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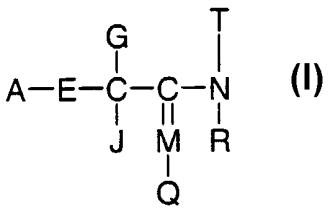
(54) Title: COMPOUNDS USEFUL AS INSECTICIDES, COMPOUNDS USEFUL AS ACARICIDES, AND PROCESSES TO USE AND MAKE SAME



(I)

(57) Abstract: A compound according to Formula One is provided and a process to use such compound to control insects is provided.

COMPOUNDS USEFUL AS INSECTICIDES, COMPOUNDS USEFUL AS ACARICIDES, AND PROCESSES TO USE AND MAKE SAME

PRIORITY

This application claims priority from U.S. provisional application 60/229,110 which was filed on August 30, 2000.

FIELD OF THE INVENTION

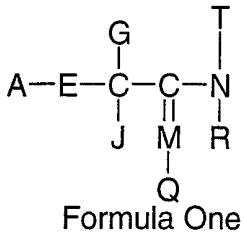
This invention provides compounds that are useful as insecticides and compounds that are useful as acaricides, and processes of making and using these compounds.

BACKGROUND OF THE INVENTION

There is an acute need for new insecticides and acaricides. Insects and mites are developing resistance to the insecticides and acaricides in current use. At least 400 species of arthropods are resistant to one or more insecticides. The development of resistance to some of the older insecticides, such as DDT, the carbamates, and the organophosphates, is well known. But resistance has even developed to some of the newer pyrethroid insecticides and acaricides. Therefore a need exists for new insecticides and acaricides, and particularly for compounds that have new or atypical modes of action.

SUMMARY OF THE INVENTION

It is an object of this invention to provide compounds that are useful as insecticides and compounds that are useful as acaricides, and processes of making and using these compounds. In accordance with this invention compounds of Formula One are provided, as well as, processes to make and use same.



Formula One

DETAILED DESCRIPTION OF THE INVENTION

In Formula One A represents a five or six membered heterocyclic ring containing at least one heteroatom selected from the group consisting of an oxygen, sulfur, or nitrogen. Currently, it is preferred when a six membered heterocyclic ring is used. It is even more preferred when such six membered heterocyclic ring contains one or two nitrogen atoms as the heteroatoms.

This heterocyclic ring may be substituted by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, iodine, C_{1-10} alkyl, halo C_{1-10} alkyl, nitro, cyano, C_{1-10} alkoxy, C_{1-10} alkylthio, C_{1-10} alkylsulfinyl, C_{1-10} alkylsulfonyl, C_{1-10} alkenyl, halo C_{1-10} alkoxy, halo C_{1-10} alkylthio, halo C_{1-10} alkenyl, acylamino, haloacylamino, C_{1-10} alkoxycarbonyl, C_{1-10} alkynyl, amino, C_{1-10} alkylamino, C_{1-10} dialkylamino, C_{3-12} cycloalkyl, C_{1-10} alkoxyalkyl, acyl, formyl, C_{6-12} aryl, mono-or poly substituted C_{6-12} aryl, heteroaryl, and mono-or poly substituted heteroaryl (where said heteroaryl has 5-12 atoms in the ring, and where 1-3 of said atoms in said ring are selected from the group consisting of nitrogen, oxygen, and sulfur, and where the rest of said atoms in said ring are carbon atoms) and where the substituents are selected from the group consisting of halo, C_{1-10} alkyl, halo C_{1-10} alkyl, C_{1-10} alkoxy, nitro, cyano, and C_{6-12} aryloxy).

In the above notations, and throughout this document, it is preferred when the C_{1-10} is a C_{1-6}, and it is more preferred when the C_{1-10} is a C_{1-4}.

Currently, if the heterocyclic ring is substituted, it is preferred when it is mono-substituted with either methyl, ethyl, fluoro, chloro, or bromo. Currently, it is preferred when the substituent is ortho to a heteroatom.

E is selected from the group consisting of O, SO_n where n is 0-2, NH, and NX where X is selected from the group consisting of C_{1-10} alkyl or halo C_{1-10} alkyl. Currently, it is preferred when E is O.

J and R are independently selected from the group consisting of H, C_{1-10} alkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, halo C_{1-10} alkyl, and C_{1-10} alkoxyalkyl. Currently, it is preferred when J and R are H.

M is selected from the group consisting of N and CZ, where Z is selected from the group consisting of H and C(=O)H. Currently, it is preferred when CH is used.

Q is selected from the group consisting of NO_2, CN, and $C(=O)CF_3$. Currently, it is preferred when Q is NO_2.

G and T are independently selected from the group consisting of H, C_{1-10} alkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, halo C_{1-10} alkyl, and C_{1-10} alkoxyalkyl. Currently, it is preferred when G and T are methyl or ethyl.

G and T can also be joined together by a single bond, or through a connecting bridge, where such connecting bridge is selected from the group consisting of CH_2, $CHCH_3$, $C(CH_3)_2$, CH(halo C_{1-10} alkyl), C(halo C_{1-10} alkyl)$_2$, CHF, CF_2, O, SO_n where n is 0-2, NH, and NX where X is selected from the group consisting of C_{1-10} alkyl or halo C_{1-10} alkyl. Currently, it is preferred when the connecting bridge is a single bond or a CH_2.

All salts and esters of these compounds and all the optical isomers thereof are contemplated as part of this invention.

Throughout this document, all temperatures are given in degrees Celsius, and all percentages are weight percentages unless otherwise stated.

Unless otherwise indicated, when it is stated that a group may be substituted with one or more substituents selected from an identified class, it is intended that the substituents may be independently selected from the class.

The compounds of the invention are useful for the control of insects, mites, and aphids. Therefore, the present invention also is directed to a method for inhibiting an insect, mite, or aphid which comprises applying to a locus of the insect or mite an insect- or mite-inhibiting amount of a compound of Formula One. In particular, these compounds control insects in the order Homoptera, including the families Aphididae (aphids), Aleyrodidae (whiteflies), Delphacidae (planthoppers), and Cicadellidae (leafhoppers). They also control insects in the order Coleoptera (beetles), including the family Chrysomelidae (leaf beetles).

The compounds are useful for reducing populations of insects and mites and are useful in a method of inhibiting an insect or mite population which comprises applying to a locus of the insect or mite an effective insect- or mite-inactivating amount of a compound of Formula One.

The "locus" of insects or mites is a term used herein to refer to the environment in which the insects or mites live or where their eggs are present, including the air surrounding them, the food they eat, or objects or materials which they contact. For example, plant-ingesting insects or mites can be controlled by applying the active compound to plant parts that the insects or mites eat, particularly the foliage. Soil-inhabiting insects such as termites can be controlled by applying the active compound to the soil that the insects move through. Insects such as fleas that infest animals can be controlled by applying the active compound to the animal that is infested.

It is contemplated that the compounds might also be useful to protect textiles, paper, stored grain, or seeds by applying an active compound to such substance.

The term "inhibiting an insect or mite" refers to a decrease in the numbers of living insects or mites, or a decrease in the number of viable insect or mite eggs. The extent of reduction accomplished by a compound depends, of course, upon the application rate of the compound, the particular compound used, and the target insect or mite species. At least an inactivating amount should be used.

The terms "insect-inactivating amount" and "mite-inactivating amount" are used to describe the amount, which is sufficient to cause a measurable reduction in the treated insect or mite, population. Generally an amount in the range from about 1 to about 1000 ppm by weight active compound is used. In a preferred embodiment, the present invention is directed to a method for inhibiting a mite or aphid which comprises applying to a plant an effective mite- or aphid- inactivating amount of a compound of Formula One.

The compounds of this invention are applied in the form of compositions which comprise a compound of this invention and a phytologically-acceptable inert carrier. The compositions are either concentrated formulations which are dispersed in water for application, or are dust or granular formulations which are applied without further treatment. The compositions are prepared according to procedures and formulae which are conventional in the agricultural chemical art, but which are novel and important because of the presence therein of the compounds of this invention.

The dispersions in which the compounds are applied are most often aqueous suspensions or emulsions prepared from concentrated formulations of the compounds. Such water-soluble, water-suspendable or emulsifiable formulations are either solids, usually known as wettable powders, or liquids usually known as emulsifiable concentrates or aqueous suspensions. Wettable powders, which may be compacted to

form water dispersible granules, comprise an intimate mixture of the active compound, an inert carrier, and surfactants. The concentration of the active compound is usually from about 10% to about 90% by weight. The inert carrier is usually chosen from among the attapulgite clays, the montmorillonite clays, the diatomaceous earths, or the purified silicates.

Effective surfactants, comprising from about 0.5% to about 10% of the wettable powder, are found among the sulfonated lignins, the condensed naphthalenesulfonates, the naphthalenesulfonates, the alkylbenzenesulfonates, the alkyl sulfates, and nonionic surfactants such as ethylene oxide adducts of alkyl phenols.

Emulsifiable concentrates of the compounds comprise a convenient concentration of a compound, such as from about 50 to about 500 grams per liter of liquid, equivalent to about 10% to about 50%, dissolved in an inert carrier which is either a water miscible solvent or a mixture of water-immiscible organic solvent and emulslfiers. Useful organic solvents include aromatics, especially the xylenes, and the petroleum fractions, especially the high-boiling naphthalenic and olefinic portions of petroleum such as heavy aromatic naphtha. Other organic solvents may also be used, such as the terpenic solvents including rosin derivatives, aliphatic ketones such as cyclohexanone, and complex alcohols such as 2-ethoxyethanol. Suitable emulsifiers for emulsifiable concentrates are chosen from conventional nonionic surfactants, such as those discussed above.

Aqueous suspensions comprise suspensions of water-insoluble compounds of this invention, dispersed in an aqueous vehicle at a concentration in the range from about 5% to about 50% by weight. Suspensions are prepared by finely grinding the compound, and vigorously mixing it into a vehicle comprised of water and surfactants chosen from the same types discussed above. Inert ingredients, such as inorganic salts and synthetic or natural gums, may also be added, to increase the density and viscosity

of the aqueous vehicle. It is often most effective to grind and mix the compound at the same time by preparing the aqueous mixture, and homogenizing it in an implement such as a sand mill, ball mill, or piston-type homogenizer.

The compounds may also be applied as granular compositions, which are particularly useful for applications to the soil. Granular compositions usually contain from about 0.5% to about 10% by weight of the compound, dispersed in an inert carrier which consists entirely or in large part of clay or a similar inexpensive substance. Such compositions are usually prepared by dissolving the compound in a suitable solvent and applying it to a granular carrier which has been pre-formed to the appropriate particle size, in the range of from about 0.5 to 3 mm. Such compositions may also be formulated by making a dough or paste of the carrier and compound and crushing and drying to obtain the desired granular particle size.

Dusts containing the compounds are prepared simply by intimately mixing the compound in powdered form with a suitable dusty agricultural carrier, such as kaolin clay, ground volcanic rock, and the like. Dusts can suitably contain from about 1% to about 10% of the compound.

The active compositions may contain adjuvant surfactants to enhance deposition, wetting and penetration of the compositions onto the target crop and organism. These adjuvant surfactants may optionally be employed as a component of the formulation or as a tank mix. The amount of adjuvant surfactant will vary from 0.01 percent to 1.0 percent v/v based on a spray-volume of water, preferably 0.05 to 0.5 percent. Suitable adjuvant surfactants include ethoxylated nonyl phenols, ethoxylated synthetic or natural alcohols, salts of the esters of sulphosuccinic acids, ethoxylated organosilicones, ethoxylated fatty amines, crop oil concentrates containing high molecular weight paraffinic oils and blends of surfactants with mineral and vegetable oils.

It is equally practical, when desirable for any reason, to apply the compound in the form of a solution in an appropriate organic solvent, usually a bland petroleum oil, such as the spray oils, which are widely used in agricultural chemistry.

Insecticides and acaricides are generally applied in the form of a dispersion of the active ingredient in a liquid carrier. It is conventional to refer to application rates in terms of the concentration of active ingredient in the carrier. The most widely used carrier is water.

The compounds of the invention can also be applied in the form of an aerosol composition. In such compositions the active compound is dissolved or dispersed in an inert carrier, which is a pressure-generating propellant mixture. The aerosol composition is packaged in a container from which the mixture is dispensed through an atomizing valve. Propellant mixtures comprise either low-boiling halocarbons, which may be mixed with organic solvents, or aqueous suspensions pressurized with inert gases or gaseous hydrocarbons.

The actual amount of compound to be applied to loci of insects, mites, and aphids is not critical and can readily be determined by those skilled in the art in view of the examples above. In general, concentrations of from-10 ppm to 5000 ppm by weight of compound are expected to provide good control. With many of the compounds, concentrations of from 100 to 1500 ppm will suffice.

The locus to which a compound is applied can be any locus inhabited by an insect or arachnid, for example, vegetable crops, fruit and nut trees, grape vines, and ornamental plants.

Because of the unique ability of mite eggs to resist toxicant action, repeated applications may be desirable to control newly emerged larvae, as is true of other known acaricides.

In addition to being effective against mites, aphids, and insects when applied to foliage, compounds of Formula One have systemic activity. Accordingly, another aspect of the invention is a method of protecting a plant from insects which comprises treating plant seed prior to planting it, treating soil where plant seed is to be planted, or treating soil at the roots of a plant after it is planted, with an effective amount of a compound of Formula One.

The action of the inventive compounds can be broadened by adding other, for example insecticidally, acaricidally, and/or nematocidally active, ingredients. For example, one or more of the following compounds can suitably be combined with the compounds of the invention:

organophosphorus compounds such as acephate, azinphosmethyl, cadusafos, chlorethoxyfos, chlorpyrifos, coumaphos, dematon, demeton-S-methyl, diazinon, dichlorvos, dimethoate, EPN, erthoate, ethoprophos, etrimfos, fenamiphos, fenitrothion, fensulfothion, fenthion, fonofos, formothion, fosthiazate, heptenophos, malathion, methamidophos, methyl parathion, mevinphos, monocrotophos, parathion, phorate, phosalone, phosmet, phosphamidon, phosphocarb, phoxim, profenofos, propaphos, propetamphos, prothiofos, pyrimiphos-methyl, pyrimiphos-ethyl, quinalphos, sulprofos; tebupirimphos, temephos, terbufos, tetrachlorvinphos, thiafenox, thiometon, triazophos, and trichlorphon;

carbamates such as aldicarb, bendiocarb, benfuracarb, bensultap, BPMC, butoxycarbocim, carbaryl, carbofuran, carbosulfan, cloethocarb, ethiofencarb, fenobucarb, furathiocarb, methiocarb, isoprocarb, methomyl, oxamyl, pirimicarb, promecarb, propoxur, thiodicarb, and thiofurox;

pyrethroids such as acrinathrin, allethrin, beta-cyfluthrin, bifenthrin, bioresmethrin, cyfluthrin; cyhalothrin; lambda-cyhalothrin; gamma-cyhalothrin, cypermethrin; alpha-

cypermethrin; zeta-cypermethrin; deltamethrin, esfenvalerate, fenvalerate, fenfluthrin, fenpropathrin, flucythrinate, flumethrin, fluvalinate, tau-fluvalinate, halfenprox, permethrin, protrifenbute, resmethrin, silafluofen, tefluthrin, tetramethrin, tralomethrin, fish safe pyrethroids for example ethofenprox, natural pyrethrin, tetramethrin, s-bioallethrin, fenfluthrin and prallethrin;

acylureas, other types of insect growth regulators and insect hormone analogs such as buprofezin, chromfenozide, chlorfluazuron, diflubenzuron, fenoxycarb, flufenoxuron, halofenozide, hexaflumuron, hydroprene, leufenuron, methoprene, methoxyfenozide, novaluron, pyriproxyfen, teflubenzuron and tebufenozide, N-[3,5-dichloro-2-fluoro-4-(1,1,2,3,3,3-hexafluoropropoxy)phenyl]-N'(2,6-difluorobenzoyl)urea;
neonicotnioids and other nicotinics such as acetamiprid, AKD-1022, cartap, TI-435, clothiamidin, MTI-446, dinotefuran, imidacloprid, nicotine, nitenpyram, thiamethoxam, thiacloprid;

macrolides such as avermectins, milbemycins,or spinosyns for example such as abamectin, ivermectin, milbemycin, emamectin benzoate and spinosad; and

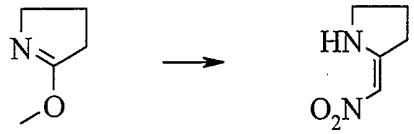
other insecticidal, acaricidal, mollscicial and nematocidal compounds or actives such as aldrin, amitraz, azadirachtin, azocyclotin. bifenazate, bromopropylate, chlordimeform, chlorfenapyr, chlofentezine, chlorobenzilate, chlordane, cyhexatin, cyromazin, DDT, dicofol, dieldrin, DNOC, endosulfan, ethoxazole, fenazaquin, fenbutatin oxide, fenproximate, beta-fenpyroximate, fipronil, flubenzimine, hexythiazox, IKI-220, indoxacarb, lindane, methiocarb, metaldehyde, methoxychlor, neem, petroleum and vegetable oils, pyridaben, pymetrozine, pyrimidifen, rotenone, S-1812, S-9539, spirodiclofen, sulfur, tebufenpyrad, tetradifon, triazamate, an insect-active extract from a plant; a preparation containing insect-active nematodes, a preparation obtainable from *Bacillus subtilis, Bacillus thuringiensis,* a nuclear polyhedrosis virus, or other like organism genetically modified or native, as well as

synergists such as piperonyl butoxide, sesamax, safroxan and dodecyl imidazole, and phagostimulants such as cucurbitacin, sugars and Coax.

EXAMPLES

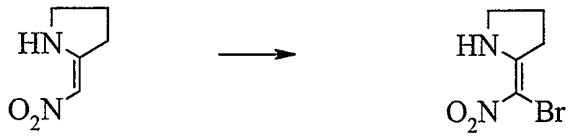
These examples are provided to further illustrate the invention. They are not meant to be construed as limiting the invention.

Preparation of (2*Z*)-3-bromo-2-(nitromethylene)pyrrolidine (Allylic Bromide I)



(2*Z*)-2-(nitromethylene)pyrrolidine

A solution of 4.00 g (40.3 mmol) of the methyl imidate (see Chem. Ber., **104**, 924, 1971) and 1.23 g (20.1 mmol) of nitromethane was heated at 100 °C for 40h and was allowed to cool. The mixture was concentrated *in vacuo* to remove volatiles and the residue was dissolved in dichloromethane and was chromatographed on silica gel (230-400 mesh) eluting with dichloromethane/ethyl acetate mixtures to give 2.1 g (42%) of the nitroethene.



(2*E*)-2-[bromo(nitro)methylene]pyrrolidine

To a vigorously stirred mixture of 328 mg (2.56 mmol) of the nitroethene at room temperature was added in one portion 478 mg (2.68 mmol) of *N*-bromosuccinimide. The mixture was stirred overnight and was then filtered to afford 711 mg which was chromatographed on silica gel using dichloromethane as the eluant to give 420 mg (79%) of the vinyl bromide.

(2*Z*)-3-bromo-2-(nitromethylene)pyrrolidine

(Allylic Bromide I)

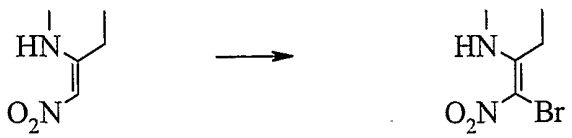
To 130 mL of refluxing xylenes was added in portions over a 5-10 min period 2.0 g (9.7 mmol) of the vinyl bromide. Reflux was continued for 8h and the mixture was allowed to cool. Concentration *in vacuo* gave a solid which was loaded dry onto a column of silica gel and was eluted with dichloromethane/ethyl acetate mixtures to afford 1.10 g (55%) of the Allylic Bromide I.

Preparation of (1*Z*)-3-bromo-*N*-methyl-1-nitrobut-1-en-2-amine

(Allylic Bromide II)

(1*Z*)-*N*-methyl-1-nitrobut-1-en-2-amine

To a solution of 29.3 g (0.290 mol) of the methyl imidate (see Chem Ber., **104**, 924, 1971) and 31.4 mL (35.4 g, 0.58 mol) of nitromethane was heated at 90-95 °C for 17h and was allowed to cool. The solution was concentrated to a residue which was chromatographed on silica gel using dichloromethane/ethyl acetate mixtures to give 22.5 g (60%) of the nitroethene.



(1*E*)-1-bromo-*N*-methyl-1-nitrobut-1-en-2-amine

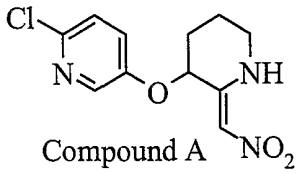
To a solution at 20-23 °C of 6.95 g (53.4 mmol) of the nitroethene in 430 mL of

carbon tetrachloride was added 10.3 g (57.8 mmol) of *N*-bromosuccinimide over a 5-10 min period. The contents were stirred overnight and were filtered. The filtrate was concentrated to give 10.5 g (94%) of the vinyl bromide. mp 79-81 °C.

(1*Z*)-3-bromo-*N*-methyl-1-nitrobut-1-en-2-amine

(Allylic Bromide II)

To 200 mL of carbon tetrachloride vigorously stirred at 48-52 °C was added over a 2-3 min period 3.07 g (14.7 mmol) of the vinyl bromide. The contents were stirred for 25 min and were then cooled in ice to 10 °C. Collection of the precipitate afforded 1.35 g (44%) of the Allylic Bromide II.



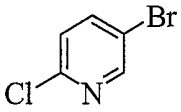
Compound A

Preparation of 3-[(6-chloro-3-pyridinyl)oxy]-2-(nitromethylene)piperidine

(Compound A)

A solution of 329 mg (25.5 mmol) of compound 3 in 10 mL of dry THF was treated with 109 mg (27.3 mmol) of 60% NaH-oil dispersion under nitrogen at room temperature. After gas evolution had subsided, the gray suspension was treated with 500 mg (22.6 mmol) of 3-bromo-2-nitromethylenopiperidine [Ger. Offen. 2,321,523 (1973)] and heated to 65° C. After 1.5 hr, the brown reaction mixture was partitioned between 1 M HCl and dichloromethane. The organic layer was washed with dilute potassium carbonate solution and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel using a 50% mixture of EtOAc/ petroleum ether as eluant. The yellow solid obtained was

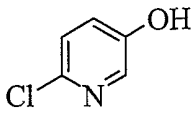
further extracted with ether to remove a byproduct leaving 244 mg (40%) of desired product as a white solid.



Compound 2

Preparation of 5-bromo-2-chloropyridine (Compound 2)

To a stirred solution of 100.0 g (0.578 mol) of 2-amino-5-bromopyridine in 600 mL of conc. HCl cooled to -4°C was added dropwise a solution of 51.8 g (0.751 mol) of sodium nitrite in 100 mL of water over 50 min keeping the temperature below 8°C. The slurry was allowed to warm to 15°C and was then poured over 1800 mL of ice. The precipitated product was collected by filtration and washed with water. The product was dissolved in methylene chloride, washed with water and dried over Na_2SO_4. The solvent was removed *in vacuo* affording 53.0 g (47.6%) of white crystalline solid.

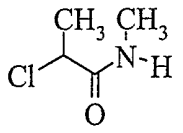


Compound 3

Preparation of 6-chloro-3-pyridinol (Compound 3)

A solution of 48.2 g (0.250 mol) of compound 2 in 500 mL of dry diethyl ether was cooled to -76°C under nitrogen and treated dropwise with 107.2 mL (0.268 mol) of a 2.5 M solution of n-butyllithium in hexane such that the temperature remained below -71 °C. The resulting slurry was allowed to stir an additional 30 min and then treated with 29.3 mL (0.268 mol) of trimethyl borate keeping the temperature below -100°C. The orange slurry was allowed to warm to 0°C and then cooled down to -75°C and 54.4 mL of 32% peracetic acid in acetic acid was added dropwise over 15 min. The yellow slurry was allowed to warm to room temperature. To the mixture was added 150 mL of water and 150 mL of diethyl ether. The layers were separated and the organic layer was washed with saturated sodium bisulfite in water. The organic layer

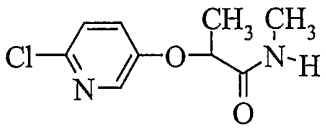
was reduced *in vacuo* and the crude product dissolved in 150 mL of 2 N NaOH. The basic layer was extracted with diethyl ether and acidified with 41.4 g (0.300 mol) of $NaHSO_4.H_2O$ with the desired product precipitating. The product was extracted into diethyl ether and the organic layer dried over $MgSO_4$. The solvent was removed *in vacuo* affording 23.6 g (86 %) of cream-colored product.



Compound 4

Preparation of 2-chloro-*N*-methylpropanamide (Compound 4)

A solution of 25.0 g (0.197 mol) of 2-chloropropionyl chloride in 100 mL of THF was added dropwise to 197 mL (0.394 mol) of 2M methylamine in THF at -45°C to -25°C. The slurry was stirred 1 hr at –45 to -65°C and allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue dissolved in methylene chloride and washed with water. The organic layer was dried over Na_2SO_4 and the solvent removed in vacuo leaving 16.8 g (70.1%) of desired product. Distillation afforded 12.6 g (52.6%) of colorless product.

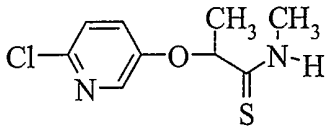


Compound 5

Preparation of 2-[(6-chloro-3-pyridinyl)oxy]-*N*-methylpropanamide (Compound 5)

To a slurry of 8.21 g (0.0634 mol) of compound 3 and 8.09 g (0.0665 mol) of compound 4 in 100 mL of acetonitrile was added 9.20 g (0.0665 mol) of powdered potassium carbonate and 1.0 g (6.02 mmol) of potassium iodide. The slurry was heated under nitrogen at reflux for 64 hr and cooled. The solvent was removed *in vacuo* and the residue partitioned between methylene chloride and water. The organic layer was washed with 1N NaOH, water and dried over Na_2SO_4. Removal of solvent

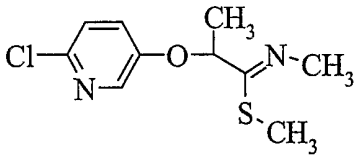
in vacuo afforded 7.43 g (54.6%) of desired product. Trituration with hot methylcyclohexane and cooling gave 7.05 g (51.8%) of white crystalline product.



Compound 6

Preparation of 2-[(6-chloro-3-pyridinyl)oxy]-*N*-methylpropanethioamide (Compound 6)

To a slurry of 6.78 g (0.0316 mol) of compound 5 in 100 mL of toluene was added 6.39 g (0.0158 mol) of Lawesson's Reagent. The slurry was heated at reflux for 2 hr and cooled. The solvent was removed *in vacuo* and the residue remaining was dissolved in methylene chloride and loaded on a silica gel column. Initial elution with methylene chloride gave the Lawesson's Reagent byproduct. Elution with 35% EtOAc/hexane afforded 6.23 g (85.4%) of white crystalline product.

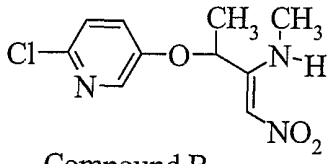


Compound 7

Preparation of methyl (1E/Z)-2-[(6-chloro-3-pyridinyl)oxy]-*N*-[(E/Z)-methyl]propanimidothioate (Compound 7)

Sodium hydride (1.14 g, 0.0286 mole, 60% oil dispersion) was washed with hexane and transferred to a flask under nitrogen and covered with 15 mL of dry DMF. To the slurry was added dropwise a solution of 6.0 g (0.0260 mol) of compound 6 in 50 mL of DMF at room temperature. Gas evolution occurred and the light yellow solution was stirred at room temperature for 1 hr. To this mixture was added a solution of 4.06 g (0.0286 mol) of methyl iodide in 5 mL of DMF. The solution was stirred at room temperature overnight and poured onto 300 mL of ice. The resulting mixture was extracted with diethyl ether. The organic layer was washed with water and dried over

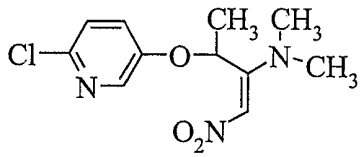
$MgSO_4$. The solvent was removed *in vacuo* affording 5.57g (87.6%) of desired product as a light yellow oil.



Compound B

Preparation of (1E/*Z*)-3-[(6-chloro-3-pyridinyl)oxy]-*N*-methyl-1-nitro-1-buten-2-amine (Compound B)

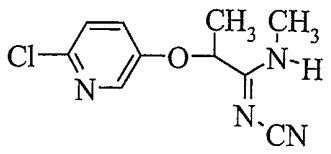
A solution of 2.85 g (0.0116 mol) of compound 7 in 50 mL of nitromethane was heated at 100°C for 4 days under nitrogen. The solvent was removed *in vacuo* and the residue remaining purified by column chromatography using initially methylene chloride and then 50% EtOAc/ hexane as eluents. Fractions containing product were combined and solvent removed *in vacuo* affording 0.69 g of desired product which was triturated with hot EtOAc. Cream-colored product was obtained, 0.57 g (19%).



Compound C

Preparation of (1*E*)-3-[(6-chloro-3-pyridinyl)oxy]-*N*,*N*-dimethyl-1-nitro-1-buten-2-amine (Compound C)

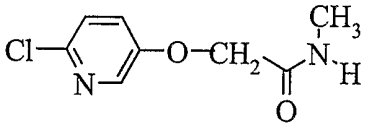
To a slurry of 0.22 g (5.50 mmol) of 60% NaH-oil dispersion and 5 mL of dry DMF was added a solution of 1.0 g (3.88 mmol) of compound B in 10 mL of DMF over 10 min. Gas evolution occurred and the temperature rose to 31°C. After stirring 30 min, 0.35 mL of methyl iodide was added. The mixture was stirred 1.5 hr and poured over 20 mL of ice. The white crystalline product was collected by filtration, washed with water and hexane. There remained 0.641 g (61%) of desired product.



Compound D

Preparation of 2-[(6-chloro-3-pyridinyl)oxy]-*N*'-cyano-*N*-methylpropanimidamide (Compound D)

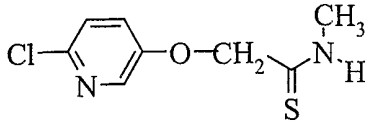
To a solution of 2.44 g (10.0 mmol) of compound 7 in 10 mL of ethanol was added a solution of 1.65 g (39.4 mmol) of cyanamide in 15 mL of ethanol. The solution was stirred at room temperature for 45 min and at reflux for 30 min and cooled. The solvent was removed *in vacuo* leaving an oil which was slurried in 35 mL of methylene chloride. A white crystalline byproduct precipitated and was collected by filtration. The filtrate was loaded on a silica gel and the column was initially eluted with methylene chloride and then 50% EtOAc/hexane. The fractions containing product were combined and solvent removed *in vacuo* affording 2.10 (88.2 %) of white crystalline product.



Compound 11

Preparation of 2-[(6-chloro-3-pyridinyl)oxy]-*N*-methylacetamide (Compound 11)

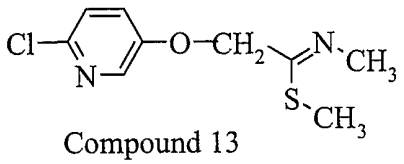
To a slurry of 8.35 g (0.0637 mol) of compound 3 and 7.19 g (0.0669 mol) of commercially available N-methyl-2-chloroacetamide in 100 mL of acetonitrile was added 9.24 g (0.0669) of powdered potassium carbonate. The slurry was heated at reflux for 2.5 hr and cooled. The solvent was removed *in vacuo* leaving a tan solid residue which was slurried in water. The cream-colored product was collected by filtration, washed with water and dried. There remained 8.49 g (66.9%) of product.



Compound 12

Preparation of 2-[(6-chloro-3-pyridinyl)oxy]-*N*-methylthioacetamide (Compound 12)

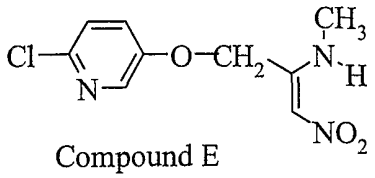
To a slurry of 8.43 g (0.0420 mol) of compound 11 in 100 mL of toluene was added 8.50 g (0.0210 mol) of Lawesson's Reagent. The slurry was heated at reflux for 2 hr and cooled. The solvent was removed *in vacuo* and the residue remaining was dissolved in methylene chloride and loaded on a silica gel column. Initial elution with methylene chloride gave the Lawesson's Reagent byproduct. Elution with 25% EtOAc/hexane afforded 8.17 g (90%) of white crystalline product.



Compound 13

Preparation of methyl (1E/Z)-2-[(6-chloro-3-pyridinyl)oxy]-*N*-[(E/Z)-methyl]acetimidothioate (Compound 13)

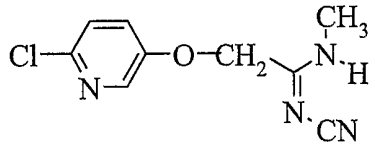
Sodium hydride (1.62 g, 0.0406 mol, 60% oil-dispersion) was washed with hexane and transferred to a flask under nitrogen and covered with 15 mL of dry DMF. To the slurry was added dropwise a solution of 8.0 g (0.0369 mol) of compound 12 in 50 mL of DMF. Gas evolution occurred and the light brown solution was stirred at room temperature for 30 min. To this mixture was added 5.76 g (0.0406 mol) of methyl iodide. The solution was stirred at room temperature overnight and poured over 500 mL of ice. On stirring, the product crystallized and was collected by filtration. The product was dissolved in methylene chloride, washed with water and dried over Na_2SO_4. Removal of solvent *in vacuo* afforded 5.84 g (68.7%) of white crystalline product.



Compound E

Preparation of (1E/Z)-3-[(6-chloro-3-pyridinyl)oxy]-*N* -methyl-1-nitro-1-propen-2-amine (Compound E)

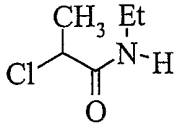
A solution of 2.57 g (11.1 mmol) of compound 13 in 40 mL of nitromethane was heated at 100°C for 4 days under nitrogen. The solvent was removed *in vacuo* and the residue dissolved in methylene chloride and loaded on a silica gel column. The column was eluted initially with methylene chloride and then 40% EtOAc/hexane. The fractions containing product were combined and solvent removed *in vacuo* affording 0.67 g (24.8%) of cream-colored product.



Compound F

Preparation of 2-[(6-chloro-3-pyridinyl)oxy]-*N*'-cyano-*N*-methylethananimidamide (Compound F)

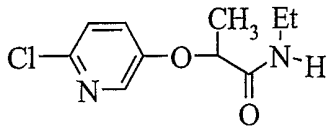
To a slurry of 3.0 g (13.0 mmol) of compound 13 in 30 mL of ethanol was added 2.15 g (51.2 mmol) of cyanamide. The slurry was stirred at room temperature for 30 min and at reflux for 25 min. After stirring at room temperature overnight, the crystalline product was collected by filtration and washed with ethanol. There remained 2.20 g (75.9%) of white crystalline product.



Compound 16

Preparation of 2-chloro-*N*-ethylpropanamide (Compound 16)

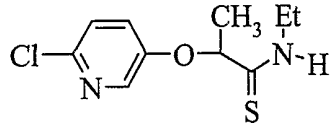
To a solution of 98.5 mL (0.197 mol) of 2.0M ethylamine in tetrahydrofuran cooled to –25 ° to –45 °C was added dropwise over a ten minute period a solution of 12.5 g (0.0984 mol) of 2-chloropropionyl chloride in 50 mL of tetrahydrofuran. The mixture was stirred in this temperature range for 1h and then at –45 to –65 °C for 1h. The mixture was then allowed to warm to room temperature and stir for 2h. The tetrahydrofuran was removed *in vacuo* and the residue was taken up in 75 mL of dichloromethane, washed two times with 75 mL of water, and dried over Na_2SO_4. Concentration gave 11.1 g (83%) of the amide as a clear, colorless liquid.



Compound 17

Preparation of 2-[(6-chloro-3-pyridinyl)oxy]-*N*-ethylpropanamide (Compound 17)

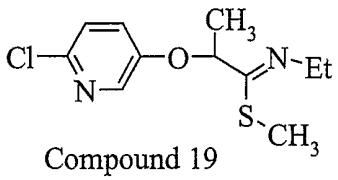
A mixture of 9.41 g (72.6 mmol) of compound 3, 10.0 g (72.6 mmol) of anhydrous potassium carbonate, 9.85 g (72.6 mmol) of compound 16, and 1.1 g (6.6 mmol) of potassium iodide in 100 mL of acetonitrile was heated at reflux for 48 h. After cooling, the mixture was filtered, the filtrate was concentrated to a brown oil which was partitioned between 300 mL of ethyl ether and 36 mL (72 mmol) of 2.0N sodium hydroxide and 75 mL of water. The layers were separated, the aqueous phase was extracted with 200 mL of ether and the combined organic layers were dried over $MgSO_4$. Concentration *in vacuo* gave 13.2 g of a solid which was triturated with hexane to afford 10.7 g (64%) of the desired amide as a tan solid.



Compound 18

Preparation of 2-[(6-chloro-3-pyridinyl)oxy]-*N*-ethylpropanethioamide (Compound 18)

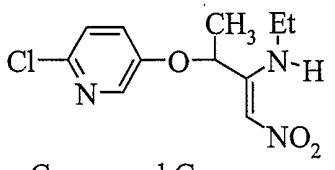
A solution of 6.80 g (29.7 mmol) of compound 17 and 6.06 g (15.0 mmol) of Lawesson's reagent in 100 mL of dry toluene was heated at reflux for 3h and allowed to cool. The solvent was removed *in vacuo* leaving a solid which was taken up in dichloromethane (40-50 mL) and chromatographed on silica gel (230-400 mesh) affording 6.8 g (93%) of the thioamide.



Compound 19

Preparation of methyl (1E/Z)-2-[(6-chloro-3-pyridinyl)oxy]-*N*-[(E/Z)-ethyl]propanimidothioate (Compound 19)

To a mixture cooled in ice of 1.11 g (27.8 mmol) of 60% sodium hydride-mineral oil dispersion in 10 mL of dry DMF was added portionwise over a 10-15minute period 6.80 g (27.8 mmol) of compound 18 followed by 15 mL of DMF. The dark brown mixture was allowed to warm to room temperature and after 1h was cooled again in ice and treated dropwise with a solution of 4.34 g (30.6 mmol) of methyl iodide in 10 mL of DMF. The mixture was stirred overnight at room temperature and added to 300 mL of ice water. The mixture was extracted once with 350 mL of diethyl ether. The extract was then washed two times with water and dried over $MgSO_4$. Concentration gave 6.56 (91%) of the desired product as a dark brown liquid.

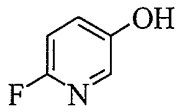


Compound G

Preparation of (1E/Z)-3-[(6-chloro-3-pyridinyl)oxy]-*N*-ethyl-1-nitro-1-buten-2-amine (Compound G)

A solution of 2.93 g (11.3 mmol) of compound 19 in 30 mL of nitromethane was heated at 100 °C for 70h and allowed to cool. The solution was concentrated to an oil

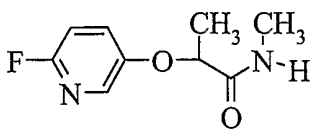
which was chromatographed on silica gel (230-400 mesh) eluting with dichloromethane to afford 600 mg of a solid. This material was recrystallized from hexane/EtOAc (1:1) to give 473 mg (15%) of the desired product.



Compound 21

Preparation of 6-fluoro-3-pyridinol (Compound 21)

A 2.5 M solution of n-butyllithium (44 mL, 0.11 mol) in hexane was added over 24 min to a –70 °C mechanically stirred solution of 5-bromo-2-fluoropyridine (17.6 g, 0.10 mol) in diethyl ether (150 mL). The resultant yellow orange slurry was stirred at this temperature for 25 min., then trimethyl borate (11.4 g, 0.10 mol) was added via syringe over 5-10 min. After 15 min., the cooling bath was removed and the white slurry stirred for 1hr while warming to 5°C. The reaction was then cooled back to -70 °C and 32 wt% peracetic acid (26.1 g, 0.11 mol, 23 mL) added over 15 min., resulting in an exotherm to –40 °C. The cooling bath was removed and the reaction stirred overnight at ambient temperature. Water (100 mL) was added and the mixture stirred until all solids had dissolved. Solid sodium bisulfite was then added in portions until the aqueous layer gave a negative starch-iodide paper test. The layers were separated and the aqueous layer extracted with ethyl acetate (2 x 100 mL). The combined organic layers were concentrated *in vacuo*, the cream- colored residue taken up in toluene (75 mL) and stripped four times to remove residual acetic acid and water. The product was then suspended in toluene (40 mL), filtered and air-dried overnight affording 9.9 g (87%) of product as an ivory powder.

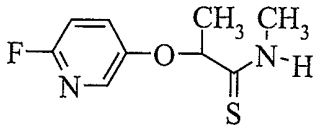


Compound 22

Preparation of 2-[(6-fluoro-3-pyridinyl)oxy]-*N*-methylpropanamide

(Compound 22)

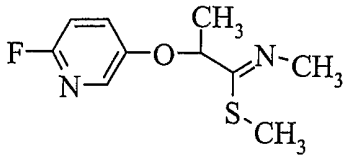
A 350 mL Hastelloy autoclave was loaded with compound 21 (6.80 g, 60.1 mmol), compound 4 (8.8 g, 72.2 mmol), potassium carbonate (10.0 g, 72.2 mmol) and acetonitrile (100 mL). The vessel was purged with nitrogen, then pressurized to 50 psi with nitrogen and heated at 150°C for 12 hr. After cooling, the solvent was removed *in vacuo*, the light brown residue taken up in methylene chloride (200 mL) and washed with dilute aqueous sodium hydroxide (2 x 100 mL), removing the majority of color. The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* leaving 10.2 g (86%) of desired product as a beige powder.



Compound 23

Preparation of 2-[(6-fluoro-3-pyridinyl)oxy]-*N*-methylpropanethioamide (Compound 23)

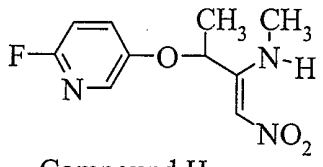
A solution of compound 22 (10.2 g, 51.5 mmol) and Lawesson's Reagent (10.4 g, 25.7 mmol) in toluene (125 mL) was heated at reflux for 1.5 hour. The solvent was then removed *in vacuo* and the residue taken up in minimal methylene chloride. This was loaded onto a silica column (250 g) and eluted with methylene chloride (ca. 1 L) to remove Lawesson's Reagent byproduct and majority of yellow color. The eluent was switched to 2:1 hexane/EtOAc. Fractions containing product were combined and concentrated leaving 9.2 g (84%) of a pale yellow powder.



Compound 24

Preparation of methyl (1E/Z)-2-[(6-fluoro-3-pyridinyl)oxy]-*N*-[(E/Z)-methyl]propanimidothioate (Compound 24)

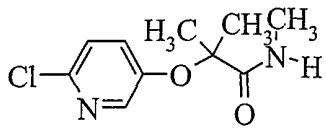
A 60 wt% oil dispersion of sodium hydride (0.84 g, 21.0 mmol) was added in one portion to a stirred solution of compound 23 (4.3 g, 20.0 mmol) in dry THF (100 mL). After 30 min, iodomethane (3.0 g, 21 mmol) was added dropwise and the reaction stirred overnight. The reaction mixture was poured into water (50 mL) and THF removed *in vacuo*. The residue was extracted with ether (3 x 50 mL). The combined organics were washed with brine, dried over $MgSO_4$, and reduced *in vacuo* leaving 5 g of residue which contains product and oil. Half the material was used as is in the next step and half purified by chromatography (3:1 hexanes/ethyl acetate). Fractions containing product were combined and concentrated leaving 1.1 g of product as a pale yellow oil.



Compound H

Preparation of (1E/Z)-3-[(6-fluoro-3-pyridinyl)oxy]-*N*-methyl-1-nitro-1-buten-2-amine (Compound H)

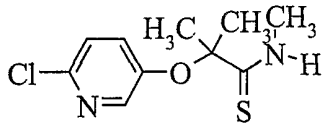
A 2.5 g portion of the crude compound 24 was stirred at reflux in nitromethane (35 mL) while monitoring by proton nmr. After 40 hr, the solvent was removed *in vacuo* and the residue (2.8 g) triturated with hexanes (3 x 5 mL) to remove oil, unreacted thioimidate and less polar impurities. The residue remaining (2.6 g) was subjected to silica gel chromatography using 1:1 hexane/EtOAc. Fractions containing product were combined and concentrated leaving a light brown oil which slowly solidified. Trituration with a small amount of a warm solution of 3:1 hexanes/EtOAc removed the majority of color leaving 590 mg (2.4 mmol) product as a cream-colored powder.



Compound 26

Preparation of 2-[(6-chloro-3-pyridinyl)oxy]-*N*,2-dimethylpropanamide (Compound 26)

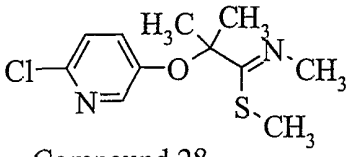
A slurry of compound 3 (6.5 g, 50 mmol), N-methyl 2-bromoisobutyramide (9.0 g, 50 mmol), and silver oxide (11.6 g, 50 mmol) in acetonitrile (250 mL) was stirred at reflux under nitrogen for 2 h. After cooling, the solids were removed by filtration through celite and the mother liquor concentrated in vacuo. The pale peach residue was taken up in methylene chloride (200 mL) and shaken with dilute aqueous sodium hydroxide (100 mL). This was allowed to stand overnight prior to separation. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* leaving 9.6 g (84%) of desired product as a beige powder.



Compound 27

Preparation of 2-[(6-chloro-3-pyridinyl)oxy]-*N*,2-dimethylpropanethioamide (Compound 27)

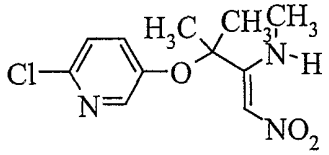
A solution of compound 26 (9.3 g, 40.7 mmol) and Lawesson's reagent (8.3 g, 20.6 mmol) in toluene (90 mL) was heated at reflux for 1 hr. The solvent was then removed *in vacuo* and the residue taken up in minimal methylene chloride. This was loaded onto a silica column (250 g) and eluted with methylene chloride (ca. 1 L) to remove Lawesson's byproduct and majority of yellow color. The eluent was changed to 2:1 hexanes/EtOAc. Fractions containing product were combined and concentrated leaving 8.0 g (80%) of desired product as a pale yellow powder.



Compound 28

Preparation of methyl (1E/Z)-2-[(6-chloro-3-pyridinyl)oxy]-*N*-[(E/Z),2-dimethyl]propanimidothioate (Compound 28)

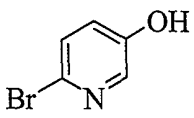
A 60 wt% oil dispersion of sodium hydride (0.10 g, 2.5 mmol) was added in one portion to a stirred solution of compound 27 (512 mg, 2.1 mmol) in dry DMF (14 mL). After 30 min, iodomethane (355 mg, 2.5 mmol) was added and the reaction stirred overnight. The reaction was quenched with water (10 mL) and extracted with ether (3 x 30 mL). Combined organic layers were washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, and reduced *in vacuo* leaving 0.5 g residue which contains product and oil. Purification by chromatography (3:1 hexanes/EtOAc) gave desired product as an oil.



Compound I

Preparation of (1E/Z)-3-[(6-chloro-3-pyridinyl)oxy]-*N*,3-dimethyl-1-nitro-1-buten-2-amine (Compound I)

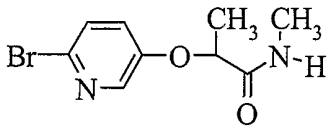
A solution of compound 28 (272 mg) and nitromethane (10 mL) was heated at 150°C in a sealed Parr vessel for 12 hour. The solvent was removed *in vacuo* and the residue subjected to silica gel chromatography using 5 vol% CH_3CN in CH_2Cl_2. Fractions containing product were combined and concentrated leaving 50 mg of desired product as a light brown oil.



Compound 30

Preparation of 6-bromo-3-pyridinol (Compound 30)

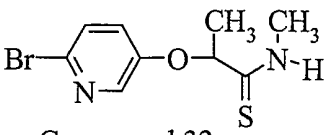
A solution of 23.4 g (99 mmol) of 2,5-dibromopyridine in 1 L of dry diethyl ether was cooled to –70°C under nitrogen and treated dropwise with 45 mL (113 mmol) of a 2.5 M solution of n-butyllithium in hexane such that the temperature remained below –65° C. The resulting slurry was allowed to stir for an additional 20 min, then treated dropwise with 14 mL (125 mmol) of trimethyl borate, again keeping the temperature below -105° C. The slurry, which had turned orange, was stirred an additional 20 min. and then treated with 24 mL (125 mmol) of 32% peracetic acid in acetic acid. The yellow mixture was warmed to 0° C and quenched with sodium bisulfite and water, extracted with diethyl ether and dried over Na_2SO_4. The solvent was removed *in vacuo* to leave 16.5 g of a tan solid. Recrystallization from EtOAc yielded 13.2 g (77%) of desired product as a yellow solid.



Compound 31

Preparation of 2-[(6-bromo-3-pyridinyl)oxy]-*N*-methylpropanamide (Compound 31)

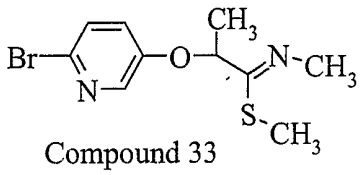
A solution of 4.0 g (23 mmol) of compound 30 in 50 mL of dry DMF was treated with 3.2 g (23 mmol) of potassium carbonate, 3.1g (25 mmol) of compound 4 and 0.38g (2.3 mmol) potassium iodide under nitrogen and heated to 100° C. After 24 hr, the mixture was diluted with 1 M HCl, extracted with methylene chloride and dried over Na_2SO_4. The solvent was removed *in vacuo* affording 4.8 g of a brown solid. Recrystallization from ethyl acetate yielded 2.50 g (42%) of desired product as a gray-brown solid.



Compound 32

Preparation of 2-[(6-bromo-3-pyridinyl)oxy]-*N*-methylpropanethioamide (Compound 32)

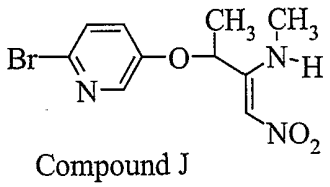
A suspension of 2.3 g (8.9 mmol) of compound 31 in 40 mL of toluene was treated with 1.9 g (4.7 mmol) of Lawesson's Reagent and heated to 110° C for 2.5 hours. The supernatant liquid was then decanted and the solvent removed *in vacuo* to leave a soft brown solid. This residue was then purified on silica gel by first washing away the byproduct with dichloromethane and then eluting the desired product with a 35% EtOAc/petroleum ether mixture. The solvent was again removed *in vacuo* to leave 1.68 g (69%) of desired product as a white solid.



Compound 33

Preparation of methyl (1E/Z)-2-[(6-bromo-3-pyridinyl)oxy]-*N*-[(Z)-methyl]propanimidothioate (Compound 33)

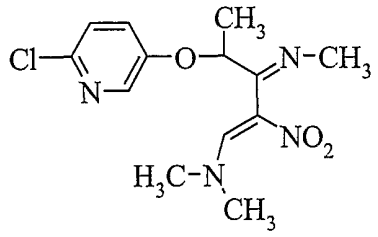
A solution of 1.57 g (5.43 mmol) of compound 32 in 15 mL of dry DMF was treated with 245 mg (6.12 mmol) of 60% NaH in oil dispersion under nitrogen at room temperature. After gas evolution had subsided, the green-blue mixture was treated with 0.50 mL (8.0 mmol) of MeI. The resulting yellow mixture was partitioned between water and diethyl ether and the organic layer dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue partitioned between acetonitrile and petroleum ether. The solvent was again removed *in vacuo* affording 1.00 g (64%) of desired product as a yellow liquid.



Compound J

Preparation of 1(E/Z)-3-[(6-bromo-3-pyridinyl)oxy]-*N*-methyl-1-nitro-1-buten-2-amine (Compound J)

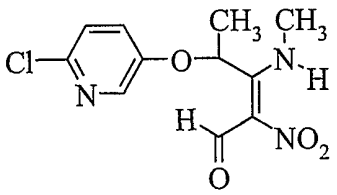
A solution of 950 mg (3.29 mmol) of compound 33 in 10 mL of nitromethane was stirred at 100°C for 3.5 days. The solvent was removed *in vacuo* and the residue washed with small portions of diethyl ether to give 496 mg of a fairly pure brown solid. Further extraction with small portions of acetonitrile afforded 258 mg (26%) of desired product as a light brown solid.



Compound 35

Preparation of 1-dimethylamino-3-methylimino-1-nitro-4-[(2-chloropyridin-5-yl)oxy-1-pentene (Compound 35)

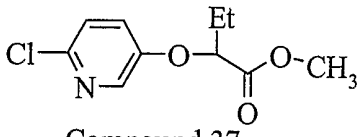
A solution of 315 mg (1.22 mmol) of compound B and 291 mg (2.44 mmol) of dimethylformamide dimethylacetal in 5 mL of dry toluene was heated at 100 °C for 4h and was allowed to cool. The solution was concentrated to a solid which was triturated under ethyl ether. Collection afforded 204 mg of a light brown solid which was found to consist of desired product contaminated with 22% by weight of starting material. The filtrate of this filtered material was concentrated to give 200 mg of a residue which was chromatographed on silica gel (230-400 mesh) using ethyl acetate as the eluant to afford 24 mg (6%) of the nitropentene.



Compound K

Preparation of 3-Methylamino-1-nitro-4-[(2-chloropyridin-5-yl)oxy-2-pentenal (Compound K)

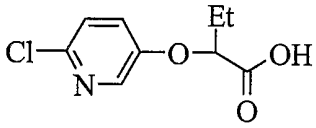
A mixture of 202 mg (0.504 mmol) of the crude compound 35 (78% by weight) in 3 mL of methanol was treated with 0.279 mL (0.559 mmol) of 2.0N sodium hydroxide. The contents were stirred at room temperature for 3h and were then treated with 0.56 mL (0.56 mmol) of 1.0N hydrochloric acid. The mixture was concentrated to remove volatiles and the residue was dissolved in 150 mL of dichloromethane and was dried over magnesium sulfate. Concentration gave 310 mg of an oil which was chromatographed on silica gel using chloroform as eluant and increasing in polarity to 95/5 chloroform/methanol. The pentenal was obtained in 69% yield (100 mg).



Compound 37

Preparation of Methyl 2-[(6-chloro-3-pyridinyl)oxy]-butyrate (Compound 37)

To a slurry of 15.0 g (0.116 mol) of compound 3 and 14.7 mL (0.127 mol) of methyl 2-bromobutyrate in 150 mL of acetonitrile was added 17.6 g (0.127 mol) of powdered potassium carbonate and 1.0 g (6.02 mmol) of potassium iodide. The slurry was heated under nitrogen at reflux for 4 hr and cooled. The solvent was removed *in vacuo* and the residue partitioned between methylene chloride and water. The organic layer was washed with 1N NaOH, saturated brine and dried over Na_2SO_4. Removal of solvent *in vacuo* afforded 24.2 g (91.0%) of desired product as a brown oil.

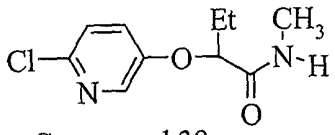


Compound 38

Preparation of 2-[(6-Chloro-3-pyridinyl)oxy]-butyric acid (Compound 38)

To a slurry of 20.8 g (0.316 mol) of 85% KOH pellets in 100 mL of ethanol was added a solution of 24.2 g (0.105 mol) of compound 37 in 150 mL of ethanol. An exotherm took place with the temperature rising to 50°C and the KOH dissolved. To the solution was added 50 mL of water and the solution was stirred at ambient

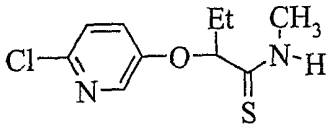
temperature for 3 hr. To this solution was then added 150 mL of water and 43.6 g (0.316 mol) of sodium bisulfate H_2O. A white solid precipitated and was collected by filtration. The aqueous filtrate was extracted with methylene chloride (2X 100 mL). The combined organic layers were dried over Na_2SO_4. Removal of solvent *in vacuo* afforded 20.2 g (89.2%) of cream-colored product.



Compound 39

Preparation of 2-[(6-Chloro-3-pyridinyl)oxy]-N-methylbutyranamide (Compound 39)

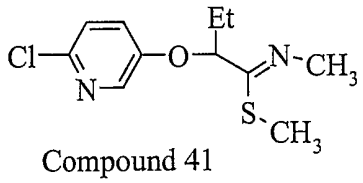
To a slurry of 19.7 g (0.0912 mol) of compound 38 in 150 mL of benzene was added 7.32 mL (0.100 mol) of thionyl chloride and four drops of DMF. The slurry was heated under nitrogen for 1 hr with the starting material dissolving. The solvent was removed *in vacuo* leaving 23.3 g of desired acid chloride which was dissolved in 50 mL of methylene chloride. This solution was then added dropwise to a solution of 137 mL (0.274 mol) of 2 M methylamine in tetrahydrofuran at 0°C. An additional 300 mL of methylene chloride was added and the slurry was allowed to warm to room temperature. The reaction mixture was washed with water, 0.50 M NaOH and dried over Na_2SO_4. The solvent was removed *in vacuo* leaving 19.4 g (93.0%) of desired product. Trituration with hot methyl cyclohexane afforded 18.5 g (88.7%) of off-white crystalline product.



Compound 40

Preparation of 2-[(6-Chloro-3-pyridinyl)oxy]-N-methylbutanethioamide (Compound 40)

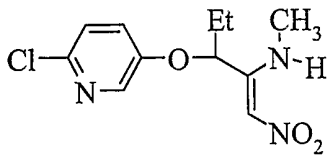
To a slurry of 18.2 g (0.0796 mol) of compound 39 in 100 mL of toluene was added 16.6 g (0.0398 mol) of Lawesson's Reagent. The slurry was heated under nitrogen at reflux for 2 hr and cooled. The solvent was removed *in vacuo* and the residue remaining was dissolved in methylene chloride and loaded on a silica gel column. Initial elution with methylene chloride gave the Lawesson's Reagent byproduct. Elution with 35% EtOAc/hexane afforded 19.0 g (98.0%) of white crystalline product.



Compound 41

Preparation of Methyl (1E/Z)-2-[(6-chloro-3-pyridinyl)oxy]-N-[(E/Z)-methyl]butanimidothioate (Compound 41)

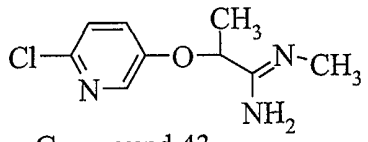
Sodium hydride (1.53 g, 0.0382 mol, 60% oil dispersion) was washed with hexane and transferred to a flask under nitrogen and covered with 15 mL of dry DMF. To the slurry was added dropwise a solution of 8.50 g (0.0347 mol) of compound 40 in 75 mL of DMF at room temperature. Gas evolution occurred and the solution was stirred at room temperature for 15 min. To this mixture was added a solution of 5.42 g (0.0382 mol) of methyl iodide. The solution was stirred at room temperature overnight and poured over 200 mL of ice. The resulting mixture was extracted with diethyl ether. The organic layer was washed with water and dried over Na_2SO_4. Removal of solvent *in vacuo* afforded 7.77 g (86.3%) of desired product as a light yellow oil, which crystallized on standing.



Compound L

Preparation of (1E/Z)-3-[(6-chloro-3-pyridinyl)oxy]-N-methyl-1-nitro-1-penten-2-amine (Compound L)

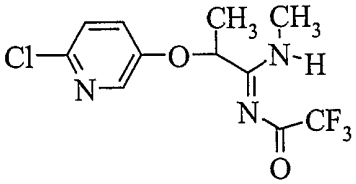
A solution of 3.0 g (0.0116 mol) of compound 41 in 30 mL of nitromethane was heated at 100°C for 3 days under nitrogen. The solvent was removed in vacuo and the residue remaining was purified by column chromatography using initially methylene chloride and then 40% EtOAc/ hexane as eluents. Fractions containing product were combined and solvent removed in vacuo affording 0.488 g (15.5%) of desired product as a crystalline solid after triturating with 40% EtOAc/hexane.



Compound 43

Preparation of 2-[(6-chloro-3-pyridinyl)oxy]-1-amino-1-methylimino-propane (Compound 43)

A solution of 3.0 g (0.0123 mol) of compound 7 and 31 mL (0.0615 mol) of 2 M methylamine in methanol in a sealed tube was heated in an oil bath at 80°C for 8 hr. The solution was cooled and the solvent removed *in vacuo* leaving 2.58 g (98.5%) of desired product. Trituration with hot EtOAc afforded 2.26 (86.3%) of white crystalline product.

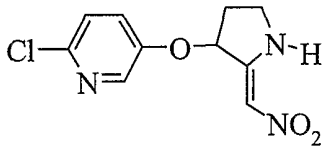


Compound M

Preparation of 1-Trifluoroacetylimino-2-methylamino-3-[(6-chloro-3-pyridinyl)oxy]propane (Compound M)

To a slurry of 0.50 g (2.34 mmol) of compound 43 in 15 mL of methylene chloride was added a catalytic amount of DMAP and 0.35 mL (2.46 mmol) of trifluoroacetic anhydride. The solution was stirred under nitrogen for 48 hr and partitioned between methylene chloride and water. The organic layer was washed with saturated $NaHCO_3$ and dried over Na_2SO_4. Removal of solvent *in vacuo* afforded 0.59 g (81.9%) of

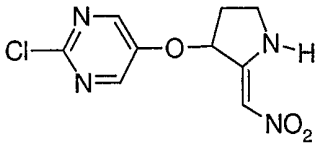
desired product. Recrystallization from ethanol afforded 0.074 g (10.3%) of desired product.



Compound N

Preparation of 2-chloro-5-{[(2Z)-2-(nitromethylene)pyrrolidin-3-yl]oxy}pyridine (Compound N)

To a suspension cooled in ice of 33 mg (0.82 mmol) of 60% sodium hydride/mineral oil dispersion in 2 mL of dry dimethylformamide (DMF) was added in portions 75 mg (0.58 mmol) of the compound 3 over a five minute period. After stirring 15-20 min, 120 mg (0.57 mmol) of the Allylic Bromide I in 2 mL of DMF was added dropwise via syringe. The mixture was stirred overnight at room temperature and was poured onto 20 mL of ice water and was extracted twice with dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated to give 120 mg of a residue which was chromatographed on silica gel using 4/1 dichloromethane/ethyl acetate to give 30 mg (20%) of the nitroethene.

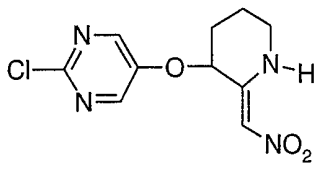


Compound O

Preparation of 2-chloro-5-{[(2Z)-2-(nitromethylene)pyrrolidin-3-yl]oxy}pyrimidine (Compound O)

To a suspension cooled in ice of 104 mg (2.59 mmol) of 60% sodium hydride/mineral oil dispersion in 2 mL of dry dimethylformamide (DMF) was added in portions 338 mg (2.59 mmol) of the 2-chloro-5-hydroxy pyrimidine (see J. Chem. Soc., 7116, 1965) over a five minute period. After stirring 30 min, 536 mg (2.59 mmol) of the Allylic Bromide I was added in portions followed by 1 mL of DMF. The mixture was

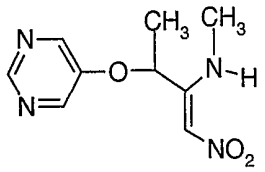
stirred overnight at room temperature and was poured onto 100 mL of dichloromethane and was filtered and concentrated to a residue which was chromatographed on silica gel using 4/1 dichloromethane/ethyl acetate to give 91 mg (14%) of the nitroethene.



Compound P

Preparation of 2-chloro-5-{[(2Z)-2-(nitromethylene)piperidin-3-yl]oxy}pyrimidine (Compound P)

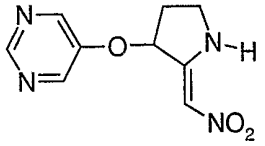
2-chloro-5-hydroxy pyrimidine (70 mg, 0.54 mmol, J. Chem. Soc., 7116, 1965)) was dissolved in 2 mL of dry DMF and was treated with 23 mg (0.57 mmol) of 60% sodium hydride/mineral oil dispersion in one portion. After stirring for 30 min, a solution of 118 mg (0.534 mmol) of 3-bromo-2-nitromethylenopiperidine [Ger. Offen. 2,321,523 (1973)] in 2 mL of DMF was added dropwise via syringe. The contents were stirred at room temperature overnight and were then treated with 35 mL of ice water. The mixture was extracted three times with ether and twice with dichloromethane and the combined extracts were dried ($MgSO_4$). Concentration gave a residue which was chromatographed on silica gel eluting with dichloromethane/ethyl acetate mixtures to give 69 mg (48%) of the nitroethene.



Compound Q

Preparation of (1*Z*)-*N*-methyl-1-nitro-3-(pyrimidin-5-yloxy)but-1-en-2-amine (Compound Q)

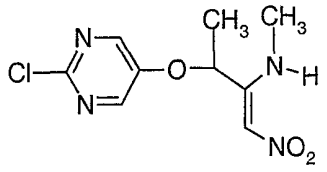
To a suspension of 91.4 mg (2.28 mmol) of 60% sodium hydride/mineral oil dispersion in 1 mL of dry DMF cooled in ice was added dropwise via syringe a solution of 219 mg (2.28 mmol) of 5-hydroxy pyrimidine (Ger. Offen., 3,423,622 (1986) in 2 mL of DMF. After 10-15 min a solution of 478 mg (2.28 mmol) of the Allylic Bromide II in 2 mL of dry tetrahydrofuran and 1 mL of DMF was added dropwise. The contents were stirred at room temperature overnight and were then diluted with 100 mL of dichloromethane and filtered. The filtrate was dried over magnesium sulfate and was concentrated to give 510 mg which was chromatographed on silica gel eluting with 95/5 dichloromethane/methanol to give 115 mg (22%) of the nitroethene.



Compound R

Preparation of 5-{[(2Z)-2-(nitromethylene)pyrrolidin-3-yl]oxy}pyrimidine (Compound R)

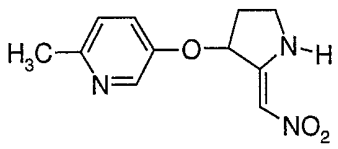
To a suspension of 101mg (2.52 mmol) of 60% sodium hydride/mineral oil dispersion in 1 mL of dry THF cooled in ice was added in portions 183 mg (1.91 mmol) of 5-hydroxy pyrimidine (Ger. Offen., 3,423,622 (1986) followed by 1 mL of THF. After 10-15 min 434 mg (2.10 mmol) of the Allylic Bromide II was added in one portion. The contents were diluted with 1 mL of DMF and were stirred overnight at room temperature. The contents were diluted with ice water and were extracted three times with dichloromethane and were dried ($MgSO_4$). Concentration gave 230 mg which was chromatographed on silica gel eluting with 9/1 dichloromethane/methanol to give 85 mg (20%) of the nitroethene.



Compound S

Preparation of (1Z)-3-[(2-chloropyrimidin-5-yl)oxy]-*N*-methyl-1-nitrobut-1-en-2-amine (Compound S)

To a suspension of 91.3 mg (2.28 mmol) of 60% sodium hydride/mineral oil dispersion in 1 mL of dry DMF cooled in ice was added in portions 298 mg (2.28 mmol) of 2-chloro-5-hydroxy pyrimidine (J. Chem. Soc., 7116, 1965) followed by 1 mL of DMF. After 10-15 min a solution of 478 mg (2.28 mmol) of the Allylic Bromide II was added in one portion. The contents were stirred at room temperature overnight, were treated with ice water, then extracted three times with dichloromethane. The combined extracts were dried over magnesium sulfate and were concentrated to give 540 mg which was chromatographed on silica gel eluting with 97/3 dichloromethane/methanol to give 101 mg (17%) of the nitroethene.

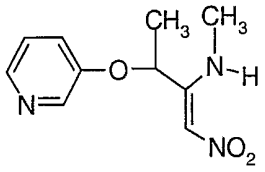


Compound T

Preparation of 2-methyl-5-{[(2Z)-2-(nitromethylene)pyrrolidin-3-yl]oxy}pyridine (Compound T)

To a suspension of 93 mg (2.3 mmol) of 60% sodium hydride/mineral oil dispersion in 1 mL of dry DMF cooled in ice was added in portions 208 mg (1.91 mmol) of 5-hydroxy 2-methyl pyridine. After 10-15 min 400 mg (1.93 mmol) of the Allylic Bromide I was added in one portion. The contents were stirred at room temperature overnight, were treated with ice water, then extracted three times with dichloromethane. The combined extracts were dried over magnesium sulfate and were

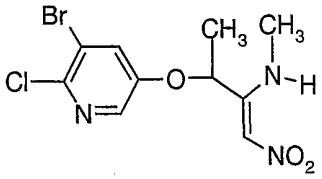
concentrated to give an oil which was chromatographed on silica gel eluting with 95/5 dichloromethane/methanol to give 50 mg (11%) of the nitroethene.



Compound U

Preparation of (1*Z*)-*N*-methyl-1-nitro-3-(pyridin-3-yloxy)but-1-en-2-amine (Compound U)

To a suspension of 99 mg (2.5 mmol) of 60% sodium hydride/mineral oil dispersion in 1 mL of dry DMF cooled in ice was added in portions 235 mg (2.5 mmol) of 3-hydroxypyridine. After 10-15 min 517 mg (2.5 mmol) of the Allylic Bromide II was added in one portion. The contents were stirred at room temperature overnight, were treated with ice water, then extracted three times with dichloromethane. The combined extracts were dried over magnesium sulfate and were concentrated to give 400 mg of an oil which was chromatographed on silica gel eluting with 95/5 dichloromethane/methanol to give 25 mg (4%) of the nitroethene.

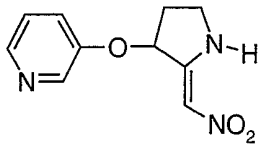


Compound V

Preparation of (1*Z*)-3-[(5-bromo-6-chloropyridin-3-yl)oxy]-*N*-methyl-1-nitrobut-1-en-2-amine (Compound V)

To a suspension of 93 mg (2.3 mmol) of 60% sodium hydride/mineral oil dispersion in 1 mL of dry DMF cooled in ice was added in portions 485 mg (2.32 mmol) of 3-bromo-2-chloro-5-hydroxy pyridine (see Synthesis, 499, 1990). After 10-15 min 486 mg (2.32 mmol) of the Allylic Bromide II was added in one portion. The contents were stirred at room temperature overnight, were treated with ice water, then extracted

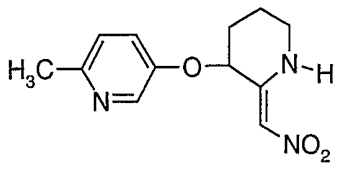
three times with dichloromethane. The combined extracts were dried over magnesium sulfate and were concentrated to give a residue which was chromatographed on silica gel eluting with 95/5 dichloromethane/methanol to give 113 mg (14%) of the nitroethene.



Compound W

Preparation of 3-{[(2Z)-2-(nitromethylene)pyrrolidin-3-yl]oxy}pyridine (Compound W)

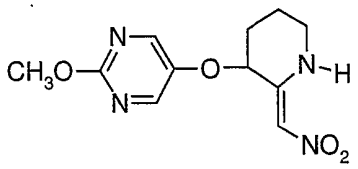
To a suspension of 73 mg (1.8 mmol) of 60% sodium hydride/mineral oil dispersion in 1 mL of dry DMF cooled in ice was added in portions 174 mg (1.83 mmol) of 3-hydroxypyridine. The mixture was allowed to warm to room temperature and after 10-15 min was cooled again in ice and 380 mg (1.83 mmol) of the Allylic Bromide I was added in one portion. The contents were stirred at room temperature overnight, were treated with ice water, then extracted three times with dichloromethane. The combined extracts were dried over magnesium sulfate and were concentrated to give 230 mg of a residue which was chromatographed on silica gel eluting with 95/5 dichloromethane/methanol to give 20 mg (5%) of the nitroethene.



Compound X

Preparation of 2-methyl-5-{[(2Z)-2-(nitromethylene)piperidin-3-yl]oxy}pyridine (Compound X)

Sodium hydride (0.220 g,.0055 mol, 60% oil dispersion) was added to a flask containing 3 ml of anhydrous DMF under a nitrogen atmosphere. The flask was cooled to 0° C. A solution of 5-hydroxy-2-methylpyridine (0.620 g, 0.0057 mol) in 4 ml of DMF was added dropwise with stirring. Gas evolution occurred. The mixture was stirred at 0° C for 30 minutes, and a solution of the 3-bromo-2-nitromethylenepiperidine (1.01g, 0.0046 mol, Ger. Offen. 2,321,523 (1973)) in 4 ml of DMF was then added dropwise with stirring. The flask was allowed to warm to room temperature, and the mixture stirred overnight. The mixture was poured over 40 ml of ice water and extracted with 4 – 75 ml portions of dichloromethane. The extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography using 4% methanol/ dichloromethane as eluents. Fractions containing the desired product were combined, and the solvent removed *in vacuo*. Trituration under ether yielded 0.57 g (50.2%) of the desired product as a goldenrod powder.

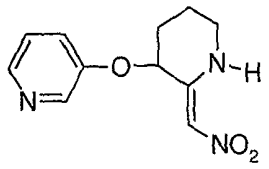


Compound Z

Preparation of 2-methoxy-5-{[(2Z)-2-(nitromethylene)piperidin-3-yl]oxy}pyrimidine (Compound Z)

Sodium hydride (0.158 g,.0040 mol, 60% oil dispersion) was added to a flask containing 3 ml of anhydrous THF under a nitrogen atmosphere. The flask was cooled to 0° C. A solution of 5-hydroxy-2-methoxypyrimidine (0.500 g, 0.0040 mol, Can. J. Chem., **62**, 1176 (1984)) in 20 ml of THF was added to the solution dropwise with stirring. Gas evolution occurred. The mixture was stirred at 0° C for 30 minutes, and a solution of the 3-bromo-2-nitromethylenepiperidine (0.875 g, 0.0040 mol, Ger. Offen. 2,321,523 (1973)) in 4 ml of THF was then added dropwise with stirring. The flask was gradually heated to 65° C in an oil bath and stirred for 4 h. The mixture was then

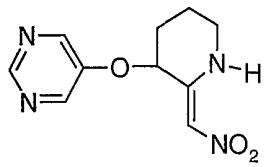
cooled to room temperature and stirred overnight. The mixture was poured over 40 ml of ice water and extracted with 4 – 100 ml portions of dichloromethane. The extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated under ether to afford 0.480 g (45%) of product as a light orange powder.



Compound AA

Preparation of 3-{[(2Z)-2-(nitromethylene)piperidin-3-yl]oxy}pyridine (Compound AA)

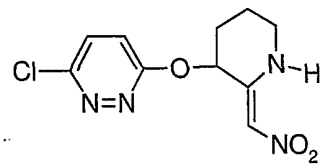
Sodium hydride (0.105 g,.0026 mol, 60% oil dispersion) was added to a flask containing 3 ml of anhydrous DMF under a nitrogen atmosphere. The flask was cooled to 0° C. A solution of 3-hydroxypyridine (0.250 g, 0.0026 mol) in 3 ml of DMF was added to the solution dropwise with stirring. Gas evolution occurred. The mixture was stirred at 0° C for 30 minutes, and a solution of the 3-bromo-2-nitromethylenepiperidine (0.580 g, 0.0026 mol, Ger. Offen. 2,321,523 (1973)) in 4 ml of DMF was then added dropwise with stirring. The flask was allowed to warm to room temperature, and the mixture stirred overnight. The mixture was poured over 40 ml of ice water and extracted with 4 – 75 ml portions of dichloromethane. The extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography using 4% methanol/ dichloromethane as eluents. Fractions containing the desired product were combined, and the solvent removed *in vacuo*. The residue was triturated under ether to afford 0.074 g (12.1%) of the desired product as a rust-colored powder.



Compound AB

Preparation of 5-{[(2Z)-2-(nitromethylene)piperidin-3-yl]oxy}pyrimidine (Compound AB)

Sodium hydride (0.104 g,.0026 mol, 60% oil dispersion) was added to a flask containing 3 ml of anhydrous DMF under a nitrogen atmosphere. The flask was cooled to 0° C. A solution of 5-hydroxypyrimidine (0.250 g, 0.0026 mol, Ger. Offen., 3,423,622 (1986)) in 3 ml of DMF was added to the solution dropwise with stirring. Gas evolution occurred. The mixture was stirred at 0° C for 30 minutes, and a solution of the 3-bromo-2-nitromethylenepiperidine (0.575 g, 0.0026 mol, Ger. Offen. 2,321,523 (1973)) in 4 ml of DMF was then added dropwise with stirring. The flask was allowed to warm to room temperature, and the mixture stirred overnight. The mixture was poured over 40 ml of ice water and extracted with 4 – 75 ml portions of dichloromethane. The extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in boiling 50% ethyl acetate/ methanol solution, and insoluble material was filtered. Concentrated filtrate *in vacuo* to afford 0.240 g (39.1%) of the desired product as a brown powder.

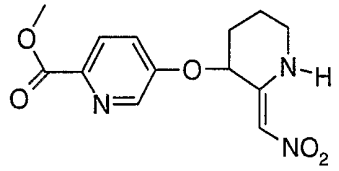


Compound AC

Preparation of 3-chloro-6-{[(2Z)-2-(nitromethylene)piperidin-3-yl]oxy}pyridazine (Compound AC)

A slurry of the 3-bromo-2-nitromethylenepiperidine (0.369 g, 0.0028 mol, Ger. Offen. 2,321,523 (1973)), silver carbonate (1.560 g, 0.0057 mol), and 3-chloro-6-

hydroxypyridazine (0.625 g, 0.0028 mol) in 45 ml of methylcyclohexane was stirred at 100° C for 12 h in the dark. The mixture was filtered through celite. The celite was rinsed with ethyl acetate until the washings were colorless, and the washings were concentrated *in vacuo*. The residue was purified by column chromatography, using 15% ethyl acetate/ hexanes as the eluents. Fractions containing the crude product were combined and concentrated *in vacuo*. The crude product was further purified by preparative TLC, using 50% ethyl acetate/ dichloromethane as the eluents. The silica containing the desired product was collected, and the material removed from the silica using ethyl acetate as the eluent. The material was filtered, dried over $MgSO_4$ and concentrated *in vacuo* to afford 0.040 mg (5.2%) of the desired product.

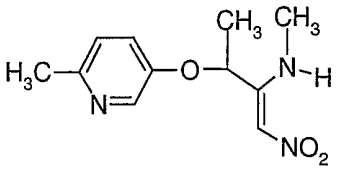


Compound AE

Preparation of methyl 5-{[(2Z)-2-(nitromethylene)piperidin-3-yl]oxy}pyridine-2-carboxylate (Compound AE)

Sodium hydride (0.131 g,.0033 mol, 60% oil dispersion) was added to a flask containing 3.5 ml of anhydrous DMF under a nitrogen atmosphere. The flask was cooled to 0° C. A solution of 5-hydroxy-2-pyridine carboxylic acid methyl ester (0.500 g, 0.0033 mol, Aust. J. Chem., **24**, 385 (1971)) in 3 ml of DMF was added to the solution dropwise with stirring. Gas evolution occurred. The mixture was stirred at 0° C for 30 minutes, and a solution of the 3-bromo-2-nitromethylenepiperidine (0.722 g, 0.0033 mol, Ger. Offen. 2,321,523 (1973)) in 7 ml of DMF was then added dropwise with stirring. The flask was allowed to warm to room temperature, and the mixture stirred overnight. The mixture was poured over 40 ml of ice water and extracted with 3 – 75 ml portions of dichloromethane. The extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Residue was triturated under ether to afford 0.312

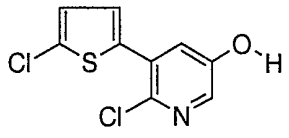
mg of product as a brown powder. The powder was recrystallized from boiling methanol to yield 0.113 mg (11.9%) tan powder.



Compound AF

Preparation of (1*Z*)-*N*-methyl-3-[(6-methylpyridin-3-yl)oxy]-1-nitrobut-1-en-2-amine (Compound AF)

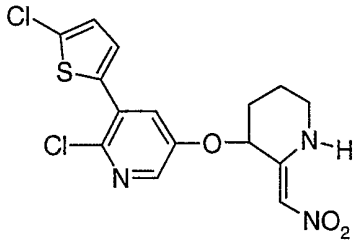
Sodium hydride (0.092 g,.0023 mol, 60% oil dispersion) was added to a flask containing 3 ml of anhydrous DMF under a nitrogen atmosphere. The flask was cooled to 0° C. A solution of 5-hydroxy-2-methylpyridine (0.250 g, 0.0023 mol) in 3 ml of DMF was added to the solution dropwise with stirring. Gas evolution occurred. The mixture was stirred at 0° C for 30 minutes, then the Allylic Bromide II (0.478 g, 0.0023 mol) was added to the reaction flask neat. The flask was allowed to warm to room temperature, and the mixture stirred overnight. The mixture was poured over 40 ml of ice water, and the pH was adjusted to 7 with 1 N HCl. The mixture was extracted with 2 – 75 ml portions of dichloromethane. The extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography using 5% methanol/ dichloromethane as eluents. Fractions containing the desired product were combined, and the solvent removed *in vacuo* to obtain 0.010 g (1.8%) of the desired product as pale yellow crystals.



Compound PAG

Preparation of 6-chloro-5-(5-chlorothien-2-yl)pyridin-3-ol

3-Bromo-2-chloro-5-hydroxypyridine (0.560 g, 0.0027 mol, Synthesis, 499, 1990), 5-chlorothiophene-2-boronic acid (0.581 g, 0.0036 mol), $Pd(PPh_3)_2Cl_2$ (0.094 g, 0.0001 mol), tri(*o*-tolyl)phosphine (0.082 g, 0.0003 mol), and sodium carbonate (0.427 g, 0.0040 mol) were combined in flask containing 26.5 ml DME and 7 ml water. The mixture was heated at reflux for 9 h, then cooled to room temperature. The mixture was diluted with 100 ml of dichloromethane. The solution was washed with 2 – 100 ml portions of brine, followed by 2 – 100 ml portions of water. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography using first 100% dichloromethane, then 5% methanol/ dichloromethane as eluents. Fractions containing the desired product were combined, and the solvent removed *in vacuo* to obtain crude product. The material was further purified using preparative HPLC (40% water/ acetonitrile, flow rate 8 ml/min). The fractions containing product were collected and concentrated *in vacuo* to obtain 0.055 g of the desired product as an off-white solid.

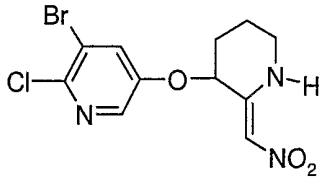


Compound AG

Preparation of 2-chloro-3-(5-chlorothien-2-yl)-5-{[(2Z)-2-(nitromethylene)piperidin-3-yl]oxy}pyridine (Compound AG)

Sodium hydride (0.009 g,.0002 mol, 60% oil dispersion) was added to a flask containing 1 ml of anhydrous DMF under a nitrogen atmosphere. The flask was cooled to 0° C. A solution of the compound PAG (0.055 g, 0.0002 mol) in 0.5 ml of DMF was added to the solution dropwise with stirring. Gas evolution occurred. The mixture was stirred at 0° C for 30 minutes, then a solution of 3-bromo-2-nitromethylenepiperidine (0.123 g, 0.0006 mol, Ger. Offen. 2,321,523 (1973)) on 0.5

ml of DMF was added dropwise with stirring. The flask was allowed to warm to room temperature, and the mixture stirred for 2 days. The mixture was poured over 40 ml of ice water and extracted with 4 – 10 ml portions of dichloromethane. The extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography using first 100% dichloromethane, then 2% methanol/dichloromethane as eluents. Fractions containing product were collected and concentrated *in vacuo*, then further purified by preparative HPLC (20% water/ acetonitrile, flow rate 9 ml/ min). The fraction containing product was collected and concentrated *in vacuo*, then extracted with 3 – 10 ml portions of dichloromethane. The material was dried over $MgSO_4$ and concentrated *in vacuo* to afford 0.023 g (25.9%) of the desired product as a yellow oil.



Compound AH

Preparation of 3-bromo-2-chloro-5-{[(2Z)-2-(nitromethylene)piperidin-3-yl]oxy}pyridine (Compound AH)

Sodium hydride (0.056 g,.0014 mol, 60% oil dispersion) was added to a flask containing 5 ml of anhydrous DMF under a nitrogen atmosphere. The flask was cooled to 0° C. A solution of 3-bromo-2-chloro-5-hydroxypyridine (0.294 g, 0.0014 mol, Synthesis, 499, 1990) in 6 ml of DMF was added to the solution dropwise with stirring. Gas evolution occurred. The mixture was stirred at 0° C for 30 minutes, and a solution of 3-bromo-2-nitromethylenepiperidine (0.780 g, 0.0035 mol, Ger. Offen. 2,321,523 (1973)) in 7 ml of DMF was then added dropwise with stirring. The flask was allowed to warm to room temperature, and the mixture stirred overnight. The mixture was poured over 40 ml of ice water and extracted with 3 – 75 ml portions of dichloromethane. The extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography using first 1% methanol/

dichloromethane, then 10% ethyl acetate/ dichloromethane as eluents. The fractions containing the desired product were combined and concentrated *in vacuo* to afford 0.150 g of the desired product as a colorless oil. The oil was triturated under ether to obtain 0.110 g (22.4%) of product as an off-white solid.

Biological Testing

Cotton Aphid (*Aphis gossypii*) - Squash Spray Method

Yellow crookneck squash, *Cucurbita pepo*, is planted in 3 inch pots and placed in a greenhouse. Plants are watered regularly for 5 to 7 days until they reach the first emergent leaf stage. Plants are then trimmed to a single cotyledon. The squash assay consists of four squash plants per treatment with each plant cotyledon considered a replicate. Four additional plants are used as a control treatment (receiving solvent blank application only). Twenty-four hours prior to application, a leaf section of heavily infested squash plant from the aphid colony is placed onto each cotyledon, allowing a mixed population of *A. gossypii* nymphs and adults to migrate and infest the test plants. The pre-infested squash cotyledons are sprayed on both the upper and lower surfaces using an airbrush sprayer set at 2 psi. Formulation is an aqueous solution containing 5% solvent and 0.025% Tween 20 surfactant to yield a concentration of 50 ppm of the test compound. Plants are sprayed to runoff. Tests are held in ambient laboratory temperatures for three days. At 3 days after application (DAA) the number of live aphids are counted with the aid of a dissecting microscope. The number of live aphids in the treatment is compared to the number of live aphids in the solvent blank-treated controls and percent mortality is calculated.

Two-spotted Spider Mite (*Tetranychus urticae*) - Squash Spray Method

Either mixed-age mobile mites or mite nymphs are transferred to 5 to 7 day old squash plants trimmed to a single cotyledon. Four mite-infested plants per rate are sprayed to runoff with a 50 ppm solution of test compound using a hand syringe equipped with a spray nozzle. Eight solvent blank-treated plants are held as negative controls. Plants

are held at ambient temperature and humidity in the laboratory and then graded at 4 days after application. The number of dead mites in each treatment is compared to the number dead in the controls and percent mortality is calculated.

Sweetpotato Whitefly (*Bemisia tabaci*) - Cotton Spray Method

Technical materials are dissolved in a mixture of 90:10 acetone:ethanol; this is then diluted in water containing 0.05% v/v Tween 20 surfactant to produce a spray eggs on the plants for 2 to 3 days. solution containing 200 ppm of the test compound. Four week-old cotton (*Gossypium hirsutum*) plants are trimmed to the first two true leaves and *B. tabaci* adults are allowed to lay eggs on the leaves over a 48 hour period. Solutions of the test compounds are applied to both sides of each cotton leaf using a hand syringe equipped with spray nozzle. A total of four leaves are treated with test compound, eight leaves are treated with a solvent blank control. After 12 to 14 days, the number of live whitefly nymphs on the treated plants are counted and compared to the number in the control treatment and percent mortality is calculated.

Systemic Insecticide method for brown planthopper (*Nilaparvata lugens*) and green leafhopper (*Nephotettix cincticeps*)

The test compound is dissolved in acetone, making a 10,000 ppm solution. Out of this 10,000 ppm solution, 0.1 ml are added to 99.9 ml of water to produce 100 ml of a 10 ppm test solution. Twenty-five ml of 10 ppm test solution are added to each of four glass cylinder cages. Within each cylinder, roots of several four week-old rice (*Oryza sativa*) seedlings are submerged in the solution of test compound. Five laboratory-reared third instar nymphs of either brown planthopper or green leafhopper are introduced into the glass cylinder cages. The cylinders (four replicates per treatment) are held in a growth chamber at 28° C and 75% relative humidity, with a photoperiod of 14 hours. The number of dead insects is counted 6 days after application and percent mortality is calculated.

Foliar insecticidal method for brown planthopper (*Nilaparvata lugens*)

and green leafhopper (*Nephotettix cincticeps*)

The test compound is dissolved in acetone and further diluted in water to make a 200 ppm solution. Several four week-old rice seedlings are placed in glass cylinder cages, supported by plastic mesh, 4 glass cylinders are used in each treatment. Using a small spraying device, 0.5 ml of test compound solution is sprayed onto the rice seedlings in each glass cylinder. After the plants have dried, 5 laboratory-reared third instar nymphs of either brown planthopper or green leafhopper are introduced into the glass cylinder cages. The cylinders are held in a growth chamber at 28° C and 75% relative humidity, with a photoperiod of 14 hours. The number of dead insects is counted 6 days after application and percent mortality is calculated.

Topical method for insecticidal activity against Colorado potato beetle (*Leptinotarsa decemlineata*)

The test compound is dissolved in acetone to yield a concentration of 5 micrograms per microliter. One microliter of this solution is pipetted on to the dorsal surface of third instar *L. decemlineata* larvae, achieving a dose of 5 micrograms per larva. Six larvae are treated with each solution. The larvae are placed on potato (*Solanum tubersum*) foliage and held at ambient temperature and humidity in the laboratory for 2 days. After 2 days, the number of dead larvae are counted and percent mortality is calculated.

Green Peach Aphid Bioassay

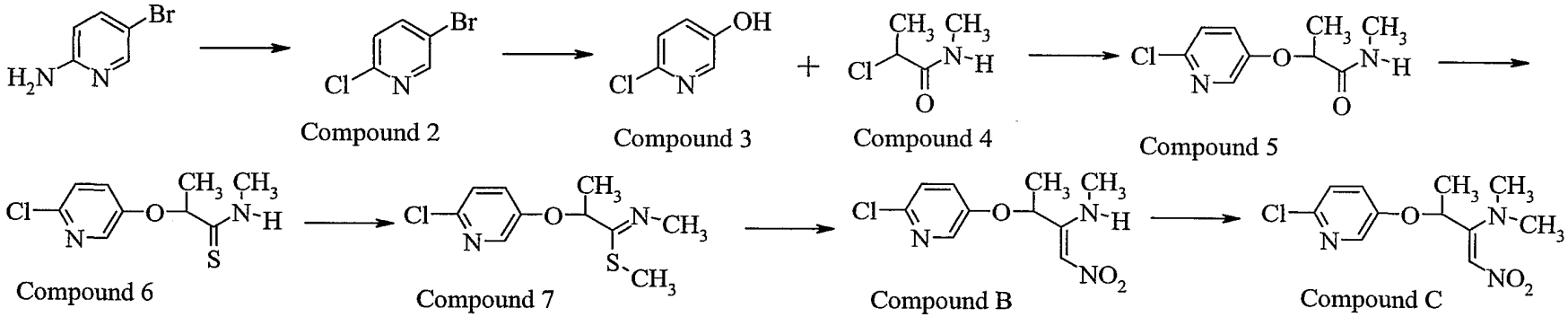
Plant Preparation and Infestation: Head cabbage seedlings, (*Brassica oleracea capitat*), at the 2-4 leaf stage, approximately 12 days old, are infested with all stages of Green peach aphid (*Myzus persicae*) by shaking heavily infested, colony, leaf sections above the cabbage seedlings 4 days prior to the application of the test material. The aphids moved to the succulent plant material and settled to feed predominantly on the underside of the leaves. The plants are examined for good infestation prior to application of experimental compounds.

Spray Solution Preparation: Technical material of each experimental compound is dissolved at 1 mg/ml in 90:10 acetone:alcohol, then diluted in tap water containing 0.05% Tween 20. Additional serial dilutions are made to yield subsequent solutions of 50, 12.5, 3.13, 0.78, 0.195 and 0.049 ppm.

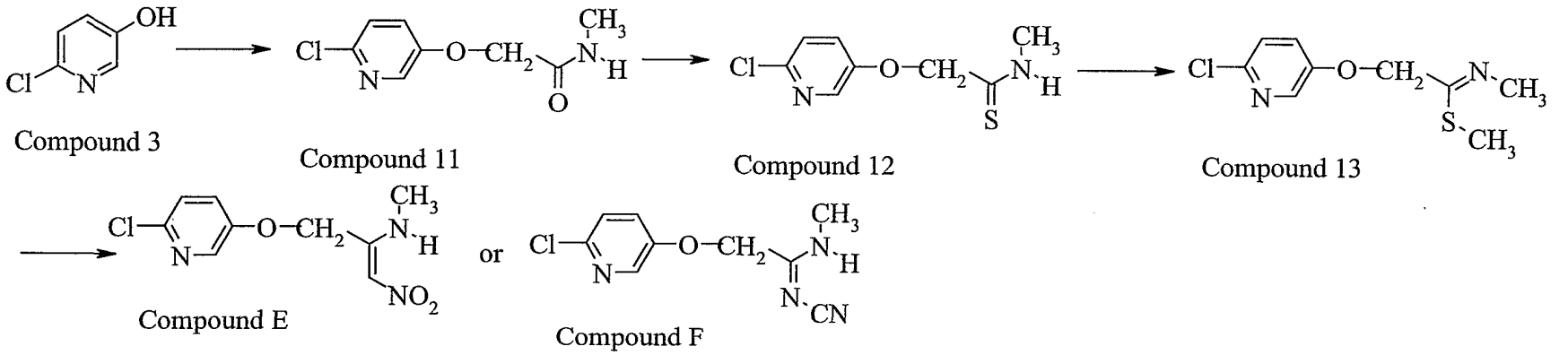
Application is made with a hand-held air-brush sprayer. The cabbage seedlings are sprayed on both the upper and lower surfaces of the cotyledon until runoff and then all plants within the treatment are sprayed evenly until the remaining spray solution is completely used. Each rate has 4 reps (plants). Controls consist of 8 plants treated with diluent prepared with a blank stock solution only.

Tests are held in a holding room for 72 hours at approximately 74°F and 40° relative humidity, 24 hour photoperiod prior to grading. Tests are graded 3 days after application by assessing the live aphid count (all non-winged stages) on the underside of each leaf using a dissecting binocular microscope. Live count results are used to calculate a percent control based on comparison to the aphid population on the solvent blank controls.

Route to Compounds B, C and D



Route to Compounds E and F



The routes used to prepare Compounds G, H, I, and J utilize these chemical routes.

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TABLE ONE – PERCENT MORTALITY RANGE LISTED BELOW COMPOUND											
Common name Scientific name	Method Time of Rating Rate	F	E	D	B	G	H	C	A	J	K
COTTON APHID *APHIS GOSSYPII*	Squash spray 3 DAA 50 ppm	<30	>80	>80	>80	>80	>80	>80	>80	>80	>80
SWEETPOTATO WHITEFLY *BEMISIA TABACI*	Cotton spray 13 DAA 200 ppm	30-50	30-50	<30	>80	50-80	50-80	<30	<30	50-80	---
GREEN RICE LEAFHOPPER *NEPHOTETTIX CINCTICEPS*	Rice foliar spray 6 DAA 200 ppm	---	50-80	<30	30-50	>80	>80	<30	>80	>80	---
	Rice systemic 6 DAA 10 ppm	---	<30	50-80	30-50	50-89	>80	50-80	50-80	50-80	---
BROWN PLANTHOPPER *NILAPARVATA LUGENS*	Rice foliar spray 6 DAA 200 ppm	---	<30	50-80	50-80	<30	50-80	<30	>80	50-80	---
	Rice systemic 6 DAA 10 ppm	---	<30	<30	30-50	50-80	50-80	30-50	50-80	50-80	---
COLORADO POTATO BEETLE *LEPTINOTARSA DECEMLINEATA*	Topical application, 2 DAA 5 micrograms per larva	<30	>80	<30	>80	>80	>80	>80	>80	>80	
TWOSPOTTED SPIDER MITE *TETRANYCHUS URTICAE*	Squash spray 4 DAA 50 ppm	<30	<30	30-50	50-80	30-50	<30	<30	<30	30-50	30-50

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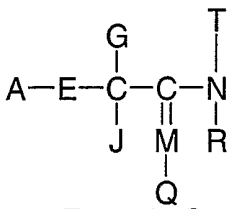
TABLE TWO - **PERCENT MORTALITY RANGE**							
Compound	Cotton aphid	Green peach aphid (Myzus persicae) at 50 ppm	Sweetpotato whitefly	Brown planthopper (foliar spray)	Brown planthopper (systemic)	Green leafhopper (foliar spray)	Green leafhopper (systemic)
M	<30		50-80				
X	>80	>80	<30	30-50	30-50	50-80	50-80
N	>80	<30	>80				
Z	30-50		<30	<30	30-50	<30	30-50
L	>80	<30	>80	<30	>80	30-50	50-80
P	>80		>80	>80	>80	30-50	>80
AA	>80		<30	50-80	<30	>80	>80
Q	>80	<30	>80	50-80	>80	50-80	50-80
AB	>80		<30	<30	<30	50-80	>80
AC	>80		<30			50-80	50-80
AE	<30		<30	<30	30-50	<30	50-80
AF	>80					<30	<30
AG	<30			<30	<30		
O	>80		>80	>80	>80	<30	30-50
R	>80	<30	<30			>80	>80
S	>80	>80	>80	50-80	50-80		
T	>80	<30	<30			50-80	50-80
AH	>80	<30	<30	<30	50-80		
U	>80					<30	<30
V	>80		50-80				
W	>80						

WE CLAIMED:

1. A compound according to Formula One



Formula One

wherein

A represents a five or six membered heterocyclic ring containing at least one heteroatom selected from the group consisting of an oxygen, sulfur, or nitrogen, where said heterocyclic ring may be substituted by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, iodine, C_{1-10} alkyl, halo C_{1-10} alkyl, nitro, cyano, C_{1-10} alkoxy, C_{1-10} alkylthio, C_{1-10} alkylsulfinyl, C_{1-10} alkylsulfonyl, C_{1-10} alkenyl, halo C_{1-10} alkoxy, halo C_{1-10} alkylthio, halo C_{1-10} alkenyl, acylamino, haloacylamino, C_{1-10} alkoxycarbonyl, C_{1-10} alkynyl, amino, C_{1-10} alkylamino, C_{1-10} dialkylamino, C_{3-12} cycloalkyl, C_{1-10} alkoxyalkyl, acyl, formyl, C_{6-12} aryl, mono-or poly substituted C_{6-12} aryl, heteroaryl, and mono-or poly substituted heteroaryl (where said heteroaryl has 5-12 atoms in the ring, and where 1-3 of said atoms in said ring are selected from the group consisting of nitrogen, oxygen, and sulfur, and where the rest of said atoms in said ring are carbon atoms) and where the substituents are selected from the group consisting of halo, C_{1-10} alkyl, halo C_{1-10} alkyl, C_{1-10} alkoxy, nitro, cyano, and C_{6-12} aryloxy);

E is selected from the group consisting of O, SO_n where n is 0-2, NH, and NX, where X is selected from the group consisting of C_{1-10} alkyl or halo C_{1-10} alkyl.

J and R are independently selected from the group consisting of H, C_{1-10} alkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, halo C_{1-10} alkyl, and C_{1-10} alkoxyalkyl;

M is selected from the group consisting of N and CZ, where Z is selected from the group consisting of H and C(=O)H;

Q is selected from the group consisting of NO_2, CN, and $C(=O)CF_3$;

G and T are independently selected from the group consisting of H, C_{1-10} alkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, halo C_{1-10} alkyl, and C_{1-10} alkoxyalkyl; optionally, G and T can also be joined together by a single bond, or through a connecting bridge, where such connecting bridge is selected from the group consisting of CH_2, $CHCH_3$, $C(CH_3)_2$, CH(halo C_{1-10} alkyl), C(halo C_{1-10} alkyl)$_2$, CHF, CF_2, O, SO_n where n is 0-2, NH, and NX where X is selected from the group consisting of C_{1-10} alkyl or halo C_{1-10} alkyl.

2. A compound according to claim 1 wherein said heterocyclic ring is a six membered heterocyclic ring

3 A compound according to claim 2 wherein said heterocyclic ring contains one or two nitrogen atoms as the heteroatoms.

4. A compound according to claim 3 wherein said heterocyclic ring is mono-substituted with either methyl, ethyl, fluoro, chloro, or bromo.

5. A compound according to claim 4 wherein said substituent is ortho to a heteroatom.

6. A compound according to claim 1 wherein E is O.

7. A compound according to claim 1 wherein J and R are H.

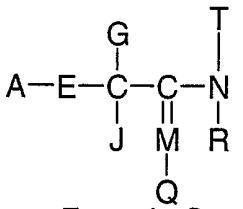
8. A compound according to claim 1 wherein M is CH.

9. A compound according to claim 1 wherein Q is NO_2.

10. A compound according to claim 1 wherein G and T are methyl or ethyl.

11. A compound according to claim 1 wherein G and T are connected with a connecting bridge that is a single bond or a CH_2.

12. A process comprising inhibiting an insect or mite by applying a compound according to Formula One to a locus of an insect or mite



Formula One

wherein

A represents a five or six membered heterocyclic ring containing at least one heteroatom selected from the group consisting of an oxygen, sulfur, or nitrogen, where said heterocyclic ring may be substituted by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, iodine, C_{1-10} alkyl, halo C_{1-10} alkyl, nitro, cyano, C_{1-10} alkoxy, C_{1-10} alkylthio, C_{1-10} alkylsulfinyl, C_{1-10} alkylsulfonyl, C_{1-10} alkenyl, halo C_{1-10} alkoxy, halo C_{1-10} alkylthio, halo C_{1-10} alkenyl, acylamino, haloacylamino, C_{1-10} alkoxycarbonyl, C_{1-10} alkynyl, amino, C_{1-10} alkylamino, C_{1-10} dialkylamino, C_{3-12} cycloalkyl, C_{1-10} alkoxyalkyl, acyl, formyl, C_{6-12} aryl, mono-or poly

substituted C_{6-12} aryl, heteroaryl, and mono-or poly substituted heteroaryl (where said heteroaryl has 5-12 atoms in the ring, and where 1-3 of said atoms in said ring are selected from the group consisting of nitrogen, oxygen, and sulfur, and where the rest of said atoms in said ring are carbon atoms) and where the substituents are selected from the group consisting of halo, C_{1-10} alkyl, halo C_{1-10} alkyl, C_{1-10} alkoxy, nitro, cyano, and C_{6-12} aryloxy);

E is selected from the group consisting of O, SO_n where n is 0-2, NH, and NX, where X is selected from the group consisting of C_{1-10} alkyl or halo C_{1-10} alkyl.

J and R are independently selected from the group consisting of H, C_{1-10} alkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, halo C_{1-10} alkyl, and C_{1-10} alkoxyalkyl;

M is selected from the group consisting of N and CZ, where Z is selected from the group consisting of H and C(=O)H;

Q is selected from the group consisting of NO_2, CN, and $C(=O)CF_3$;

G and T are independently selected from the group consisting of H, C_{1-10} alkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, halo C_{1-10} alkyl, and C_{1-10} alkoxyalkyl; optionally, G and T can also be joined together by a single bond, or through a connecting bridge, where such connecting bridge is selected from the group consisting of CH_2, $CHCH_3$, $C(CH_3)_2$, CH(halo C_{1-10} alkyl), C(halo C_{1-10} alkyl)$_2$, CHF, CF_2, O, SO_n where n is 0-2, NH, and NX where X is selected from the group consisting of C_{1-10} alkyl or halo C_{1-10} alkyl.

13. A process according to claim 12 wherein said heterocyclic ring is a six membered heterocyclic ring

14 A process according to claim 13 wherein said heterocyclic ring contains one or two nitrogen atoms as the heteroatoms.

15. A process according to claim 14 wherein said heterocyclic ring is mono-substituted with either methyl, ethyl, fluoro, chloro, or bromo.

16. A process according to claim 15 wherein said substituent is ortho to a heteroatom.

17. A process according to claim 12 wherein E is O.

18. A process according to claim 12 wherein J and R are H.

19. A process according to claim 12 wherein M is CH.

20. A process according to claim 12 wherein Q is NO_2.

21. A process according to claim 12 wherein G and T are methyl or ethyl.

22. A process according to claim 12 wherein G and T are connected with a connecting bridge that is a single bond or a CH_2.

23. A composition comprising a compound according to claim 1 and at least one other compound selected from the group consisting of insecticides, acaricides, nematocides, and adjuvant surfactants.