatoms; and

R₃ and R₄ independently represent H, C₁-C₆ 15 alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, aryl or heteroaryl or R₃ and R₄ taken together with =C represent a 5- or 6-membered saturated ring; and

agriculturally acceptable derivatives of the carboxylic acid, with the proviso that when X 20 represents Cl, then Y and Z are not both Cl, in admixture with an agriculturally acceptable adjuvant or carrier.

6. An herbicidal composition of claim 5 wherein:

25 X represents H, halogen or trifluoromethyl;

Y represents halogen, aryloxy, heteroaryloxy or trifluoromethyl;

Z represents halogen; and

W represents $-NR_1R_2$

where

R₁ and R₂ independently represent H, C₁-C₆
5 alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl or R₁ and R₂ taken
together with N represent a 5- or 6-membered saturated
ring which may contain additional O or N heteroatoms;
and

10 agriculturally acceptable salts, esters or amides of
the carboxylic acid.

7. An herbicidal composition of claim 5 or
claim 6

wherein:

X represents H or F;

15 Y represents F, Cl, Br or aryloxy;

Z represents Cl; and

W represents $-NH_2$.

8. An herbicidal composition of any one of
claims 5-7

20 wherein:

Y represents a phenoxy group substituted
with halogen or C₁-C₄ alkyl groups in the 3-position.

9. An herbicidal composition of claim 5 containing 4-amino-3,6-dichloropyridine-2-carboxylic acid or an agriculturally acceptable salt, ester or amide thereof.

5 10. A method of controlling undesirable
vegetation which comprises contacting the vegetation
or the locus thereof with or applying to the soil to
prevent the emergence of vegetation an herbicidally
effective amount of an herbicidal composition of any
10 one of claims 5-9.

ABSTRACT

4-Aminopicolinic acids, having halogen, alkoxy, alkylthio, aryloxy, heteroaryloxy or trifluoromethyl substituents in the 3-, 5- and 6-
5 positions, and their amine and acid derivatives are potent herbicides demonstrating a broad spectrum of weed control.

4-AMINOPICOLINATOS Y SU USO COMO HERBICIDAS

Esta invención se relaciona con ciertos 4-aminopicolinatos novedosos y sus derivados y con el uso de estos compuestos como herbicidas.

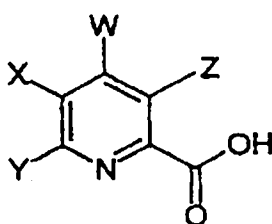
Un numero de ácidos picolínicos y sus propiedades pesticidas se han descrito en la técnica. Por ejemplo, la patente estadounidense 3,285,925 describe derivados de ácidos 4-amino-3,5,6-tricloropicolínico y su uso como agentes de control en el crecimiento de planta y herbicidas. La patente estadounidense 3,325,272 describe derivados de ácido 4-amino-3,5-dicloro-picolínico y su uso para el control del crecimiento de plantas. La patente estadounidense 3,317,549 describe derivados de ácido 3,6-dicloropicolínico y su uso como agentes de control en el crecimiento de plantas. La patente estadounidense 3, 317, 549 describe derivados de ácido 3, 6-dicloropicolínico y su uso como agentes de control en el crecimiento de plantas. La patente estadounidense 3, 334, 108 describe derivados de ácido ditiopicolínico clorado y su uso como parasiticidas. La patente

estadounidense 3,234,229 describe 4-amino-policloro-2-triclorometilpiridinas y su uso como herbicidas. En Applied and Environmental Microbiology, vol. 59, No. 7, julio 19993, pp. 2251-2256, se identifica ácido 4-amino-3,6-dicloropicolínico como un producto de degradación anaerobica de ácido 4-amino-3,5,6-dicloropicolínico, el herbicida comercialmente disponible picloran.

Mientras que el picloran se recomienda para el control de plantas leñosas y malezas de hoja ancha en ciertas aplicaciones, sus propiedades no son ideales. Sería altamente deseable descubrir compuestos relacionados que sean más potentes, más selectivos o de espectro más amplio en su actividad herbicida y/o que tengan propiedades toxicológicas o ambientales mejoradas.

Se ha encontrado ahora que ciertos ácidos 4-amino-picolínico y sus derivados tienen sustituyentes seleccionados en las posiciones 3-, 5-, y 6- que son potentes herbicidas con un amplio espectro de control de malezas y excelente selectividad de cultivos. Los compuestos poseen además excelentes perfiles toxicológicos o ambientales.

La invención incluye compuestos de fórmula I



I

En donde

X representa H, halógeno, C₁-C₆ alcoxi, C₁-C₆ alquiltio, ariloxi, nitro o trifluorometilo;

Y representa halógeno, alcoxi C₁-C₆ alquitio, ariloxi, heteroariloxi, o trifluorometilo;

Z representa halógeno, alcoxi C₁-C₆, alquiltio, C₁-C₆ ariloxi o nitro;

W representa -NO₂, -N₃, -NR₁R₂, -N=CR₃R₄ o -NHN=CR₃R₄

Donde

R_1 y R_2 independientemente representan H, alquilo C_1-C_6 , alqueno C_3-C_6 , alquino C_3-C_6 , arilo, heteroarilo, hidroxilo, alcoxi C_1-C_6 , amino, acilo, C_1-C_6 , carboalcoxi C_1-C_6 , alquilcarbamilo, C_1-C_6 , alquilsulfonilo C_1-C_6 , trialquisililo C_1-C_6 dialquilsulfonilo C_1-C_6 R_1 y R_2 tomados juntos con N representan un anillo saturado o insaturado de 5 o 6 miembros que puede contener heteroátomos O, S o N adicionales;

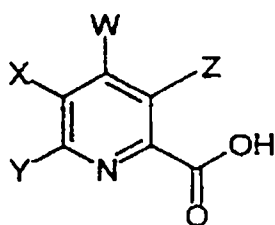
R_3 o R_4 independientemente representa H, alquilo C_1-C_6 , alquino C_3-C_6 , arilo o heteroarilo o R_3 y R_4 tomados juntos con = C representan un anillo saturado de 5- o 6- miembros;

Los derivados agrícolamente aceptables del ácido carboxílico, con la condición de que cuando X representa H o CL, entonces Y y Z no son juntos CL.

Los compuestos de fórmula I en donde X representa H o F, en donde Y representa F, CL, BR o

ariloxi, en donde Z representa CL en donde R_1 y R_2 representan H son independientemente preferidos.

La invención incluye composiciones herbicidas que comprenden una cantidad herbicídamente efectiva de un 4-amino-picolinato de fórmula I:



I

En donde

X representa H, halógeno, alcoxi C_1-C_6 , alquiltio C_1-C_6 , ariloxi, nitro o trifluorometilo;

Y representa halógeno, alcoxi C_1-C_6 , alquiltio, ariloxi, heteroariloxi, o trifluorometilo;

Z representa halógeno, alcoxi C_1-C_6 , alquiltio, C_1-C_6 ariloxi o nitro;

W representa $-NO_2$, $-N_3$, $-NR_1R_2$, $-N=CR_3R_4$ o $-NHN=CR_3R_4$

Donde

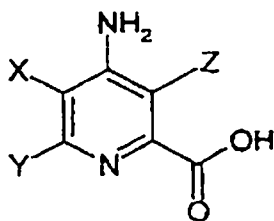
R_1 y R_2 independientemente representan H, alquilo, C_1-C_6 alquenilo C_3-C_6 , alquinilo C_3-C_6 , arilo, heteroarilo, hidroxilo, alcoxi C_1-C_6 , amino, acilo C_1-C_6 , carboalcoxi C_1-C_6 , alquilcarbamililo C_1-C_6 , alquilsulfonilo C_1-C_6 , trialquisililo C_1-C_6 o dialquilsulfonilo C_1-C_6 o R_1 y R_2 tomados juntos con N representan un anillo saturado o insaturado de 5 o 6 miembros que puede contener heteroátomos O, S o N adicionales;

R_3 o R_4 independientemente representa H, alquilo C_1-C_6 , alquenilo C_3-C_6 , alquinilo C_3-C_6 , arilo o heteroarilo o R_3 o R_4 tomados juntos con $=C$ representan un anillo saturado de 5 o 6 miembros; y

Los derivados agrícolamente aceptables del ácido carboxílico, con la condición de que cuando X representa CL, entonces Y y Z no son ambos CL.

En mezcla con un adyuvante o portador agrícola o portador agrícolamente aceptable. La invención también incluye un método de uso de los compuestos y composiciones de la presente invención para matar o controlar vegetación indeseable mediante la aplicación de una cantidad herbicida del compuesto a la vegetación o al locus de la vegetación así como también al suelo antes de la emergencia de la vegetación. El uso de los compuestos para matar o controlar plantas leñosas y malezas de hoja ancha en cultivos de pastos es una utilidad preferida y una aplicación post emergente de los compuestos a la vegetación indeseable en un método preferido de aplicación.

Los compuestos herbicidas de la presente invención son derivados de ácidos 4-aminopicolínico:



Estos compuestos están caracterizados por poseer sustituyentes alógeno, alcoxi C₁-C₆, alquiltio C₁-C₆, ariloxi o nitro en la posición 3, siendo el alógeno el preferido y el cloro siendo más preferido; al poseer sustituyentes hidrogeno, halógeno, alcoxi C₁-C₆, alquiltio C₁-C₆, ariloxi, nitro o trifluorometilo en la posición 5 con hidrógeno y flúor, siendo los preferidos; y al poseer sustituyentes alógeno, alcoxi C₁-C₆, alquiltio C₁-C₆, ariloxi, heteroariloxi o trifluorometilo en la posición 6 siendo los preferidos flúor, cloro, cloro, bromo o ariloxi. Los grupos ariloxi preferidos en la posición 6 son grupos fenoxi 3-sustituidos, más preferiblemente grupos fenoxi sustituidos con alógeno o grupos alquilo C₁-C₄ en la posición 3.

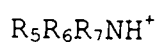
El grupo amino en la posición 4 puede ser no sustituido o sustituido con uno o más alquilo C₁-C₆,

alquienilo C₃-C₆, arilo, heteroarilo, hidroxilo, alcoxi C₁-C₆ o sustituyentes amino. El grupo amino puede ser adicionalmente derivado como una amida, un carbamato, una urea, un sulfonamida, una sililamina, un fosforamidato, una imina o una hidrazona. Tales derivados son capaces de componerse en la amina. El preferido es un grupo amino no sustituido o uno sustituido con uno o más sustituyentes alquilo.

Los ácidos carboxílicos de la fórmula I se cree que son los compuestos que matan o controlan la vegetación indeseable y son típicamente preferidos. Los análogos de estos compuestos en los cuales el ácido o grupo amino del ácido picolínico se deriva para formar un sustituyente relacionado que se puede transformar con plantas o el ambiente a un grupo ácido posee esencialmente los mismos efectos herbicidas y están dentro del alcance de la invención. Por lo tanto, un "derivado agrícolamente aceptable", cuando se utiliza para describir el ácido carboxílico funcionalmente en la posición 2, se define como cualquier sal, éster, acilhidrazida, imidato, tiomidato, amidina, amida, ortoéster, acilcianida, acilhaluro, tioéster, tionoéster, ditioléster, nitrilo, o

cualquier otro derivado ácido bien conocido en la técnica el cual (a) no afecta sustancialmente la actividad herbicida del ingrediente activo, es decir, el ácido 4-aminopicolínico, y (b) es o se puede hidrolizar en plantas o en suelo al ácido picolínico de la fórmula I que, dependiendo del pH, esta en la forma disociada o no disociada. De manera similar, un "derivado agrícolamente aceptable", cuando se utiliza para describir la funcionalidad amina en la posición 4, se define como cualquier sal, sililamina, fosforilamina, fosfinimina, fosforamidato, sulfonamida, sulfinimina, sulfoximina, amina, hemiaminal, amida, tioamida, carbamato, tiocarbamato, amidina, urea, imina, nitro, nitroso, azido, o cualquier otro hidrógeno que contiene derivados bien conocidos en la técnica los cuales (a) no afectan sustancialmente la actividad herbicida del ingrediente activo, es decir, el ácido 4-aminopicolínico, y (b) es o se puede hidrolizar en plantas o suelo a una amina libre de fórmula I. Los N-óxidos que también son capaces de descomponerse en piridina padre de la fórmula están también cubiertos por el alcance de esta invención.

Las sales adecuadas incluyen aquellos derivados de álcalis o metales alcalino térreos de aquellos derivados de amonio y aminas. Los cationes preferidos incluyen sodio, potasio, magnesio, y cationes aminio de la fórmula:



En donde $R_5R_6R_7$ cada uno, representan independientemente hidrogeno o alquilo C_1-C_{12} , alquenilo C_3-C_{12} o alquinilo C_3-C_{12} , cada uno de los cuales es opcionalmente sustituido por uno o más grupos hidroxí, alcoxi C_1-C_4 , alquiltio C_1-C_4 o fenilo, con la condición de que R_5 , R_6 , y R_7 son estéricamente compatibles. Adicionalmente, dos cualquiera de R_5 , R_6 , y R_7 juntos pueden representar una porción disfuncional alifática que contiene de 1 a 12 átomos de carbono y hasta dos átomos de oxígeno o azufre. Las sales de los compuestos de fórmula I se pueden preparar mediante tratamiento de compuestos de fórmula I con un metal hidróxido, tales como hidróxido de sodio, o una amina tal como amonio, trimetrilamina, dietanolamina, 2-metil-triopropilamina, bisalilamina, 2-butoxietylamina, morfolina,

ciclododecilamina, o benzilamina. Las sales de amina son a menudo formas preferidas de los compuestos de fórmula I en razón a que ellas son solubles en agua y se prestan para la preparación de composiciones herbicidas deseables basadas en agua.

Los ésteres adecuados incluyen aquellos derivados de alcoholes alquilo C_1-C_{12} , alquenilo C_3-C_{12} o alquinilo C_3-C_{12} , tales como metanol, iso-propanol, butanol, 2-etilhexanol, butoxietanol, metoxipropanol, alil alcohol, propargilalcohol o cicloexanol. Los ésteres se pueden preparar mediante el acoplamiento de ácido picolínico con el alcohol utilizando cualquier numero de agentes de activación adecuados tales como aquellos utilizados para acoplamientos péptidos tales como diciclohexilcarbodiimida (DCC) o carbonil diimidazola (CDI), al reaccionar el correspondiente cloruro ácido de un ácido picolínico de la fórmula I con un alcohol apropiado o al reaccionar el correspondiente picolínico de la fórmula I con un alcohol apropiado en la presencia de un catalizador ácido. Las amidas adecuadas incluyen aquellas derivadas de amonio o de aminas de alquilo C_1-C_{12} , alquinilo C_3-C_{12} o alquinilo C_3-C_{12} , mono o

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disustituidas, tales como pero no limitadas a dimetilamina, dietanolamina, 2-metiltiopropil-amina, bisalilamina, 2-butoxiethylamina, ciclo-dodecilamina, bencilamina o aminas cíclicas o aromática con o sin heteroátomos adicionales tales como pero no limitadas a aziridina, azetidina, pirolidina, pirol, imidazol, tetrazol, o morfolino. Las amidas se pueden preparar para hacer reaccionar el correspondiente cloruro de ácido picolínico, anhídrido mezclado, o éster carboxílico de fórmula I con amonio o una amina apropiada.

Los términos "alquilo", "alquenilo" y "alquinilo" así como también los términos derivados tales como "alcoxi", "acil", "alquiltio", y "alquilsulfonil", como se utilizan aquí incluyen dentro de su alcance porciones de cadena recta, cadena ramificada y cíclicos. A menos que se especifique otra cosa, cada uno puede ser no sustituido o sustituido con uno o más sustituyentes seleccionados pero no limitados a alógenos, hidroxil, alcoxi, "alquiltio", acilo C₁-C₆, formilo, ciano, ariloxi, o arilo, con la condición de que los sustituyentes sean estéricamente compatibles y las reglas del enlace químico y la energía de tensión se satisfaga. Los términos

"alquenilo" y "alquinilo" pretenden incluir uno o más enlaces insaturados.

El término "arilo", así como también los términos derivados tales como "ariloxi", se refieren a un grupo fenilo o naftilo. El término "heteroarilo", así como también los términos derivados tales como "heteroariloxi" se refieren a un anillo aromático de 5 o 6 miembros que contiene uno o más heteroátomos, sean, N, O o S; estos anillos heteroaromáticos pueden estar fusionados a otros sistemas aromáticos. Los sustituyentes arilo o heteroarilo pueden ser no sustituidos o sustituidos con uno o más sustituyentes seleccionados de alógeno, hidroxilo, nitro, ciano, ariloxi, formilo, alquilo C₁-C₆, alquenilo C₂-C₃, alquinilo C₂-C₆, alcoxi C₁-C₆, alquilo C₁-C₆ alogenado, acilo C₁-C₆, alquitio C₁-C₆, alquilsufinilo C₁-C₃, alquilsulfonilo C₁-C₆, arilo, OC(O)alquilo C₁-C₆, NHC(O)alquilo C₁-C₆, C(O)OH, C(O) o alquilo C₁-C₆, C(O)NH₂, C(O)NH alquilo C₁-C₆, C(O)N(alquilo)₂ C₁-C₆, con la condición de que los sustituyentes sean estéricamente compatibles y las reglas de enlace químico y de energía de tensión se satisfagan.

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A menos que se especifique otra cosa el término alógeno incluye flúor, cloro, bromo y yodo.

Los compuestos de fórmula I se pueden hacer utilizando procedimientos químicos bien conocidos. Los materiales de partida requeridos están comercialmente disponibles o son fácilmente sintetizados utilizando procedimientos estándar.

En general, la reducción de N-óxido de picolinato se puede preparar para utilizar los correspondientes picolinatos. La deshalogenación electrolítica de picolinatos 5-halogenados se puede utilizar para preparar picolinatos 5-H(no sustituidos), y la hidrólisis de piridinas sustituidas en la posición 2 mediante nitrilos, amidas, ésteres y otras funcionalidades hidrolizables se pueden utilizar para preparar los picolinatos deseados.

Los derivados amino 4-N-amida carbamato, urea, sulfonamida, sililamina y fosforamidato se pueden preparar mediante la reacción del compuesto amino libre

Los análogos 3- 5 5-alcoxi y ariloxi se pueden preparar mediante reducción de los correspondientes derivados 4-azido, los que a su vez se pueden preparar mediante desplazamiento nucleofílico de las correspondientes 4-bromopiridinas con NaN_3 . Las requeridas 3- y 5- alcoxi-4-bromopiridinas se pueden preparar de acuerdo a los procedimientos de la literatura.

Los análogos 6-alcoxi, alquiltio, ariloxi y heteroariloxi se pueden preparar mediante desplazamiento nucleofílico con alcóxido, tioalcóxido, arilóxido o heteroarilóxido sobre la apropiada 6-halopiridina.

Los análogos 3-y 5- alquiltio se pueden preparar mediante litiación de las apropiadas cloropiridinas a baja temperatura y tratamiento secuencial con alquil disulfuros y óxido de carbono. La reacción de los resultantes ácidos picolínicos con hidróxido de amonio dio los productos deseados.

Los análogos 6-ciano se pueden preparar mediante aminación del apropiado 4-halo-6-cianopicolinato. Los 4-halo -6-cianopicolinatos se pueden preparar mediante acción de trimetilsilil cianuro (TMSCN) sobre los apropiados N-óxido de piperidina, los cuales se pueden preparar mediante la oxidación mediada por peróxido de hidrogeno de la correspondiente piridina.

Los análogos 3- y 5- se pueden preparar mediante acción de KCN sobre la fluoropiridina apropiada a alta temperatura. Los análogos 3- y 5-fluor, bromo, yodo y nitro se pueden preparar mediante reacción electrofílica del precursor no sustituido con el halógeno positivo o las fuentes nitro tales como gas de flúor, bromo, yodo y con humos de ácido nítrico respectivamente.

Los análogos de 6-trifluorometil se pueden preparar mediante aminación de metil trifluorometil-picolinato fácilmente disponible (oxidación de halogenación de la posición 4 seguida por desplazamiento con amonio o una amina equivalente) seguido mediante cloración de las posiciones 3- y 5-.

Los análogos de 3- y 5-trifluorometilo se pueden preparar mediante manipulaciones estándar conocidas por aquellos expertos en la técnica que inician desde los compuestos conocidos 2-fluoro-3-cloro-5-trifluorometilpiridina y 2,5-dicloro-3-trifluorometilpiridina.

Los análogos 4-amino sustituidos se pueden preparar al hacer reaccionar el correspondiente 4-halopiridina-2-carboxilato o cualquier otro 4-sustituyente desplazable con la amina sustituida.

Los compuestos de fórmula I, obtenidos mediante cualquiera de estos procesos, se puede recuperar por medios convencionales. Químicamente, la mezcla de reacción se acidifica con el ácido acuoso, tal como ácido clorhídrico, y se extracta con un solvente orgánico, tal como acetato de etilo o diclorometano. El solvente orgánico y otros volátiles se pueden remover mediante destilación o evaporación para obtener el compuesto deseado de fórmula I, que se puede purificar mediante

procedimientos estándar, tales como recristalización o cromatografía.

Los compuestos de fórmula I se han encontrado como herbicidas de pre-emergencia y post-emergencia útiles. Ellos se pueden emplear a índices no selectivos (mayores) de aplicación para controlar un amplio espectro de la vegetación en un área a unos índices inferiores de aplicación para el control selectivo de vegetación no deseada. Las áreas de aplicación incluyen tierras de pastos, bordes de caminos, derechos de caminos, y cultivos tales como maíz, arroz y cereales. Usualmente se prefiere emplear los compuestos de post-emergencia. Es adicionalmente preferido utilizar los compuestos para controlar un amplio espectro de malezas de hojas anchas que incluyen las especies DOCK (*Rumex* spp), cardo canadiense (*Cirsium arvense*), especies de maleza de cerdo (*Amaranthus* spp.), especies Senna (*Cassia* spp.), especies de euforbio (*Euforbia* spp), especies de ambrosia (*Ambrosia* spp), especies de sida (*Sida* spp.), enredadera de campo (*Convolvulus arvensis*), y especies de centaurea negra (*Centaurea* spp.), entre otros. El uso de los compuestos para controlar vegetación indeseable en

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áreas de pastos es especialmente indicado. Mientras que cada uno de los compuestos de 4-aminopicolinato comprendidos por La fórmula I están dentro del alcance de la invención, el grado de actividad herbicida, la selectividad del cultivo y el espectro de control de malezas obtenido varía dependiendo de los sustituyentes que se presenten. Un compuesto apropiado para cualquier utilidad herbicida se puede identificar al utilizar la información presentada aquí y los ensayos de rutina.

El término herbicida se utiliza aquí para significar un ingrediente activo que mata, controla o modifica de otra forma de manera adversa el crecimiento de plantas. Una cantidad herbicidamente efectiva o que controla la vegetación es una cantidad de ingrediente activo que origina un efecto de modificación adverso y que incluye desviaciones del desarrollo natural, muerte, regulación, desecación, retardo, y similar. Los términos plantas y vegetación incluyen semillas germinantes plántulas emergentes y vegetación establecida.

La actividad herbicida se exhibe por los compuestos de la presente invención cuando ellos se aplican

directamente a la planta o al locus de la planta en cualquier etapa de crecimiento o antes de la plantación o emergencia. El objeto observado depende del crecimiento de la planta, los parámetros de aplicación de dilución y el tamaño de la gota de rociado, el tamaño de la partícula de los componentes sólidos, las condiciones ambientales en el momento de uso, el compuesto específico empleado, los adyuvantes específicos y los portadores empleados, el tipo de suelo, y similar. Así como también la cantidad de químico aplicado. Estos y otros factores se pueden ajustar como es conocido en la técnica para promover acción herbicida no selectiva o selectiva. De manera general, se prefiere aplicar los compuestos de fórmula I post-emergencia a vegetación indeseable relativamente inmadura para lograr el control máximo de las malezas.

Los índices de aplicación de 1 a 500 g/Ha son generalmente empleados en operaciones post-emergencia; para aplicaciones preemergencia, los índices de 10 a 100 g/Ha son empleados de manera general. Los índices mayores designados generalmente dan un control no selectivo de una variedad amplia de vegetación no deseada. Los índices

inferiores típicamente dan control selectivo y se pueden emplear en el locus de cultivos.

Los compuestos herbicidas de la presente invención son a menudo mejor aplicados en conjunto con uno o más de otros herbicidas para obtener control de una amplia variedad de vegetación no deseada. Cuando se utiliza en conjunto con otros herbicidas, los compuestos reivindicados en la presente invención se pueden formular con el otro herbicida o herbicidas, mezclados en tanque con el otro herbicida o herbicidas, o aplicado secuencialmente con el otro herbicida o herbicidas. Algunos de los herbicidas se pueden emplear en conjunto con los compuestos de la presente invención incluidas sulfonamidas tales como metosulam, flumetosulam, cloransulam-metilo, diclosulam y florasulam, sulfonilureas tales como clorimuron, nicosulfuron, y metsulfuron, imidazolinonas tales como imazaquin, imazapic, imazetapir e imazamox, ácidos fenoxialcanoicos tales como 2,4-Dy MCPA, ácidos piridiniloxiacéticos tales como triclopir y fluroxipir, ácidos carboxílicos. Tales como clopiralid y dicamba, dinitroanilinas tales como trifluralin y pendimetalin, cloroacetanilidas tales como

alaclor, acetoclor, y metolaclor y otros herbicidas comunes que incluyen acifluorfen, bentazon, clomazona, fumiclorac, fluometuron, fomesafen, lactofen, linuron, isoproturón, y metribuzin. Las combinaciones particularmente preferidas son aquellas con florasulam, 2,4-Dy fluroxipir, los cuales, contra algunas especies de malezas, pueden exhibir sinergia. Una respuesta sinérgica se puede también obtener con compuestos de la presente invención cuando se mezclan con inhibidores de transporte de auxina tales como diflufenzopir y clorflurenol. Los compuestos herbicidas de la presente invención pueden, además, ser utilizados en conjunto con grifotas y glufosinato sobre cultivos tolerantes aglifosato o glufosinato. Se prefieren generalmente utilizar los compuestos de la invención en combinación con herbicidas que son selectivos para el cultivo que esta siendo tratado y que complementa el espectro de malezas controladas por los compuestos en el índice de aplicación empleado. Se prefiere además generalmente aplicar los compuestos de la invención y otros herbicidas complementarios a la vez, bien sea como una formulación en combinación o como una mezcla en tanque.

Los compuestos de la presente invención pueden ser generalmente empleados en combinación con aseguradores de herbicidas conocidos, tales como cloquintocet, furilazole, diclormid, benoxacor, mefenpri-etilo, fenclorazol-etilo, flurazole, y fluxofenim, para mejorar su selectividad. Ellos pueden adicionalmente ser empleados para controlar vegetación indeseada en muchos cultivos que se han hecho tolerantes o resistentes a ellos o a los otros herbicidas mediante manipulación genética o mediante mutación y selección. Por ejemplo, se pueden tratar al maíz, trigo, arroz, soja, remolacha, algodón, cáñola, y otros cultivos que se han hecho tolerantes o resistentes a los compuestos que son inhibidores de acetolactato sintasa en plantas sensibles. Muchos cultivos tolerantes glifosato y glufosinato se pueden tratar también, solo que en combinación con estos herbicidas. Algunos cultivos (por ejemplo algodón) se han hecho tolerantes a herbicidas auxínicos tales como 2,4-diclorofenoxiacético. Estos herbicidas se pueden utilizar para tratar tales cultivos resistentes u otros cultivos tolerantes auxina.

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Mientras que es posible utilizar los compuestos de 4-amino-picolinato de fórmula I directamente como herbicidas, es preferible utilizarlos en mezclas que contienen una cantidad herbicídamente efectiva del compuesto junto con al menos un adyuvante o portador agrícolamente aceptable. Adyuvantes o portadores adecuados no deben ser fitotóxicos a los cultivos valiosos, particularmente en la concentración empleada en la aplicación de las composiciones para controlar malezas selectivas en la presencia de cultivos, y no deben reaccionar químicamente con los compuestos de fórmula I u otros ingredientes de la composición. Tales mezclas se pueden diseñar para la aplicación directamente a las malezas o su locus o pueden ser concentrados o formulaciones que son normalmente diluidos con portadores adicionales y adyuvantes antes de aplicación. Ellos pueden ser sólidos, tales como, por ejemplo, polvos, gránulos, gránulos dispersables en agua, o polvos humectables, o líquidos, tales como, por ejemplo, concentrados emulsificables, soluciones, emulsiones o suspensiones.

Los adyuvantes y portadores agrícolas adecuados que son útiles en la preparación de mezclas herbicidas de la invención son bien conocidos por los expertos en la técnica.

Los portadores líquidos que se pueden emplear incluyen agua, tolueno, xileno, nafta de petróleo, aceite de cultivo, acetona, metil etil cetona, ciclohexanona, tricloroetileno, percloroetileno, etil acetato, amil acetato, butil acetato, propilen glicol monometil éter y dietilen glicol monometil éter, metanol, etanol, isopropanol, amil alcohol, etileno glicol, propileno glicol, glicerina, y similares. El agua es generalmente el portador de escogencia para la dilusión de concentrados.

Los portadores sólidos adecuados incluyen talco, arcilla de pirofilita, sílice, arcilla atapulgus, arcilla de caolin, kieselgur, yeso, tierras diatomáceas, limo, carbonato de calcio, arcilla de bentonita, tierra de fuller, vainas de semilla de algodón, harina de trigo, harina de soja, piedra pómez, harina de madera, harina de concha de nogal lignina, y similares.

Es usualmente deseable incorporar uno o más agentes activos d superficie activa en las composiciones de la presente invención. Los agentes de superficie activa son ventajosamente empleados tanto en composiciones sólidas como líquidas, especialmente aquellos designados para ser diluidos con portadores antes de aplicación. Los agentes de superficie activa pueden ser aniónicos, catiónicos o no iónicos en carácter y se pueden emplear como agentes emulsificantes, agentes humectantes, agentes de suspensión, o para otros propósitos. Los agentes de superficie activa típicos incluyen sales o alquilsulfatos, tales como dietilamonio lauril sulfato; sales de alquilarilsulfonato, tales como dodecilbenzonosulfonato de calcio; productos de adición de óxido de alquilfenol-alquilenos, tales como nonifenol-C18, etoxilato; productos de adición de óxido de alcohol-alquilenos, tales como tridecil alcohol -C16 etoxilato; Jabones, tales como estearato de sodio; sales de alquil naftalenosulfonato, tales como dibutilnaftalenosulfonato de sodio; ésteres de dialquilo de sales de sulfosuccinato, tales como di(2-etilhexil)sulfosuccinato de sodio; ésteres desorbitol, tales como oleato de

sorbitol; aminas cuaternarias, tales como cloruroetileno de lauril trimetil-amonio; ésteres de polietilen glicol de ácidos grasos, tales como estearato de polietilen glicol; copolímeros de bloque de óxido de etileno y óxido de propileno; y sales de ésteres de mono y de dialquil fosfato.

Otros adyuvantes común mente utilizados en composiciones agrícolas incluyen agentes compatibilizantes, agentes antiespumantes, agentes secuestrantes, agentes neutralizantes y amortiguadores, inhibidores de la corrosión, tintes, odorantes, agentes de rociado, agentes de ayuda de penetración, agentes para adherencia, agentes dispersantes, agentes espesantes, supresores de punto de congelamiento, agentes antimicrobianos, y similares. Las composiciones también podrían contener otros componentes compatibles por ejemplo, otros herbicidas, reguladores de crecimiento de planta, fungicidas, insecticidas, y similares y se pueden formular con fertilizantes líquidos o sólidos, portador de fertilizantes en partículas tales como nitrato de amonio, urea y similares.

La concentración de los ingredientes activos en las composiciones herbicidas de esta invención son generalmente de 0,001 a 98% en peso. Las concentraciones de 0,01 a 90% en peso se emplean a menudo. En las composiciones designadas a ser empleadas como concentrados, el ingrediente activo está generalmente presente en una concentración de 5 a 98% en peso, preferiblemente 10 a 90% en peso. Tales composiciones son típicamente diluidas con un portador inerte tales como agua, antes de aplicación. Las composiciones diluidas usualmente aplicadas a las malezas o al locus de malezas generalmente contienen 0,0001 a 1 por ciento en peso de ingrediente activo y preferiblemente contienen 0,0001 a 0,05 por ciento en peso.

Las composiciones presentes se pueden aplicar a malezas o su locus mediante el uso de aplicadores de polvo molido convencional o aéreo, y aplicadores de gránulos, mediante la adición de aguas de irrigación, y mediante otros medios convencionales conocidos por aquellos expertos en la técnica.

Los siguientes ejemplos se presentan para ilustrar varios aspectos de esta invención y no se deben considerar como limitaciones a las reivindicaciones

Ejemplos

1. Preparación de ácido 4-amino-3,6-dicloropiridina-2-carboxílico (Compuesto 1)

En un beaker de 3 litros (L) se agregaron 2000 gramos (g) de agua caliente, 115,1 g de NaOH, al 50% en peso, y 200 g de ácido 4-amino-3,5-tricloro-piridina-2-carboxílico húmedo (79,4%). La solución se agitó durante 30 minutos (min), se filtró a través de un papel de filtro, y se transfirió a un tanque de alimentación/recirculación de 5 L. Esta solución pesó 2315 g y contenía 6,8% del ácido 4-amino-3,5,6-tricloro-piridina-2-carboxílico. Esta alimentación se recirculó a un índice de aproximadamente 9,46 L/min y un temperatura de 30° C a través de una celda electroquímica individual que tiene un ánodo Hastelloy C y un cátodo de pantalla de malla de lata expandido. Después de la anodización normal

a +0,7 voltios (v), la polaridad de la celda se reversó y se inició la electrólisis. El potencial de trabajo del cátodo se controló a -1,1 a -1,4 v con relación a un electrodo con referencia Ag/AgCl (3,0 de Cl^- M). Mientras que se recircula la alimentación, una solución al 50% de NaOH se bombea lentamente dentro del tanque de recirculación para mantener la concentración de NaOH a un exceso en porcentaje de 1,5 a 2,0. Después de aproximadamente 15 horas (h) la electrólisis se terminó y el efluente de celda se filtró a través del papel de filtro. La solución se neutralizó con HCl concentrado y se concentró a aproximadamente 750 g de concentrado crudo. El concentrado se calentó a 85° C con agitación y el pH se ajustó a menos de 1 con HCl concentrado durante 30 min. La lechada resultante se enfrió a temperatura ambiente y se filtró. La torta del filtro se lavó con 3 x 200 mililitros (mL) de agua y se secó bajo vacío a 80° C. el producto seco, 118,1 g ensayado a 90,6% de producto deseado; la cromatografía de gas (GC) indicó aproximadamente un resto de ácido 4-amino-3,5,6-tricloropiridin-2-carboxílico como impureza. Una muestra purificada de ácido 4-amino-3,6-dicloropiridin-2-carboxílico tuvo un punto de fusión (pf) de 185-187° C

(dec.); ^1H RMN (DMSO-d_6): δ 13,9 (br, 1H), 7,0 (br m, 2H), 6,8 (s, 1H); ^{13}C RMN $\{^1\text{H}\}$ (DMSO-d_6): 111,0 (1C), 108,1 (1C).

2. Preparación de 2-etilhexil 4-amino-3,6-dicloropiridina-2-carboxilato (compuesto 2)

A una solución de 2-etilhexanol (10 ml) y ácido sulfúrico (1 ml) se agregó ácido 4-amino-3,6-dicloropiridina-2-carboxílico (0,0097 mol, 2,0 g). Después de calentamiento la reacción a reflujo durante toda la noche, la mezcla de reacción se enfrió, se virió en agua (75 ml), y se extrajo con etilacetato (75 ml). La fase orgánica se lavó con bicarbonato de sodio (75 ml), se secó (Na_2SO_4), y se concentró. El sólido resultante se recrystalizó sin diclorometano y hexano y se filtró para dar 2-etilhexil 4-amino-3,6-dicloropiridina-2-carboxilato (0,0074 mol, 2,36 g) como un sólido cristalino (pf 55°C). ^1H RMN (CDCl_3): δ 0,9 (7 H, 1m), 1,3 (7 H, m), 1,7 (1 H, m), 4,3 (2 H, d), 5,1 (2 H, bs), 6,7 (1 H, s).

Los siguientes ésteres de ácido 4-amino -3,5,6-tricloro-piridina-2-carboxílico se prepararon de acuerdo con el procedimiento del ejemplo 2:

Metilo 4-amino-3,6-dicloropiridina-2-carboxilato
(compuesto 3); pf 134-135° C.

Etilo 4-amino-3,6-dicloropiridina-2-carboxilato
(compuesto 4); pf 98-99° C.

n-propilo 4-amino-3,6-dicloropiridina-2-carboxilato
(compuesto 5); pf 94-95° C.

i-propilo 4-amino-3,6-dicloropiridina-2-carboxilato
(compuesto 6); pf 114-115° C.

n-butilo 4-amino-3,6-dicloropiridina-2-carboxilato
(compuesto 7); pf 78-79° C.

n-pentilo 4-amino-3,6-dicloropiridina-2-carboxilato
(compuesto 8); pf 134-135° C.

n-hexilo 4-amino-3,6-dicloropiridina-2-carboxilato
(compuesto 9); pf 65-66° C.

butoxietilo 4-amino-3,6-dicloropiridina-2-carboxilato (compuesto 10); pf 64-7° C; como monohidrato.

3. Preparación de 4-amino-3,6-dicloropiridin-2-carboxamida (Compuesto 11)

A un recipiente de fondo redondeado de tres cuellos de 250 ml ajustado por un agitador mecánico se agregaron metilo 750 (10,0 g, 45 mmol) y NH_4OH acuoso al 28% (35 ml) a 0° C. La suspensión se agitó vigorosamente durante 24 h mientras que se calentó gradualmente hasta 25° C. la suspensión fue filtrada por succión, y la torra del filtro se lavó sobre el filtro con agua fría (2 x 100 ml). Después de secar al aire sobre el filtro, el producto sólido blanco analíticamente puro se recolectó para dar 4-amino-3,6-dicloropiridin-2-carboxamida 11 (8,58 g, 92% de producción); pf 240-241° C.

4. Preparación de metilo N-acetilo 4-amino-3,6-dicloropiridin-2-carboxilato (compuesto 21) y N,N-diacetil 4-amino-3,6-dicloropiridin-2-carboxilato (compuesto 13)

A una solución de anhídrido acético (75 ml) y metil 4-amino-3,6-dicloropiridin-2-carboxilato (0,00904 mol, 2,0 g) se agitó y calentó a reflujo durante toda la noche. La solución se enfrió, se concentró, tomó de acetato de etilo (100 ml), se lavó con agua (100 ml). La fase orgánica se lavó con bicarbonato de sodio saturado (100 ml), se secó (Na_2SO_4), y se concentró. La solución se purificó mediante cromatografía sobre sílica gel. La mancha de corrimiento frontal se aisló y dio un aceite amarillo identificado como el compuesto 13 de 4-amidadiacilado (0,0023 mol, 0,700 g). ^1H RMN 2,2 (6 H, s), 3,9 (3 H, s), 7,3 (1 H, s). La segunda mancha dio un sólido amarillo identificado como el compuesto 12 de 4-amida monoacilado (0,0035 mol, 0,920 g); pf 102-103° C.

5. preparación de ácido 4-amino-6-bromo-3-cloropiridin-2-carboxílico (Compuesto 14)

A. N-óxido, metilo 6-bromo-3-cloropiridina-2-carboxilato

A una solución de metil 6-bromo-3-cloro-piridin-2-carboxilato (0,13 mol, 32,1 g) en ácido trifluoroacético (75 ml) y anhídrido trifluoroacético (40 ml) se agregó de

manera cautelosa peróxido de hidrógeno al 50% (0,17 mol, 13 g). La reacción fue hexotérmica hasta reflujo. Después de agitación durante 30 min, la solución se vertió en una mezcla de hielo y 10% de bisulfito de sodio (150 ml). El sólido resultante se recolectó y se secó in vacuo para dar un sólido blanco (0,08 mol, 21,4 g). ^1H RMN (CDCl_3): δ 4,1 (3H, s), 7,3 (1H, d), 7,7 (1H, d).

B. N-óxido, metil 6-bromo-3-cloro-4-nitropiridin-2-carboxilato

A una solución de humo de ácido nítrico (10 ml) y humo de ácido sulfúrico (10 ml) se agregó N-óxido, metil 6-bromo -3-cloropiridin-2-carboxilato, y la reacción se calentó hasta 70° C en un baño de aceite durante 4 h. La mezcla se vertió sobre agua de hielo (100 ml) y se extrajo con acetato de etilo (3 x 73 ml) y los extractos combinados se retrolavaron con agua salobre, se secaron (Na_2SO_4) y se concentraron. El aceite oscuro se cromatografió sobre sílice en 4:1 de EtOAc /hexano para dar N-óxido, 6-bromo-3-cloro-4-nitropiridin-2-carboxilato, (0,007 mol, 2,2 g). ^1H RMN (CDCl_3): δ 4,1 (3H, s), 8,4 (1H, s).

C. metilo 4-amino-6-bromo-3-cloropiridin-2-
carboxilato

A una solución de tetracloruro de titanio (0,015 mol, 2,8 g) en tetrahidrofurano (50 ml) se agregó hidruro de aluminio litio (0,0175 mol, 0,07 g). La lechada negra se agitó 15 min antes de agregar el N-óxido, metil 6-bromo-3-cloro-4-nitropiridin-2-carboxilato, (0,007 mol, 2,3 g) en THF (25 ml). La solución se agitó 1 h antes de verter en H₂O/N₄OH 1:1 y filtrar. El filtrado se extrajo con EtOAc (2 x 75 ml). La fase orgánica se secó (Na₂SO₄) y se concentró. El rojo sólido se cromatografió sobre sílice en EtOAc/hexano 4:1 para dar metil 4-amino-6-bromo-3-cloropiridin-2-carboxilato (0,003 mol, 0,8 g); pf en 194-5° C. ¹H RMN (CDCl₃): δ 3,95 (3H, s), 5,3 (2H, bs), 6,9 (1H, s).

C. Ácido 4-amino-6-bromo-3-cloropiridin-2-
carboxílico (compuesto 14)

A metilo 4-amino-6-bromo-3-cloropiridin-2-
carboxilato (200 mg; 0,8 mmol) en 10 ml de metanol se

agregó un exceso de NaOH 2N (10 mL). La mezcla se agitó durante 1 h a temperatura ambiente y luego se evaporó hasta sequedad in vacuo. El residuo se disolvió en agua y dietiléter. Después de la separación de las fases, la capa acuosa se acidificó con HCl 1N a un pH = 2. La capa acuosa se evaporó hasta sequedad y el residuo se disolvió en 50 ml de metanol y se filtró. El filtrado se evaporó bajo presión reducida y el residuo se trituro con dietiléter al 5% en éter de petróleo para dar 70 mg de ácido 4-amino-5-6-bromo-3-cloropiridin-2-carboxílico, pf 182-183° C.

6. preparación de metilo 4-aminometilo-3-cloro-6-fluoro-piridin-2-carboxilato (compuesto 15)

A. metilo 3-cloro-6-fluoro-piridin-2-carboxilato

A una solución de metilo 3,4,6-tricloropiridin-2-carboxilato (0,010 mol, 2,4 g) en DMSO (10 ml) se agregó fluoruro de cesio (0,038 mol, 3,8 g) y la suspensión se calentó durante 2 h a 100° C. la mezcla de reacción se disolvió en HCl diluido y se extrajo con acetato de etilo (EtOAc). La capa orgánica se trató con (trimetilsilil) diazometano (TMSCHN₂) para reesterificar cualquier éster

hidrolizado. La mezcla se concentró y el residuo resultante se cromatografió sobre sílice con 10% de EtOAc/hexano para dar metilo 3-cloro-4,6-difluoropiridin-2-carboxilato (0,072 mol, 1,5 g). ^1H RMN (CDCl_3): δ 4,00 (3H, s), 6,95-6,90 (1H, m), ^{19}F RMN $\{^1\text{H}\}$: δ -65,0 (d, $J = 17$ Hz), 95,8 (d, $J = 17$ Hz).

B. metilo 4-amino-3-cloro-6-fluoropiridin-2-carboxilato (Compuesto 15)

A azido de sodio (0,0086 mol, 0,60 g) se agregó una solución de metilo 3-cloro-4,6-difluoropiridin-2-carboxilato (0,0072 mol, 1,5 g) en 15 ml de dimetilformamida (DMF). La solución se agitó 10 min a temperatura ambiente antes de verter en 350 ml de agua y extraer la mezcla acuosa con EtOAc (2 x 100 ml). La fase orgánica se secó (Na_2SO_4) y luego se trató con un exceso de NaBH_4 se apagó con EtOH acuoso y la mezcla se diluyó con agua (200 ml). La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (2 x 200 ml). Las capas orgánicas combinadas se secaron (Na_2SO_4) y se concentraron a un polvo blanco apagado que se purificó mediante HPLC de fase reversa para dar metilo 4-amino-3-cloro-6-

fluoropiridin-2-carboxilato (0,0059 mol, 1,2 g). ^1H RMN (CDCl_3): δ 3,95 (3H, s), 5,2-5,1 (2H, bs), 6,36 (1H, s), ^{19}F RMN $\{^1\text{H}\}$: δ -72,7.

7. Preparación de ácido 4-amino-3-difluoro-6-bromopiridin-2-carboxílico (compuesto 16)

A. Preparación de 4-amino 3,5,6-trifluoro-2-cianopiridin

A una solución de 3,4,5,6-tetrafluoro-2-cianopiridin en DMF (75 ml) a 0°C se agregó lentamente hidróxido de amonio concentrado (15 ml) la reacción se agitó 15 min adicionales y la solución se diluyó con agua (150 ml). El sólido se recolectó y se secó al aire para dar 4-amino - 3,5-trifluoro-2-cianopiridino (25,5 g, 0,16 mol, 92%); pf $291-3^\circ\text{C}$.

B. Preparación de metilo, 4-amino-6-bromo-3,5-difluoropiridil-2-carboxilato (compuesto 16)

Una solución de 4-amino-3,5,6-trifluoro-2-cianopiridin (19 g, 0,12) en bromuro de hidrógeno al 30%

en ácido acético (150 ml) se colocó en una bomba Para y se calentó a 110° C durante 3 h. La reacción se diluyó con agua (300 ml) y se recolectó un sólido (4-amino-6-cloro-3,5-difluoropiridin-2-carboxamida). Este material, sin purificación adicional, se convirtió en lechada con metanol (500 ml) y se agregó ácido clorhídrico concentrado. La lechada se calentó bajo reflujo durante 4 h, y luego bajo enfriamiento a temperatura ambiente, se diluyó en agua (1.000 ml) y el sólido se recolectó y se secó para dar metilo 4-amino-6-bromo-3,5-difluoropiridin-2-carboxilato (9,6 g, 0,04 mol, 25%); pf 110-111° C.

8. Preparación de ácido 4-amino-3,6-dibromopiridin-2-carboxílico (compuesto 17)

3,4,5,6-tetrabromopiridin-2-carboxamida (5,0 g) se aminató selectivamente con gas amonio a temperatura ambiente en 100 ml de metanol. La solución resultante se concentró hasta un sólido blanco apagado y se hidrolizó con ácido sulfúrico concentrado (25 ml) a 140° C durante 3H. La mezcla se hizo básica con NaOH, se extrajo con EtOAc (2 x 100 ml), se acidificó y se filtró para dar 1,4 g de ácido 4-amino-3,6-dibromopiridino-2-carboxílico puro; pf 205° C.

9. Preparación de metilo 4-amino-3,5,6-tribromopiridin-2-carboxilato (compuesto 18)

Metilo 4-amino-3,5,6-tribromopiridin-2-carboxilato se preparó mediante aminación de metil 3,4,5,6-tetrabromopiridin-2-carboxilato siguiendo el procedimiento del ejemplo 6B. ^1H RMN (CDCl_3): δ 3,95 (3H, s), 6,9-6,8 (2H, bs).

10. Preparación de ácido 4-amino-3,6-dicloro-5-fluoropiridin-2-carboxílico (compuesto 19)

A una solución de 4-amino-3,6-dicloro-piridin-2-carboxilato (1,5 g, 6,8 mmol) en 20 ml de acetonitrilo seco se agregó 1-(clorometil)-4-fluoro-1,4-diazoniabicyclo [2.2.2] octano bis (tetrafluoroborato) (SelectfluorTM de Aldrich Chemical Company, Inc.; 2,9 g, 2,59 mmol) [F^-]/g). La mezcla resultante se calentó en reflujo durante 3 h, entonces se le permitió enfriarse hasta temperatura ambiente. Este material fue tomado Et_2O y lavado con H_2O . La capa orgánica se secó sobre MgSO_4 , se filtró y se concentró para producir un aceite café. El

producto crudo se purificó y la fase HPLC fase reversa (50% de acetonitrilo/agua) para dar 0,37 g de un sólido blanco que se agitó en NaOH durante 1H luego se acidificó con HCl concentrado. El precipitado blanco sólido se recolectó con succión, se lavó con H₂O se secó bajo vacío para dar 170 mg de ácido 4-amino-3,6-dicloro-5-fluoropiridin-2-carboxílico (11% de producción); pf 214° C dec.

11.Preparación de ácido 4-amino-3,6-dicloro-5-bromopiridin-2-carboxílico (compuesto 20)

A una solución de metilo 4-amino-3,6-dicloropiridin-2-carboxilato (18 g, 81 mmol) en 100 ml se agregó de humos de ácido sulfúrico se agregó bromo (15 ml, en exceso). La mezcla resultante se calentó a 70° C durante 30 min, luego se le permitió enfriarse hasta temperatura ambiente. Este material se virió en agua con hielo (1.000 ml) y se extrajo con EtOAc (4 x 500 ml). Los extractos orgánicos combinados se secaron (MgSO₄), se filtraron y se concentraron para producir un sólido café. En el producto crudo se purificó vía HPLC de fase reversa (50% de acetonitrilo/agua) para dar 21 g de ácido 4-

amino-3,6-dicloro-5-bromopiridin-2-carboxílico como un sólido blanco (91% de reducción); pf 201-202° C.

12. Preparación de ácido 4-amino-3,6-dicloro-5-trifluorometilpiridin-2-carboxílico (compuesto 21)

Una solución de 4-amino-3,6-dicloro-5-trifluorometil-2-cianopiridin (0,5 g, 1,96 mol) en 10 ml de H₂SO₄ al 85% se agitó a 140° C durante 0, h. La mezcla de reacción se le permitió enfriarse a hielo. El sólido blanco precipitado se recolectó con succión, se enjuagó varias veces más con agua y se le permitió secarse con agua para dar 0,33 g del producto como u sólido blanco (61,4% de producción); pf 173° C.

13. Preparación de ácido 4-amino-3,6-dicloro-5-metoxipiridin-2-carboxílico (compuesto 22)

A. N-óxido, metil 3-cloro-5-metoxipiridin-2-carboxilato

En un frasco de fondo redondeado de tres cuellos seco se agregó N-óxido, metilo 3,5-dicloropiridin-2-

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carboxilato (5,0 g, 22,5 mmol) a 25 ml de metanol para dar una lechada. Una solución al 25% de metóxido de sodio en metanol (5,40 ml, 23,62 mmol) se agregó y calentó a reflujo durante 1,5 h. La mezcla de reacción se diluyó en acetato de etilo y se agregó H₂O. Las capas se separaron y la capa acuosa se saturó con H₂O salobre y se extrajo dos veces más en etilacetato. Las capas orgánicas combinadas se secaron (MgSO₄) y se concentraron para dar un sólido blanco. Purificación mediante cromatografía de columna (sílica gel) utilizando un eluente de 50% de Et₂O/éter de petróleo (1,5 l) luego 100% de Et₂O para dar 1,76 g de un sólido blanco; pf 154-156° C.

B. N-óxido metilo 3-cloro-5-metoxi-4-nitropiridin-2-carboxilato

A N-óxido, metilo 3-cloro-5-metoxipiridin-2-carboxilato, (1,41 g, 5,97 mmol) en H₂SO₄ enfriado a 0° C se agregó lentamente una mezcla 50/50 de óleo al 30% y humos de HNO₃. La mezcla de reacción se agitó durante 30 min a temperatura ambiente y luego se calentó a 70° C durante 3 días. La mezcla de reacción se diluyó con acetato de etilo y se enfrió a 0° C. se agregó cuidadosamente carbonato de sodio saturado y las capas se

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separaron. La capa acuosa se elaboró dos veces más con acetato de etilo. Las capas orgánicas combinadas se secaron (MgSO_4) y se concentraron hasta sequedad. Purificación mediante cromatografía de columna (sílica gel) utilizando un eluyente de etilacetato/hexano al 20% dio 300 mg de un sólido amarillo; pf 160°C .

C. metilo 3,6-dicloro-5-metoxi-4-nitro-piridin-2-
carboxilato

A metilo 3-cloro-5-metoxi-4-nitro-piridin-2-
carboxilato

A metilo 3-cloro-5-metoxi-4-nitro-piridin-2-carboxilato, N-óxido (0,300 g, 1,12 mmol) en 5 ml de cloroformo se agregó PCl_3 (0,664 mL, 7,62 mmol). La mezcla de reacción se calentó hasta reflujo durante 8 h y luego se concentró hasta sequedad in vacuo para dar 300 mg de un sólido blanco.

D. Metilo 4-amino-3,6-dicloro-5-metoxipiridin-2-
carboxilato

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A metilo 3,6-dicloro-5-metoxi-4-nitropiridin-2-carboxilato (0,300 g, 1,06 mmol) en 5 ml de acetato de etilo se agregó $\text{SnCl}_2 \times 2\text{H}_2\text{O}$ (1,60 g, 7,1 mmol). La mezcla de reacción se calentó a 70°C durante 30 min y luego se enfrió a temperatura ambiente. Se agregaron bicarbonato de sodio saturado y solución saturada de KHF_2 a la mezcla de reacción. La mezcla se trajo con acetato de etilo y las capas se separaron. La capa acuosa se lavó dos veces más con acetato de etilo. Las capas orgánicas combinadas se secaron (MgSO_4) se concentraron hasta sequedad para dar 0,250 g de un sólido amarillo.

E. ácido 4-amino-3,6-dicloro-5-metoxipiridin-2-carboxílico (compuesto 22)

Acido 4-amino-3,6-dicloro-5-metoxipiridin-2-carboxílico se preparó mediante saponificación del éster de metilo de acuerdo con el ejemplo 17 (D); pf $154-156^\circ \text{C}$.

14. Preparación de ácido 4-amino-3,6-dicloro-5-metiltiopiridin-2-carboxílico (compuesto 23)

Se preparó 4-amino-3,6-dicloro-5-metiltiopiridino-2-carboxílico mediante analogía a la preparación del ácido 4-amino-3,6-dicloro-5-metoxipiridin-2-carboxílico siguiendo el procedimiento del ejemplo 13 utilizando tiometóxido de sodio en lugar de metóxido de sodio; pf 160° C dec.

15. Preparación de 4-amino-3,6-dicloro-5-feniltiopiridin-2-carboxilato (compuesto 24)

Ácido 4-amino-3,6-dicloro-5-feniltiopiridin-2-carboxílico se preparó mediante analogía a la preparación de ácido 4-amino-3,6-dicloro-5-metoxipiridin-2-carboxílico siguiendo el procedimiento del ejemplo 13 utilizando tiofenóxido de sodio en lugar de metóxido de sodio; pf 160° C dec.

16. Preparación de metilo 4-amino-3,6-dicloro-5-nitropiridin-2-carboxilato (compuesto 25)

A una solución que contiene ácido 4-amino-3,6-dicloropiridin-2-carboxílico (0,5 g, 2,43 mmol) y 10 ml de H₂SO₄ concentrado se agregó gota a gota de una mezcla de HNO₃/H₂SO₄ concentrado (1 ml/1 ml) a temperatura

ambiente. Después de agitar durante 5 min, la mezcla de reacción se agregó a hielo y el sólido se recolectó mediante filtración en vacío. El sólido resultante se disolvió en MeOH/EtOAc al 20% y trimetilsilil diazometano (TMSCHN_2) se agregó entonces hasta que se completó la reacción. La mezcla de reacción se concentró bajo presión reducida, se virtió en Et_2O y se lavó con NaHSO_3 , se secó sobre MgSO_4 , se filtró y se concentró para dar un aceite café. El producto crudo se purificó mediante cromatografía, diluyendo con etilacetato-hexano al 10% para dar 80 mg de metiléster como un sólido amarillo; pf $127-8^\circ \text{C}$.

17. Preparación de ácido 4-N-metilamida-3,6-dicloro-
piridin-2-carboxílico (compuesto 26)

A. Metilo 3,6-dicloropiridin-2-carboxilato

A un frasco de fondo redondeado de tres cuellos equipado con un condensador de reflujo se agregó ácido 3,6-dicloropiridin-2-carboxílico (50,0 g, 260,42 mmol) en metanol (200 ml). $\text{HCl}_{(g)}$ se burbujeó hasta que la solución se saturó y se agitó a temperatura ambiente durante 2 h. La solución se concentró hasta sequedad in vacuo. Se

agregó dietiléter para hacer una lechada que se agregó subsecuentemente a un recipiente llenado con una mezcla 1:1 de bicarbonato de sodio/dietiléter y se agitó durante 10 min. La fase acuosa se extrajo con dietiléter (3 x 300 ml). Los extractos combinados se secaron (MgSO_4) y se concentraron para dar 46,6 g de un sólido amarillo claro. ^1H RMN (CDCl_3): δ 4,00 (s, 3H), 7,41 (d, 1H), 7,80 (d, 1H).

B. N-óxido metilo 3,6-dicloropiridin-2-carboxilato

Metilo 3,6-dicloropicolinato (20,0 g, 97,07 mmol) se disolvió en la cantidad mínima de ácido trifluoroacético (TFA). En un recipiente separado se agitó anhídrido trifluoroacético (TFAA, 38 mL) y H_2O_2 al 50% (9,9 g, 145,61 mmol) el cual se agregó a la solución TFA. La mezcla de reacción se agitó a reflujo durante un ácido se concentró a sequedad. El aceite de naranja se disolvió en acetato de etilo y bicarbonato de sodio saturado. Las fases se separaron y la fase acuosa se extrajo con acetato de etilo (2 x 200 mL). Los extractos combinados se secaron (MgSO_4) y concentraron en un sólido amarillo. Purificación mediante cromatografía de columna (sílica

gel) utilizando un eluente de acetato de etilo/hexano al 50% dio 12,13 g de un sólido amarillo. ^1H NMR (CDCl_3): δ 4,00 (s, 3H); 7,25 (d, 1H); 7,50 (d, 1H).

C. Metilo 3,4,6-tricloropiridin-2-carboxilato

A N-óxido metilo 3,6-dicloropinato (5,0 g, 22,52 mmol) disuelto en 15 mL de acetonitrilo se agregó POCl_3 (4,20 mL, 45,04 mmol). La mezcla de reacción se agitó a reflujo durante 5 h, se enfrió a temperatura ambiente y se concentro antes de quedar in vacuo. El aceite de naranja resultante se disolvió en dietiléter. Se agregó cuidadosamente bicarbonato de sodio saturado y la base acuosa se extrajo con dietiléter (2 x 100 mL). Los extractos combinados se secaron (MgSO_4) y se concentraron hasta sequedad. Purificación mediante cromatografía de columna (sílica gel) utilizando un eluente de 20% de acetato de etilo /hexano dio 5,89 g de un sólido amarillo claro. ^1H RMN (CDCl_3): δ 4,00 (s, 3H); 7,55 (s, 1H).

D. Acido 3,4,6-tricloropiridin-2-carboxílico.

A metilo 3,4,6-tricloropicolinato (3,57 g, 14,85 mmol) en 20 mL de metanol se agregó NaOH 1N (14,85 mL, 14,85 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1h y luego se concentró hasta sequedad in vacuo. 100 mL cada uno de dietil éter y H₂O se agregaron. La capa acuosa se acidificó con HCl 1N hasta un pH=2. Se agregó cloruro de metileno y la fase acuosa se extrajo con CH₂Cl₂ (2 x 100 mL). Los extractos combinados se secaron (MgSO₄) y se concentraron hasta dar 3,13 g de un sólido blanco. ¹H RMN (CDCl₃): δ 7,50 (s, 1H).

E. Acido 4-N-metilamino-3,6-dicloropiridin-2-carboxílico (compuesto 26)

Acido 3,4,6-tricloropiridin -2-carboxílico (1,56 g, 6,89 mmol) se disolvieron en metilamina y se colocaron en una bomba Parr a 800 C durante dos días. La mezcla de reacción se enfrió hasta temperatura ambiente y se diluyó con acetato de etilo. Se agregó HCl 1N hasta un pH=2. La fase acuosa se extrajo con acetato de etilo (2 x 50 mL) y los extractos combinados se secaron (MgSO₄) y concentraron hasta sequedad. El producto deseado se

trituro de dietil éter/éter pet al 5%; el sólido se filtró y se secó para dar 0,600 g de un sólido amarillo claro. ^1H RMN (CDCl_3): δ 2,75 (s, 3H); 5,70 (s, 1H); 6,30 (s, 1H); pf 170-172°C.

Los siguientes análogos N-alquilo de ácido 4-amino - 3,6-dicloropiridin-2-carboxílico se prepararon de acuerdo con el procedimiento del ejemplo 17:

Ácido 4-N-etilamino-3,6-dicloropiridin-2-carboxílico (compuesto 27); pf 136-137°C

Acido 4-N-isopropilamino-3,6-dicloropiridin-2-carboxílico (compuesto 28); pf 146-147° C.

Acido 4-N-butilamina-3,6-dicloropiridina-2-carboxílico (compuesto 29); pf 96-97° C.

Acido 4-N-alilamino-3,6-dicloropiridina-2-carboxílico (compuesto 30), pf 128-131° C.

Acido 4-N-hidroxietilamino-3,6-dicloropiridin-2-carboxílico (compuesto 31), pf 140-141°C.

Acido 4-N-metoxilamina-3,6-dicloropiridin-2-carboxílico (compuesto 32), pf 97-99°C.

Acido 4-N, N-dimetilamina--3,6-dicloropiridin-2-carboxílico (compuesto 33), pf 110° C.

Acido 4-N-hidroxi-N-metil-amino-3,6-dicloropiridin-2-carboxílico (compuesto 34), pf 140-1° C.

Acido 4-N-metoxi-N-metil-amino-3,6-dicloropiridin-2-carboxílico (compuesto 35), pf 98-99°C.

Acido 4-pirrolidino-3,6-dicloropiridino-2-carboxílico (compuesto 36), pf 153-5° C.

Acido 4-pirrolo-3,6-dicloropiridin-2-carboxílico (compuesto 37), pf 155-156° C.

18. Preparación de ácido metilo 4-azido-6-bromo-3-cloropiridina-2-carboxílico (Compuesto 38)

A una solución de metilo 4,6-dibromo-3-cloropiridin-2-carboxilato (6,0 g 0,018 mol) en DMF (50 ml) se agregó

azido de sodio (2,0 g, 0,03 ml) y la solución se calentó hasta 50° C durante 1 h. La reacción se diluyó con agua (200 ml) se enfrió a 0° durante 1 h. El sólido se recolectó para dar metilo 4-azido-6-bromo-3-cloropiridin-2-carboxilato (4,4 g, 0,012 mol, 66%); pf 84-86° C:

19. Preparación de ácido 4-nitro-3,6-dicloropiridin-2-carboxílico (Compuesto 39)

N-óxido metilo 3,6-dicloropiridin-2-carboxilato (5,0 g, 22,52 mmol) se disolvieron en una cantidad mínima de H₂SO₄. La mezcla se enfrió en un baño de hielo/agua y a este se agregó lentamente el 30% de óleo (9,6 ml) y humos de HNO₃ (9,6 ml), se calentó gradualmente hasta 65° C y se agitó hasta 48 h. La mezcla de reacción enfriada se diluyó con acetato de etilo (200 ml) y a este se agregó cuidadosamente bicarbonato de sodio saturado. El producto se extrajo con acetato de etilo (2 x 150 ml) y los extractos combinados se secaron (MgSO₄) y se concentraron para dar 0,10 g de un sólido amarillo; pf 192-193° C.

20. Preparación de ácido 4-N,N-dimetilformamidino-3,6-dicloropiridin-2-carboxílico (compuesto 40).

A una suspensión de ácido metilo 4-amino-3,6-dicloroíridin-2-carboxílico (2,07 g, 10,0 mmol) en THF (50 ml) se agregó 5,0 eq de N,N-dimetilformamida dimetilacetal (50 mmol). La mezcla se calentó a 50° durante 1 h tiempo durante el cual la suspensión se hizo una solución homogénea. La mezcla de reacción enfriada se concentró in vacuo, se trituro con hexanos hasta un sólido amorfo blanco y se secó bajo alto vacío para dar 2,5 g de un polvo blanco altamente higroscópico (95% de producción); ^1H RMN (DMSO) δ 8,211 (1H, s), 7,95 (1H, s), 3,17 (3H, s).

21. Preparación de ácido 4-amino-6-bromo-3-metoxipiridin-2-carboxílico (compuesto 41)

A. metilo 4,6-dibromo-3-metoxipiridin-2-carboxilato

A metilo 4,6-dibromo-3-hidroxipiridin-2-carboxilato 3,98 g (3,98 g, 12,81 mmol) en 40 ml de acetona se agregó K_2CO_3 (2,0 g, 14,47 mmol) y dimetilsulfato (1,20 ml, 12,37 mmol). La mezcla de reacción se reflujo durante toda la noche y se concentró hasta sequedad. El residuo se disolvió en acetato de etilo y bicarbonato de sodio

saturado. Las fases se separaron y la fase acuosa se extrajo con acetato de etilo (3 x 100 ml). Los extractos combinados se secaron (MgSO_4) y se concentraron hasta sequedad. El residuo se purificó mediante cromatografía (sílica gel). Elusión con 15% de acetato de etilo/hexano dio 0,980 g de un sólido blanco. ^1H RMN (CDCl_3): δ 3,95 (s, 3H); 3,90 (s, 3H); 7,80 (s, 1H).

B. Metilo 4-azido-6-bromo-3-metoxipiridin-2-carboxilato

Metilo 4,6-dibromo-3-metoxipiridin-2-carboxilato (0,980 g, 3,02 mmol) se disolvieron en una cantidad mínima de DMF. Se agregó azido de sodio lentamente (0,216 g, 3,32 mmol) seguido mediante H_2O para formar una solución homogénea. La mezcla de reacción fue calentada a 60 °C y agitada durante 2 días. La mezcla de reacción fue agregada a un frasco cargado con agua y hielo y extraído con acetato de etilo (3 x 50 mL). Los extractos fueron combinados y de nuevo lavados con H_2O , secados (MgSO_4) y concentrados para dar 0,500 g de un aceite naranja. ^1H RMN (CDCl_3): δ 3,90 (s, 3H); 3,95 (s, 3H); 7,20 (s, 1H).

C. Metilo 4-amino-6-bromo-3-metoxipiridina-2-carboxilato

A metil 4-azido-6-bromo-3-metoxipiridina-2-carboxilato (0,500 g, 1,74 mmol). En 10 ml de metanol se la agregó NaBH_4 (0,046 g, 1,22 mmol). La mezcla de reacción fue agitada a temperatura ambiente durante 10 minutos. El acetato de etilo y el agua fueron agregados y las fases fueron separadas. La fase orgánica fue lavada con H_2O y se secó (MgSO_4) y se concentro hasta el secado en vacío. El residuo fue purificado por cromatografía (gel de sílice). La elusión con 100% de acetato de etilo dio 0,300 g de un sólido blanco. ^1H RMN (CDCl_3): δ 3,90 (s, 1H); 3,95 (s, 1H); 4,60, (s, 2H); 6,85 (s, 1H).

D. Acido metil 4-amino-6-bromo-3-metoxipiridina-2-carboxílico (compuesto 41)

A metil 4-amino-6-bromo-3-metoxipiridina-2-carboxilato (0,300 g, 1,15 mmol) in 10 mL de metanol se agregó NaOH 1N (1,15 mL, 1,15 mmol). La mezcla de reacción fue agitada a temperatura ambiente durante una

hora y el concentrado hasta el secado en vacío. El éter de dietilo y el H₂O fueron agregados. La capa acuosa fue acidificada con HCl al 1N hasta que el pH igual a 2 y el concentrado hasta el secado. Se agregó metanol (50 mL) al sólido blanco. La mezcla fue filtrada y el filtrado concentrado hasta el secado. Se trituro con 5% de éter de dietilo/éter pet y que dio 0,180 g de un sólido rosado claro. ¹H RMN (DMSO): δ 3,60 (s, 3H); 6,80 (s, 1H).

Preparación del ácido 4-amino-6-bromo-5-cloro-3-metoxipiridina-2- carboxílico (compuesto 42)

A. metil 4-amino-6-bromo-5-cloro-3-metoxipiridina-2- carboxilato.

A metil 4-amino-6-bromo-3-metoxipiridina-2-carboxilato (1,45 g, 5,56 mmol) en 10 ml de acetonitrilo se agregó cloruro de sulforilo, en exceso a través de una pipeta hasta que la solución permaneció amarilla. La solución fue calentada hasta el reflujo durante 5 minutos. La mezcla de reacción fue agregada al bicarbonato de sodio saturado y la fase acuosa fue extraída con dietil éter (3x). Los extractos orgánicos combinados fueron secados (MgSO₄), filtrados y

concentrados en vacío para dar un sólido amarillo. El sólido fue lavado en dietil éter/éter de petróleo al 10% y el sólido filtrado para dar 0,580 g de un sólido blanco.

B. Acido de 4-amino-6-bromo-5-cloro-3-metoxipiridina-2- carboxílico (compuesto 42)

A metil-4-amino-6-bromo-5-cloro-3-metoxipiridina-2-carboxilato (0,300 g, 1,02 mmol) en 10 mL de metanol se agregó NaOH 1N (1,10 mL, 1,10 mmol). La mezcla de reacción fue agitada a temperatura ambiente durante 4 horas y fue entonces concentrada hasta el secado en vacío. La capa acuosa resultante fue acidificada con HCl concentrado. El sólido blanco fue recolectado por filtración y fue enjuagado con H₂O. El sólido fue secado a 50° C bajo vacío para dar 0,230 g de un sólido lanudo blanco; pf 154-156° C.

23 Preparación del ácido 4-amino-5, 6-dicloro-3-fluoropiridina-2- carbo xílico (compuesto 43)

A. 4-Amino-5,6-dicloro-2-triclorometil-piridina

A una solución de 4,5,6-tricloro-2-triclorometilpiridina (2 g, 6,7 mmol) en DMF acuoso se agregó NaN_3 (0,5 g, 7,7 mmol). La mezcla resultante fue calentada a 70°C durante 2 horas, agregada a H_2O y extraída (3x) con Et_2O . La capa orgánica fue concentrada para dar un sólido blanco, que fue disuelto en 10 ml de Me OH, el exceso de NaBH_4 fue agregado y la mezcla de reacción fue agitada a temperatura ambiente durante 0.5 horas. Este material fue agregado al H_2O , extraído (3x) con Et_2O , secado sobre MgSO_4 y concentrado en vacío. El sólido resultante fue lavado varias veces con hexano para dar 1,3 g de 4-amino-5,6-dicloro-2-triclorometilpiridina.

B. Acido de 4-amino-5,6-dicloro-3-fluoropiridina-2-carboxílico (compuesto 43)

A una solución de 4-amino-5,6-dicloro-2-triclorometilpiridina (1,25 g, 4,46 mmol) en 20 mL de acetonitrilo seco se agregó SelecfluorTM (1,9 g, 2,59 mmol $[\text{F}^+]/\text{g}$). La mezcla resultante fue calentada a reflujo durante 72 horas, luego se le permitió enfriarse a

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temperatura ambiente. Este material fue retirado con Et₂O y lavado con H₂O. La capa orgánica fue secada sobre Mg SO₄, filtrada y concentrada para dar un aceite oscuro. El producto crudo fue purificado a través de fase inversa HPLC (75% de acetonitrilo/agua) para dar 0,2 g de sólido blanco que fue agitado en 80% de H₂SO₄ a 155° C durante 0,5 horas. La mezcla de reacción se la permitió enfriarse y se extrajo varias veces con 10% de MeOH/CH₂Cl₂. La capa orgánica fue secada sobre MgSO₄, filtrada y concentrada para dar un sólido blanco que fue lavado varias veces con hexano-dietil éter para dar 60 mg de ácido de 4-amino-5,6-dicloro-3-fluoropiridina-2- carboxílico; pf 208°C dec.

24. Preparación de ácido de 4-amino-3-bromo-4-cloropiridina-2- carboxílico (compuesto 44)

A. Metil-3-bromo-4-cloropiridina-2-carboxilato

A una solución de ácido de 3-bromo-4-cloropiridina-2-carboxílico (1,75 7,4 mmol) in Me OH se agregó HCl anhidroso. La mezcla resultante fue agitada a temperatura ambiente durante 18 horas. La mezcla de reacción fue

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concentrada para dar un sólido del cual es particionado entre Et₂O y NaHCO₃ saturada. La capa orgánica fue secada sobre MgSO₄, filtrada y concentrada para dar un residuo café. Este material fue purificado a través de cromatografía de columna flash para dar 1,35 g de producto como un aceite amarillo pálido.

B Metil-3-bromo-4,6-dicloropiridina-2-carboxilato

A una solución de metil 3-bromo-4-cloropiridina-2-carboxilato (1,35 g, 5,4 mmol) en 5 mL de TFA se agregó H₂O₂ al 30% (1 g, 9,8 mmol). La mezcla resultante fue agitada a 75° C durante 0,5 horas y se le permitió enfriarse a temperatura ambiente. Se agregó Et₂O. Y la capa orgánica fue lavada cuidadosamente con NaOH₃ saturado, secado sobre MgSO₄, filtrada y concentrada para dar el N-óxido intermedio correspondiente como un sólido blanco. Este material fue retirado con acetonitrilo (5 mL) POCl₃ (2-3 mL) y fue calentado a reflujo durante 2 horas. La mezcla de reacción se le permitió enfriarse, se agregó al Et₂O y se lavo cuidadosamente con NaHCO₃ saturada, se secó sobre MgSO₄, filtrado y concentrado para dar 0,9 g de producto como un aceite café claro

Este material fue lo suficientemente puro para llevar a cabo la siguiente etapa.

C. Acido de 4-amino-3bromo-6-cloropiridina-carboxílico (compuesto 44)

A una solución de metil 3-bromo-4, 6-dicloropiridina-2-carboxilato (0,9 g 3,2 mmol) en DMF acuoso se agregó NaN_3 (0,25 g, 3,8 mmol). La mezcla resultante fue calentada a 60 °C durante 1 hora, agregada a H_2O y extraída (3x) con Et_2O . La capa orgánica fue concentrada para dar un sólido blanco que fue disuelto en 10 mL de MeOH. EL exceso de NaBH_4 fue agregado y la mezcla de reacción agitada a temperatura ambiente durante 0,5 horas. Este material se agregó al H_2O , se extrajo (3x) con Et_2O , se secó sobre MgSO_4 y se concentro. El sólido resultante fue agitado en NaOH al 1N por una hora, se hizo con HCl concentrado y se concentro hasta el secado. Este material fue extraído con MeOH, concentrado para dar 220 mg de ácido de 4-amino-3-bromo-6-cloropiridina-2-carboxílico; pf 175° C dec.

25. Preparación de ácido 4-amino-3, 5-dicloro-6-
trifluoro-metilpiridina-2-carboxílico
(compuesto 45)

A. Metil 4-cloro-6-trifluorometilpiridina-2-
carboxilato

A una solución de ácido de 6-trifluorometilpicolínico (8,6 g 45 mmol; preparado del 6-trifluorometil-2-cianopiridina correspondiente) en 25 mL de TFA se agregó 30 % de H_2O_2 (7,8 g, 67,5 mmol). La mezcla de reacción fue agitada a 70 °C durante 18 horas y concentradas para dar 8,0 g del N-óxido. Este material fue agitado en una solución de HCl/MeOH durante 18 horas. La mezcla de reacción fue concentrada para dar un residuo en peso que fue particionado entre Et_2O y NaHCO_3 saturada. La capa orgánica fue secada sobre MgSO_4 , filtrada y concentrada para dar 5,0 g de un aceite amarillo. POCl_3 nítido fue agregado y agitado a reflujo durante 2 horas. La mezcla se le permitió enfriarse, se agregó cuidadosamente al NaHCO_3 saturado y se extrajo (3x) con Et_2O . La capa orgánica fue secada sobre MgSO_4 , filtrada y concentrada para dar un sólido café. Este material fue purificado a través de cromatografía de columna flash

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para dar 2,64 g del producto como un sólido blanco; pf 62-3°C.

B. Metil 4-amino-6-trifluorometilpiridina-2-carboxilato

A una solución de metil 4-cloro-6-trifluorometilpiridina-2-carboxilato (2,44 g 10,12 mmol) en DMF acuoso se agregó NaN_3 (0,7 g, 10,8 mmol). La mezcla resultante fue calentada a 70 °C durante 18 horas, agregada a H_2O y extraída (3x) con Et_2O . LA capa orgánica fue concentrada para dar un sólido blanco que fue disuelto en 10 ml de MeOH. El exceso de NaBH_4 y la mezcla de reacción agitada a temperatura ambiente durante 0,5 horas. Este material fue agregado al H_2O extraído (3x) con Et_2O . EL extracto fue secado sobre MgSO_4 y concentrado. EL residuo resultante fue purificado a través de cromatografía de columna flash para dar 0,95 del producto como un sólido blanco; pf 113°C.

C Metil 4-amino-3-5-dicloro-6-trifluorometilpiridina-2-carboxilato

A una solución de metil 4-amino-6-trifluorometilpiridina-2-carboxilato (0,75 g, 3,4 mmol) en 5 ml de acetonitrilo seco se agregó SO_2Cl_2 (0,55 ml, 6,88 mmol). La mezcla resultante fue calentada a reflujo durante 0,5 horas, luego se le permitió enfriarse a temperatura ambiente. Este material fue retirado en Et_2O y lavado con NaHCO_3 saturada. La capa orgánica fue secada sobre MgSO_4 , filtrada y concentrada para dar sólido. El material crudo fue purificado mediante cromatografía de columna de flash para dar 0,28 g de producto como un sólido blanco; pf 135-6°C.

D Preparación de 4-amino-3,5-dicloro-6-trifluorometilpiridina-2-carboxilato (compuesto 45)

A una solución de metil 4-amino-3,5-dicloro-6-trifluorometilpiridina-2-carboxilato (0,16 g, 0.56 mmol) en 5 ml de MeOH se agregó exceso de NaOH al 1N. La mezcla de reacción resultante fue agitada a temperatura ambiente durante 1 hora, luego se hizo acídica con HCl concentrado. El sólido blanco precipitado fue recolectado

22A

con succión, lavado con H₂O y secado bajo vacío para dar 80 mg del compuesto 45; pf 178° C. Dec.

26. Preparación del ácido de 4-amino-3-cloro-6-trifluorometilpiridina-2-carboxílico (compuesto 46)

A una solución que contenía éster de metil de ácido 4-amino-6-trifluorometilpiridina-2-carboxílico. (0,75 g, 3,4 mmol) en 5 ml de CH₃CN se agregó gota a gota una solución de cloruro de sulforilo (0,27, ml, 3,4 mmol) en 1 ml de CH₃CN. Después de agitar a temperatura ambiente durante 1 hora, la mezcla de reacción fue agregada a 50 ml de Et₂O y lavada con NaHCO₃ acuoso, secada sobre MgSO₄, filtrada y concentrada para dar un sólido. El producto crudo fue purificado por cromatografía, diluyendo con 10% de acetato de etilo-hexano para dar 200 mg de producto como un sólido blanco; pf 131-3° C.

27 Preparación de ácido 4-amino-3-cloro-6-(3, 5-dicloro-fenoxi)piridina-2-carboxílico (compuesto 47)

A. Preparación de metil 3-cloro-6-(3, 5-dicloro-fenoxi)piridina-2-carboxilato N-óxido

En un frasco de fondo redondo de 3 cuellos seco se agregó 60% de NaH (0,435 g, 10,81 mmol), THF seco (30 ml) y 3,5-diclorofenol (1,76 g, 10,81 mmol). La mezcla fue agitada hasta que la evolución de H₂ (g) cesó. Se agregó N-óxido de metil 3,6-dicloropiridina-2-carboxilato (2,0 g, 9,00 mmol) en una porción y se agitó a temperatura ambiente durante 3 horas, se diluyó con acetato de etilo y 100 ml de agua. La fase acuosa fue extraída con acetato de etilo (2 x 200 ml). Los extractos combinados fueron secados (MgSO₄) y concentrados para dar 2,40 g de Sólido blanco.

B Preparación de metil 3,4-dicloro-6-(3, 5-dicloro-fenoxi)piridina-2-carboxilato

Al N-óxido de ácido metil 3-cloro-6-(3, 5-dicloro-fenoxi)piridina -2-carboxílico (2,40 g, 6,89 mmol) se disolvió en 50 ml de acetonitrilo fueron agregados POCl_3 (1,28 ml, 13,77 mmol). La mezcla fue agitada a reflujo durante la noche después de lo cual fue enfriada a temperatura ambiente y concentrada hasta secado en vacío. El aceite naranja resultante fue disuelto en dietil éter y en bicarbonato de sodio saturada. Fue agregado cuidadosamente. La fase acuosa fue extraída con dietil éter (2 x 100 ml). Los extractos orgánicos combinados fueron secados (MgSO_4) y concentrados hasta secado. La purificación por cromatografía de columna (gel de sílice) usando un eluyente de 20 % de dietil éter /hexano dio 1,93 g de sólido blanco.

C. Preparación de metil 4-amino-3-cloro-6-(3, 5-diclorofenoxi)piridina-2-carboxilato

Acido de metil 4-amino-3,4 -dicloro-6-(3, 5-diclorofenoxi)piridina-2-carboxílico (1,93 g, 5,26 mmol) fue disuelto en una cantidad mínima de DMF y a este se agregó cuidadosamente NaN_3 (0,444 g, 6,84 mmol) y agua para formar una mezcla homogénea que fue calentada a 70°

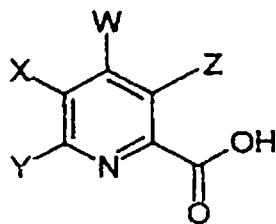
C y agitada durante la noche. La mezcla de reacción fue vertida en una mezcla de agua con hielo y el producto fue extraído con acetato de etilo (3 x 100 ml). Los extractos combinados fueron lavados con pet éter/agua (200 ml), secados (MgSO_4) y concentrado hasta el secado en vacío. El aceite resultante fue disuelto en metanol y a este se le agrega NaBH_4 (0,200 g, 5,26 mmol) y se agitó a temperatura ambiente durante 1,5 horas. Acetato de etilo y agua fueron agregados y la fase acuosa fue extraída con acetato de etilo (2 x 100 ml) los extractos combinados fueron secados (MgSO_4) y concentrados hasta secado. La purificación por cromatografía de columna (gel de sílice) usando un eluyente de 20% de dietil éter/ hexano -50% de d-etil éter/hexano para dar 0,900 g de un sólido claro.

D. Preparación de ácido de 4-amino-3-cloro-6-(3,5-diclorofenoxi)piridina-2-carboxílico (compuesto 47)

Al ácido metil 4-amino-3-cloro-6-(3,5-diclorofenoxi)piridina-2-carboxílico (0,720 g, 2,07 mmol) en 20 ml de metanol se agregó NaOH al 1N (2,07 ml) y se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción fue concentrada hasta el secado en vacío y 100

REIVINDICACIONES

1. Un compuesto de fórmula I:



I

En donde

X representa H, halógeno, alcoxi C₁-C₆, alquiltio C₁-C₆, ariloxi, nitro o trifluorometilo;

Y representa halógeno, alcoxi C₁-C₆ alquiltio, ariloxi, heteroariloxi, o trifluorometilo;

Z representa halógeno, alcoxi C₁-C₆, alquiltio, C₁-C₆ ariloxi o nitro;

W representa $-\text{NO}_2$, $-\text{N}_3$, $-\text{NR}_1\text{R}_2$, $-\text{N}=\text{CR}_3\text{R}_4$ o $-\text{NHN}=\text{CR}_3\text{R}_4$

Donde

R_1 y R_2 independientemente representan H, alquilo, $\text{C}_1\text{-C}_6$ alquenilo $\text{C}_3\text{-C}_6$, alquinilo $\text{C}_3\text{-C}_6$, arilo, heteroarilo, hidroxilo, alcoxi $\text{C}_1\text{-C}_6$, amino, acilo $\text{C}_1\text{-C}_6$, carboalcoxi $\text{C}_1\text{-C}_6$, alquilcarbamilo $\text{C}_1\text{-C}_6$, alquilsulfonilo $\text{C}_1\text{-C}_6$, trialquisililo $\text{C}_1\text{-C}_6$ o dialquilsulfonilo $\text{C}_1\text{-C}_6$ o R_1 y R_2 tomados juntos con N representan un anillo saturado o insaturado de 5 o 6 miembros que puede contener heteroátomos O, S o N adicionales;

R_3 y R_4 independientemente representa H, alquilo $\text{C}_1\text{-C}_6$, alquenilo $\text{C}_3\text{-C}_6$, alquinilo $\text{C}_3\text{-C}_6$, arilo o heteroarilo o R_3 o R_4 tomados juntos con $=\text{C}$ representan un anillo saturado de 5 o 6 miembros; y

Los derivados agrícolamente aceptables del ácido carboxílico, con la condición de que cuando X representa CL, entonces Y y Z no son ambos CL.

2. Un compuesto de la fórmula 1 en donde:

X representa H, halógeno, o trifluorometilo;

Y representa halógeno, ariloxi, heteroariloxi, o trifluorometilo;

Z representa halógeno;

W representa $-NR_1R_2$

En donde R_1 y R_2 independientemente representan H, alquilo C_1-C_6 , alquenilo C_3-C_6 , alquinilo C_3-C_6 , o R_1 y R_2 tomados juntos con N representan un anillo saturado o insaturado de 5 o 6 miembros que puede contener heteroátomos O, S o N adicionales; y

Sales agriculturalmente aceptables, ésteres o amidas del ácido carboxílico.

3. Un compuesto según la reivindicación 1 o la reivindicación 2 en donde:

X representa H o F;

Y representa F, Cl, Br o ariloxy;

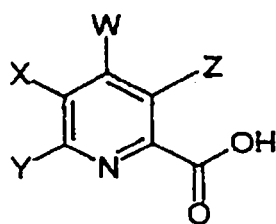
Z representa Cl; y

W representa -NH_2 .

4. Un compuesto según una cualquiera de las reivindicaciones 1 a 3 en donde:

Y representa un grupo fenoxi sustituido con halógeno o grupos alquilo con 1 a 4 átomos de carbono en la posición 3.

5. Una composición herbicida que comprende una cantidad herbicidamente efectiva de un 4-aminopicolinato de fórmula-I:



I

En donde

X representa H, halógeno, alcoxi C_1-C_6 , alquiltio C_1-C_6 , ariloxi, nitro o trifluorometilo;

Y representa halógeno, alcoxi C_1-C_6 , alquiltio C_1-C_6 , ariloxi, heteroariloxi, o trifluorometilo;

Z representa halógeno, alcoxi C_1-C_6 , alquiltio C_1-C_6 , ariloxi o nitro; y

W representa $-NO_2$, $-N_3$, $-NR_1R_2$, $-N=CR_3R_4$ o $-NHN=CR_3R_4$

Donde

R_1 y R_2 independientemente representan H, alquilo C_1-C_6 , alquenilo C_3-C_6 , alquinilo C_3-C_6 , arilo, heteroarilo, hidroxilo, alcoxi C_1-C_6 , amino, acilo C_1-C_6 , carboalcoxi C_1-C_6 , alquilcarbamilo C_1-C_6 , alquilsulfonilo C_1-C_6 , trialquilsililo C_1-C_6 o dialquilsulfonilo C_1-C_6 o R_1 y R_2 tomados juntos con N representan un anillo saturado o insaturado de 5 o 6 miembros que puede contener heteroátomos O, S o N adicionales; y

R_3 y R_4 independientemente representa H, alquilo C_1-C_6 , alquenilo C_3-C_6 , alquinilo C_3-C_6 , arilo o heteroarilo o R_3 o R_4 tomados juntos con $=C$ representan un anillo saturado de 5 o 6 miembros; y.

Los derivados agrícolamente aceptables del ácido carboxílico, con la condición de que cuando X representa Cl, entonces Y y Z no son ambos Cl, en mezcla con un adyuvante o portador agrícolamente aceptable.

6. Una composición herbicida de la reivindicación 5 en donde:

X representa H, halógeno o trifluorometilo;

Y representa halógeno, ariloxi, heteroariloxi o trifluorometilo;

Z representa halógeno; y

W representa $-NR_1R_2$

En donde

R_1 y R_2 independientemente representan H, alquilo C_1-C_6 , alquenilo C_3-C_6 , alquinilo C_3-C_6 , o R_1 y R_2 tomados juntos con N representan un anillo saturado o insaturado de 5 o 6 miembros que puede contener heteroátomos O, S o N adicionales; y

Sales agrícolas aceptables, ésteres o amidas del ácido carboxílico.

7. Una composición herbicida según la reivindicación 5 o la reivindicación 6

en donde:

X representa H, o F;

Y representa F, Cl, Br o ariloxi;

Z representa Cl; y

W representa $-NH_2$.

8. Una composición herbicida de una cualquiera de las reivindicaciones 5 a 7

en donde:

Y representa un grupo fenoxi sustituido con halógenoo grupos alquilo C_1-C_4 en la posición 3.

9. Una composición herbicida según la reivindicación 5 que contiene ácido de 4-amino-3,6-dicloropiridina-2-

carboxílico o una sal agrícolamente aceptable éster o amida del mismo.

10. Un método para controlar vegetación no deseada que comprende poner en contacto la vegetación o el locus de la misma con o aplicar al suelo para impedir la emergencia o nacimiento de vegetación una cantidad herbicídamente efectiva de una composición herbicida de cualquiera de las reivindicaciones 5 a 9.

RESUMEN

Acidos 4-aminopicolínicos, que tienen halógeno, alcoxi, alquiltio, ariloxi, heteroariloxi o sustituyentes de trifluorometilo en las posiciones 3-, 5- y 6-, y sus aminas y derivados de ácido que son potentes herbicidas que demuestran un espectro amplio de control de malezas.

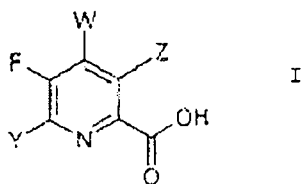
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REIVINDICACIONES

SOLICITUD DIVISIONAL

Reivindicaciones

1. Un compuesto de formula I



donde

Y representa halógeno, alcoxi C₁-C₆, alquiltio C₁-C₆, aryloxi, heteroariloxi o trifluorometilo

Z representa halógeno, alcoxy C₁-C₆, alquiltio C₁-C₆, ariloxi o nitro y

W representa -NO₂, -N₃, -NR₁R₂, -NN=CR₃R₄ o -NHN=CR₃R₄ donde

R₁ y R₂ independientemente representan Hidrógeno, alquilo C₁-C₆, alquenilo C₁-C₆, alquinilo C₃-C₆, arilo, heteroarilo, hidroxil, alcoxi C₁-C₆, amino, acilo C₁-C₆, carboalcoxy C₁-C₆, alquilcarbamil C₁-C₆, alquilsulfonilo C₁-C₆, trialquilsilil C₁-C₆, o dialquilo fosfonilo C₁-C₆ o R₁ y R₂ junto con N representa un anillo saturado o insaturado de 5 o 6 miembros, el cual puede contener heteroátomos O, S o N adicionales; y

R₃ y R₄ independientemente representan Hidrógeno, alquil C₁-C₆, alquencil C₃-C₆, alquencil C₃-C₆, arilo o heteroarilo o R₃ y R₄ tomados junto con =C representa un anillo saturado de 5 o 6 miembros; y derivados aceptables agrícolamente del ácido carboxílico.

2. Un compuesto de la reivindicación 1 en donde:

Y representa halógeno, ariloxi, heteroariloxi, o trifluorometilo

Z representa halógeno, y

W representa - NR₁R₂

Donde

R₁ y R₂ representan independientemente hidrógeno, alquilo C₁-C₆, alqueno C₃-C₆, alquinilo C₃-C₆ o R₁ y R₂ tomados junto con N representa un anillo saturado de 5 o 6 miembros, el cual puede contener heteroátomos como O o N adicionales y sales agrícolamente aceptables, esteres o amidas del ácido carboxílico.

3. Un compuesto de la reivindicación 1 o 2 donde:

Y representa F, Cl, Br o ariloxi

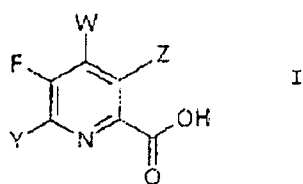
Z representa Cl y

W representa -NH₂

4. Un compuesto de cualquiera de las reivindicaciones 1-3 en donde

Y representa un grupo fenoxi sustituido con halógeno o grupos alquilo C₁-C₄ en la posición 3

5. Una composición herbicida que comprende una cantidad efectiva de un Herbicida de 4 aminopicolinato de formula I:



donde

Y representa halógeno, alcoxi C₁-C₆, alquiltio C₁-C₆, ariloxi, heteroariloxi, o trifluorometilo

Z representa halógeno, alcoxi C₁-C₆, alquiltio C₁-C₆, ariloxi o nitro y

W representa -NO₂, -N₃, -NR₁R₂, -N=CR₃R₄ o -NHN=CR₃R₄ donde

R₁ y R₂ representan independientemente hidrógeno, alquilo C₁-C₆, alquenilo C₁-C₆, alquinilo C₃-C₆, arilo, heteroarilo, hidroxilo, alcoxi C₁-C₆, amino, acilo C₁-C₆, carboalcoxi C₁-C₆, alquilcarbamil C₁-C₆, alquilsulfonilo C₁-C₆, alquilsililo C₁-C₆, o dialquilsulfonilo C₁-C₆ o R₁ y R₂ tomados junto con N representa un anillo saturado o insaturado de 5 o 6 miembros que puede contener heteroátomos como O, S, o N adicionales; y

R₃ y R₄ independientemente representa hidrógeno, alquilo C₁-C₆, alquenilo C₃-C₆, alquinilo C₃-C₆, arilo o heteroarilo o R₃ y R₄ tomados junto con =C representa un anillo saturado de 5 o 6 miembros, y derivados agrícolamente aceptable del ácido carboxílico en mezcla con un adyuvante o portador agrícolamente aceptable

6. Una composición herbicida de la reivindicación 5 donde:

Y representa halógeno, ariloxi, heteroariloxi, o trifluorometilo.

Z representa Halógeno, y

W representa -NR₁R₂

Donde

R₁ y R₂ independientemente representan H, alquilo C₁-C₆, alquenilo C₃-C₆, alquinilo C₃-C₆ o R₁ y R₂ tomados junto con N representan un anillo saturado de 5 o 6 miembros el cual puede contener heteroátomos como O o N adicionales, y sales, esteres o amidas del ácido carboxílico agrícolamente aceptables.

7. Una composición herbicida de la reivindicación 5 o 6 donde

Y representa F, Cl, Br, o ariloxi

Z representa Cl; y

W representa -NH₂

8. La composición herbicida de cualquiera de las reivindicaciones 5 a 7 donde

Y representa un grupo fenoxi sustituido por halógeno o por grupo alquilo C₁-C₄ en la posición 3

9. Un método para controlar las plantas indeseables que comprende poner en contacto la vegetación o locus de la misma para impedir el nacimiento de vegetación en una cantidad herbicidamente efectiva de una composición herbicida de cualquiera de las reivindicaciones 5 a 8.

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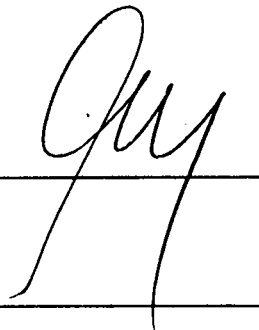
***** CONSIGNACION *****

ASITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	55800360	12/06/2007	46,385,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
1		TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL :	\$ 482,000.00

CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

6060 10995 801 012 7

STEME = pamplina (*Atellaria media*)
XANST = cadillo (*Xantium strumarium*)
CHEAL = cuartos de cordero (*Quinopodium album*)
AMARE = chual (*Amarantus retroflexus*)
ABUTH = hoja velluda (*Abutilion theoprasti*)
VIOTR = viola (*Viola tricolor*)
POLCO = alforfón salvaje (*Poligonum convolvulus*)
ALOMY = hierba negra (*Alopecurus misuroides*)
ECHCG = grama (*Equinocloa crus-gali*)
DIGSA = pasto de cangrejo (*Digitaria sanguinalis*)
SETFA = cola de zorro gigante (*Setaria faveris*)
SORBI = sorgo naranja Rox (*Sorgo bicolor*)
AVEFA = avena salvaje (*Avena fatua*)

Tabla 3

Control de varias malezas clave en arroz

Evaluación post emergencia - % de control

Comp. #	ORYZA	ECHCG	CYPES	Rata (ppm)
1	10	75	75	250
14	10	65	75	250
27	40	70	50	250

ORYZA = arroz (*Oryza sativa*)ECHCG = grama (*Equinocloa crus-galli*)CYPES = nutsedge amarilla (*Cyperus esculentus*)

Tabla 4

Control de varias malezas clave en maíz

Evaluación post emergencia - % de control

Comp #	ZEAMX	ABUTH	AMARE	XANST	Rata (ppm)
15	0	40	75	90	250
20	10	70	90	85	250
33	20	80	50	100	125
43	0	70	90	85	250

ZEAMX = maíz (*Zea mays*)

ABUTH = hoja velluda (*Abutilon theophrasti*)

AMARE = chual (*Amarantus retroflexus*)

XANST = cadillo (*Xanthium strumarium*)

Tabla 5

Control de varias malezas clave en trigo

Evaluación post emergencia - % de control

Comp #	TRZAS	STEME	CHEAL	POLCO	Rata (ppm)
14	0	70	70	90	250
23	20	30	90	98	125
41	10	20	90	100	250
46	10	50	100	100	31

TRZAS = trigo (*Triticum aestivum*)

STEME = pamplina (*Stellaria media*)

CHEAL = cuartos de cordero (*Chenopodium album*)

PALCO = alforfón salvaje (*Polygonum convolvulus*)

33. Evaluación de actividad herbicida pre-emergencia

Las semillas de las especies de plantas de ensayo deseadas fueron plantadas en una matriz de suelo preparada mezclando una arcilla de tierra (43% de tierra, 19% de arcilla y 38% de arena, con un pH de alrededor de 8,1 y un contenido de materia orgánica de alrededor de 1,5%) y arena en una proporción de 70 a 30. La matriz de tierra se colocó en vasijas plásticas con un área de superficie de 113 cm². Cuando se requirió asegurar una buena germinación y unas plantas saludables, se aplicó un tratamiento fungicida y/u otro tratamiento químico o físico.

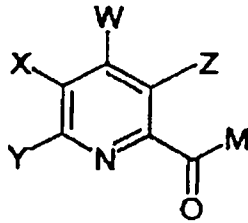
Una cantidad pesada, determinada por la rata más alta a ser ensaya, de cada compuesto de ensayo fue colocado en un frasco de vidrio de 20 ml y fue disuelto en 4 ml de una mezcla de 97:3 v/v (volumen /volumen) de acetona y dimetil sulfóxido para obtener unas soluciones de base concentradas. Si el compuesto de ensayo no se disolvió fácilmente, la mezcla fue calentada y/o sonicado. Las soluciones de base obtenidas fueron diluidas con una mezcla 99,9:0,1 de agua, y un tensoactivo Tween® 155 para obtener soluciones de

aplicación de concentración conocida. La solución que contenía la concentración más alta a ser ensayada fueron preparadas diluyendo alícuotas de 2 ml de la solución base con 15 ml de la mezcla y concentraciones bajas fueron preparadas por dilución serial de la solución de base. Una alícuota de 2,5 ml de cada solución de concentración conocida fue rociada de manera uniforme sobre la superficie de la tierra (113 cm^2) de cada vasija sembrada usando una jeringa de vidrio Cornwall 5,0 ml ajustada con una boquilla de cono hueco TeeJet TN-3 para obtener un cubrimiento parejo completo de la tierra en cada vasija. Las vasijas de control también fueron rociadas de la misma manera con la mezcla acuosa.

Las vasijas tratadas y las vasijas de control fueron colocadas en un invernadero mantenido con fotoperiodos de pax 15 horas y temperaturas de alrededor de 23 a 29° C durante el día y 22 a 28° C durante la noche. Se agregaron nutrientes y agua en una base regular y luz suplementaria fue suministrada con lámparas suspendidas de haluro de metal de 1.00 watios según fue necesario. El agua fue agregada por irrigación superior. Después de tres semanas la condición de las plantas de ensayo fue que germinaron y crecieron comparadas con aquellas de las

plantas no tratadas que germinaron y crecieron fue determinada visualmente y registrada en una escala de 0 a 100% en donde 0 corresponde a ningún daño y 100 corresponde a muerte completa o ninguna germinación. Algunos de los compuestos ensayados, las ratas de aplicación empleadas, las especies de plantas tratadas y los resultados se dan en las tablas 6 a 7.

Tabla 6

Preemergencia y control

#	M	W	X	Y	Z	% Control			Rate (ppm)
						IPQHE	AMARE	ABUTH	
1	OH	NH ₂	H	Cl	Cl	100	100	100	280
2	O-2-EH ²	NH ₂	H	Cl	Cl	100	100	100	280
3	O-Me	NH ₂	H	Cl	Cl	100	100	100	280
4	O-Et	NH ₂	H	Cl	Cl	100	100	100	280
5	O-Pr	NH ₂	H	Cl	Cl	100	100	100	280
6	O- <i>i</i> -Pr	NH ₂	H	Cl	Cl	100	100	100	280
7	O-Bu	NH ₂	H	Cl	Cl	100	100	100	280
8	O-pentyl	NH ₂	H	Cl	Cl	100	100	100	280
9	O-hexyl	NH ₂	H	Cl	Cl	100	98	100	280
10	O-BE ¹	NH ₂	H	Cl	Cl	100	100	100	280
11	NH ₂	NH ₂	H	Cl	Cl	85	0	85	560
12	O-Me	NHC(O)Me	H	Cl	Cl	100	100	95	560
13	O-Me	N(C(O)Me) ₂	H	Cl	Cl	95	100	95	560
14	OH	NH ₂	H	Br	Cl	100	90	100	560
15	OH	NH ₂	H	F	Cl	100	100	100	560
16	OH	NH ₂	F	Br	F	80	70	0	560
17	OH	NH ₂	H	Br	Br	100	100	100	560
18	O-Me	NH ₂	Br	Br	Br	30	80	98	280
19	OH	NH ₂	F	Cl	Cl	100	100	100	560
20	OH	NH ₂	Br	Cl	Cl	100	100	100	560
21	OH	NH ₂	CF ₃	Cl	Cl	90	80	80	560

22	OH	NH ₂	O-Me	Cl	Cl	100	100	100	560
23	OH	NH ₂	S-Et	Cl	Cl	0	40	40	560
24	OH	NH ₂	S-Ph	Cl	Cl	30	20	50	560
25	O-Me	NH ₂	NO ₂	Cl	Cl	nt	nt	nt	250
26	OH	NHMe	H	Cl	Cl	100	100	100	560
27	OH	NHEt	H	Cl	Cl	100	100	100	560
28	OH	NH- <i>i</i> -Pr	H	Cl	Cl	100	100	100	560
29	OH	NHBu	H	Cl	Cl	100	100	100	560
30	OH	NH(allyl)	H	Cl	Cl	85	90	95	560
31	OH	NH(CH ₂) ₂ OH	Cl	Cl	Cl	100	95	95	560
32	OH	NH(CH ₂) ₂ OMe	H	Cl	Cl	90	70	90	560
33	OH	NMe ₂	H	Cl	Cl	100	100	98	560
34	OH	NMe(OH)	H	Cl	Cl	95	100	100	560
35	OH	NMe(OMe)	H	Cl	Cl	85	95	90	560
36	OH	pyrrolidine	H	Cl	Cl	80	80	95	560
37	OH	pyrrole	H	Cl	Cl	95	100	100	560
38	O-Me	N ₃	H	Br	Cl	100	100	100	560
39 ¹	OH	NO ₂	H	Cl	Cl	100	100	100	560
40	OH	N-CH(NMe ₂)	H	Cl	Cl	100	100	100	560
41	OH	NH ₂	H	Br	O-Me	85	40	90	280
42	OH	NH ₂	Cl	Br	O-Me	100	100	100	560
43	OH	NH ₂	Cl	Cl	F	70	30	80	140
44	OH	NH ₂	H	Cl	Br	100	100	100	560
45	O-Me	NH ₂	Cl	CF ₃	Cl	100	100	90	125
46	O-Me	NH ₂	H	CF ₃	Cl	100	95	95	140
47	OH	NH ₂	H	O-3,5-DCPh ⁴	Cl	0	100	95	280
48	OH	NH ₂	H	O-Ph	Cl	100	30	100	280
49	OH	NH ₂	H	O-4-MeOPh ⁵	Cl	0	0	0	70
50	OH	NH ₂	H	O-4-MePh ⁶	Cl	0	0	0	70
51	OH	NH ₂	H	O-3,4-DCPh ⁷	Cl	0	98	80	280
52	OH	NH ₂	H	O-3-MePh ⁸	Cl	70	20	50	560
53	OH	NH ₂	H	O-3-CPh ⁹	Cl	100	0	100	560
54	OH	NH ₂	Cl	O-Ph	Cl	41	10	50	280
55	OH	NH ₂	F	O-3,4-DCPh ⁷	Cl	100	95	100	250
56	OH	NH ₂	Cl	O-2-MP ¹⁰	Cl	0	0	40	560

¹Compuesto 39 es N-óxido piridina

²O-2-EH = O-2-etilhexil

³O-BE = O-(CH₂)-OBu

⁴O-3,5-DCPh = O-3,5-dicloroC₆H₃

⁵O-4-MeOPh = O-4-metoxiC₆H₄

⁶O-3-MePh = O-4-MetilC₆H₄

⁷O-3,4-DCPh = O-3,4-ddicloroC₆H₃

⁸O-3-MePh = O-3-MetilC₆H₄

⁹O-3-CPh = O-3-cloroC₆H₄

¹⁰O-2-MP = O-2-metilpropilo

NT = no ensayado

IPOHE = gloria de la mañana (*Ipomea hederacea*)

AMARE = cual (*Amarantus retroflexus*)

ABUTH = hoja velluda (*Abutilon theoprasti*)

Tabla 7
% de Control de la Actividad Postemergencia Herbicida

Cpd. No.	Rata, G/Ha	XANST	CHEAL	AMARE	ABUTH	EPHHL	ALOMY	ECHCG	DIGSA	SETFA	SORBI	AVEFA
1	35	99	99	88	95	62	36	17	20	40	60	37
3	35	90	100	90	95	20	NT	20	40	40	30	10
14	35	100	100	100	10	70	60	40	80	98	50	40
42	35	98	90	60	80	40	30	30	30	30	20	30

Nt = sin ensayo

XANST = cadillo (*Xanthium strumarium*)

CHEAL = cuartos de cordero (*Quinopodium album*)

AMARE = chual (*Amarantus retroflexus*)

ABUTH = hoja velluda (*Abutilion theoprasti*)

EPHHL = polenta salvaje (*Euphorbia heterophilla*)

ALOMY = hierba negra (*Alopecurus misuroides*)

ECHCG = grama (*Equinocloa crus-gali*)

DIGSA = pasto de cangrejo (*Digitaria sanguinalis*)

SETFA = cola de zorro gigante (*Setaria faveris*)

SORBI = sorgo naranja Rox (*Sorgo bicolor*)

AVEFA = avena salvaje (*Avena fatua*)

34. Rango y ensayo de cosecha de pastura

Las tasas son calculadas con base en 5 dosis que han sido aplicadas. La tasa más alta (X), seguido por diluciones seriales de 1/2x, 1/4x, 1/8x y 1/16x. Los requerimientos del compuesto son basados sobre el volumen de portador de 187 l/ha, las especificaciones del sistema de suministro (rociador de camino Mandel) y generar 24 ml de material de rociado técnico para permitir para las diluciones y el cubrimiento del rociador.

$$\frac{\text{Rata g/ha}}{187 \text{ l/ha}} = \frac{x \text{ mg}}{24 \text{ ml}}$$

Ejemplo:

Rata de partida x (g/ha)	Mgs requerido
560	71,9
280	35,9
140	17,95
70	8,9

Todos los materiales técnicos fueron formulados en 97:3 (acetona: DMSO) con 0,25% de X-77. El volumen total del disolvente es mantenido a menos de 7%. Un rociador de camino Mandel suspendido calibrado para suministrar 187 L/ha fue usado para todas las aplicaciones de tratamiento (post-emergencia). El Picloram fue incluido como un tratamiento de comparación.

Las soluciones fueron aplicadas con un rociador de camino mecanizado de las siguientes capacidades:

Boquilla: 8002E

Velocidad: 2 mph (3,2 km/hr)

Presión de rociado: 40 psi (276 kPa)

Altura de rociado: 17 pulgadas (43 cm) por encima de la parte superior de las plantas

Esto suministra un volumen de aplicación de 187 l/ha

El porcentaje de control de semilla (quemado) fue evaluado tres semanas después de tratamiento. El control visual sobre una escala lineal de 0 a 100 fue usado con el cero representando ningún control y 100 representando control total. Las calificaciones de quemado fueron tomadas por especies de malezas anuales y perennes.

Algunos de los compuestos ensayados, ratas de aplicación empleadas, especies de plantas ensayadas, y resultados se dan en las tablas 8 a 10.

Tabla 8

Sales de compuesto 1

Post emergencia GR₈₀

G/Ha

Sal	CASOB	CONAR	CIRAR
Ácido libre	11	59	47
Sal de potasio	<8,8	36	27
Sal amina	<8,8	34	37
Sal dimetilamina	11,8	>140	43
Sal de monoetanolamina	11	20	18
Sal de trietilamina	<8,8	16	<8,8
Sal de triisopropanolamina	11	20	43

CASOB = Sicklepod (*Cassia obtusifolia*)

CONAR = maleza de campo (*Convolvulus arvensis*)

CIRAR = Thistel Canada (*Cirsium arvense*),

3 semanas de evaluación

Tabla 9

Control de varias malezas clave en la pastura

Evaluación post emergencia - % de control

Comp #	AGRCR	CIRAR	RUMOB	AMBEL	Rata (ppm)
3	30	90	100	100	70
6	30	95	100	93	70
26	10	90	100	Nt	70
23	30	80	100	85	70

AGRCR = cesp   de trigo encumbrado (Agropiron cristatum)

~~CIRAR = Thistel Canada (Cirsium arvense),~~

RUMOB = Asedera de hoja ancha (Rumex obtusifolia)

AMBEL = malezatr  o com  n (Ambrosia artemisiifolia)

3 semanas de evaluaci  n

nt = no ensayado

Tabla 10

Control de varias malezas clave en la pastura Clover

	GR ₂₀	GR ₈₀	GR ₈₀
Comp	TRFRE	CONAR	CIRAR
3	17,5	127,7	17,5
4	17,5	59	17,5
5	17,5	140,1	17,5
6	98,8	98,8	17,3
7	15,3	116,6	17,3
9	20,7	66	20,7

TRFRE = trébol blanco (*Trifolium repens*)

CONAR = campo malezatrabada

CIRAR = Thistel Canada (*Cirsium arvense*),

ml de dietil éter y H₂O se agregaron. La capa acuosa acidificada con HCl al 1N hasta que el pH igual 2. El cloruro de metileno fue agregado y la fase acuosa fue extrarída con CH₂Cl₂ adicional (2 x 100 ml). Los extractos combinados fueron secados (MgSO₄) y concentrados hasta el secado en vacío para dar 0,390 g de sólido blanco de ácido de 4-amino-3-cloro-6-(3,5-diclorofenoxi)piridina-2-carboxílico (compuesto 47); pf 196° C.

Los siguientes análogos 6-fenoxi de ácido 4-amino-3-cloro-6-(3, 5-diclorofenoxi)piridina-2-carboxílico fueron preparados de acuerdo con el procedimiento del ejemplo 27:

Acido de 4-amino-3-cloro-6-fenoxipiridina-2-carboxílico (compuesto 48); pf 178° C.

Acido de 4-amino-3-cloro-6-(4-metoxifenoxi)piridina-2-carboxílico (compuesto 49); pf 174° C.

Acido de 4-amino-3-cloro-6-(4-metilfenoxi)piridina-2-carboxílico (compuesto 50); pf 173° C.

Acido de 4-amino-3-cloro-6-(3,4-diclorofenoxi)piridina-2-carboxílico (compuesto 51); pf 186 a 187° C.

Acido de 4-amino-3-cloro-6-(3-metilfenoxi)piridina-2-carboxílico (compuesto 52); pf 169° C.

Acido de 4-amino-3-cloro-6-(3-clorofenoxi)piridina-2-carboxílico (compuesto 53); pf 176° C.

28. Preparación de ácido de 4-amino-3, 5-dicloro-6-fenoxipiridina-2-carboxílico (compuesto 54)

A. Preparación de metil de 4-amino-3, 5-dicloro-6-fenoxipiridina-2-carboxilato.

A una solución de ácido de 4-amino-3,5,6 de tricloropiridina-2-carboxílico (7,2 g, 0,03 mol), fenol (3,0 g, 0,036 mol) e hidróxido de sodio (2,7 g, 0,066 mol) en DMSO (60 ml) y agua (9 ml) fueron calentados hasta 130° C durante 18 horas. La reacción fue diluida con agua (250 ml) y un sólido pegajoso fue recolectado. Este material fue disuelto en metanol (100 ml) y tratado con TMSCHN₂ (25 ml al 2M en hexano). La reacción fue agitada durante 30 minutos y concentrada. El aceite resultante fue cromatografiado sobre gel de sílice (80% de hexano y 20% de acetato de etilo) para dar metil 4-amino-3,5-dicloro-6-fenoxipiridina-2-carboxilato (1,2 g, 14%); pf 88-90° C.

B. Preparación de ácido de 4-amino-3,5-dicloro-6-fenoxipiridina-2-carboxílico (compuesto 54)

A una solución de metilo 4-amino-3,5-dicloro-6-fenoxipiridina-2-carboxilato en metanol (10 ml) y agua (100 ml) se agregó hidróxido de sodio (0,5 g en exceso) y la solución calentada bajo reflujo durante 3 horas. La solución fue enfriada y concentrada con ácido clorhídrico

(2 ml) agregado. El sólido fue recolectado para dar ácido de 4-amino-3,5-dicloro-6-fenoxipiridina-2-carboxílico (1,1 g, 90%); pf 158-60° C.

29. Preparación de ácido 4-amino-3-cloro-5-fluoro-6-(3,4-diclorofenoxi)piridina-2-carboxílico (compuesto 55)

Acido de 4-amino-3-cloro-6-(3,4-diclorofenoxi)-piridina-2-carboxílico fue fluorinado con [1-(clorometil)-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octano bis (tetrafluoroborato)] (F-TEDA) en acetonitrilo en reflujo; pf 156-160° C.

30. Preparación de ácido 4-amino-3,5-dicloro-6-(2-metilpropoxi)piridina-2-carboxílico (Compuesto 56)

Acido 4-amino-3,5-dicloro-6-(2-metilpropoxi)-piridina-2-carboxílico (compuesto 56) fue preparado siguiendo el procedimiento del ejemplo 27 usando 2-metilpropanol en lugar de fenol; pf 104-6° C.

31. Preparación de composiciones herbicidas

En las siguientes composiciones ilustrativas las partes y porcentajes se dan en peso.

CONCENTRADOS EMULSIFICABLES

FORMULACION A	% peso
Éster de 4-amino-3,6-dicloropicolinato, 2-butoxiethyl	26,2
Poliglicol 26-3	5,2
Emulsificador no iónico-(di-sec-butil)fenilpoli (oxipropileno) b polímero de bloqueo con oxietileno).	
El contenido de polioxietileno es de alrededor de 12 moles	
Witconato pl2-20	5,2
(emulsificador aniónico-calcio dodecilbenceno sulfonato - 60% en peso activo)	
Aromáticos 11	63,4
(rango de xileno en disolvente aromático)	

FORMULACION B	%peso
Ester de 4-amino-3,6-dicloropicolinato, 2-etilhexil	3,5
Sunspray 11N (aceite parafínico)	40,0
Poliglicol 26-3	19,0
Ácido oléico 1,0	1,0
Disolvente aromático de rango en xileno	36,5

FORMULACION C	%peso
Éster de 4-amino-3,6-dicloropicolinato, n-butilo	13,2
Stepon C-65	25,7
Ethomen T/25	7,7
Ethomeen T/15	18,0
Disolvente aromático en rango de xileno	35,4

Estos concentrados pueden ser diluidos con agua para dar emulsiones de concentraciones adecuadas para controlar malezas.

POLVOS HUMECTANTES

FORMULACION D	%peso
Ácido 4-amino-3,6-dicloropicolínico	26,0
Poliglicol 26-3	2,0
Polifon H	4,0
Zeosil 100 (SiO ₂ precipitado hidratado)	17,0
Arcilla Barden + inertes	51,0

FORMULACION E	%peso
Ácido 4-amino-3,6-dicloropicolínico	62,4
Polifon H (sal de sodio de sulfonato de lignina)	6,0
Sellogen HR (sulfonato de naftaleno de sodio)	4,0
Zeosil 100	27,6

El ingrediente activo es aplicado a los portadores correspondientes y entonces estos son mezclados y molidos para obtener polvos humectables de excelente humectabilidad y potencia de suspensión. Diluyendo estos polvos humectables con agua es posible obtener suspensiones de concentraciones adecuadas para controlar malezas.

GRANULOS DISPERSABLES EN AGUA

FORMULACION F	%peso
Ácido 4-amino-3,6-dicloropicolínico	26,0
Sellogen HR	4,0
Polifon H	5,0
Zeosil 100	17,0
Arcilla Kaolinita	48,0

El Ingrediente activo se agregó al sílice hidratado, el cual es entonces mezclado con los otros ingredientes y molido hasta hacer un polvo. El polvo es aglomerado con agua y tamizado para suministrar gránulos en el rango de -10 a +60 de malla. Por medio de dispersar estos gránulos en agua es posible obtener suspensiones de concentraciones adecuadas para controlar malezas.

GRANULOS

FORMULACION G	%peso
Ácido 4-amino-3,6-dicloropicolínico	5,0
Celetom MP-88	95,0

El ingrediente activo es aplicado en un disolvente polar tal como N-metil-pirrolidinona, ciclohexanona, gamma-butirolactona, etc. al Celetom MP 88 portador o a otros portadores adecuados. Los gránulos resultantes pueden ser aplicados a mano, aplicador de gránulos, avión, etc. para poder controlar malezas.

FORMULACION H		%peso
Ácido 4-amino-3,6-dicloropicolínico		1,0
Polifon H		8,0
Nekal BA 77		2,0
Stearato de zinc		2,0
Arcilla Barden		87,0

Todos los materiales son mezclados y molidos hasta ser polvo entonces se agrega agua y la mezcla de arcilla es agitada hasta que se forma una pasta. La mezcla es extruída a través de una boquilla para suministrar gránulos de tamaño apropiado.

Líquidos Solubles en Agua

FORMULACION I	% peso
Ácido 4-amino-3,6-dicloropicolínico	11,2
KOH	3,7
agua	85,1

Ácido 4-amino-3,6-dicloropicolínico es dispersado en agua. El KOH es agregado lentamente para neutralizar el ácido hasta un pH que está entre 9 a 12. El tensoactivo soluble en agua puede ser agregado. Otras ayudas pueden ser incorporadas para mejorar las propiedades físicas, químicas y/o de formulación.

32. Evaluación de actividad herbicida postemergencia

Las semillas de las especies de plantas de ensayo deseadas fueron plantadas en Grace-Sierra metroMix® 306 una mezcla para plantar, la cual típicamente tiene un pH entre 6,0 a 6,8 y un contenido de manera orgánica de alrededor del 30%, en vasijs plásticas con un área e superficie de 64 cm². Cuando se requirió asegurar una

buena germinación y unas plantas saludables, un tratamiento fungicida y/u otro químico o tratamiento físico fue aplicado. Las plantas crecieron durante 7 a 21 días en invernadero con fotoperiodo de aproximadamente 15 horas el cual fue mantenido alrededor de 23 a 29° C durante el día y 22 a 28° C durante la noche. Los nutrientes y el agua fueron agregados en base regular y luz suplementaria fue suministrada con lámparas de 1.000 de haluro de metal suspendidas según fue necesario. Las plantas fueron empleadas para ensayo cuando ellas alcanzaron el primero y segundo estado de hoja verdadera.

Una cantidad pesada, determinada por la rata más alta a ser ensayada, de cada compuesto de ensayo fue colocado en un frasco de vidrio de 20 ml y fue disuelto en 4 ml de una mezcla 97:3 de v/v (volumen/volumen) de acetona y dimetilsulfóxido (DMSO) para obtener una solución de base. Si el compuesto de ensayo no se disuelve fácilmente, la mezcla fue calentada y/o sonicada. Las soluciones de base concentradas obtenidas fueron diluidas con una mezcla acuosa que contenía acetona, agua, alcohol isopropilo, DMSO, concentrado de aceite de cosecha Atplus 411F y un tensoactivo Triton x-

155 en una proporción 48,5:39:10:1,5:1,0:0,02 de v/v para obtener soluciones de aerosol de concentraciones conocidas. Las soluciones contenían la concentración más alta para ser ensayada fueron preparadas diluyendo 2 alícuotas de 2 ml de la solución base con 13 ml de la mezcla y concentraciones bajas fueron preparadas por dilución serial de la solución base. Apropiadamente alícuotas de 1,15 ml de cada solución de concentraciones conocidas fueron rociadas de manera uniforme sobre cada una de las vasijas de plantas de ensayo usando un atomizador DeVilbiss accionado por aire comprimido a presión entre 2 a 4 psi (140 a 280 kilopascales) para obtener un cubrimiento parejo de cada planta. Las plantas de control fueron rociadas de la misma manera con la mezcla acuosa. En este ensayo una rata de aplicación de 1 ppm resulta en la aplicación de aproximadamente 1 g/Ha.

Las plantas tratadas y las plantas de control fueron colocadas en el invernadero como se describió anteriormente y fueron regadas por subirrigación para impedir un lavado de los compuestos de ensayo. Después de dos semanas la condición de las plantas de ensayo según se comparó con aquellas de las plantas no tratadas fue

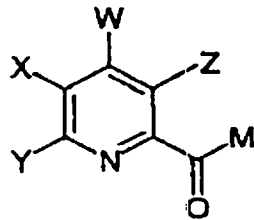
determinada visualmente y registrada sobre una escala de 0 a 100% en donde 0 corresponde ningún daño y 100 corresponde a muerte completa.

El análisis probado bien aceptado según se describió por J. Berkson en Journal of The American Statistical Society, 48, 565 (1953) y por D. Finney en "Probit Analysis" Cambridge University Press (1952), Los datos anteriores pueden ser usados para calcular valores GR_{50} y GR_{80} , que son definidos como factores de reducción de crecimiento como corresponde a la dosis efectiva de herbicida requerida para matar o controlar 50% u 80%, respectivamente, de la planta objetivo.

Algunos de los compuestos ensayados, las ratas de aplicación empleadas, las especies de plantas ensayadas, y los resultados se dan en las tablas 1 y 2. La selectividad para arroz, maíz y trigo se ilustran en las tablas 3 a 5.

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Tabla 1
Post Emergencia & Control



#	M	W	X	Y	Z	% Control			Rate (ppm)
						XANST	STEME	POLCO	
1	OH	NH ₂	H	Cl	Cl	95	100	100	125
2	O-2-EH ²	NH ₂	H	Cl	Cl	95	80	100	250
3	O-Me	NH ₂	H	Cl	Cl	100	100	100	125
4	O-Et	NH ₂	H	Cl	Cl	100	100	100	125
5	O-Pr	NH ₂	H	Cl	Cl	100	100	100	125
6	O-i-Pr	NH ₂	H	Cl	Cl	100	100	100	125
7	O-Bu	NH ₂	H	Cl	Cl	100	100	100	250
8	O-pentyl	NH ₂	H	Cl	Cl	100	90	100	250
9	O-hexyl	NH ₂	H	Cl	Cl	100	100	100	250
10	O-BE ³	NH ₂	H	Cl	Cl	90	50	100	125
11	NH ₂	NH ₂	H	Cl	Cl	80	85	95	125
12	O-Me	NHC(O)Me	H	Cl	Cl	90	30	100	125
13	O-Me	N(C(O)Me) ₂	H	Cl	Cl	95	100	80	250
14	OH	NH ₂	H	Br	Cl	85	90	50	250
15	OH	NH ₂	H	F	Cl	100	70	90	250
16	OH	NH ₂	F	Br	F	60	30	70	250
17	OH	NH ₂	H	Br	Br	100	80	100	250
18	O-Me	NH ₂	Br	Br	Br	85	90	75	250
19	OH	NH ₂	F	Cl	Cl	95	95	100	125
20	OH	NH ₂	Br	Cl	Cl	85	90	50	250
21	OH	NH ₂	CF ₃	Cl	Cl	70	20	20	250

22	OH	NH ₂	O-Me	Cl	Cl	80	90	100	250
23	OH	NH ₂	S-Et	Cl	Cl	90	90	98	125
24	OH	NH ₂	S-Ph	Cl	Cl	60	50	50	250
25	O-Me	NH ₂	NO ₂	Cl	Cl	60	50	50	250
26	OH	NHMe	H	Cl	Cl	90	90	95	125
27	OH	NHEt	H	Cl	Cl	85	100	90	125
28	OH	NH- <i>i</i> -Pr	H	Cl	Cl	95	90	95	250
29	OH	NHBu	H	Cl	Cl	95	90	90	250
30	OH	NH(allyl)	H	Cl	Cl	100	80	100	250
31	OH	NH(CH ₂) ₂ OH	Cl	Cl	Cl	40	30	70	250
32	OH	NH(CH ₂) ₂ OMe	H	Cl	Cl	80	20	100	250
33	OH	NMe ₂	H	Cl	Cl	100	100	100	250
34	OH	NMe ₂ (OH)	H	Cl	Cl	100	70	100	125
35	OH	NMe(OMe)	H	Cl	Cl	90	60	100	125
36	OH	pyrrolidino	H	Cl	Cl	50	40	80	125
37	OH	pyrrol	H	Cl	Cl	90	70	90	125
38	O-Me	N ₃	H	Br	Cl	90	50	90	125
39 ¹	OH	NO ₂	H	Cl	Cl	85	30	90	125
40	OH	N=CH(NMe ₂)	H	Cl	Cl	100	90	100	250
41	OH	NH ₂	H	Br	O-Me	80	90	100	125
42	OH	NH ₂	Cl	Br	O-Me	85	90	90	250
43	OH	NH ₂	Cl	Cl	F	90	85	60	125
44	OH	NH ₂	H	Cl	Br	90	90	95	125
45	O-Me	NH ₂	Cl	CF ₃	Cl	90	0	80	250
46	O-Me	NH ₂	H	CF ₃	Cl	90	60	100	250
47	OH	NH ₂	H	O-3,5-DCPh ⁴	Cl	100	100	100	250
48	OH	NH ₂	H	O-Ph	Cl	100	60	100	250
49	OH	NH ₂	H	O-4-MeOPh ⁵	Cl	60	0	70	250
50	OH	NH ₂	H	O-4-MePh ⁶	Cl	60	0	70	250
51	OH	NH ₂	H	O-3,4-DCPh ⁷	Cl	100	70	100	250
52	OH	NH ₂	H	O-3-MePh ⁸	Cl	70	20	90	250
53	OH	NH ₂	H	O-3-CPh ⁹	Cl	100	100	100	250
54	OH	NH ₂	Cl	O-Ph	Cl	100	0	40	250
55	OH	NH ₂	F	O-3,4-DCPh ⁷	Cl	100	95	100	250
56	OH	NH ₂	Cl	O-2-MP ¹⁰	Cl	85	30	20	250

¹Compuesto 39 es N-óxido piridina

²O-2-EH = O-2-etilhexil

³O-BE = O-(CH₂)-OBu

⁴O-3,5-DCPh = O-3,5-dicloroC₆H₃

⁵O-4-MeOPh = O-4-metoxiC₆H₄

⁶O-3-MePh = O-4-MetilC₆H₄

⁷O-3,4-DCPh = O-3,4-ddicloroC₆H₃

⁸O-3-MePh = O-3-MetilC₆H₄

⁹O-3-CPh = O-3-cloroC₆H₄

¹⁰O-2-MP = O-2-metilpropilo

NT = no ensayado

XANST = Cadillo (*Xantium strumarium*)

STEME = pamplina (*Stellaria media*)

POLCO = Alforfón salvaje (*Poligonum convolvulus*)

Tabla 2

% de Control de la Actividad Postemergencia Herbicida

Cpd. No.	Rata, Ppm	STEME	XANST	CHEAL	AMARE	ABUTH	VIOTR	POLCO	ALOMY	ECHCG	DIGSA	SETFA	SORBI	AVEFA
1	125	90	100	100	95	70	80	100	50	45	60	75	50	50
4	125	70	100	100	100	70	70	100	40	50	70	75	40	40
14	125	65	100	95	90	85	75	100	50	65	65	65	60	40
19	125	60	95	95	60	50	50	100	20	10	30	20	10	20

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 44,836
FECHA : JUNIO 4 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 01-002407- -00008-0000

Fecha: 2007-06-21 16:14:38 Dep. 2020 NUECREACION
Tra. 2 PATENTES Eve. 1 REGDEPOSITO
Act. 444 RESPUESTAREQUE Folios: 297

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	55800359	04/06/2007	54,559,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		82 INVOCAION DE UNA PRIORIDAD EN NU	135,000.00
		TOTAL :	\$ 135,000.00

SON: CIENTO TREINTA Y CINCO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

10975 801 012 9
COLO 11832 Del 124 13

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

2020
Bogotá, D.C, 17-10-07

Abogado
Emilio Ferrero
Solicitante: Dow Agrosciences LLC

ASUNTO	Radicación	00-87284A
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	13517
	Folios	000

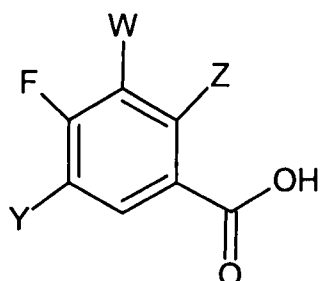
Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios: 160 a 264 como se radicó inicialmente
- 1.2. Reivindicaciones: Folios 276 a 279 , correspondientes a la división de la solicitud, original 01- por tanto el capítulo reivindicatorio, Folios 229 a 234(reivindicaciones 1 a 10)
- 1.3. Prioridad: US 60/176720. fecha 14-01-2000

2. Objeto de la invención

- Título de la solicitud: "4-aminopicolinatos y su uso como herbicidas"
- La solicitud comprende un compuesto de fórmula I (reivindicaciones 1-4)



- Composición herbicida que comprende un compuesto de la fórmula (I) en combinación con un adyuvante o portador agrícolamente aceptable.(reivindicaciones 5 a 8)
- Un método para controlar las plantas indeseables que comprende poner en contacto la vegetación o locus de la misma para impedir el nacimiento

de vegetación en una cantidad herbicidamente efectiva de la composición herbicida.

La solicitud proporciona compuestos del tipo de los ácidos 4-amino-picolínicos y sus derivados, con actividad herbicida con amplio espectro.

- Clasificación Internacional de Patentes (IPC). A01N43/40

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

En el capítulo reivindicatorio tal como se presenta, la materia a proteger, no se delimita claramente, en la reivindicación N°1 se indican en forma general los significados de Y y Z, y se hace referencia a derivados aceptables del ácido carboxílico, en la posición 2 del anillo de la piridina de fórmula I, también con respecto a los derivados agrícolamente aceptables del grupo ácido se hace mención solo en forma general, de manera que se tienen innumerables posibilidades de compuestos, los cuales además no tienen sustento suficiente en la descripción.

Con relación a la reivindicación de composición (N°5) aplica las mismas objeciones relativas al compuesto, pues realmente no se define una composición en términos de sus componentes y la proporción de cada uno de ellos en la composición.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 14 de enero de 2000, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta, los siguientes son los documentos encontrados.

	Documento	Título	Fecha
D1	BE788756	Acides 4-amino-3,5-dihalo-6-alkylpicoliniques	13-03-73
D2	US3325272	Plant growth control methods and compositions	13-06-67
D3	US3285925	Amino-trichloropicolinic acid compounds	15-11-66
D4	GB1082763	Herbicidal compositions	13-09-67

5. Análisis de patentabilidad (artículo 14 D486)

5.1. Nivel inventivo (artículo 18 D486)

De acuerdo con las reivindicaciones 1 a 4 de la solicitud en estudio se contemplan compuestos de fórmula I, del tipo de los 4-aminopicolinatos, composiciones que los contienen (reivindicaciones 5 a 8).

De acuerdo con lo divulgado en el documento D1, se revelan compuestos del tipo de los ácidos 4-amino-3,5-dihalo-6-alkilpicolínicos, los cuales presentan actividad herbicida que comprende la misma estructura piridinica con un grupo -COOH, -COOR', con un grupo amino que corresponde al grupo W de la solicitud en estudio, y X representa un halógeno, de la misma forma que Z de

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la solicitud, con la misma actividad.

D2 divulga compuestos herbicidas como el ácido 4-amino-3,5-dicloropiridin-2-carboxílico, compuesto muy próximo a los de la solicitud en estudio que presentan un grupo amino en posición 4, halógeno en posición 3,5, 6 y grupo carboxílico en posición 2, y que no presenta ningún efecto inesperado frente a los compuestos del documento D2.

En D3 igualmente se divulgan compuestos del tipo de los ácidos- 4-amino-3,5,6-tricloropiridin-2-carboxílico, en la posición 4, estos compuestos pueden presentar además de -NH₂, amino sustituido, formar heterociclo etc, compuestos que tienen múltiples aplicaciones entre ellas, como herbicidas, de manera que se trata de compuestos muy próximos a los de la solicitud en estudio que presentan el mismo núcleo piridinico, con un grupo amino, o heterociclo etc. en la posición 4 y un grupo carboxílico en la posición 2, donde por ejemplo los sustituyentes en 3 y 5 pueden ser halógenos y donde la actividad de los compuestos es la misma.

Con D4 ocurre lo mismo, se divulgan compuestos del tipo de los ácidos- 4-amino-3,5,6-tricloropiridin-2-carboxílico, compuestos que tienen actividad herbicida, de manera que se trata de compuestos muy próximos a los de la solicitud en estudio que presentan el mismo núcleo piridinico, con un grupo amino, en la posición 4 y un grupo carboxílico en la posición 2, donde por ejemplo los sustituyentes Y y Z pueden ser halógenos, e igualmente presentan actividad herbicida.

En relación con la composición, en primer lugar realmente no se ha definido ninguna composición en términos de componentes y proporciones de los mismos, simplemente se trata del compuesto activo en combinación con cualquier adyuvante o portador, de manera que de la misma forma se deriva del arte previo.

El procedimiento para combatir plantas controlar vegetación no deseada de la reivindicación N°9 corresponde a los mismos procedimientos utilizados universalmente para la aplicación de éste tipo de productos, donde no se muestra ninguna condición o forma de realización específica; procedimiento que también se contempla en los documentos citados, ahora bien resulta obvio que para que un compuesto o composición puedan ejercer su acción de acuerdo a sus propiedades, deben ser aplicados en el lugar o al elemento que se desea proteger y tratar en las dosis adecuadas.

De manera que los compuestos de la solicitud en estudio se pueden derivar de los compuestos divulgados en el arte previo, dado que son compuestos estructuralmente muy próximos a los que allí se divulgan y no presentan ningún efecto inesperado frente a lo ya conocido, además de acuerdo a como se presentan los compuestos de fórmula I, de la solicitud se puede determinar dada la amplia gama de compuestos, donde a todos se les atribuye actividad herbicida, que no existe ningún efecto inesperado.

Conclusión:

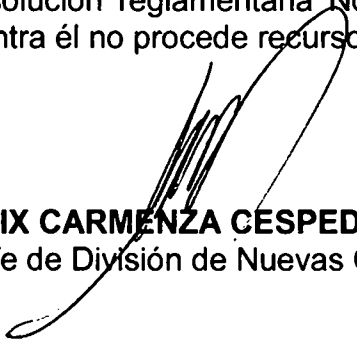
Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

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N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	BE788756	1-9	Nivel Inventivo
D2	US3325272	1-9	Nivel Inventivo
D3	US3285925	1-9	Nivel Inventivo
D4	GB1082763	1-9	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista, de fecha
25 OCT. 2007

CONCEPTO TECNICO No. 1981	EXAMINADOR TECNICO Código No. 202013
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M 286

Le Ministre des Affaires Économiques,

Vu la loi du 24 mai 1854 sur les brevets d'invention;

Vu le procès-verbal dressé le 13 septembre 1972 à 15 h. -
au Service de la Propriété industrielle;

ARRÊTE :

Article 1. — Il est délivré à la Sté dite: THE DOW CHEMICAL COMPANY,
Midland, Michigan (Etats-Unis d'Amérique),

repr. par les Bureaux Vander Haeghen à Bruxelles,

un brevet d'invention pour: Acides 4-amino-3,5-dihalo-6-alkylpicoliniques
substitués,

qu'elle déclare avoir fait l'objet d'une demande de brevet,
non encore accordée à ce jour, déposée aux Etats-Unis
d'Amérique le 2 août 1971, n° 168 349 au nom de Mr. R.H.
Rigterink dont elle est l'ayant droit.

Article 2. — Ce brevet lui est délivré sans examen préalable, à ses risques et
périls, sans garantie soit de la réalité, de la nouveauté ou du mérite de l'invention, soit
de l'exactitude de la description, et sans préjudice du droit des tiers.

Au présent arrêté demeurera joint un des doubles de la spécification de l'invention
(mémoire descriptif et éventuellement dessins) signés par l'intéressé et déposés à l'appui
de sa demande de brevet.

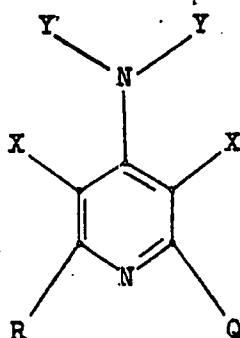
Bruxelles, le 13 mars 1973

PAR DÉLÉGATION SPÉCIALE:

Le Directeur Général,

R. RAUX.

La présente invention concerne des acides
4-amino-3,5-dihalo-6-alkylpicoliniques substitués corres-
pondant à la formule :



(I)

dans laquelle R représente un groupe alkyle de 1 à 4 at-
mes de carbone; Q représente un groupe acide carboxylique
de la formule -COOH et les sels d'addition avec un acide;
un groupe acide carboxylique substitué de la formule -COOR'
et les sels d'addition avec un acide, où R' est un groupe
alkyle de 1 à 4 atomes de carbone; ou un sel d'acide car-
boxylique de la formule -COOM , où M représente un métal
alcalin, un métal alcalino-terreux, le cuivre, le fer, le
zinc, le cobalt, le nickel, un groupe ammonium et ammonium
substitué comportant un groupe alkyle ayant de 1 à 4 atomes
de carbone, chacun des X représente indépendamment un atome
de chlore, de brome, de fluor ou d'iode; et chacun des Y
représente indépendamment de l'hydrogène ou un groupe al-
kyle de 1 à 4 atomes de carbone.

1

3,325,272

PLANT GROWTH CONTROL METHODS AND COMPOSITIONS

John W. Hamaker, Walnut Creek, Calif., and Robert T. Martin, Kuau, Hawaii, assignors to The Dow Chemical Company, Midland, Mich., a corporation of Delaware
No Drawing. Filed June 23, 1965, Ser. No. 466,469
15 Claims. (Cl. 71-2.5)

This application is a continuation-in-part of our prior application Ser. No. 258,901, filed Feb. 15, 1963, which in turn is a continuation-in-part of application Ser. No. 177,757, filed Mar. 6, 1962, both now abandoned.

This invention is related to plant growth control and is particularly directed to compositions and methods for regulating the growth of plants and seeds, both aquatic and terrestrial.

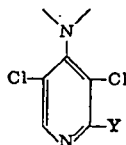
In plant growth control, the methods and compositions of the present invention are useful in the various applications of the art of growth control for which compounds having plant hormone activity are suitable. For example, the compositions and methods of the present invention may be employed to speed up, inhibit or arrest the germination of seeds, or to stimulate or suppress the formation of roots, buds and flowers. They may be used as herbicides to kill undesirable plants and weed seeds. They may also be used to produce seedless fruits without the use of pollen (parthenocarpy), and to prevent or retard the formation of the abscission layer on fruit trees, thereby preventing premature fruit drop. Other applications include causing fruit drop, setting of flowers and defoliating plants. In addition, the compositions may be applied to eradicate the lower or parasitic plants.

It is the object of the present invention to provide novel compositions and methods for treating plants and plant parts and their habitats to stimulate, inhibit or otherwise control the growth of plants. Another object of the present invention is to provide methods and compositions for the selective growth of plants. Still another object of the present invention is to provide novel compositions and methods for the eradication of weeds. Other objects will become apparent from the following specification and claims.

According to the present invention, it has been discovered that germination, growth, eradication or special control of plant or plant parts may be obtained by applying to plant parts or to the habitats of plants, a growth controlling amount of a 4-amino-3,5-dichloropicolinic acid compound.

By "4-amino-3,5-dichloropicolinic acid compound" is meant the parent amino acid and derivatives thereof wherein the amino and carboxyl groups may be further substituted or modified. Thus, the amino group may be substituted with one or more alkyl or hydroxyalkyl groups and the carboxyl group may be replaced by a carboxylic acid salt, amide, ester or hydrazide group.

The 4-amino-3,5-dichloropicolinic acid compounds useful in the methods and compositions of the present invention may be represented by the formula

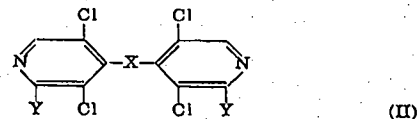


(I)

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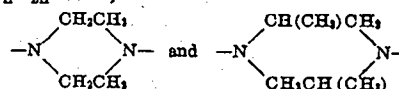
wherein —N< is a residue of a nitrogen base having a basic dissociation constant of 10^{-7} or greater and Y is a carboxylic acid derived group selected from the group consisting of carboxylic acid, carboxylic acid salt, carboxylic acid hydrazide, carboxylic acid ester and carboxylic acid amide.

The amino group, —N< , in the above formula embraces residues of such bases as ammonia, aliphatic, alicyclic and heterocyclic mono- and polyamines, as well as such basic or amino compounds as guanidine, hydrazine and substituted hydrazine, and which have a basic dissociation constant of at least 10^{-7} . The apparent oxidation state of the amino nitrogen is from -3 to 0 . The free valences may be satisfied with radicals such as hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, aralkyl, cycloalkyl, amino, dialkylamino, guanyl, aminoalkyl, poly(aminoalkylene)aminoalkyl, pyridyl, pyrimidinyl, triazinyl; alternatively, the free valences may be joined with a divalent group which with the nitrogen forms a heterocyclic ring such as ethyleneimine, trimethylethyleneimine, pyrrolidine, alkylpyrrolidine, piperidine, alkylpiperidine, piperazine, alkylpiperazine and morpholine. Moreover, the compounds of the present invention embrace those having two trichloropicolinic acid nuclei, joined either directly through the nitrogen or through a divalent group interconnecting the nitrogens; these compounds may be better illustrated by a modified formula



(II)

wherein X may be —NHNH— , $\text{—(NHC}_m\text{H}_{2m})_x\text{NH—}$, $\text{—NHC}_n\text{H}_{2n}\text{NH—}$,



wherein m , n and x are integers from 1 to 4, inclusive, or alkylene diamines which may have aminoalkyl or hydroxyalkyl substituents.

Nitrogen base suitable in forming the amino group have defined embrace such amines and basic nitrogen compounds as are hereinafter disclosed. Suitable aliphatic monoamines include mono- and dialkylamines, alkenylamines, alkynylamines, hydroxyalkylamines and aralkylamines such as ethylamine, n -propylamine, isobutylamine, sec-butylamine, sec-amylamine, 2-methyl- n -butylamine, 1,3-dimethylbutylamine, n -hexylamine, 3-amino- n -hexane, 4-amino- n -heptane, 2-amino- n -heptane, n -nonylamine, n -octylamine, decylamine, undecylamine, dodecylamine, tetradecylamine, hexadecylamine, 1,1,3,3-tetramethylbutylamine, 2-amino-2-methylbutane, pentadecylamine, heptadecylamine, hexahydrobenzylamine, and other monoalkylamines containing from 1 to 18 carbon atoms, inclusive; diethylamine, diisopropylamine, di- n -butylamine, ethylmethylamine, diisobutylamine, diethylamine, methylisopropylamine, N -methyldecylamine, N -methyl-sec-butylamine, N -methyldodecylamine, N -methyltetradecylamine, N -methyloctadecylamine, N -ethyldecylamine, ethylpropylamine, N - n -butyltetradecylamine, bis(1,3-dimethylbutyl)-amino, N -methyl-2-amino- n -pentane, di- n -heptylamine and other dialkylamines containing from 2 to 20 carbon atoms, inclusive; allylamine, methallylamine, oleylamine, 5-amino-1-pentene, 5-amino-2-hexene and other alkenylamines containing from 3 to

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Patented Nov. 15, 1966

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The amino group in the above formula is a residue of nitrogen bases having a basic dissociation constant of at least 10^{-7} and embrace residues of such bases as ammonia, aliphatic, alicyclic and heterocyclic mono and polyamines, as well as such basic or amino compounds as

L082.763



PATENT SPECIFICATION

NO DRAWINGS

L082.763

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Int. Cl.:—A 01 n 19/02

COMPLETE SPECIFICATION

Herbicidal Compositions

We, PRODUITS CHIMIQUES INDUSTRIELS ET AGRICOLES "PROCIDA", a French Body Corporate, of Saint Marcel, Marseille XI^{ème}, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel herbicidal compositions and more particularly herbicidal compositions for the selective weeding of cereals.

Selective herbicides used in agriculture are effective against one or more groups of common plants, but at present no single product permits selective and simultaneous destruction of all families of weeds.

2,4-Dichlorophenoxyacetic acid (2,4-D) and its salts, which destroy *Cirsium* sp. and *Papaver* sp., are used for cereal weeding, but these products have only a weak action upon *Galium aparine* and *Stellaria media*. 2-Methyl-4-chlorophenoxyacetic acid (MCPA) and its salts are highly active against *Sinapis arvensis* and *Thlaspi arvense*, but *Veronica persica*, *V-hederaefolia* and *Polygonum* sp. are not properly controlled by normal doses.

2-Methyl-4-chlorophenoxypropionic acid (Mecoprop) and its salts are effective against *Plantago* sp., *Rumex* sp., *Raphanus raphanistrum*, *Galium aparine* and *Stellaria media*, but are substantially inactive against *Papaver* sp. and *Fumaria* sp. 2,4-Dichlorophenoxypropionic acid (2,4-DP), which is effective against *Galium aparine*, and *Stellaria media*, is inactive against *Chrysanthemum segetum* and *Lithospermum arvense*.

Although the actions of the various above-mentioned products differ somewhat upon the weed flora of crops, and most particularly of cereal crops, their use in mixtures, while being highly desirable, does not enable a solution of all the problems of a user who is anxious to clear his crops completely.

In fact, all these herbicides belong to the

[Price 4s. 6d.]

large family of synthetic auxins, the most important representatives of which are the herbicidal derivatives of phenoxy alkyl carboxylic acids, the phenyl rings of which are generally substituted by one or more alkyl groups and/or halogen atoms. Examples of such compounds are:—

2,4 - dichlorophenoxyacetic acid (2,4-D);

2,4 - dichlorophenoxypropionic acid (2,4-DP);

2,4 - dichlorophenoxybutyric acid;

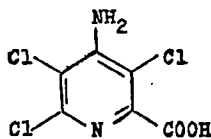
2 - methyl - 4 - chlorophenoxyacetic acid (MCPA);

2 - methyl - 4 - chlorophenoxypropionic acid (MECOPROP);

2,4,5 - trichlorophenoxyacetic acid;

2,4,5 - trichlorophenoxypropionic acid, and their salts.

It has now been found that another chemical group of weed-killers when combined with synthetic auxins provides significantly increased activity against certain species and extended spectrum of action. Thus, research has established that derivatives of picolinic acid possess interesting activities, and in particular 4-amino-3,5,6-trichloropicolinic acid (ATP) of the formula



ATP has remarkable action against *Matricaria* sp., *Galium aparine*, *Anthemis* sp., *Chrysanthemum* sp., and *Polygonum aviculare*, even in relatively advanced stages of development and in quite small doses. On the other hand, its efficiency is weak at these same doses against *Fumaria officinalis*, *Papaver* sp., *Veronica hederaefolia*, *Stellaria media*, *Sinapis arvensis*, and *Viola tricolore*.

However, the effect of this product upon