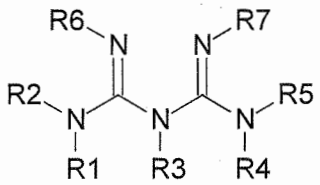
SUMMARY OF THE ~~INVENTION~~DISCLOSURE

[0007] Provided herein are compositions having at least one biguanide or related heterocyclic compound, including metformin, and methods of treatment using the compositions.

[0008] In some embodiments, the compositions herein are adapated to minimize the systemic bioavailability of the compound, e.g., reduce average systemic bioavailability of the biguanide compared to a composition having an equivalent amount of the compound formulated for immediate release. In some embodiments, the compositions described herein can be adapted for release to the upper or small intestine, to the lower or large intestine, or both. Administration of the compositions into the intestine is via any known method including oral. In some embodiments, the compositions described herein comprise a biguanide or related heterocyclic compound adapted to release a therapeutically effective amount of the biguanide or related heterocyclic compound beyond the stomach.

[0009] In certain embodiments, the biguanide or related heterocyclic compound is selected from a compound of structural Formula I,



(I)

wherein:

R1, R2, R3, R4, R5, R6, and R7 are independently selected from:

H, OH,

O-Rx, wherein Rx is alkyl, cycloalkyl, alkylcycloalkyl, acyl, ester, thioester;

optionally substituted alkyl; cycloalkyl; alkylcycloalkyl; heterocycloalkyl; alkylheterocycloalkyl; optionally substituted alkenyl; optionally substituted alkynyl;

optionally substituted aryl; optionally substituted alkylary; optionally substituted heteroaryl; optionally substituted alkylheteroaryl; and

or R6 and R7 may join to form a bond, together forming a ring including the nitrogen atoms to which they are attached;

[0071] In some embodiments, the combined amount of metformin hydrochloride is about 250 mg.

[0072] In some embodiments, the dosage form is a bi-layer tablet. In other embodiments, the dosage form is a capsule with the two components as encapsulated mini-tablets.

[0073] Also provided herein are pharmaceutical dosage forms comprising (a) a pH 6.5 enterically coated immediate release component comprising metformin hydrochloride and a pharmaceutically acceptable excipient; and (b) a pH 6.5 enterically coated extended release component comprising metformin hydrochloride and a pharmaceutically acceptable excipient; and wherein the metformin hydrochloride has reduced average systemic bioavailability.

[0074] In some embodiments, the average systemic bioavailability is less than the average systemic bioavailability of an immediate release metformin formulation having an equivalent amount of metformin. In other embodiments, the average systemic bioavailability is less than 15%.

[0075] In some embodiments, the combined amount of metformin hydrochloride is less than 400 mg.

In another aspect, there is provided use of a biguanide compound in the manufacture of a medicament for lowering blood glucose levels in a patient in need thereof, wherein the biguanide compound is in a delayed-release formulation adapted to minimize the circulating plasma concentration of the biguanide compound and/or reduce the average systemic bioavailability of the biguanide compound in the patient.

In another aspect, there is provided use of a biguanide compound in the manufacture of a medicament for treating a disorder of glucose metabolism in a patient in need thereof, wherein the biguanide compound is in a delayed-release formulation adapted to minimize the circulating plasma concentration of the biguanide compound and/or reduce the average systemic bioavailability of the biguanide compound in the patient.

INCORPORATION BY REFERENCE

[0076] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE FIGURES

[0077] FIG. 1 shows the design of the study described in Example 5.

[0078] FIG. 2 shows the events during the treatment period of the study described in Example 5.

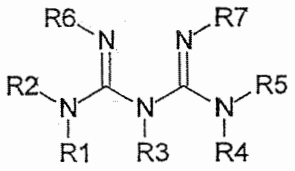
[0079] FIG. 3 shows the plasma concentration of Metformin (●) and Re-Metformin (■) (x-axis; ng/mL) as a function of time (y-axis; min) after ingestion at t = -240 and after a meal at t = 0 min.

[0080] FIG. 4A shows the plasma concentration of PYY (x-axis;pg/mL) as a function of time (y-axis; min) in subjects at baseline (□,○) or after ingestion of either Metformin (●) or Re-

CLAIMS

WHAT IS CLAIMED IS:

1. A composition comprising a biguanide or related heterocyclic compound of structural Formula I,



(I)

wherein:

R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are independently selected from:

H, OH,

O-Rx, wherein Rx is alkyl, cycloalkyl, alkylcycloalkyl, acyl, ester, thioester;

optionally substituted alkyl; cycloalkyl; alkylcycloalkyl; heterocycloalkyl; alkylheterocycloalkyl; optionally substituted alkenyl; optionally substituted alkynyl;

optionally substituted aryl; optionally substituted alkylary; optionally substituted heteroaryl; optionally substituted alkylheteroaryl; and

or R_6 and R_7 may join to form a bond, together forming a ring including the nitrogen atoms to which they are attached;

or R_1 and R_2 may together form a 3 to 8 membered heterocyclic ring, including the nitrogen atoms to which they are attached;

or R_4 and R_5 may together form a ring selected from the group aziridine, pyrrolyl, imidazolyl, pyrazolyl, indolyl, indolinyl, pyrrolidinyl, piperazinyl and piperidyl, including the nitrogen atoms to which they are attached.

wherein the composition is adapted to reduce the average bioavailability of the compound, release a therapeutically effective amount of the compound to one or more regions of the intestine of a subject, or a combination thereof.

2. A composition according to claim 1, wherein

R_2, R_3, R_4, R_5, R_6 and R_7 are independently selected from H, methyl, ethyl, propyl or isopropyl; and

R_1 is selected from:

H,

C_1 to C_{12} straight chain or branched chain alkyl optionally hetero substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl,

C_1 to C_{12} straight chain or branched chain alkenyl optionally hetero substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl,

C_1 to C_{12} straight chain or branched chain alkynyl optionally hetero substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl,

C_3 to C_7 cycloalkyl, C_2 to C_6 heterocycloalkyl, where the heterocycle comprises one or two hetero atoms selected from O, S, or N,

C_4 to C_{12} alkylcycloalkyl,

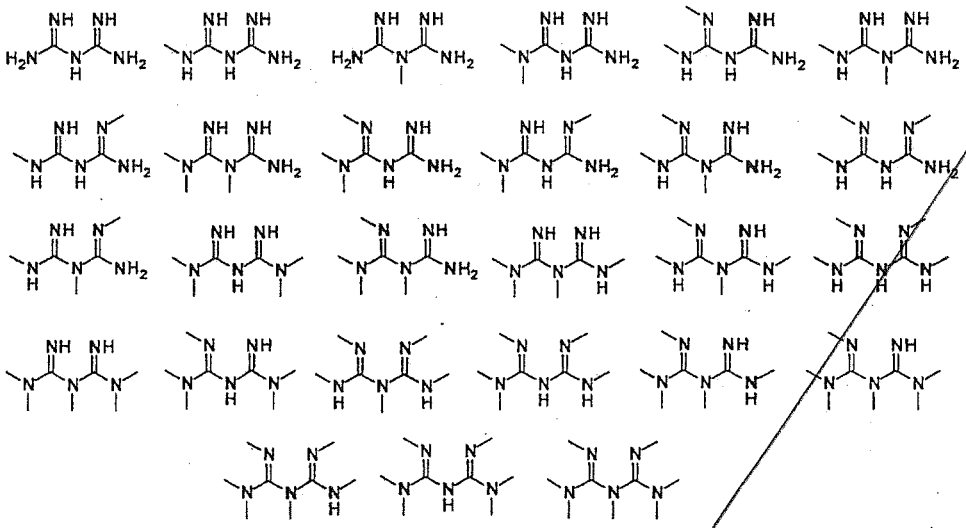
C_3 to C_{11} alkylheterocycloalkyl, where the heterocycle comprises one or two hetero atoms selected from O, S, or N and wherein N is present in the heterocyclic ring, the nitrogen atom may be in the form of an amide, carbamate or urea,

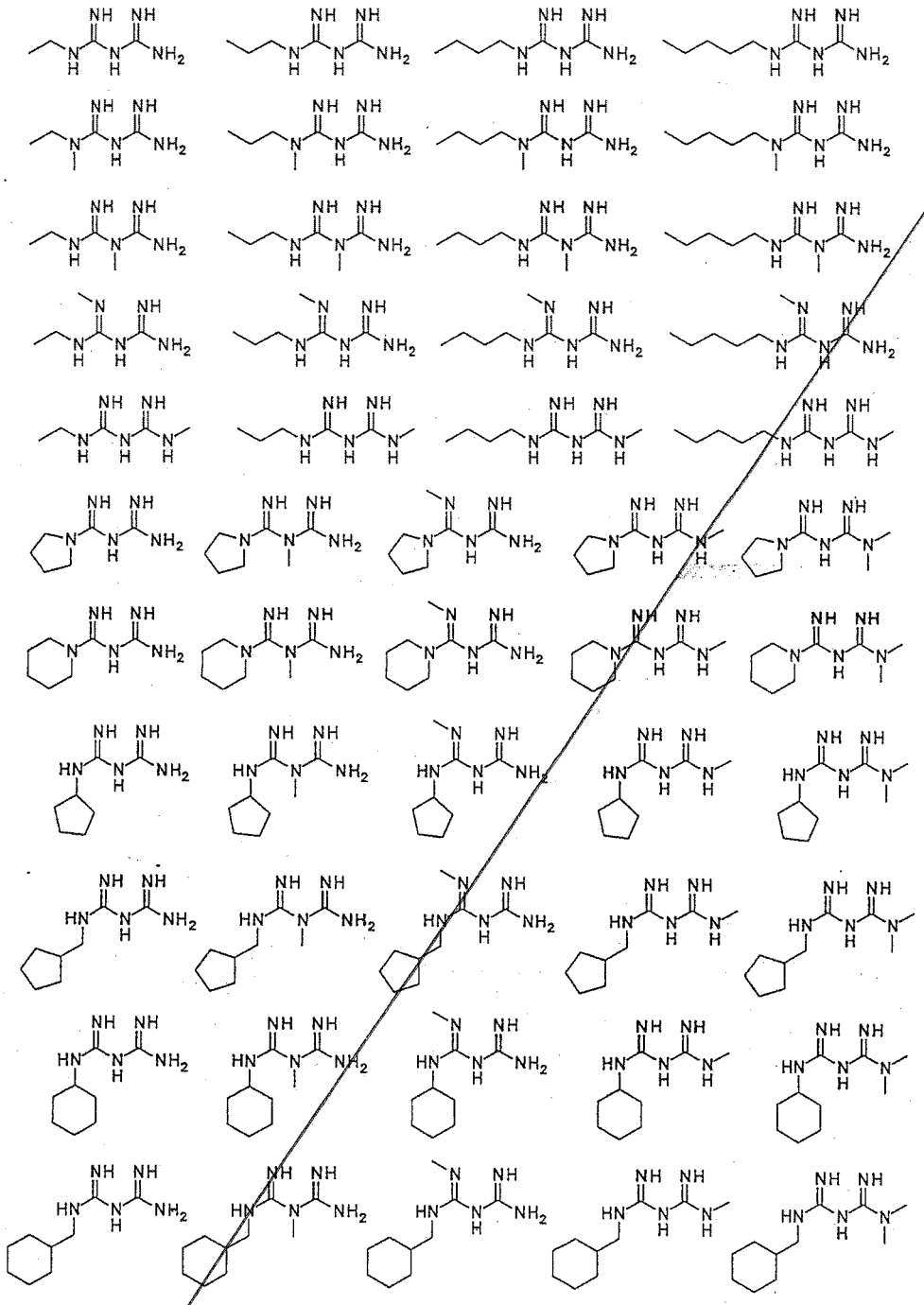
phenyl, substituted phenyl, naphthyl, substituted naphthyl,

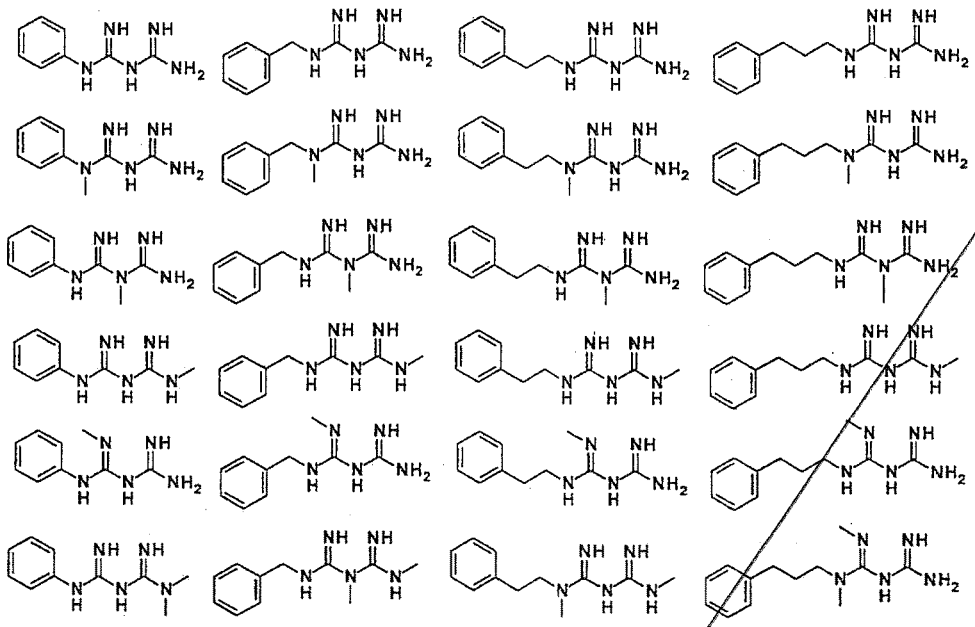
alkylphenyl, alkylsubstituted phenyl, alkylnaphthyl, alkylsubstituted naphthyl,

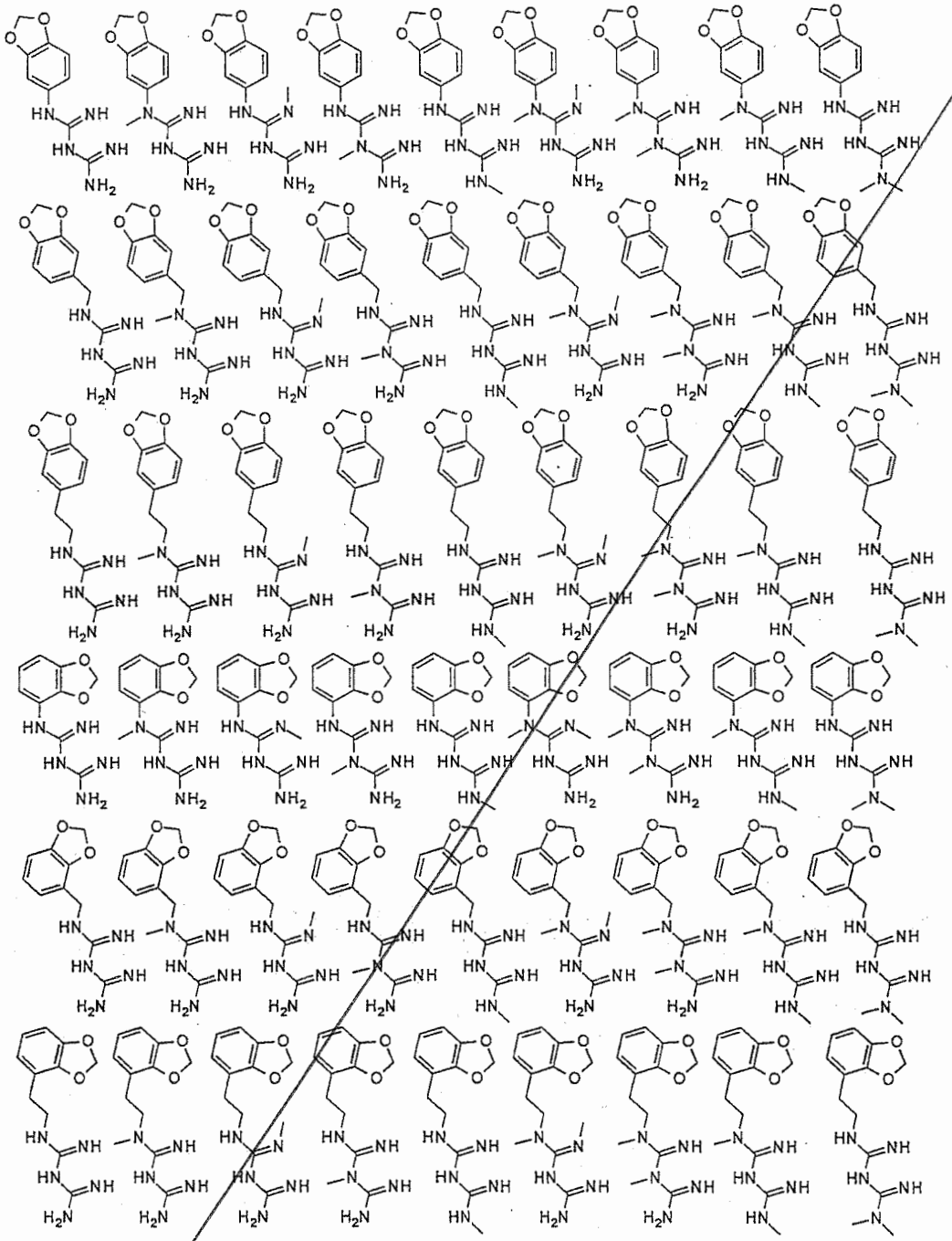
pyridyl, furanyl, thiophenyl, pyrrollyl, oxazolyl, isoxazolyl, thiazolyl, diazolyl, pyrazolyl, triazolyl all of which are optionally substituted.

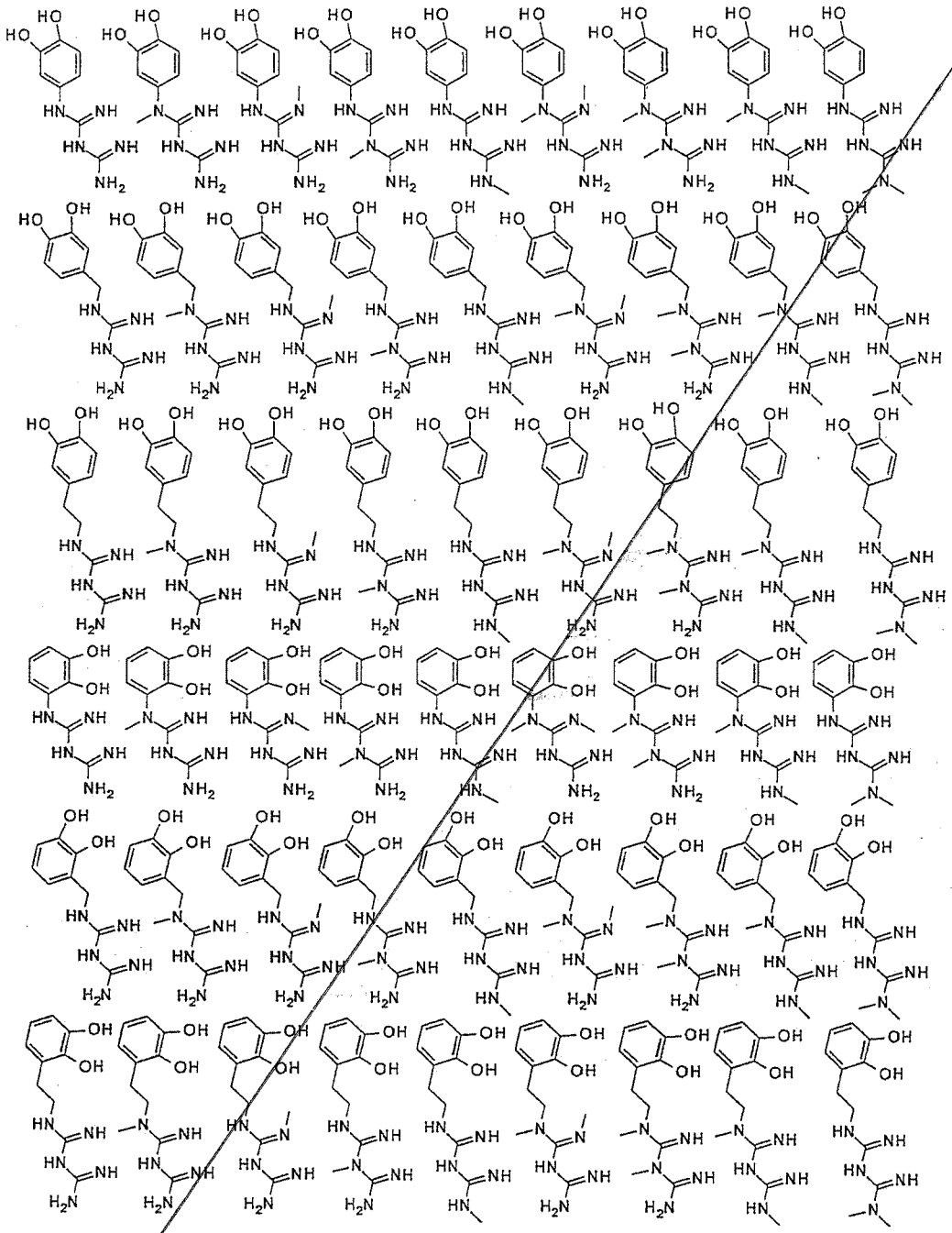
3. A composition according to claim 1, wherein the compound of Formula I is selected from the following structures:

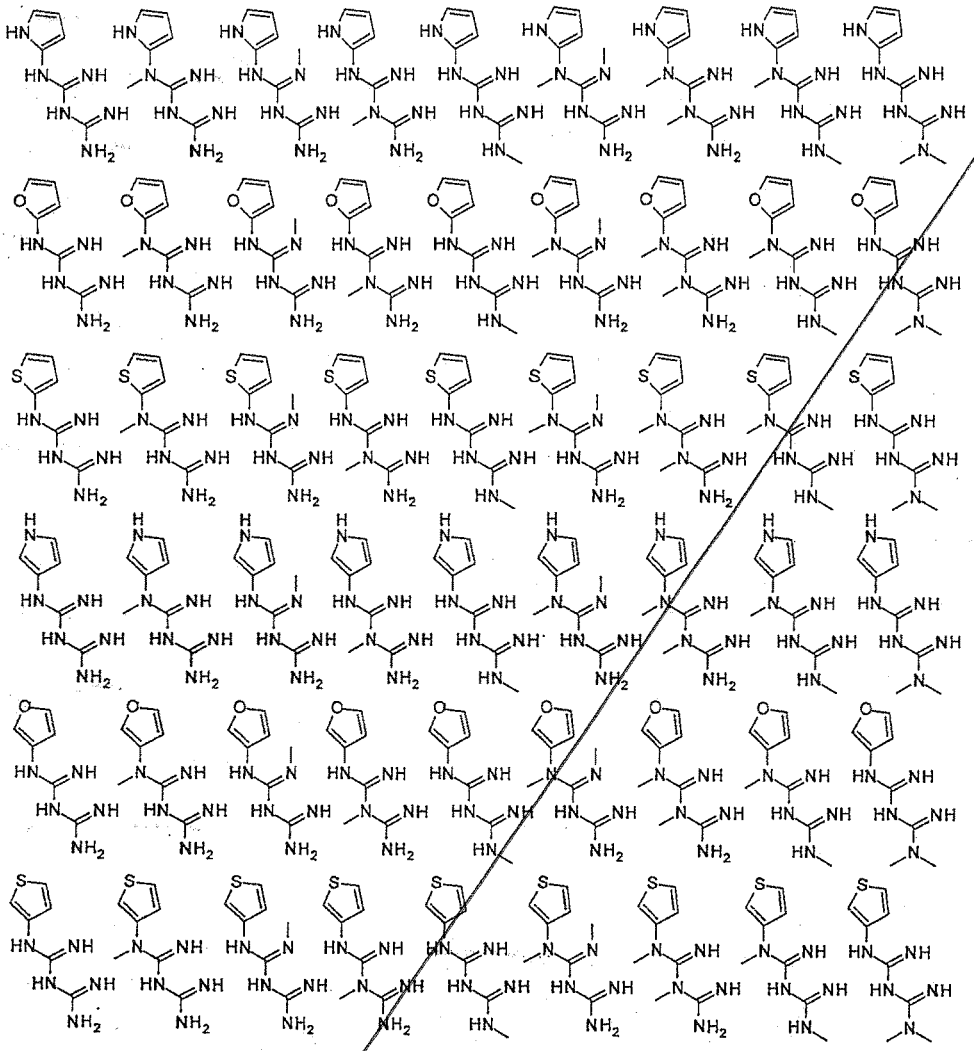


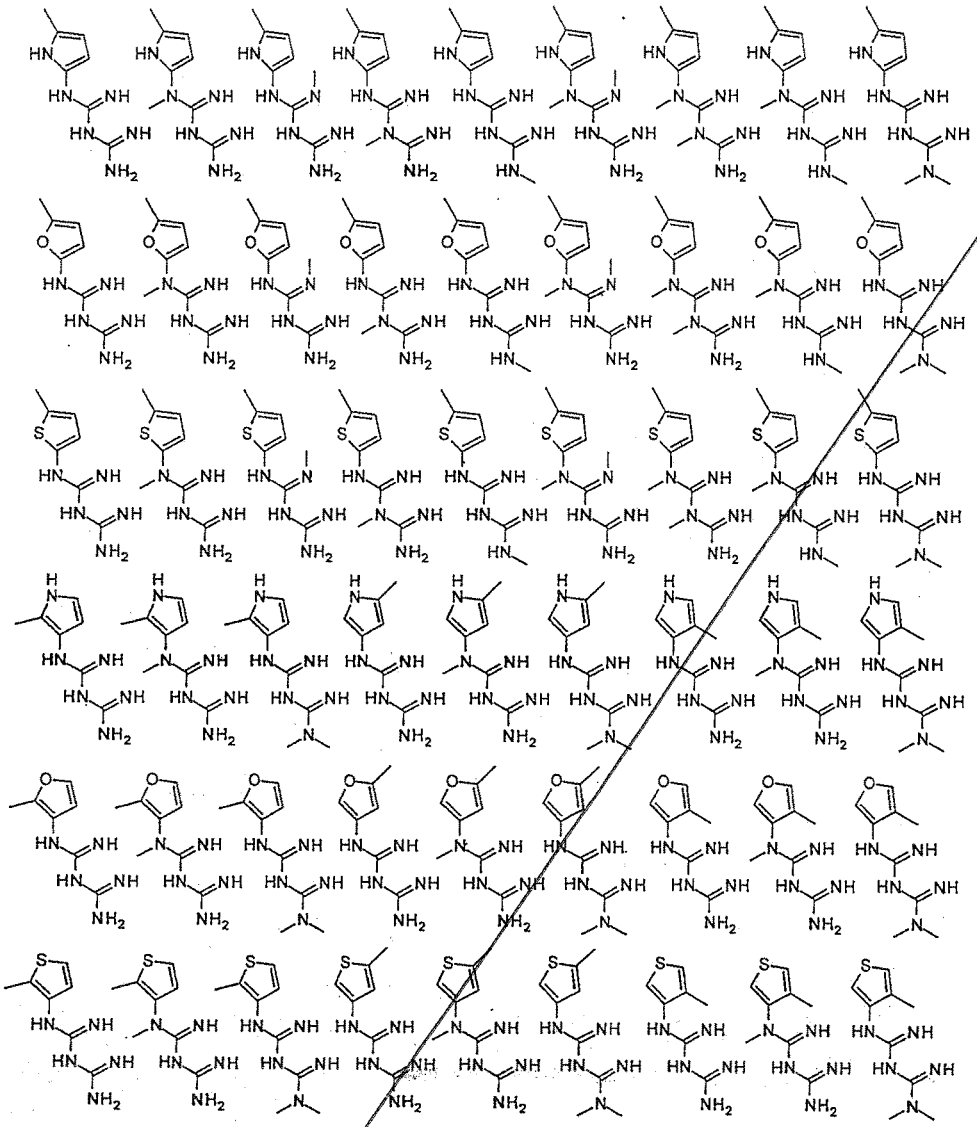


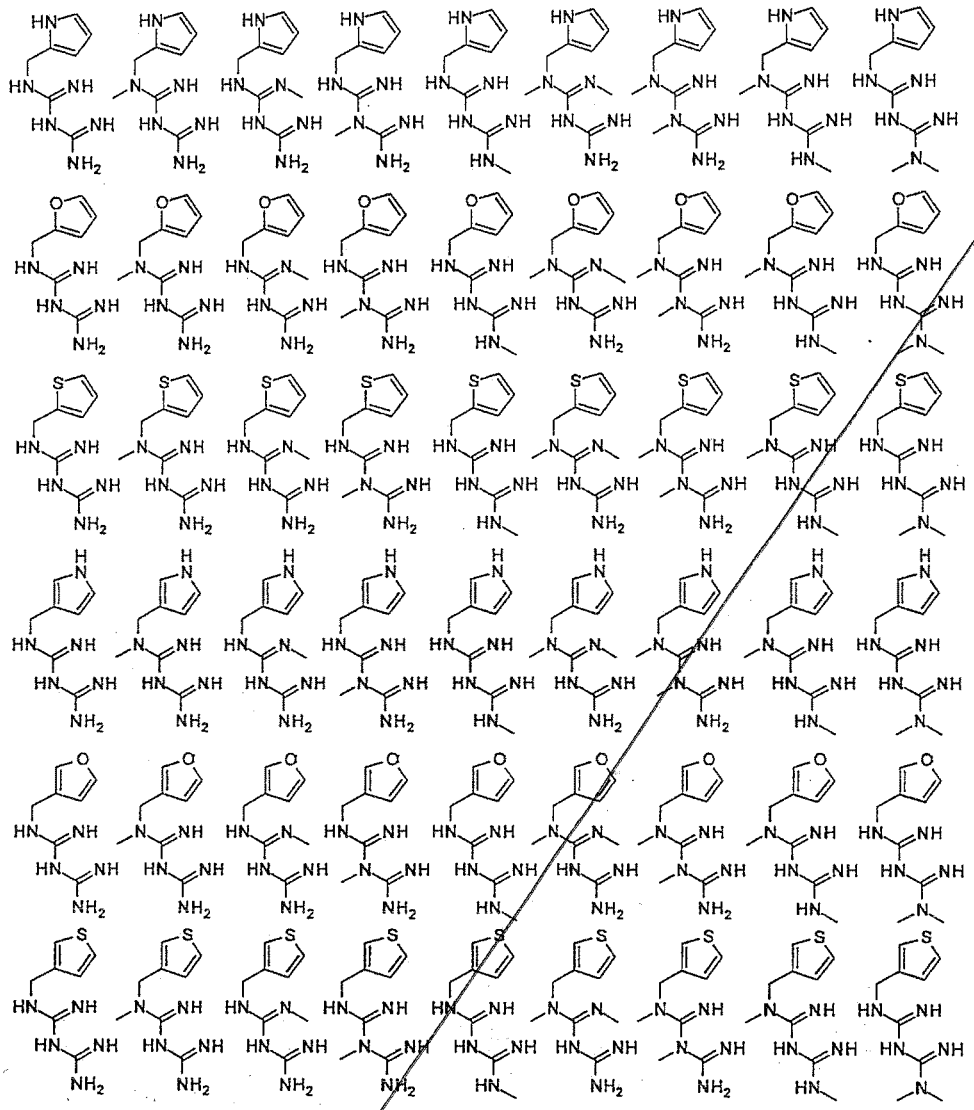


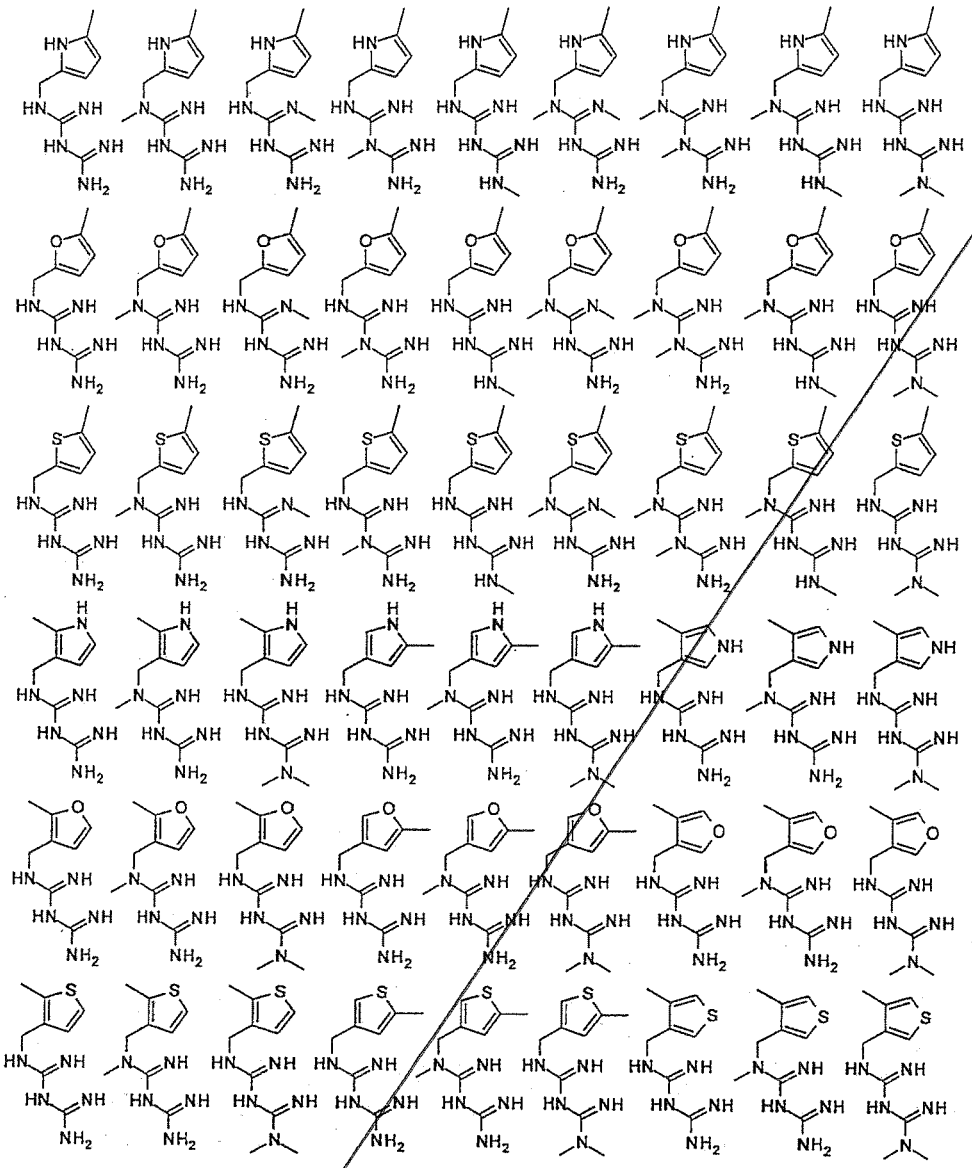


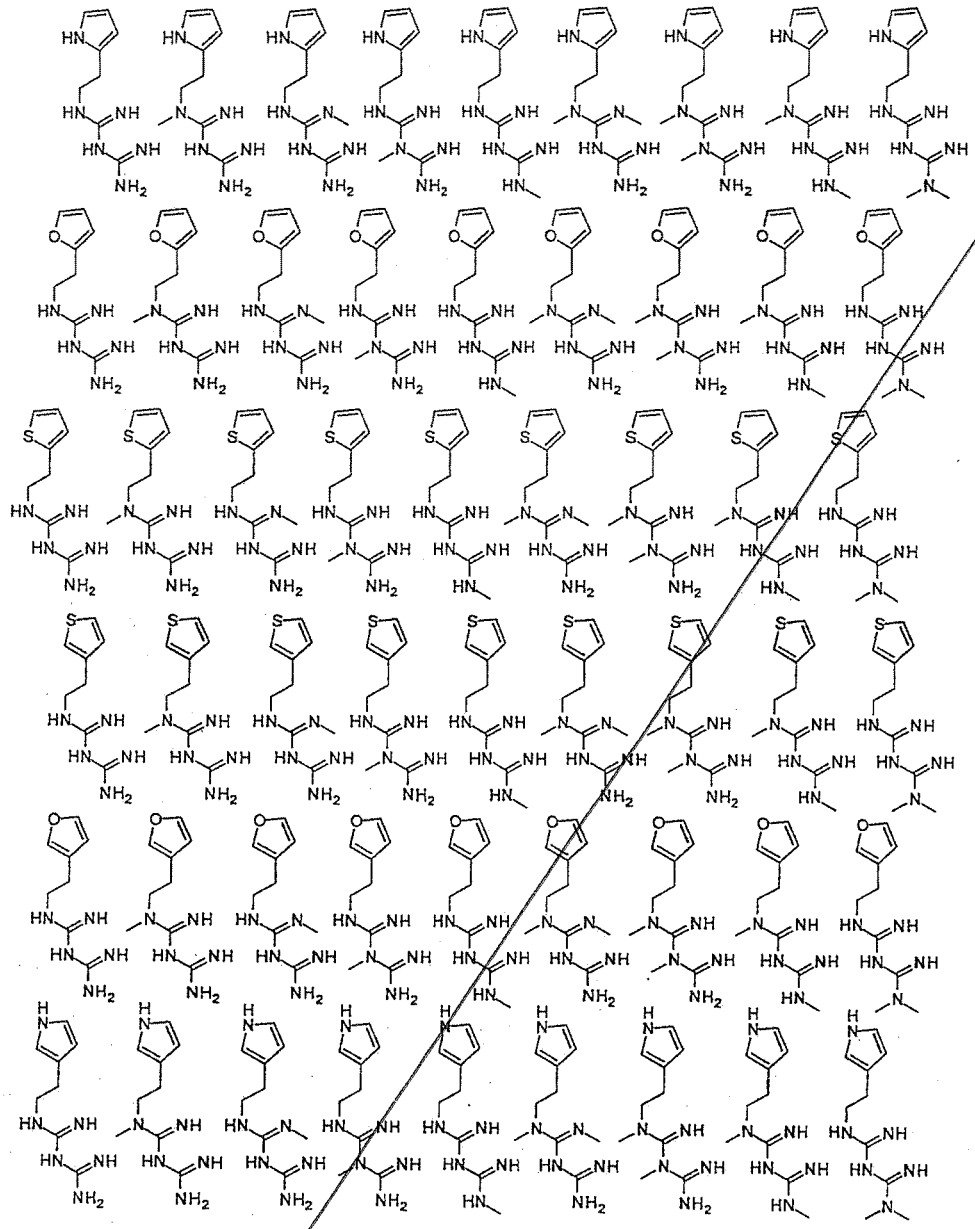


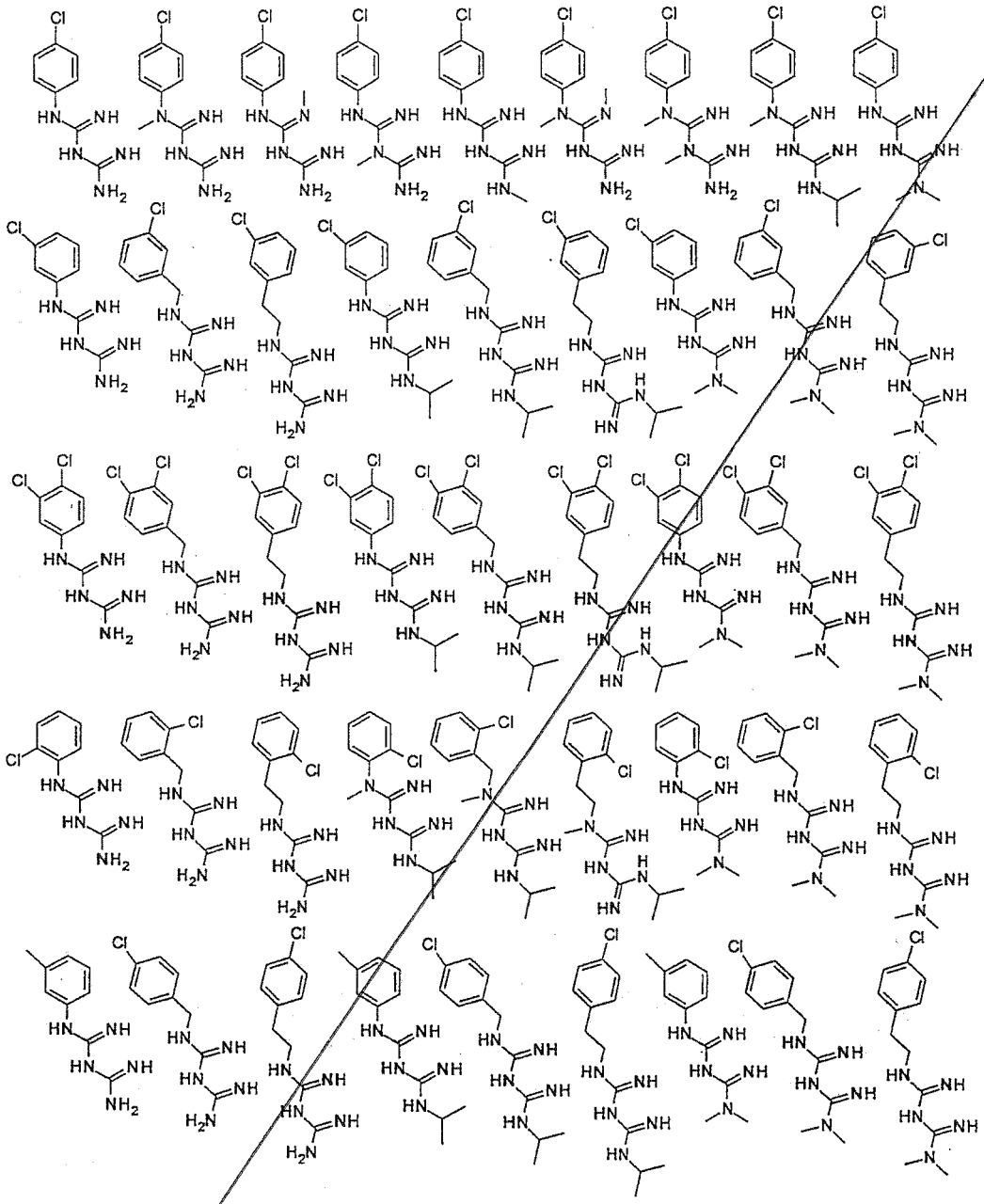


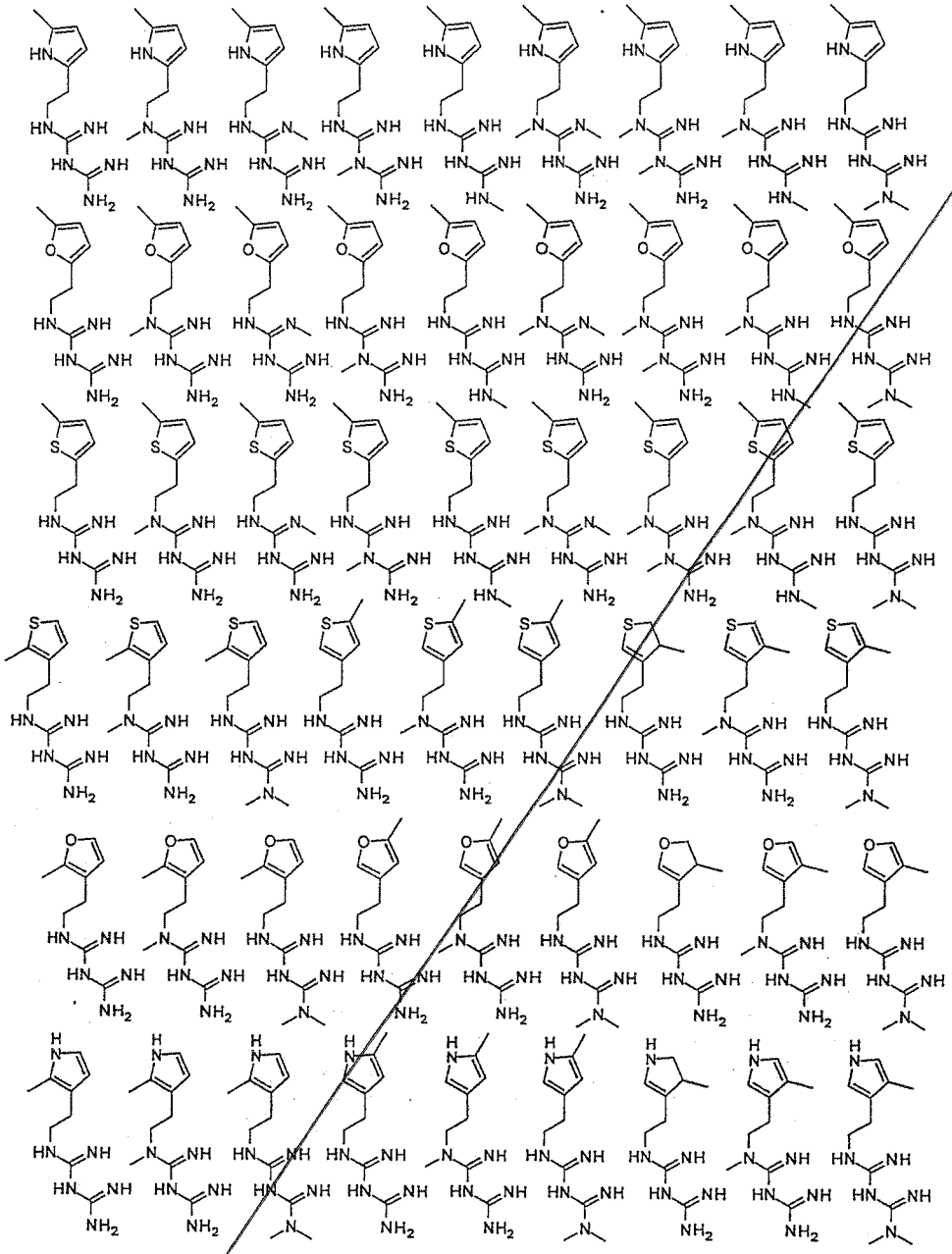




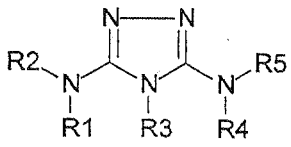








4. A composition comprising a biguanide or related heterocyclic compound of structural Formula IA,



(IA)

wherein:

R_1, R_2, R_3, R_4, and R_5 are independently selected from:

H, OH,

O-Rx, wherein Rx is alkyl, cycloalkyl, alkylcycloalkyl, acyl, ester, thioester;

optionally substituted alkyl; cycloalkyl; alkylcycloalkyl; heterocycloalkyl; alkylheterocycloalkyl; optionally substituted alkenyl; optionally substituted alkynyl;

optionally substituted aryl; optionally substituted alkylaryl; optionally substituted heteroaryl; optionally substituted alkylheteroaryl; and

or R_1 and R_2 may together form a 3 to 8 membered heterocyclic ring, including the nitrogen atoms to which they are attached;

or R_4 and R_5 may together form a ring selected from the group aziridine, pyrrolyl, imidazolyl, pyrazolyl, indolyl, indolinyl, pyrrolidinyl, piperazinyl and piperidyl, including the nitrogen atoms to which they are attached;

wherein the composition is adapted to reduce the average bioavailability of the compound, release a therapeutically effective amount of the compound to one or more regions of the intestine of a subject, or a combination thereof.

5. A composition according to claim 4, wherein:

R_2, R_3, R_4 and R_5 are independently selected from H, methyl, ethyl, propyl or isopropyl; and

R_1 is selected from:

H,

C_1 to C_{12} straight chain or branched chain alkyl optionally hetero substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl,

C_1 to C_{12} straight chain or branched chain alkenyl optionally hetero substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl,

C_1 to C_{12} straight chain or branched chain alkynyl optionally hetero substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl,

C_3 to C_7 cycloalkyl, C_2 to C_6 heterocycloalkyl, where the heterocycle comprises one or two hetero atoms selected from O, S, or N,

C_4 to C_{12} alkylcycloalkyl,

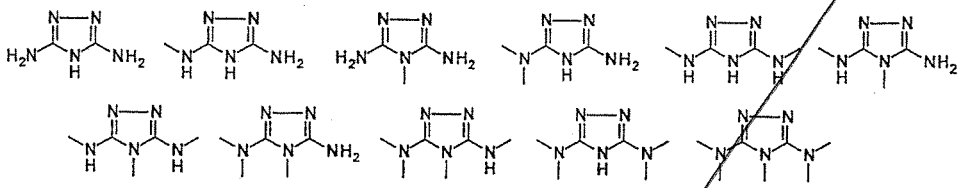
C_3 to C_{11} alkylheterocycloalkyl, where the heterocycle comprises one or two hetero atoms selected from O, S, or N and wherein N is present in the heterocyclic ring, the nitrogen atom may be in the form of an amide, carbamate or urea,

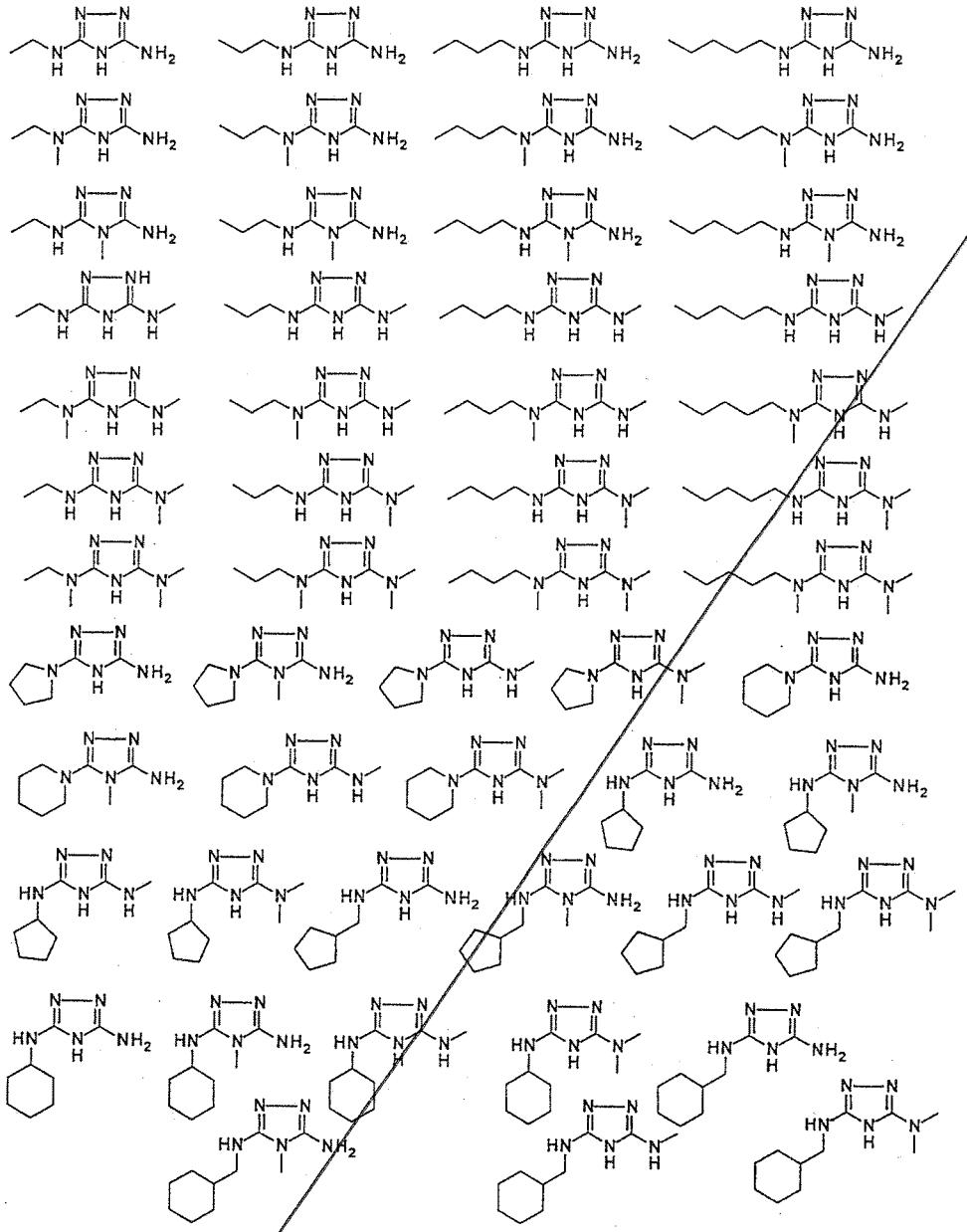
phenyl, substituted phenyl, naphthyl, substituted naphthyl,

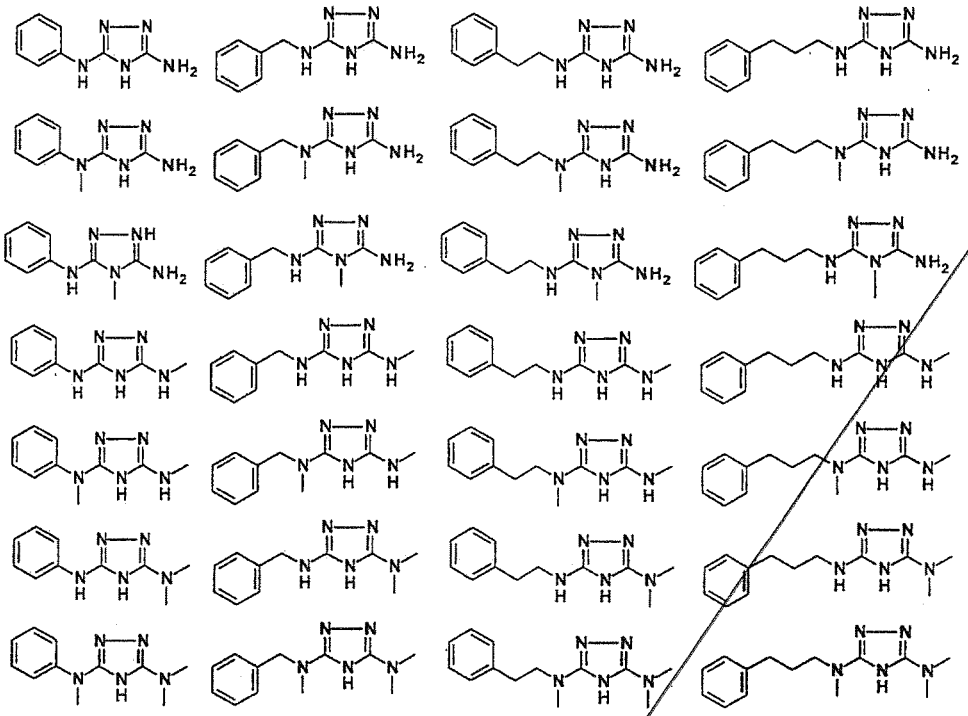
alkylphenyl, alkylsubstituted phenyl, alkylnaphthyl, alkylsubstituted naphthyl,

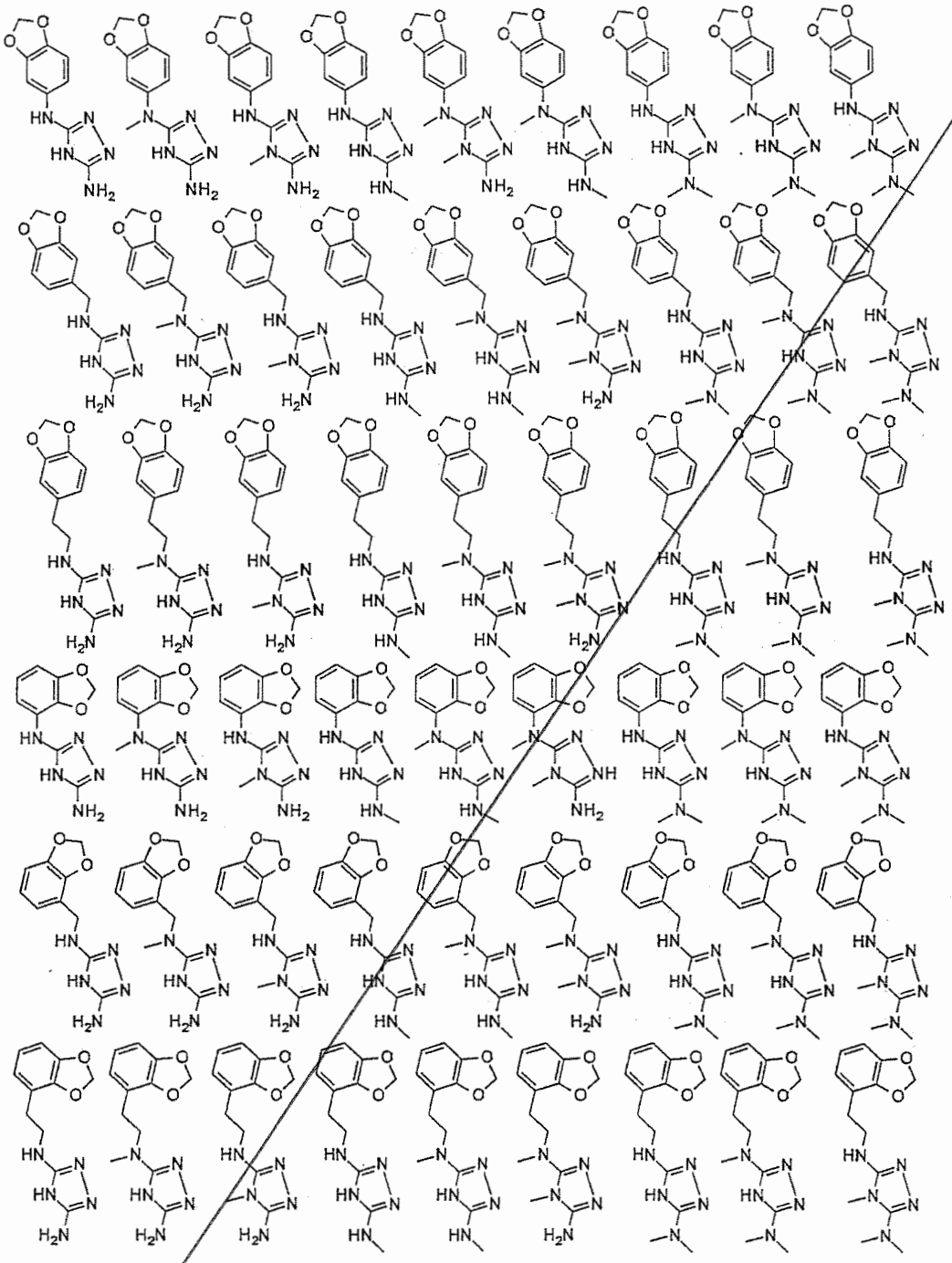
pyridyl, furanyl, thiophenyl, pyrrollyl, oxazolyl, isoxazolyl, thiazolyl, diazolyl, pyrazolyl, triazolyl all of which are optionally substituted.

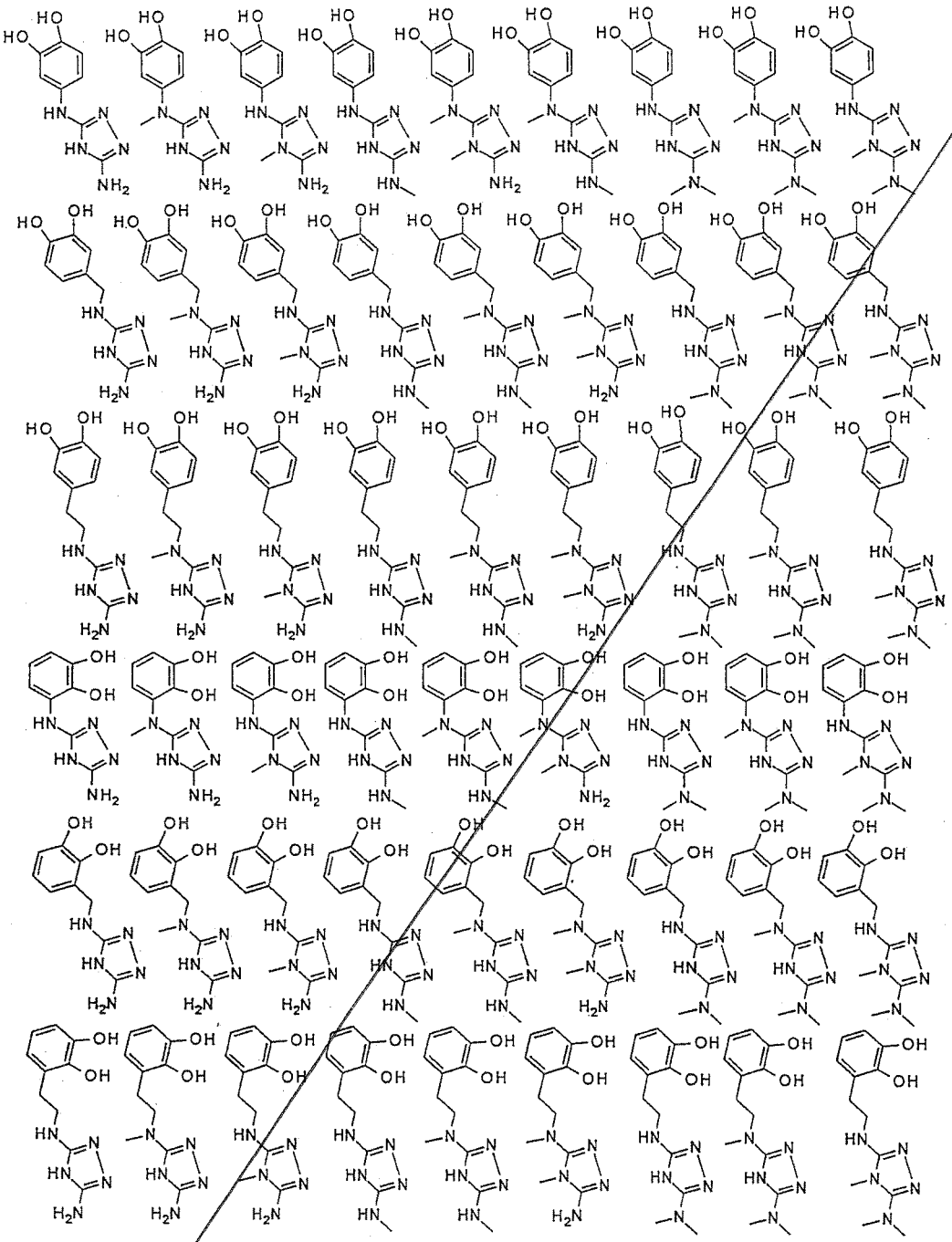
6. A composition according to claim 4, wherein the compound of Formula IA is selected from the following structures:

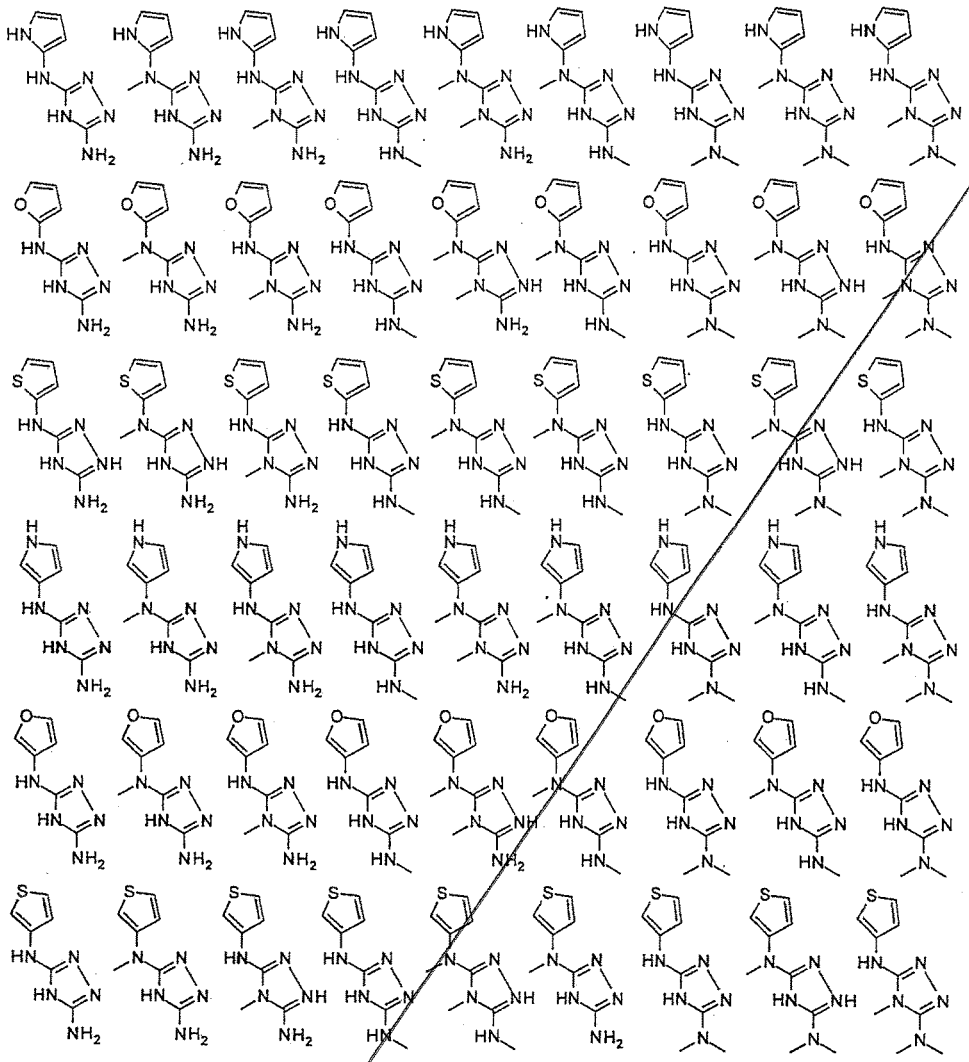


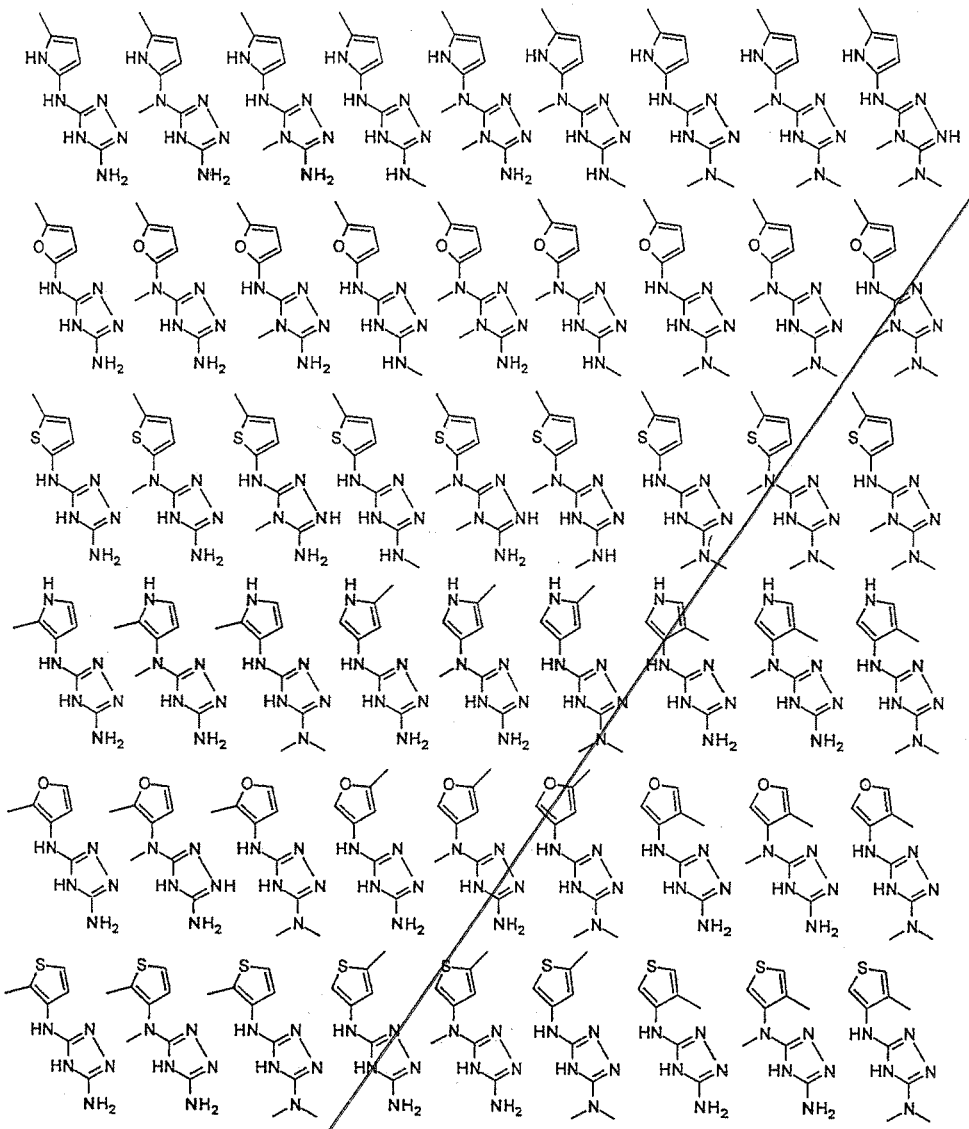


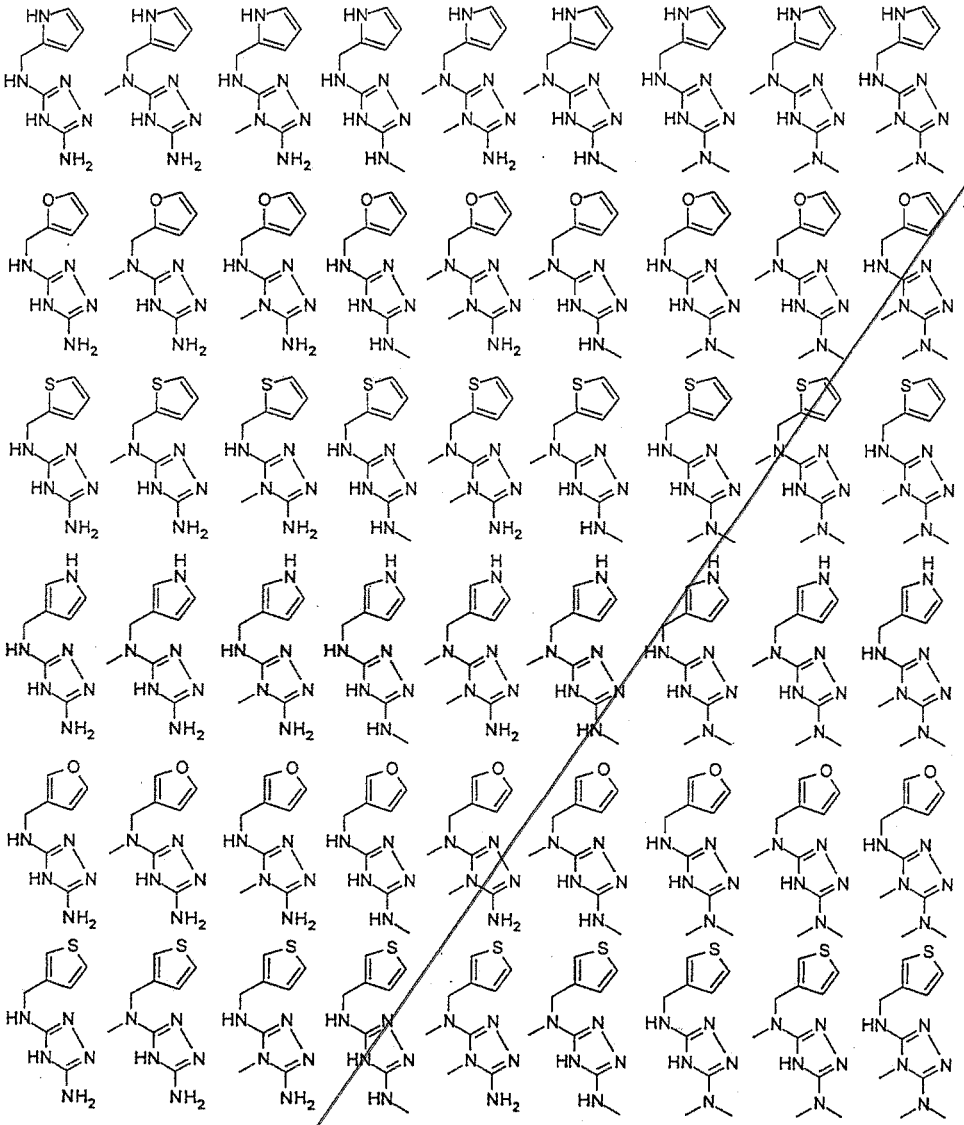


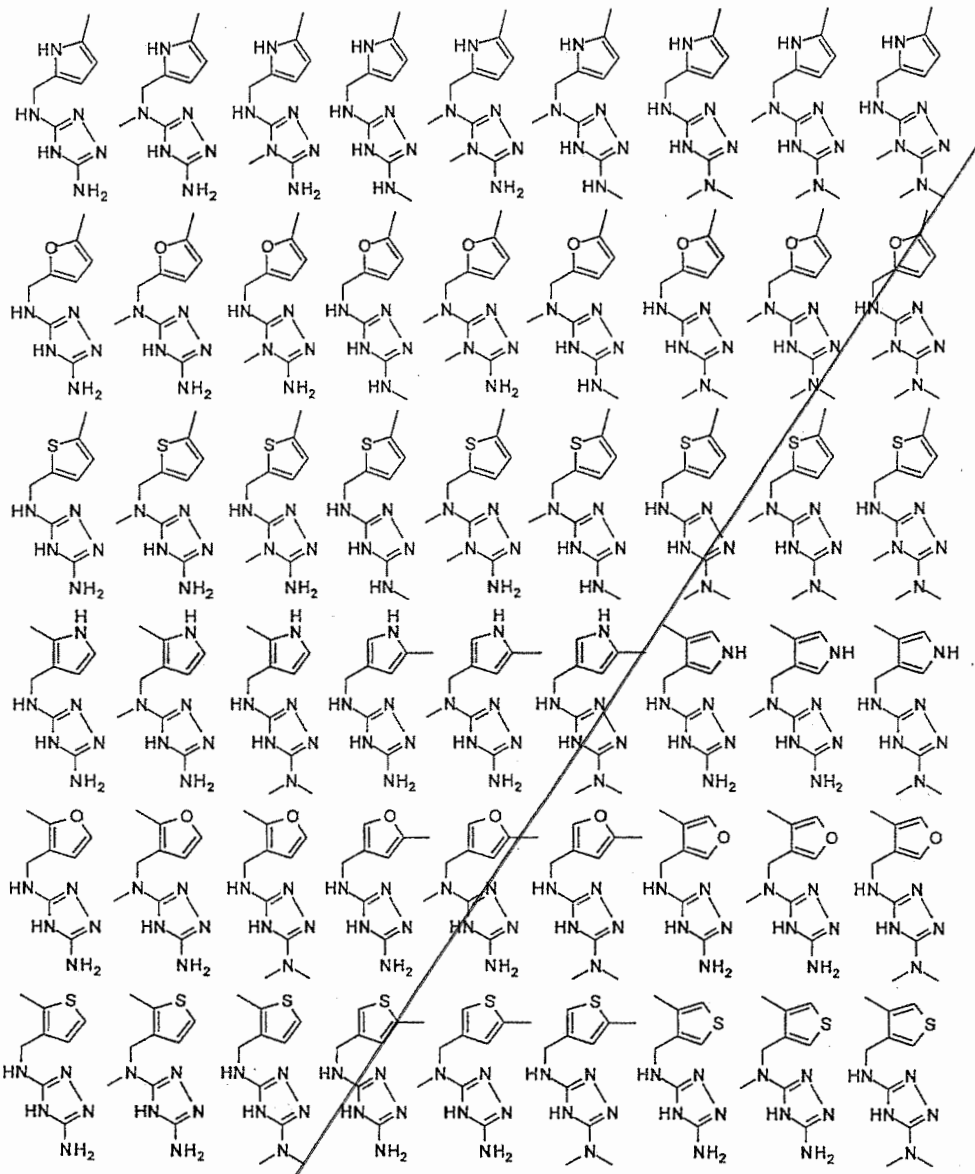


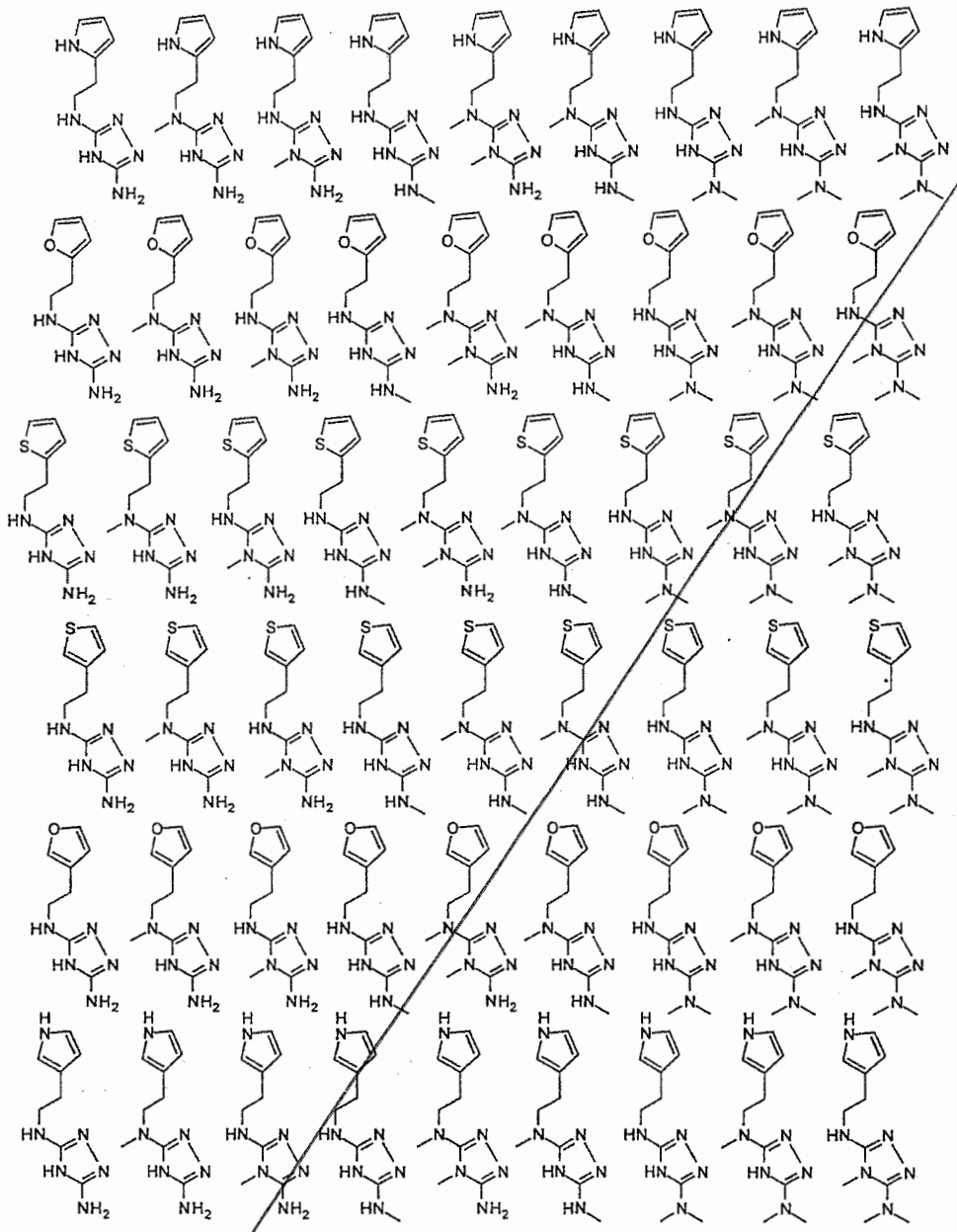


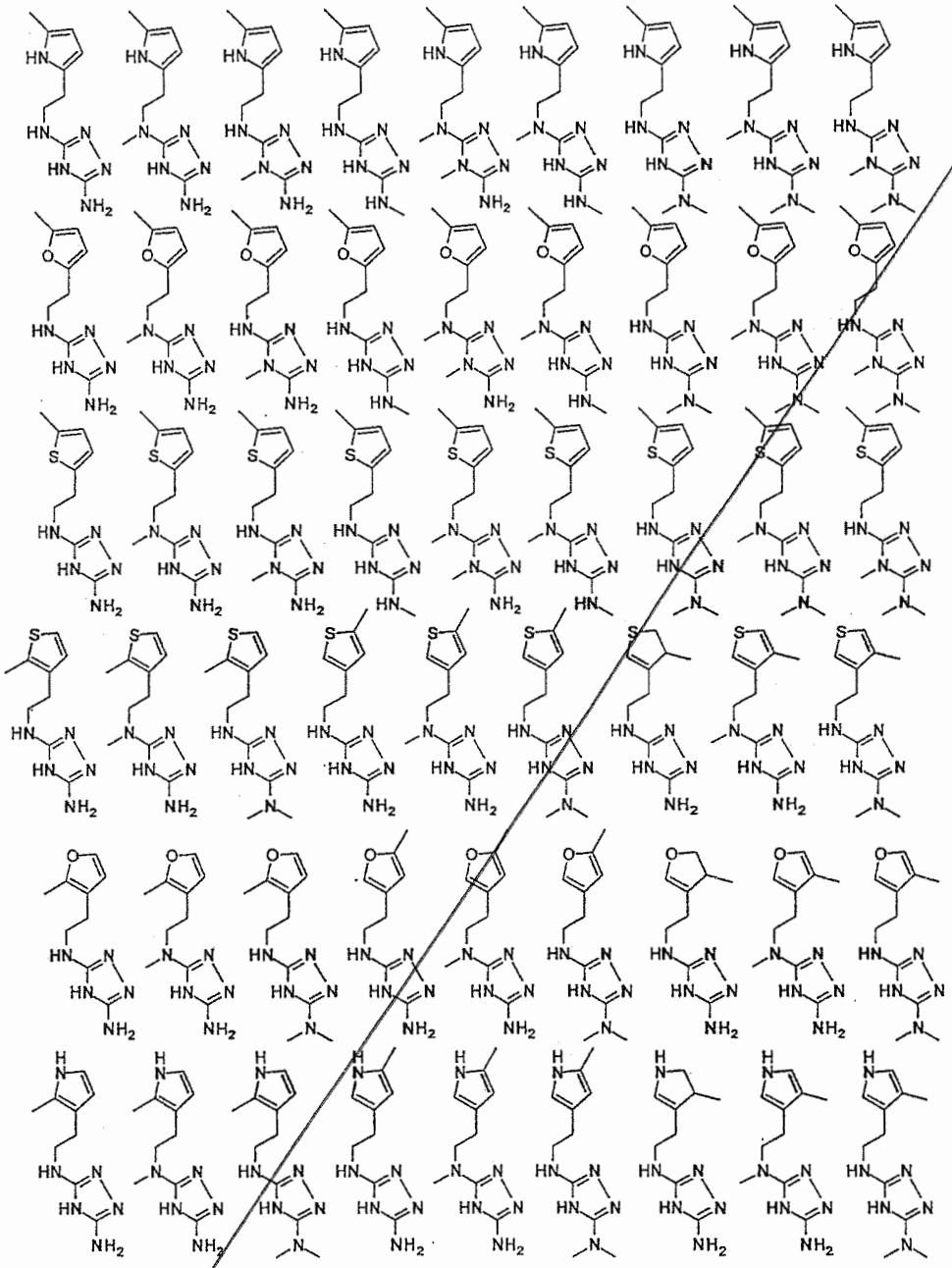


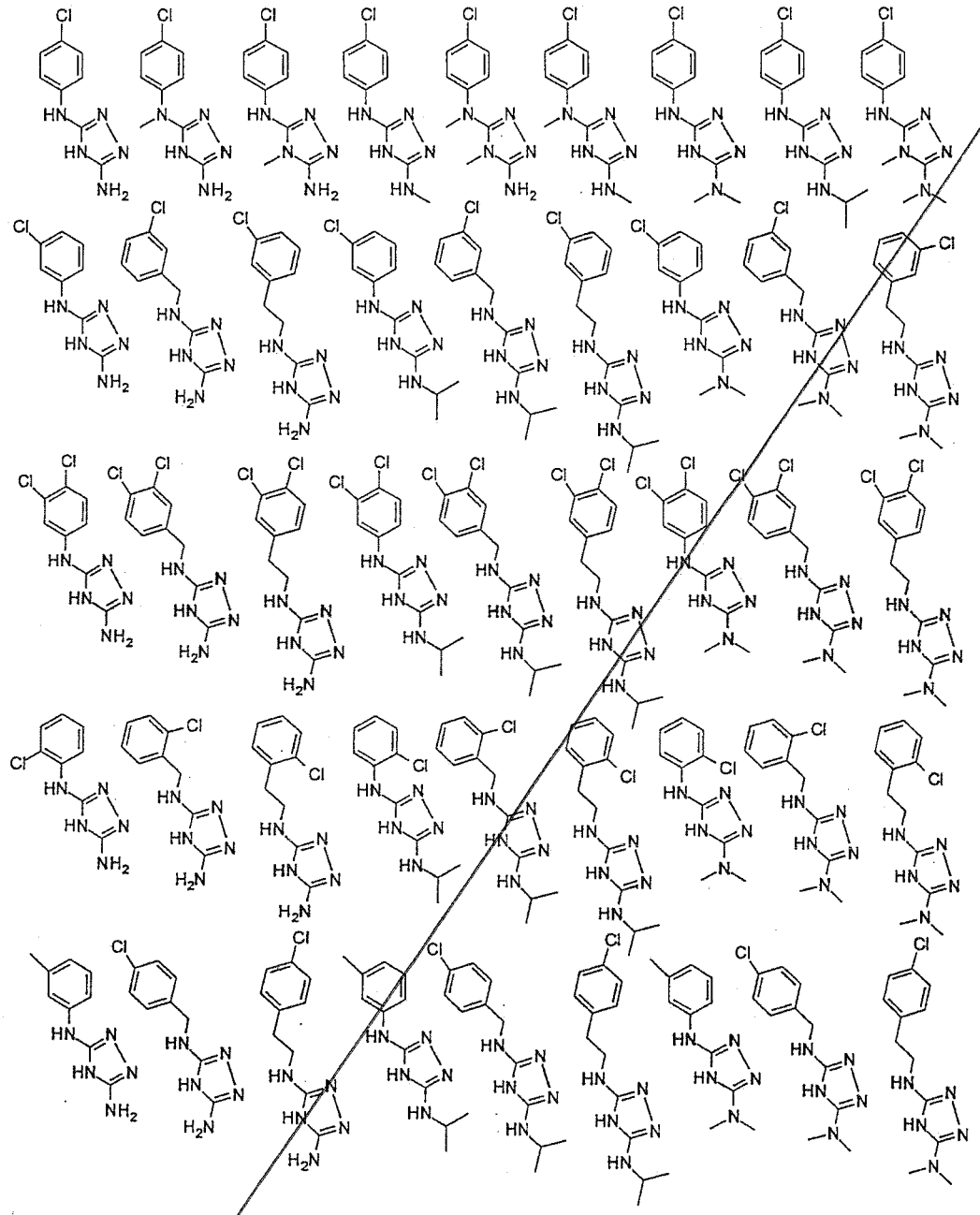




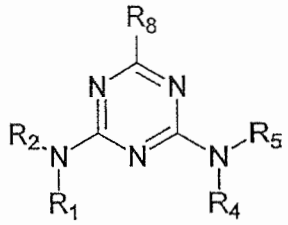








7. A composition comprising a biguanide or related heterocyclic compound of structural Formula II,



II

wherein:

R_1, R_2, R_4, and R_5, are independently selected from:

H, OH,

O-Rx, wherein Rx is alkyl, cycloalkyl, alkylcycloalkyl, acyl, ester, thioester;

optionally substituted alkyl; cycloalkyl; alkylcycloalkyl; heterocycloalkyl; alkylheterocycloalkyl; optionally substituted alkenyl; optionally substituted alkynyl;

optionally substituted aryl; optionally substituted alkylaryl; optionally substituted heteroaryl; optionally substituted alkylheteroaryl; and

or R_1 and R_2 may together form a 3 to 8 membered heterocyclic ring, including the nitrogen atoms to which they are attached;

or R_4 and R_5 may together form a ring selected from the group aziridine, pyrrolyl, imidazolyl, pyrazolyl, indolyl, indolinyl, pyrrolidinyl, piperazinyl and piperidyl, including the nitrogen atoms to which they are attached;

R_8 is selected from:

H; optionally substituted alkynyl; cycloaklyl; alkylcycloalkyl; heterocycloalkyl; alkylheterocycloalkyl; optionally substituted aryl; optionally substituted alkylaryl (e.g., alkylphenyl, alkylsubstituted phenyl, alkylnaphthyl, alkylsubstituted naphthyl); optionally substituted heteroaryl; optionally substituted alkylheteroaryl; and $-NR_aR_b$

wherein R_a and R_b are independently selected from:

H; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; cycloalkyl; alkylcycloalkyl; heterocyclalkyl; alkylheterocycloalkyl; optionally substituted aryl, optionally substituted alkylary, optionally substituted heteroaryl, and optionally substituted alkylheteroaryl;

wherein the composition is adapted to reduce the average bioavailability of the compound, release a therapeutically effective amount of the compound to one or more regions of the intestine of a subject, or a combination thereof.

8. The composition according to claim 7, wherein:

R_2, R_3, and R_4 are independently selected from H, methyl, ethyl, propyl or isopropyl;

R_5 is selected from H , CH_3, lower alkyl, NH_2, $NHCH_3$, $N(CH_3)_2$, NH-alkyl, $N(alkyl)_2$;and

R_1 is selected from:

H,

C_1 to C_{12} straight chain or branched chain alkyl optionally hetero substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl,

C_1 to C_{12} straight chain or branched chain alkenyl optionally hetero substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl,

C_1 to C_{12} straight chain or branched chain alkynyl optionally hetero substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl,

C_3 to C_7 cycloalkyl, C_2 to C_6 heterocycloalkyl, where the heterocycle comprises one or two hetero atoms selected from O, S, or N,

C_4 to C_{12} alkylcycloalkyl,

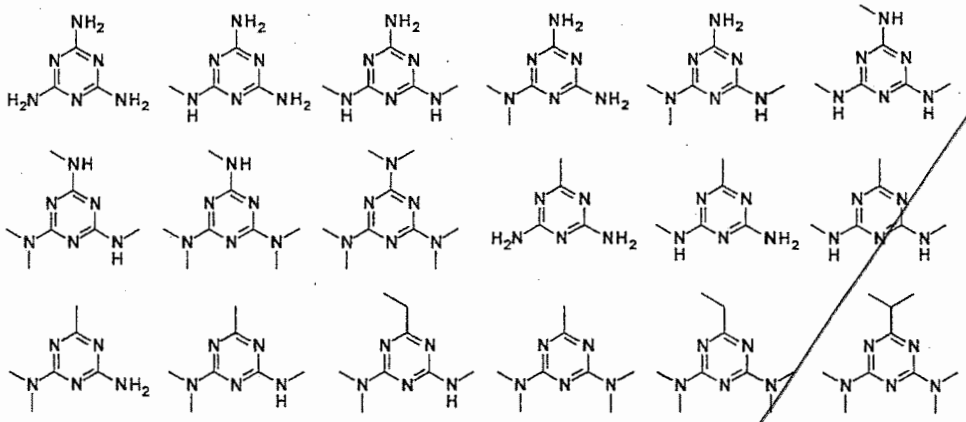
C_3 to C_{11} alkylheterocycloalkyl, where the heterocycle comprises one or two hetero atoms selected from O, S, or N and wherein N is present in the heterocyclic ring, the nitrogen atom may be in the form of an amide, carbamate or urea,

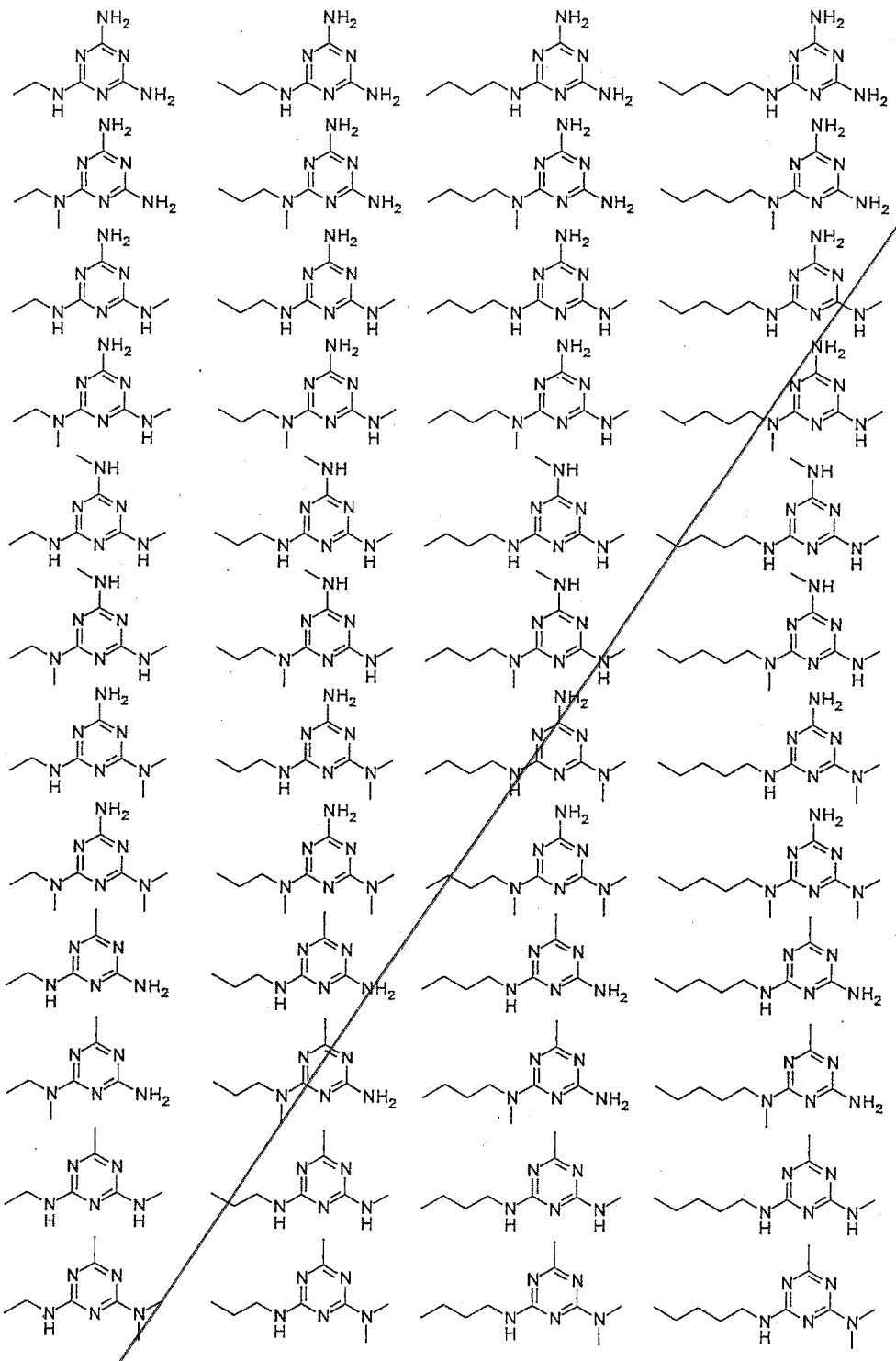
phenyl, substituted phenyl, naphthyl, substituted naphthyl,

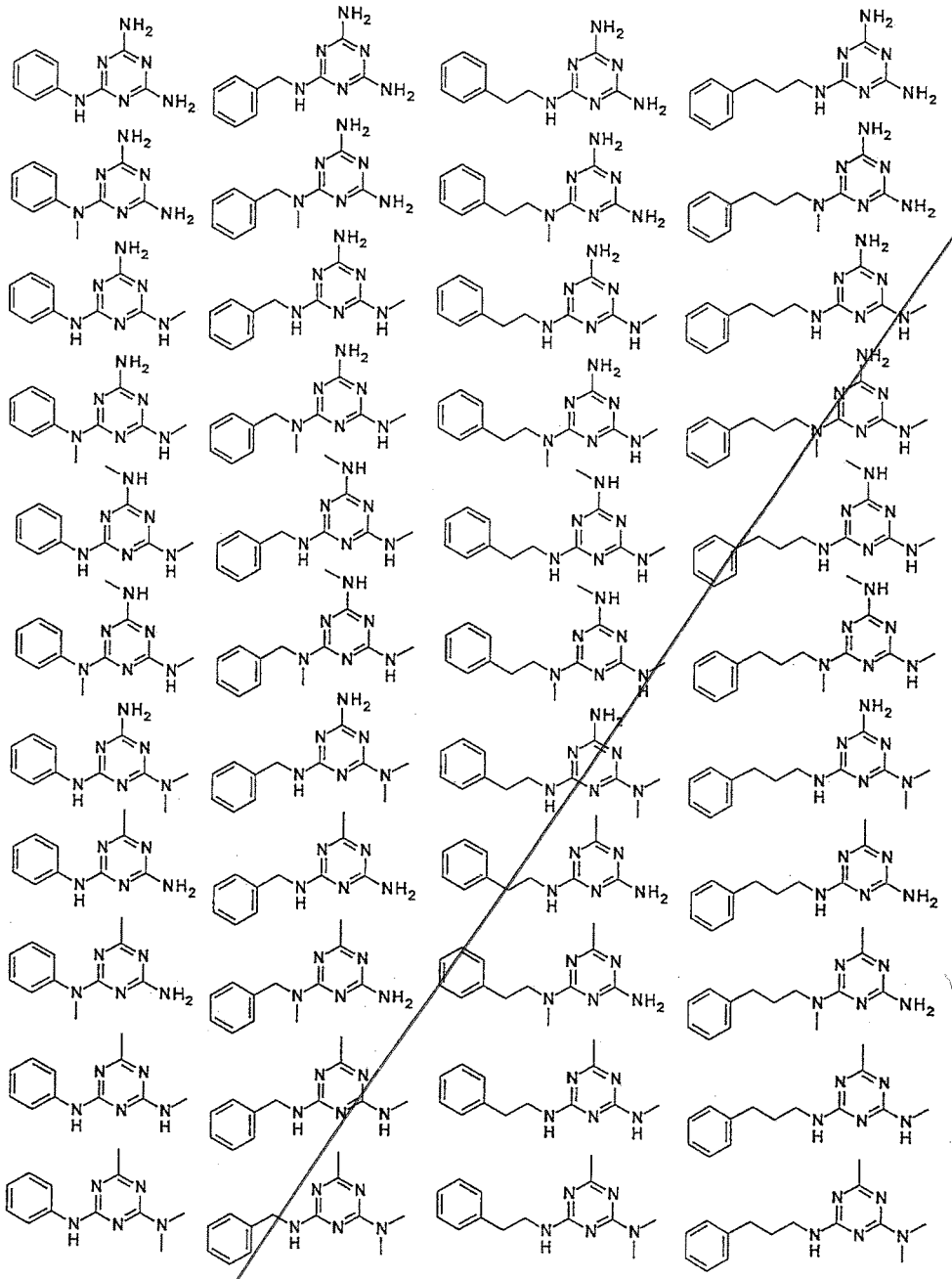
alkylphenyl, alkylsubstituted phenyl, alkylnaphthyl, alkylsubstituted naphthyl,

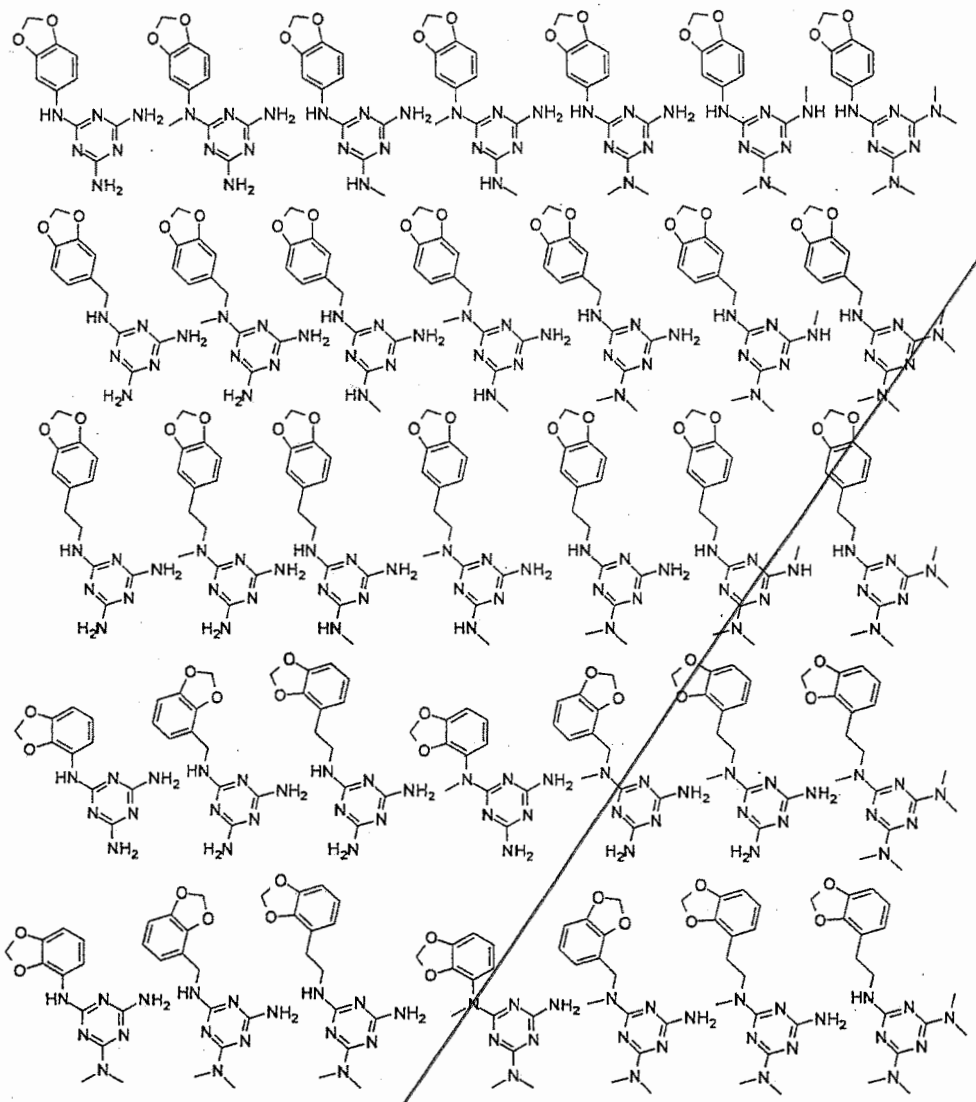
pyridyl, furanyl, thiophenyl, pyrrollyl, oxazolyl, isoxazolyl, thiazolyl, diazolyl, pyrazolyl, triazolyl all of which are optionally substituted.

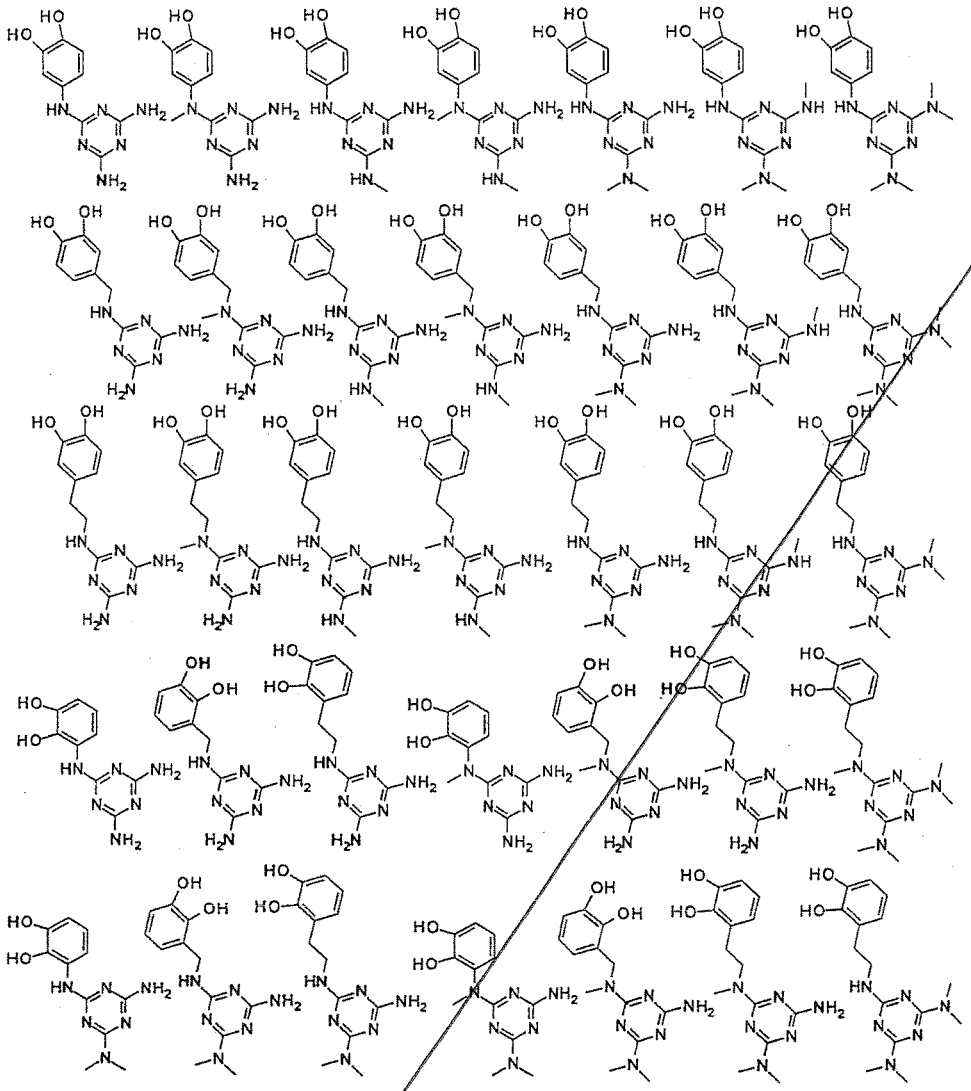
9. The composition according to claim 7, wherein the compound of Formula II is selected from the following structures:

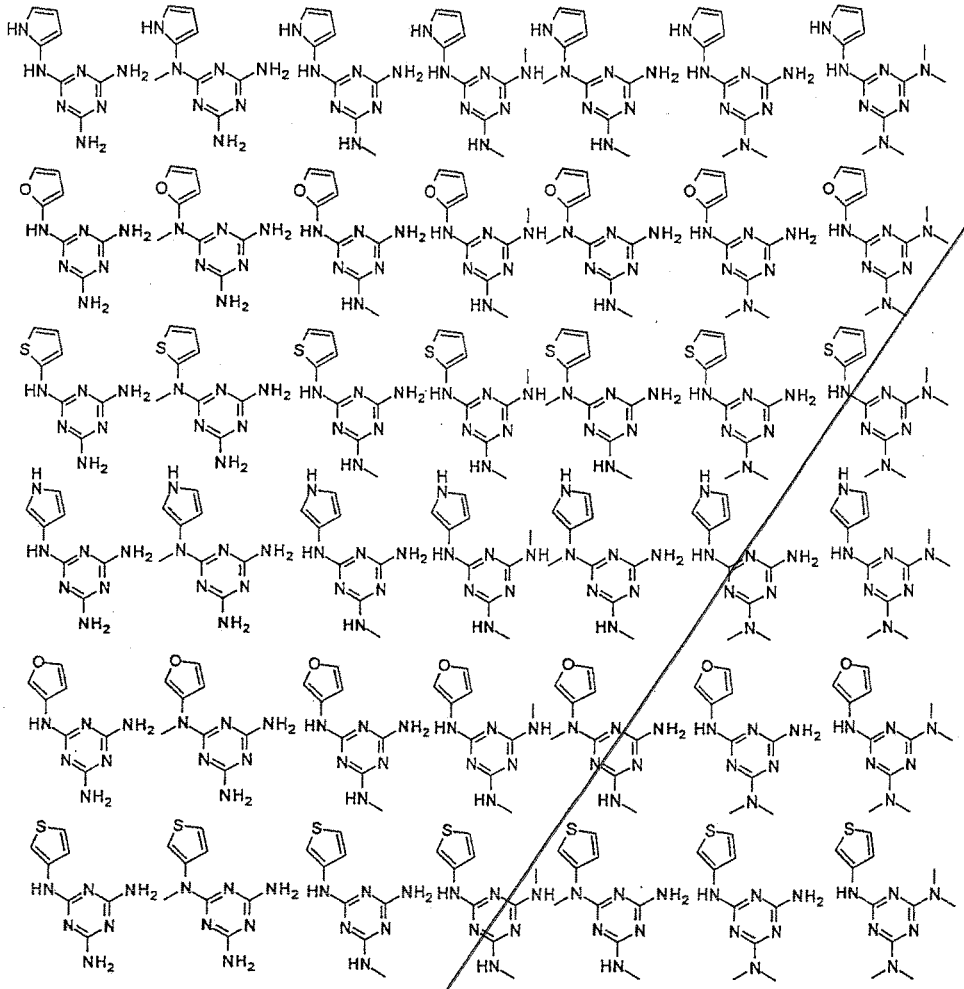


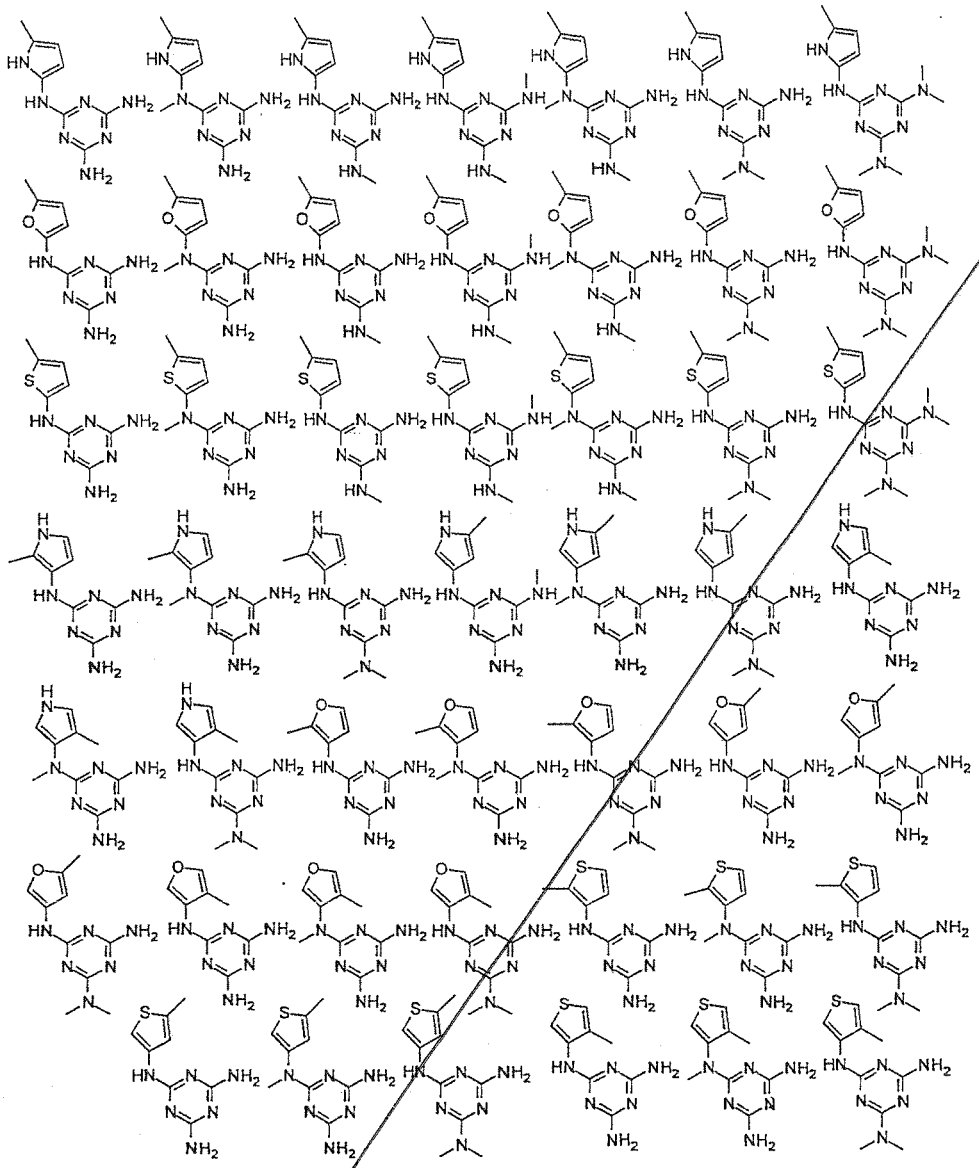


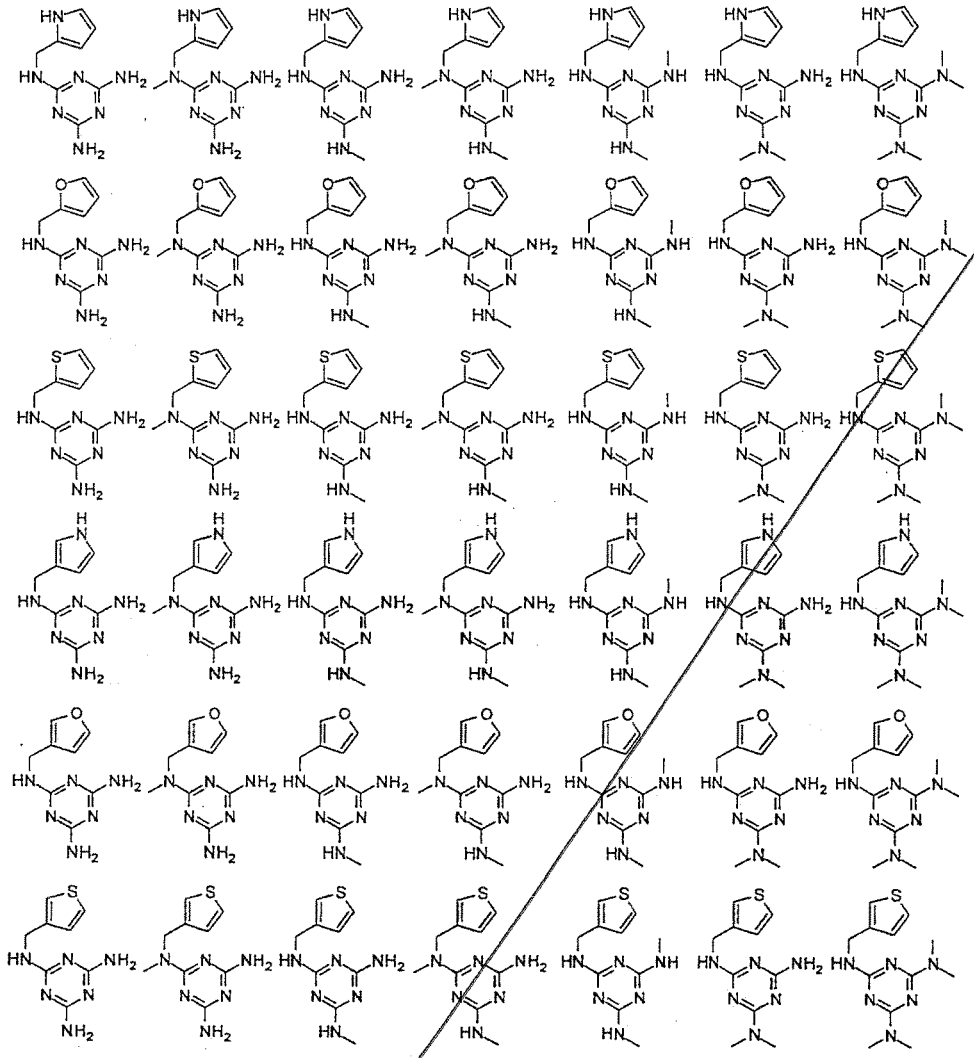


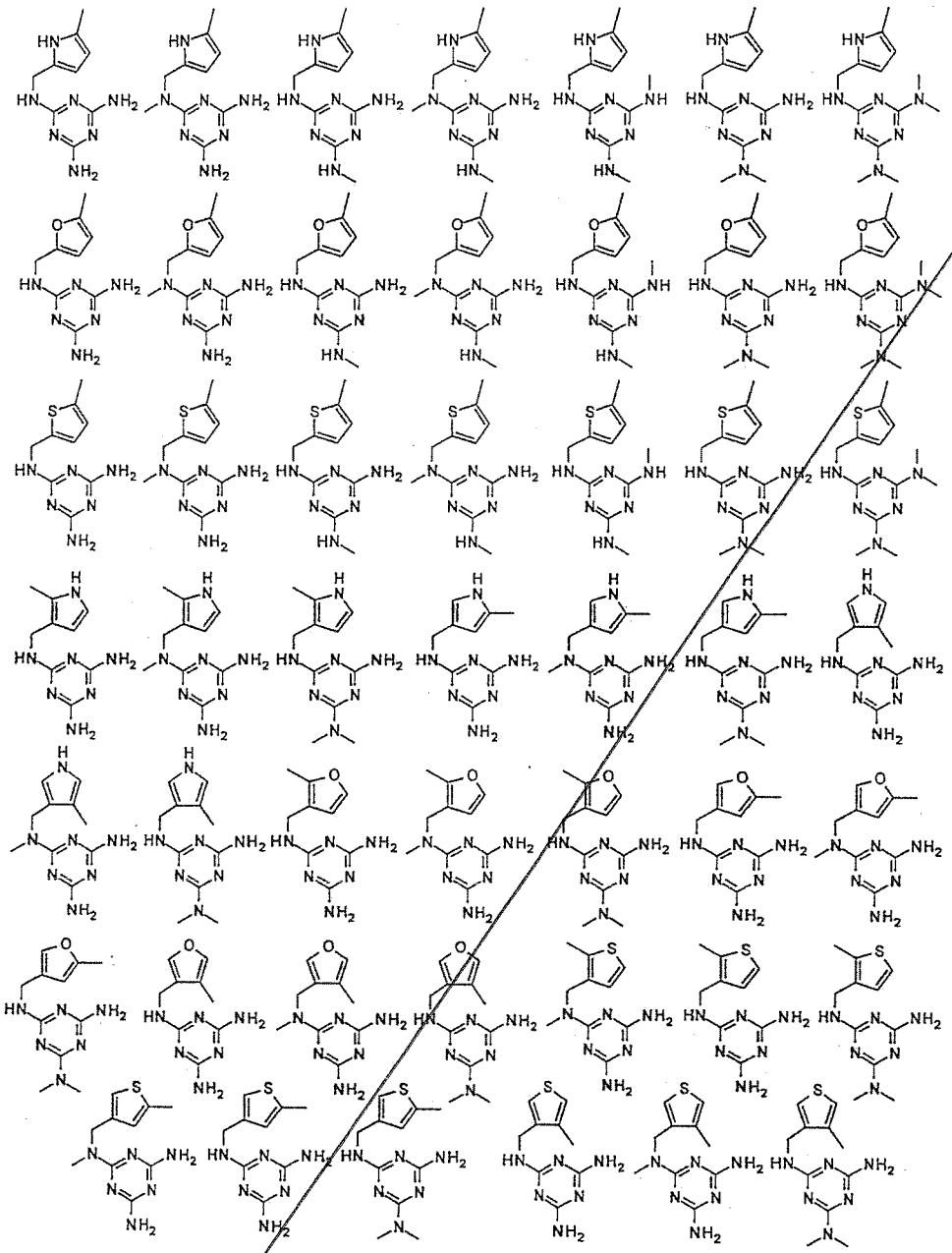


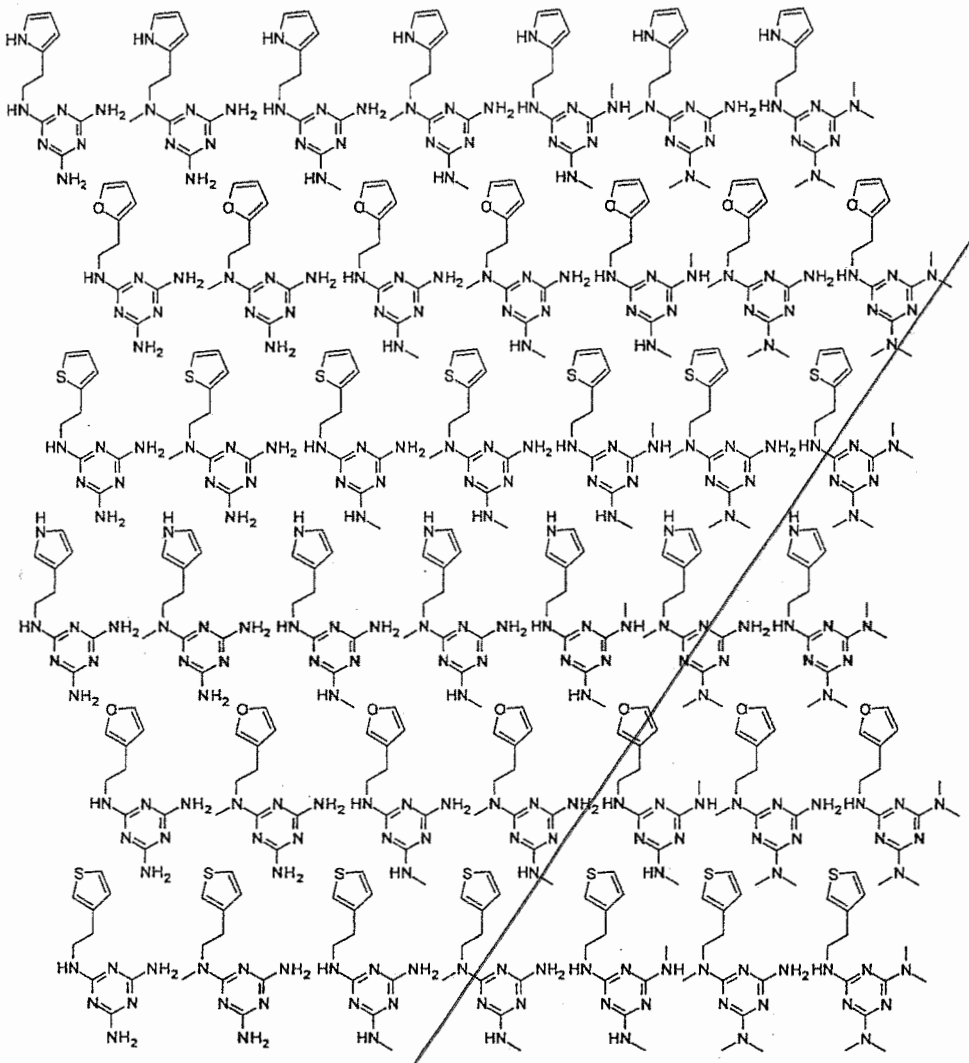


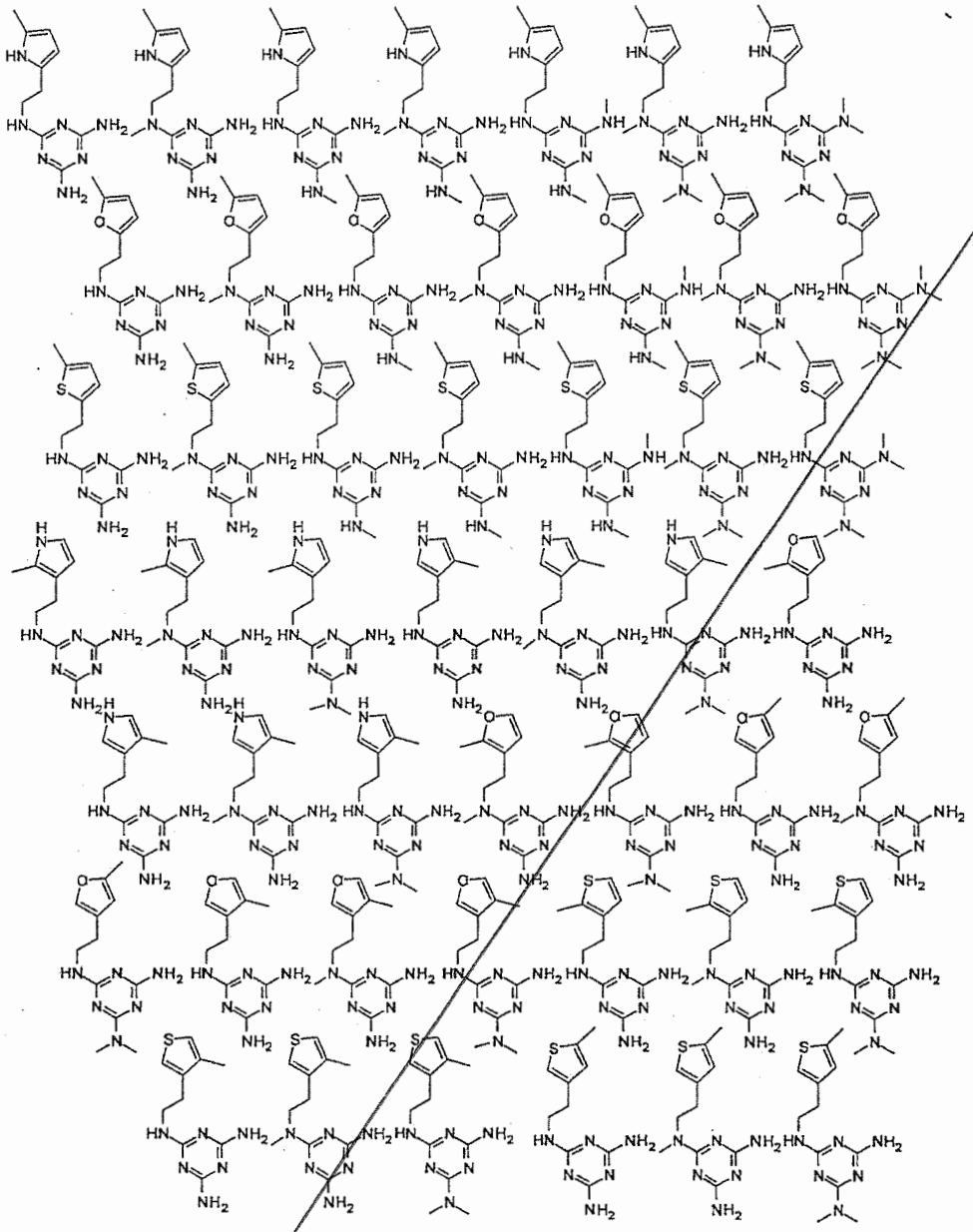


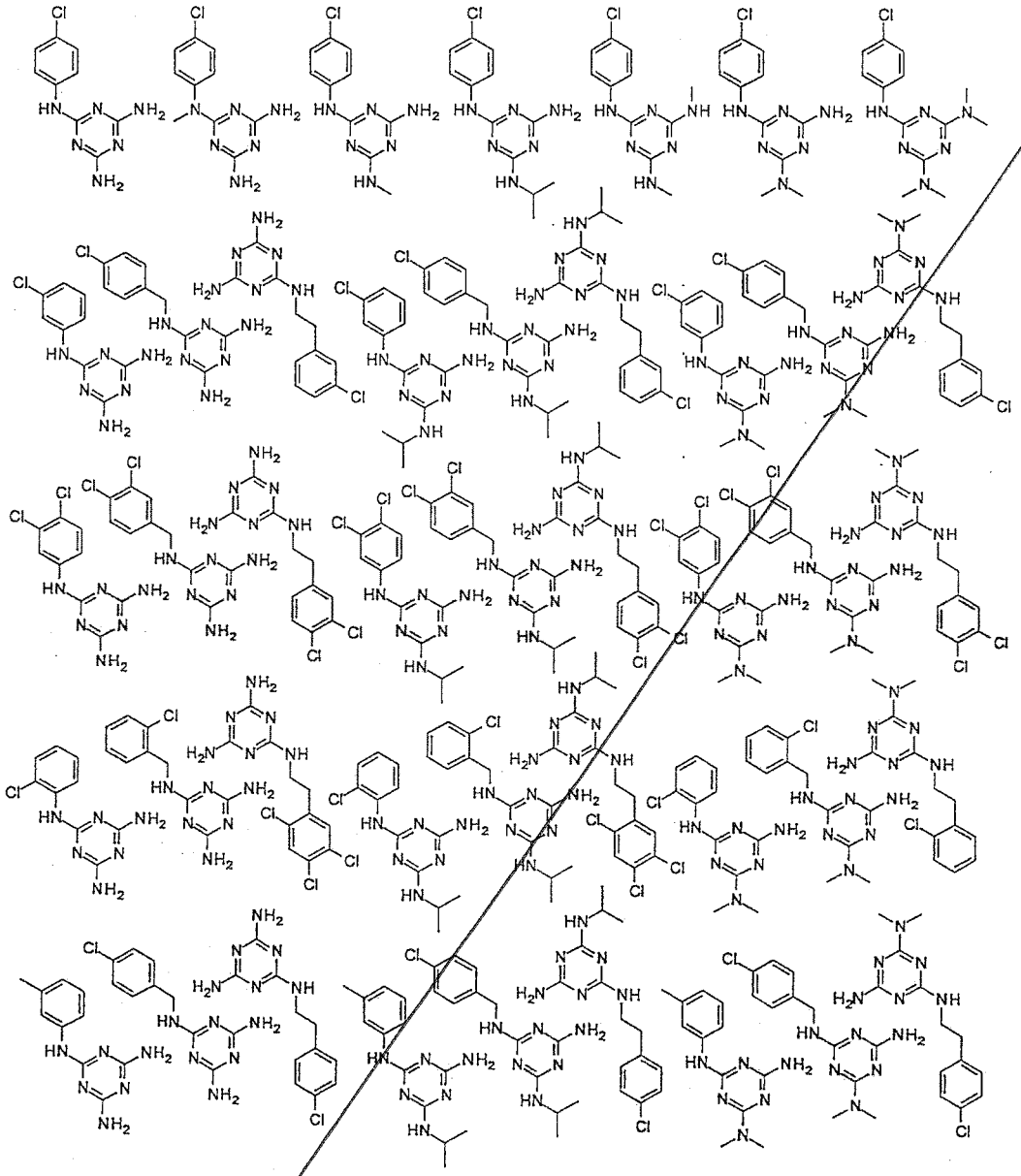




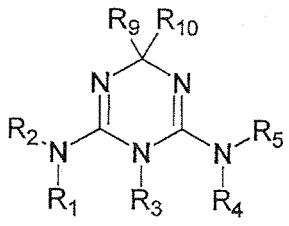








10. A composition comprising a biguanide or related heterocyclic compound of structural Formula III,



(III)

wherein:

R_1, R_2, R_3, R_4, R_5, R_9, and R_{10}, are independently selected from:

H, OH,

O-Rx, wherein Rx is alkyl, cycloalkyl, alkylcycloalkyl, acyl, ester, thioester;

optionally substituted alkyl; cycloalkyl; alkylcycloalkyl; heterocycloalkyl; alkylheterocycloalkyl; optionally substituted alkenyl; optionally substituted alkynyl;

optionally substituted aryl; optionally substituted alkylaryl; optionally substituted heteroaryl; optionally substituted alkylheteroaryl; and

or R_1 and R_2 may together form a 3 to 8 membered heterocyclic ring, including the nitrogen atoms to which they are attached;

or R_4 and R_5 may together form a ring selected from the group aziridine, pyrrolyl, imidazolyl, pyrazolyl, indolyl, indolinyl, pyrrolidinyl, piperazinyl and piperidyl, including the nitrogen atoms to which they are attached;

wherein the composition is adapted to reduce the average bioavailability of the compound, release a therapeutically effective amount of the compound to one or more regions of the intestine of a subject, or a combination thereof.

11. The composition according to claim10, wherein:

R_2, R_3, R_4, R_5, R_6 and R_7 are independently selected from H, methyl, ethyl, propyl or isopropyl; and R_1 is selected from:

H,

C_1 to C_{12} straight chain or branched chain alkyl optionally hetero substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl,

C_1 to C_{12} straight chain or branched chain alkenyl optionally hetero substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl,

C_1 to C_{12} straight chain or branched chain alkynyl optionally hetero substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl,

C_3 to C_7 cycloalkyl, C_2 to C_6 heterocycloalkyl, where the heterocycle comprises one or two hetero atoms selected from O, S, or N,

C_4 to C_{12} alkylcycloalkyl,

C_3 to C_{11} alkylheterocycloalkyl, where the heterocycle comprises one or two hetero atoms selected from O, S, or N and wherein N is present in the heterocyclic ring, the nitrogen atom may be in the form of an amide, carbamate or urea,

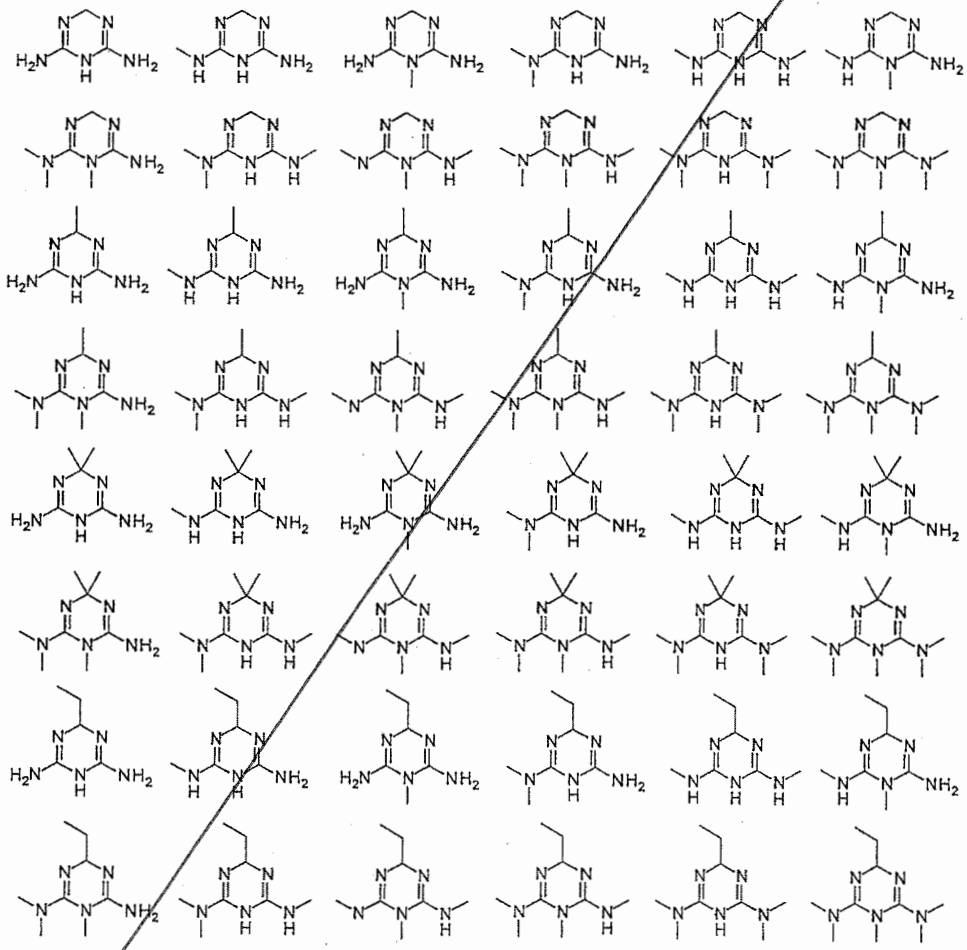
aryl, phenyl, substituted phenyl, naphthyl, substituted naphthyl,

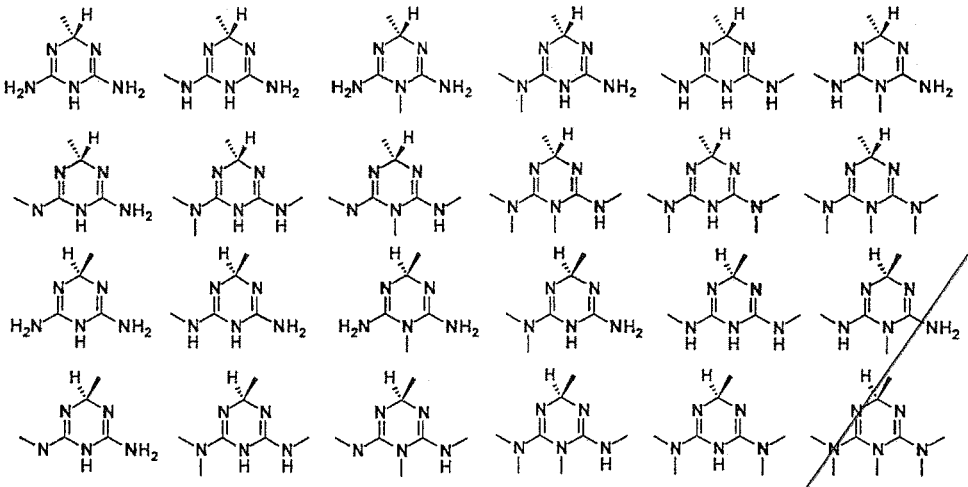
alkylaryl, alkylphenyl, alkylsubstituted phenyl, alkylnaphthyl, alkylsubstituted naphthyl,

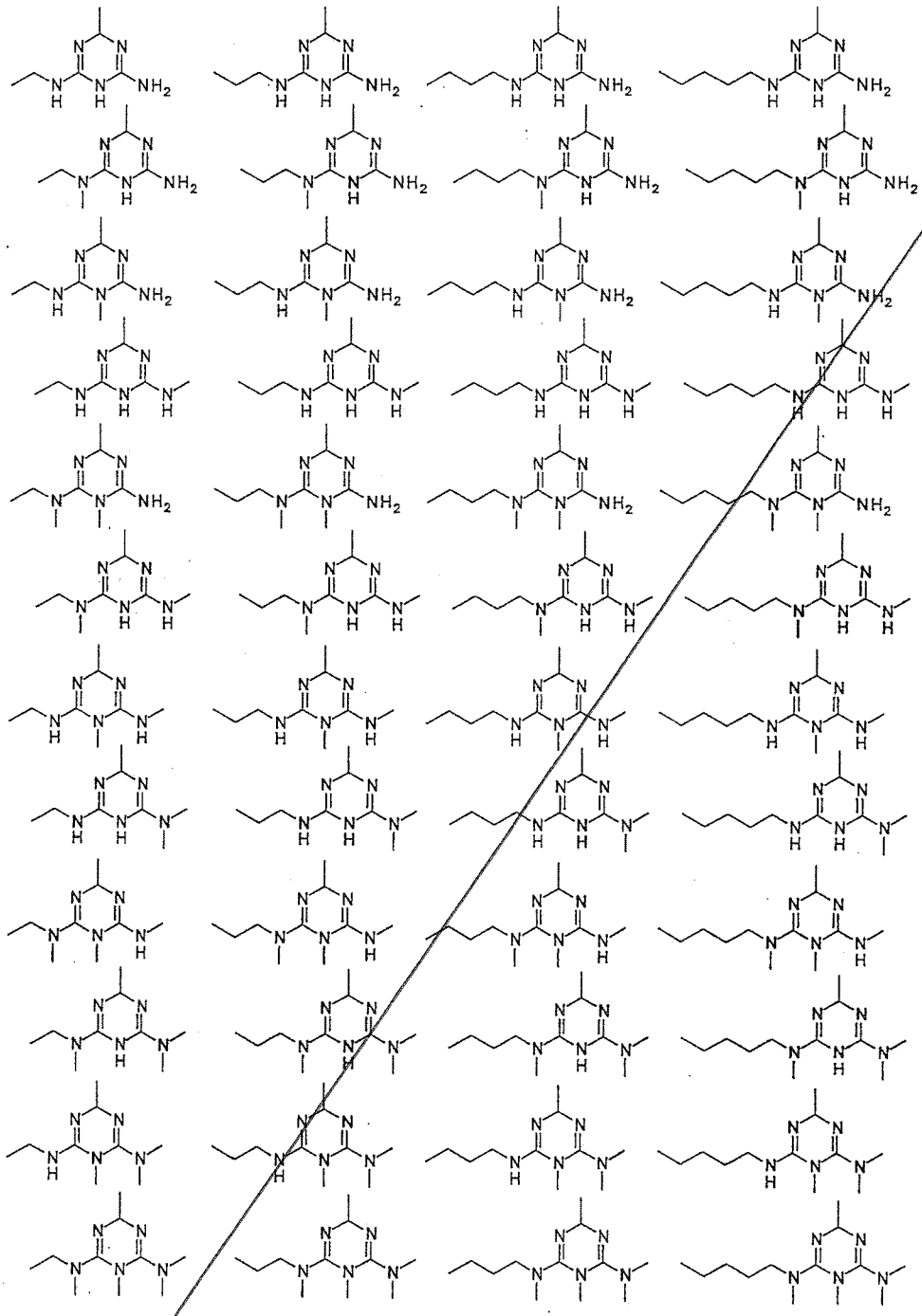
heteroaryl, pyridyl, furanyl, thiophenyl, pyrrollyl, oxazolyl, isoxazolyl, thiazolyl, diazolyl, pyrazolyl, triazolyl all of which are optionally substituted,

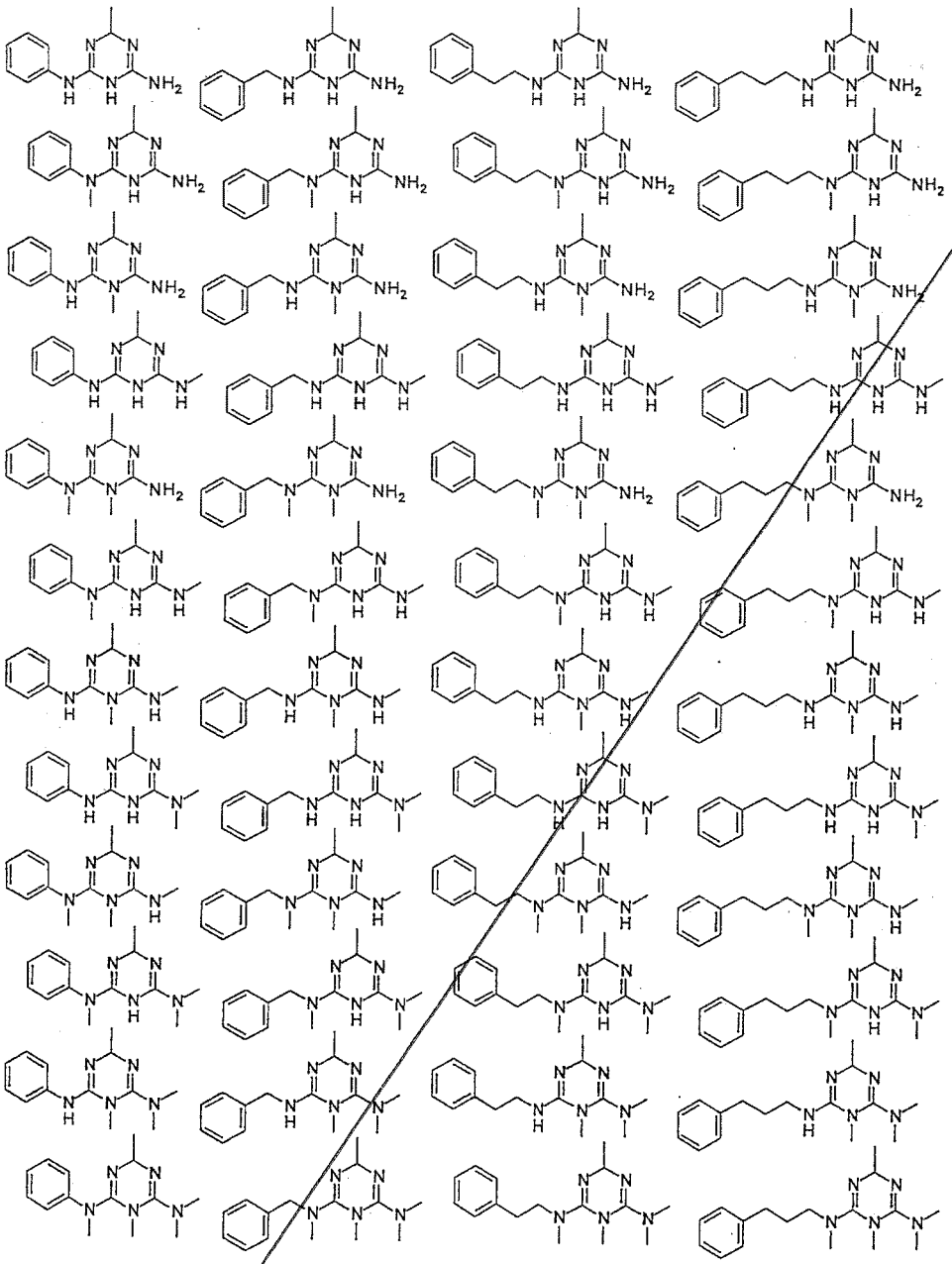
alkylheteroaryl, pyridyl, furanyl, thiophenyl, pyrrollyl, oxazolyl, isoxazolyl, diazolyl, pyrazolyl, triazolyl all of which are optionally substituted.

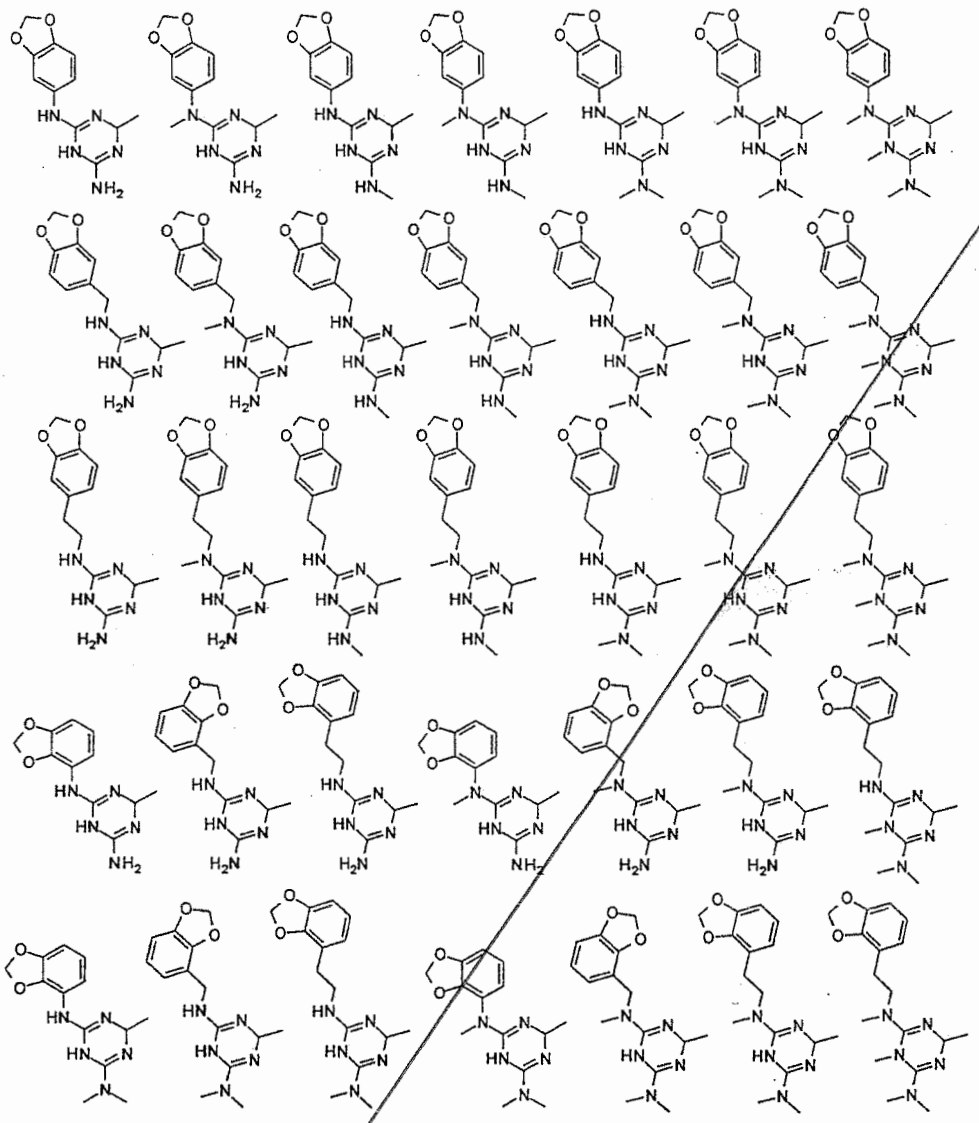
12. The composition according to claim10, wherein the compound of Formula III is selected from the following structures:

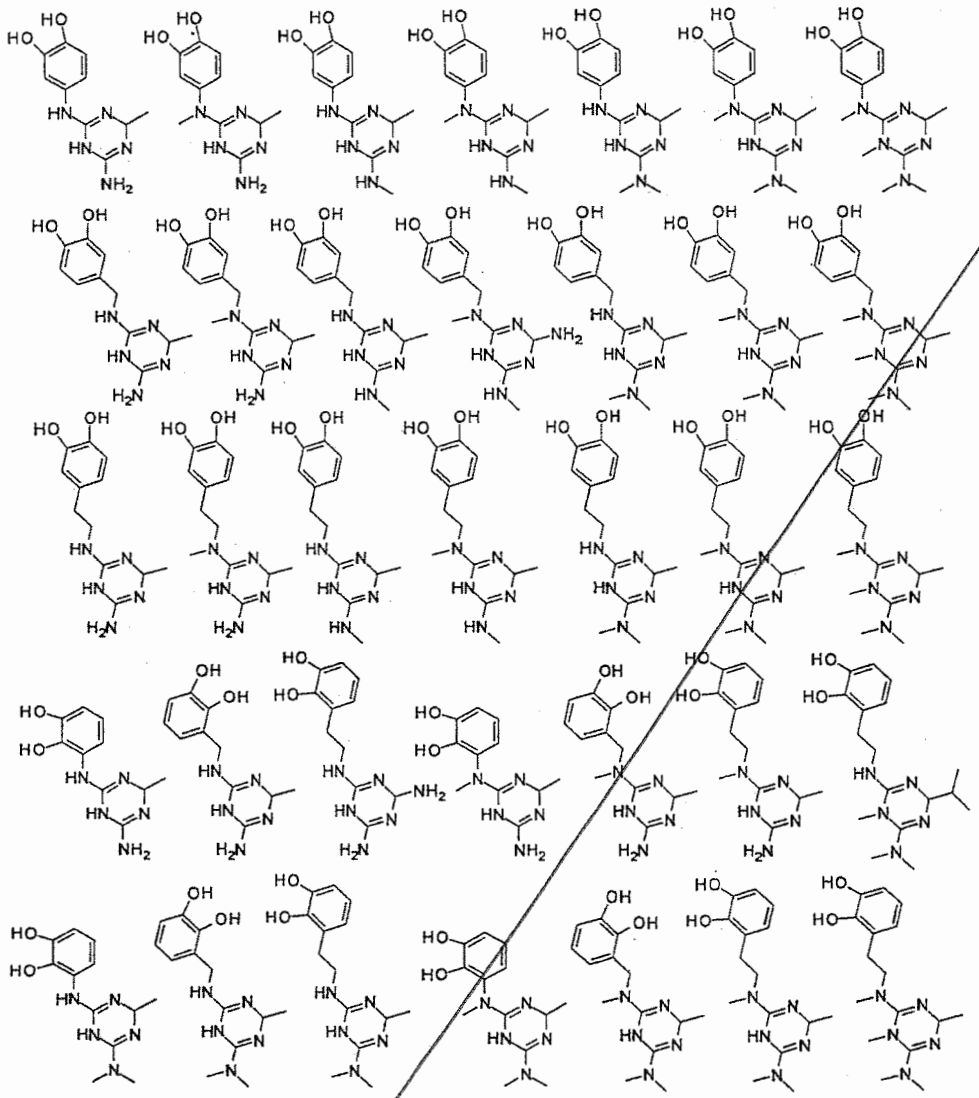


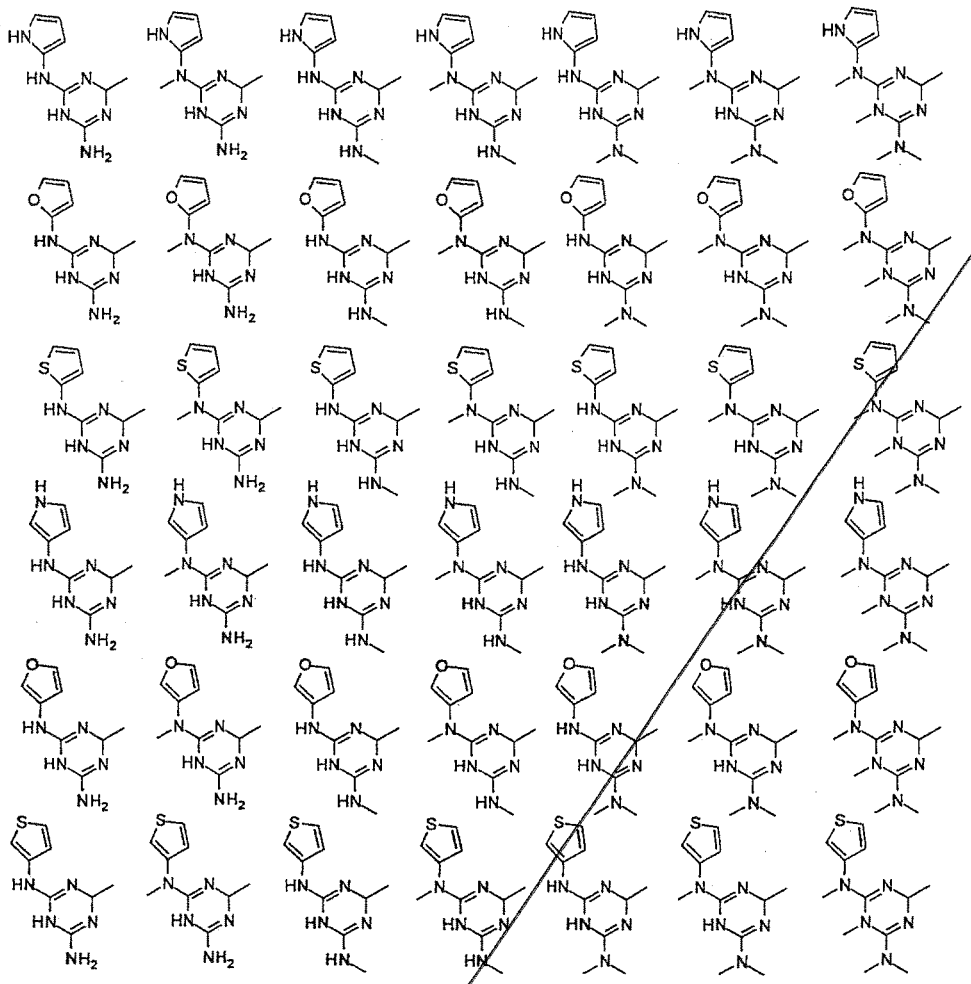


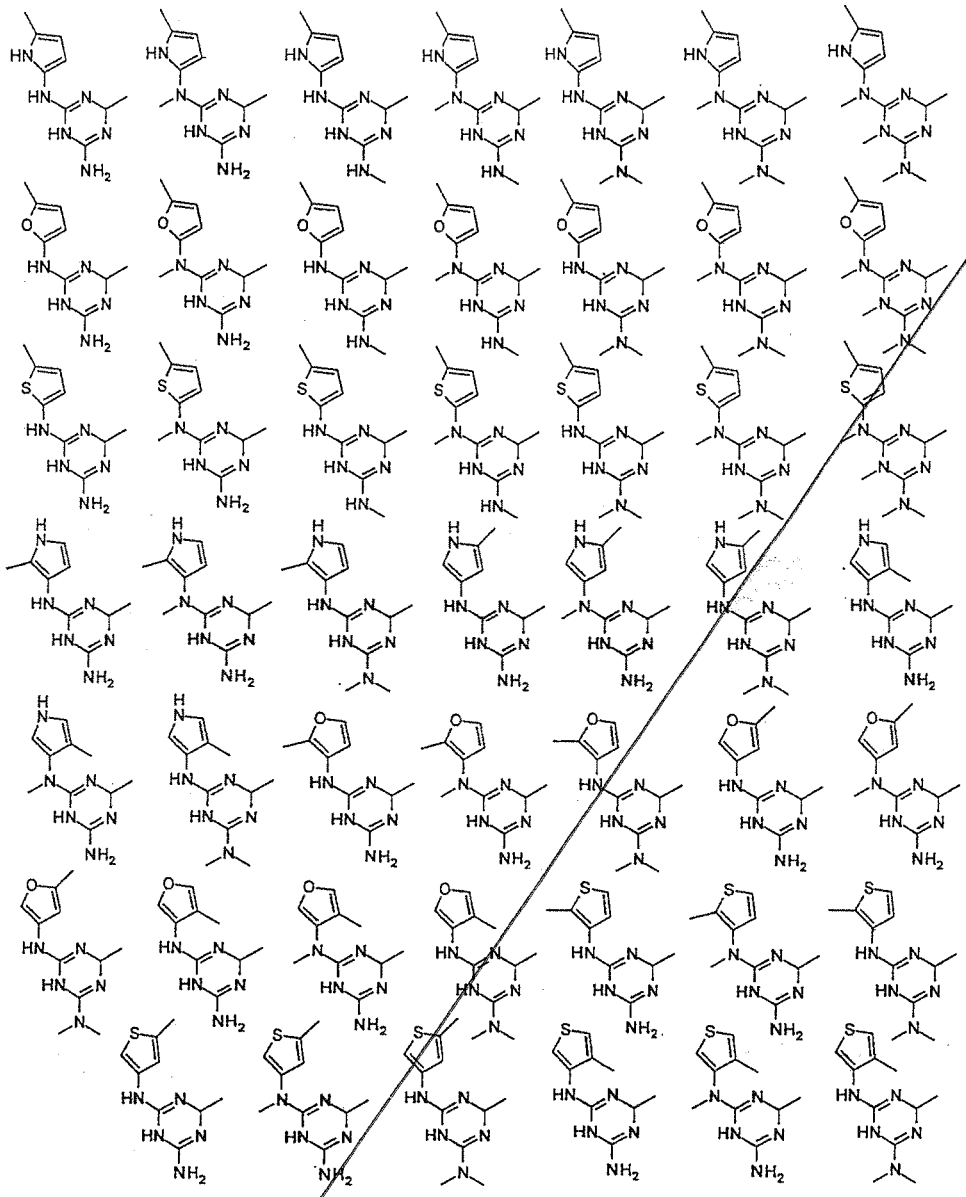


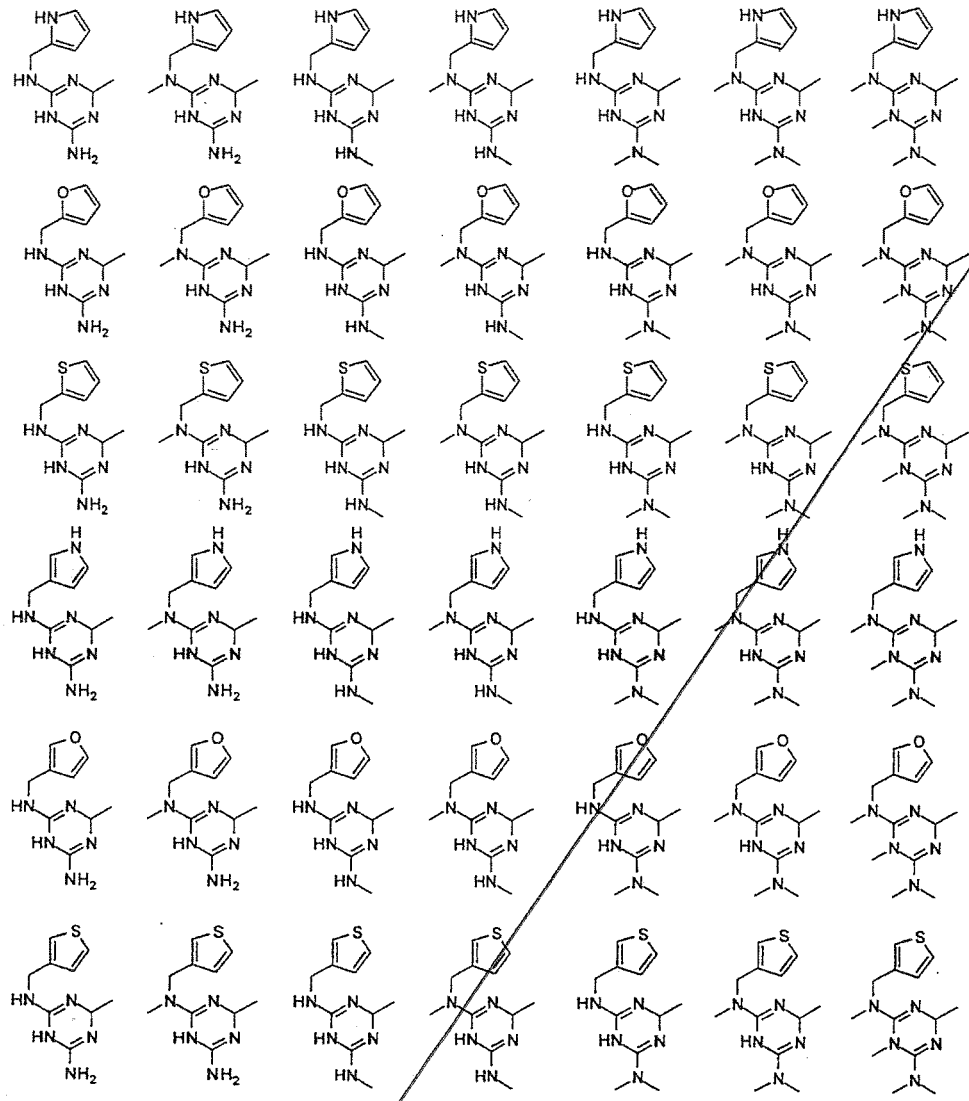


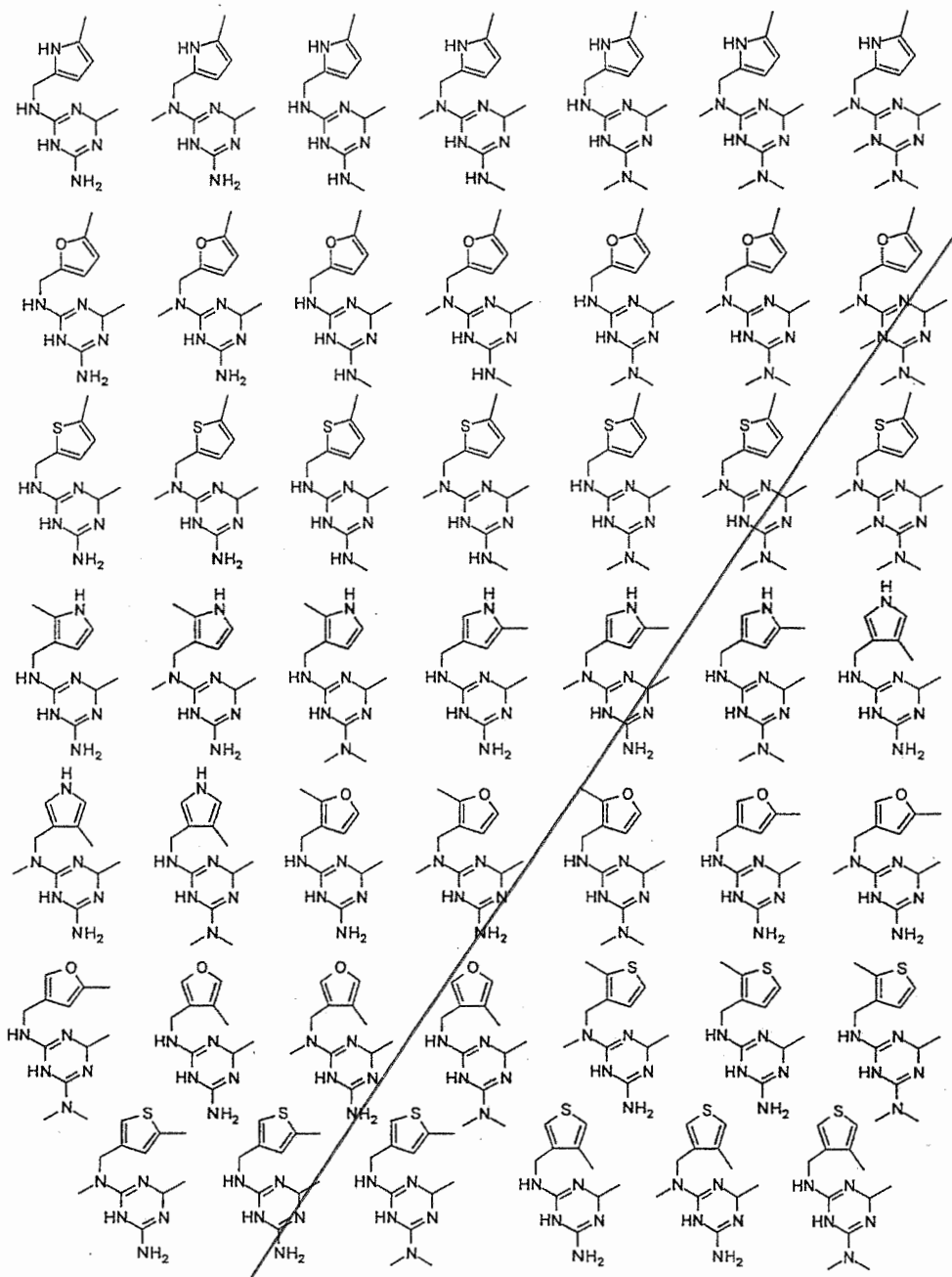


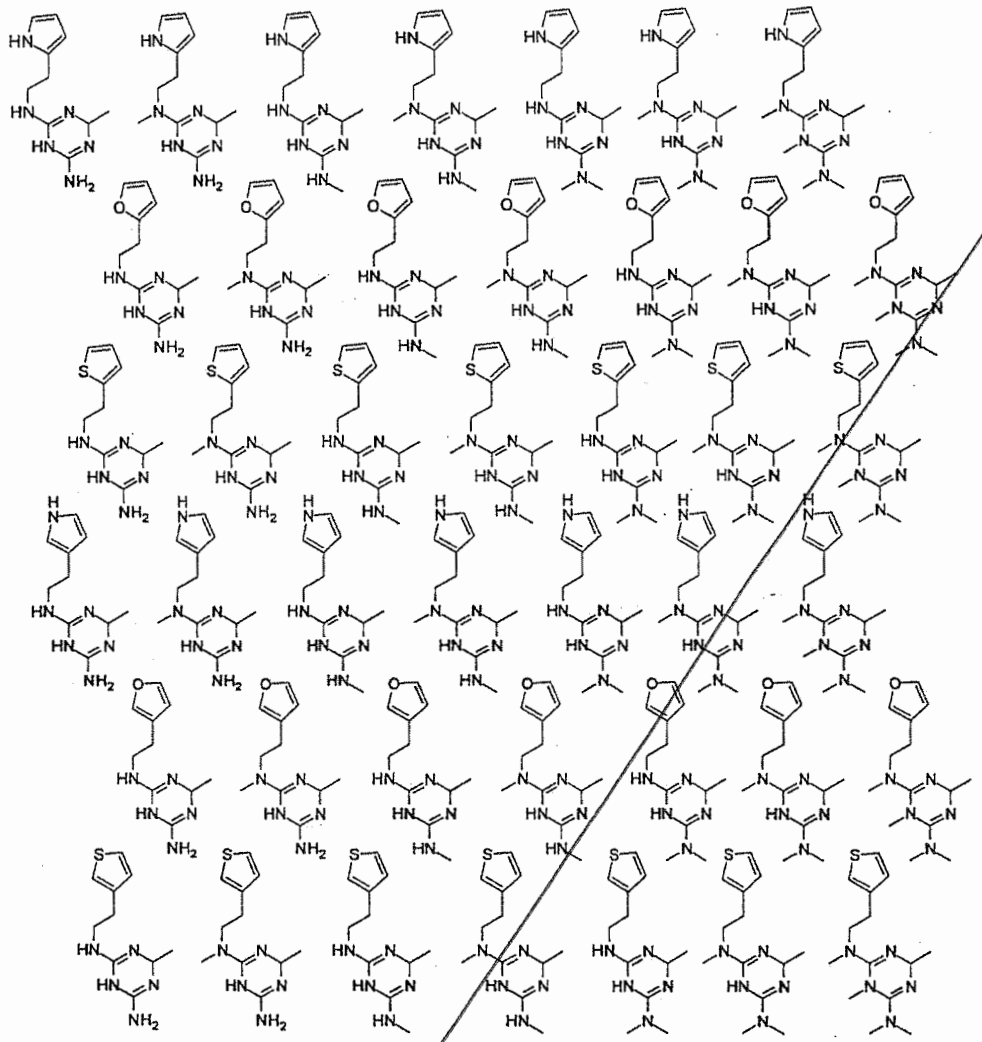


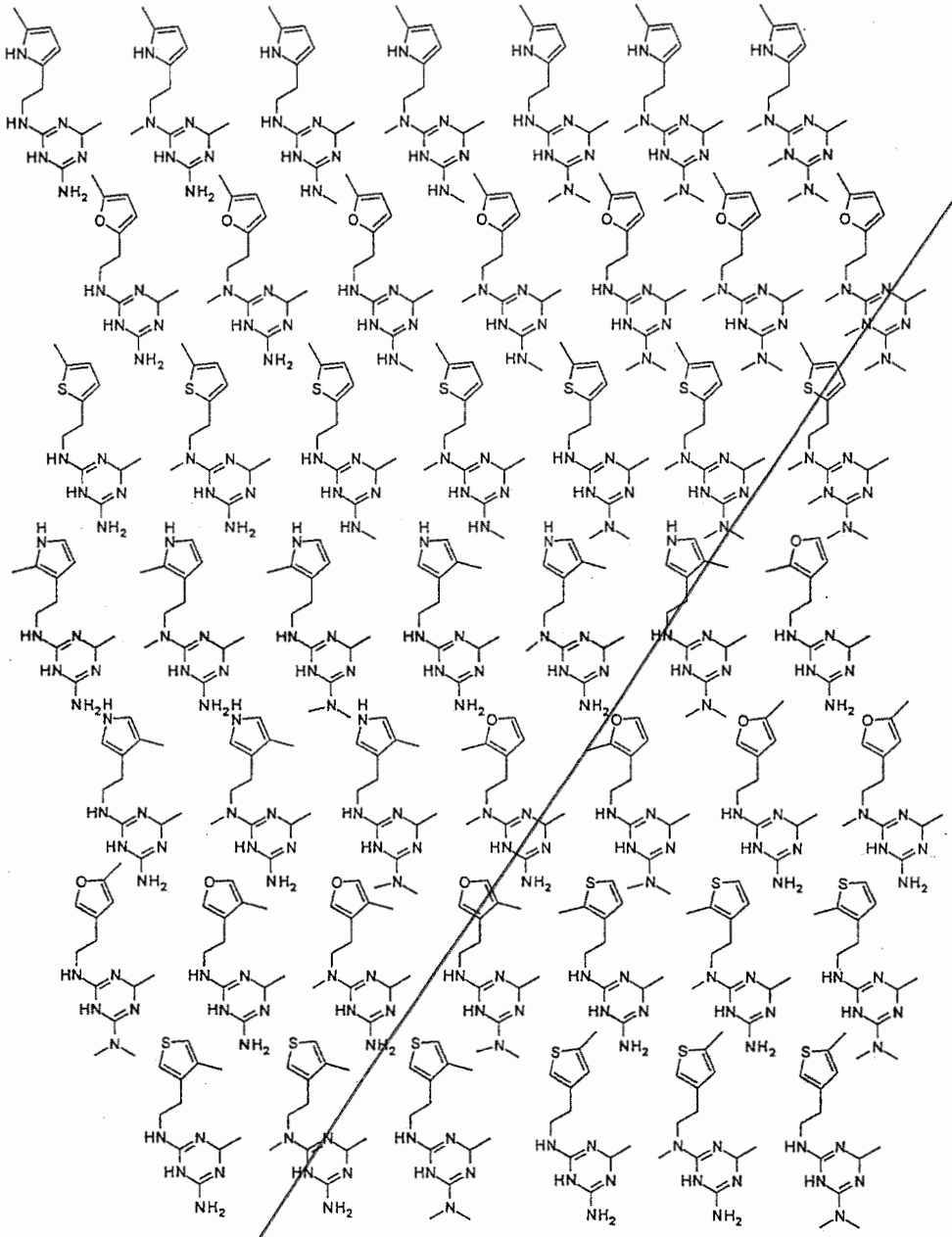


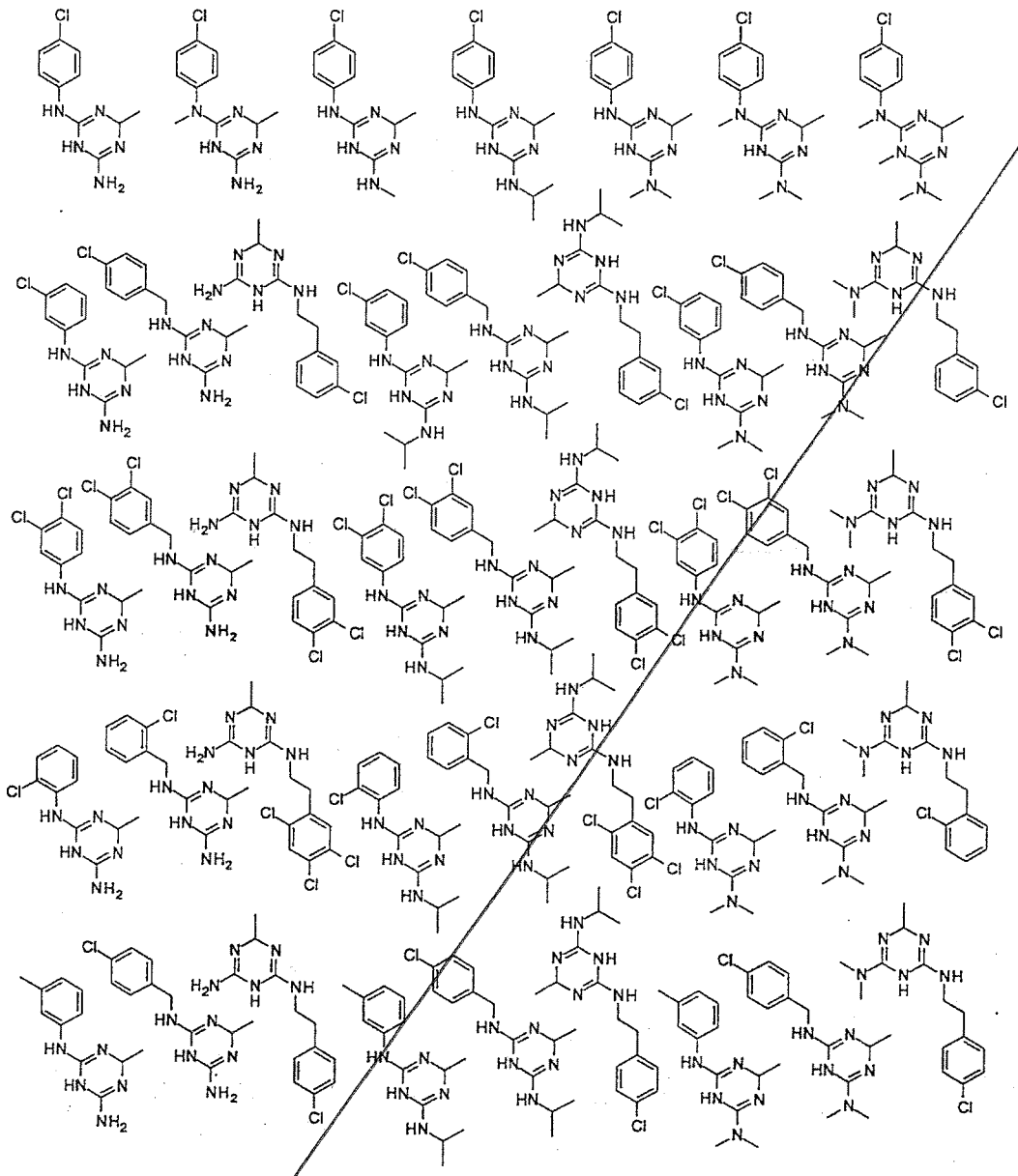




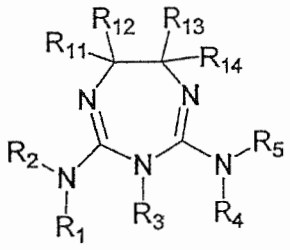








13. A composition comprising a biguanide or related heterocyclic compound of structural Formula IV,



IV

wherein:

wherein R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are independently selected from H, methyl, ethyl, propyl or isopropyl;

and wherein R_1 and R_2, and are independently selected from:

H; optionally substituted alkyl; cycloalkyl; alkylcycloalkyl; heterocycloalkyl; alkylheterocycloalkyl; optionally substituted alkenyl; optionally substituted alkynyl;

optionally substituted aryl; optionally substituted alkylaryl; optionally substituted heteroaryl; optionally substituted alkylheteroaryl; and

or R_1 and R_2 may together form a 3 to 8 membered heterocyclic ring, including the nitrogen atoms to which they are attached

wherein the composition is adapted to reduce the average bioavailability of the compound, release a therapeutically effective amount of the compound to one or more regions of the intestine of a subject, or a combination thereof.

14. The composition according to claim 13, wherein:

R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are independently selected from H or methyl; and

R_1 is selected from:

H,

C_1 to C_{12} straight chain or branched chain alkyl optionally hetero substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl,

C_1 to C_{12} straight chain or branched chain alkenyl optionally hetero substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl,

C_1 to C_{12} straight chain or branched chain alkynyl optionally hetero substituted with oxygen, silicon, sulphur or optionally substituted with OH, O-alkyl, SH, S-alkyl, NH_2, NH-alkyl,

C_3 to C_7 cycloalkyl, C_2 to C_6 heterocycloalkyl, where the heterocycle comprises one or two hetero atoms selected from O, S, or N,

C_4 to C_{12} alkylcycloalkyl,

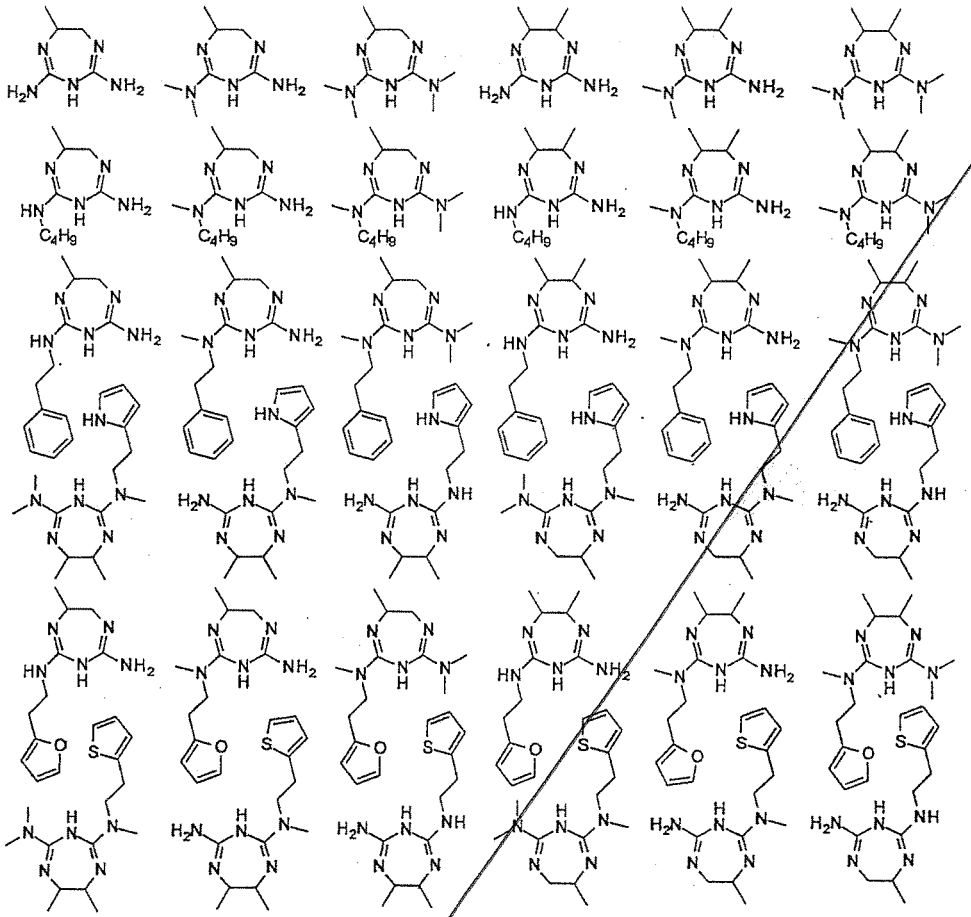
C_3 to C_{11} alkylheterocycloalkyl, where the heterocycle comprises one or two hetero atoms selected from O, S, or N and wherein N is present in the heterocyclic ring, the nitrogen atom may be in the form of an amide, carbamate or urea,

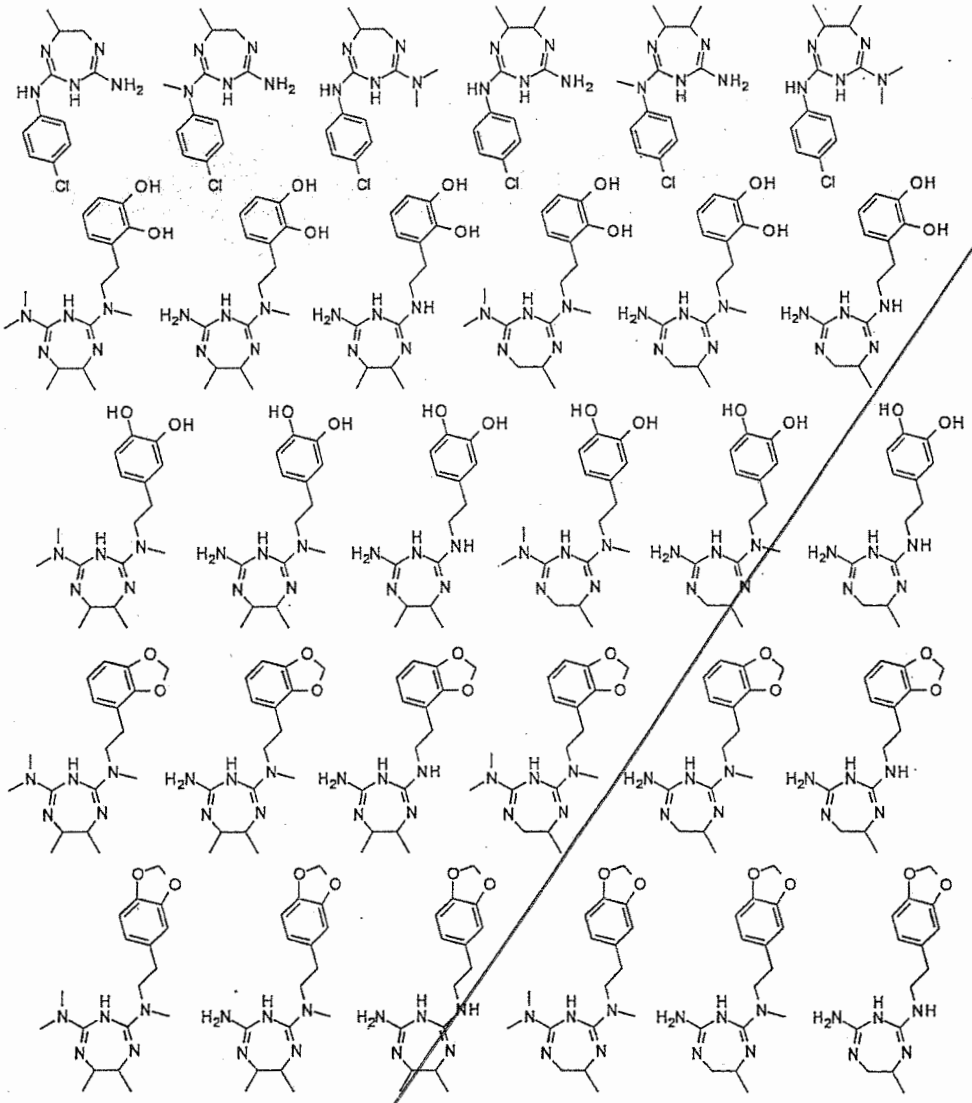
phenyl, substituted phenyl, naphthyl, substituted naphthyl,

alkylphenyl, alkylsubstituted phenyl, alkylnaphthyl, alkylsubstituted naphthyl,

pyridyl, furanyl, thiophenyl, pyrrollyl, oxazolyl, isoxazolyl, thiazolyl, diazolyl, pyrazolyl, triazolyl all of which are optionally substituted.

15. The composition according to claim 13, wherein the compound of Formula IV is selected from the following structures:





16. A composition comprising metformin or salt thereof wherein the composition is adapted to reduce the average bioavailability of the compound, release a therapeutically effective amount of the compound to one or more regions of the intestine of a subject, or a combination thereof.

17. The composition according to any one of claims 1, 4, 7, 10, 13 and 16 wherein the biguanide or related heterocyclic compound comprises an asymmetric center or centers and forms a composition of a racemic mixture, a diastereoisomeric mixture, a single enantiomer, an enantiomeric diastereomer, a meso compound, a pure epimer, or a mixture of epimers thereof, etc.

18. The composition according to any one of claims 1, 4, 7, 10, 13 and 16, wherein the biguanide or related heterocyclic compound comprises one or more double bonds, wherein the compound is a cis/trans, E/Z mixture or an E or Z geometric isomer thereof.

19. The composition according to any one of claims 1, 4, 7, 10, 13 and 16, wherein the biguanide or related heterocyclic compound is a salt selected from hydrochloride, hydrobromide, acetate, propionate, butyrate, sulfate, hydrogen sulfate, sulfite, carbonate, hydrogen carbonate, phosphate, phosphinate, oxalate, hemi-oxalate, malonate, hemi-malonate, fumarate, hemi-fumarate, maleate, hemi-maleate, citrate, hemi-citrate, tartrate, hemi-tartrate, aspartate and glutamate.

20. The composition according to any one of claims 1, 4, 7, 10, 13 and 16, wherein the biguanide or related heterocyclic compound is formulated as a composition comprising the components A, B, and C, wherein:

A is the protonated form of a natural or unnatural amino acid;

B is the dianion of an acid; and

C is the protonated form of any the biguanide or related heterocyclic compound.

21. The composition according to claim 20, wherein

A is the protonated form of a natural amino acid selected from alanine, aspartic acid, asparagine, arginine, glycine, glutamine, glutamic acid lysine, phenylalanine, tyrosine, serine, threonine, tryptophan, leucine, isoleucine, histidine, methionine, proline, cysteine, and cystine; and

B is the dianion of an acid selected from oxalic, malonic, citric, maleic, fumaric, tartaric, aspartic, and glutamic acid.

C is the protonated form of the biguanide or related heterocyclic compound.

23. The composition according to any one of claims 1, 4, 7, 10, 13 and 16, further comprising a DPP-IV inhibitor.

24. The composition according to any one of claims 1, 4, 7, 10, 13 and 16, further comprising an anti-obesity or anti-diabetes agent.

25. A composition according to any one of claims 1, 4, 7, 10, 13 and 16, the composition further comprising a chemosensory receptor ligand that is selected from the group consisting of a sweet receptor ligand, an umami receptor ligand, a fat receptor ligand, a sour receptor ligand and a bile acid receptor ligand.

26. A method of inducing feelings of happiness, well-being or contentment in subjects comprising administering at a composition according to any one of claims 1, 4, 7, 10, 13 and 16.

27. A method of treating a condition selected from metabolic syndrome, diabetes type I, diabetes type II, obesity, binge eating, undesired food cravings, food addiction, a desire to reduce food intake or to lose weight or maintain weight loss, desire to maintain healthy weight, desire to maintain normal blood glucose metabolism, anorexia, pre-diabetes, glucose intolerance, gestational diabetes mellitus (GDM), impaired fasting glycemia (IFG), post-prandial hyperglycemia, accelerated gastric emptying, dumping syndrome, delayed gastric emptying, dyslipidemia, post-prandial dyslipidemia, hyperlipidemia, hypertriglyceridemia, post-prandial hypertriglyceridemia, insulin resistance, bone loss disorders, osteopenia, osteoporosis, muscle wasting disease, muscle degenerative disorders, polycystic ovary syndrome (PCOS), non-alcoholic fatty liver disease (NAFL), non-alcoholic steatohepatitis (NASH), immune disorders of the gut, celiac disease, bowel irregularity, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, short bowel syndrome, peripheral neuropathy and diabetic neuropathy in a subject comprising administering at a composition according to any one of claims 1, 4, 7, 10, 13 and 16.

28. A method of treating a condition selected from sadness, stress, grief, anxiety, anxiety disorder (e.g., generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder or social anxiety disorder or a mood disorder (e.g., depression, bipolar disorder, dysthymic disorder and cyclothymic disorder) comprising administering at a composition according to any one of claims 1, 4, 7, 10, 13 and 16.

29. A method according to claim 27, wherein the condition is diabetes.

30. A method according to claim 27, wherein the condition is obesity.

31. A method according to claim 27, wherein the subject has undergone bariatric surgery.

32. A method according to claim 27, further comprising administration of a drug for diabetes or obesity.

33. A method of treating a defect in energy homeostasis in a subject comprising administering at a composition according to any one of claims 1, 4, 7, 10, 13 and 16.

34. A method of treating overweight in a subject by administering a composition according to any one of claims 1, 4, 7, 10, 13 and 16 to the subject.

35. A method of treating obesity in a subject by administering a composition according to any one of claims 1, 4, 7, 10, 13 and 16 to the subject.

36. A method of reducing food intake in a subject by administering a composition according to any one of claims 1, 4, 7, 10, 13 and 16 to the subject.

37. A method of treating type II diabetes in a subject by administering a composition according to any one of claims 1, 4, 7, 10, 13 and 16 to the subject.

CLAIMS

1. Use of a biguanide compound in the manufacture of a medicament for lowering blood glucose levels in a patient in need thereof, wherein the biguanide compound is in a delayed-release formulation adapted to minimize the circulating plasma concentration of the biguanide compound and/or reduce the average systemic bioavailability of the biguanide compound in the patient.

2. Use of a biguanide compound in the manufacture of a medicament for treating a disorder of glucose metabolism in a patient in need thereof, wherein the biguanide compound is in a delayed-release formulation adapted to minimize the circulating plasma concentration of the biguanide compound and/or reduce the average systemic bioavailability of the biguanide compound in the patient.

3. The use according to claim 1 or 2, wherein the average systemic bioavailability of the biguanide compound as measured by plasma AUC resulting from administration of the delayed-release formulation is less than the average systemic bioavailability of the biguanide compound as measured by plasma AUC resulting from administration of an immediate release formulation having an equivalent amount of the biguanide compound.

4. The use according to claim 1 or 2, wherein the average systemic bioavailability of the biguanide compound as measured by plasma AUC resulting from administration of the delayed-release formulation is 70%, 60%, 50%, 40%, 30% or 20% less than the average systemic bioavailability of the biguanide compound as measured by plasma AUC resulting from administration of an immediate release formulation having an equivalent amount of the biguanide compound.

5. The use according to claim 1 or 2, wherein the biguanide compound is metformin or a salt thereof.

6. The use according to claim 5, wherein the metformin plasma AUC in the patient resulting from administration of a single dose of the delayed-release formulation is $\leq$ 50% of the metformin plasma AUC resulting from administration of a single dose of GLUMETZA® having an equivalent amount of the metformin or a salt thereof.

7. The use according to claim 6, wherein the amount of the metformin or a salt thereof is 500 mg, and wherein administration of a single dose of the delayed-release formulation provides a metformin plasma AUC in the patient that is $\leq$ 2148.5 ng•hr/mL.

8. The use according to claim 6, wherein the amount of the metformin or a salt thereof is 1000 mg, and wherein administration of a single dose of the delayed-release formulation provides a metformin plasma AUC in the patient that is $\leq$ 4311.5 ng•hr/mL.

9. The use according to claim 6, wherein the amount of the metformin or a salt thereof is 1500 mg, and wherein administration of a single dose of the delayed-release formulation provides a metformin plasma AUC in the patient that is $\leq$ 6066 ng•hr/mL.

10. The use according to claim 6, wherein the amount of the metformin or a salt thereof is 2500 mg, and wherein administration of a single dose of the delayed-release formulation provides a metformin plasma AUC in the patient that is $\leq$ 9296.5 ng•hr/mL.

11. The use according to claim 1 or 2, wherein the amount of the biguanide compound is about 500 mg, and wherein the delayed-release formulation minimizes the circulating plasma concentration of the biguanide compound in the patient below about 1 μg/mL, 0.5 μg/mL, or 0.25 μg/mL.

12. The use according to claim 1 or 2, wherein the amount of the biguanide compound is about 1000 mg, and wherein the delayed-release formulation minimizes the circulating plasma concentration of the biguanide compound in the patient below about 2 μg/mL, 1 μg/mL or 0.5 μg/mL.

13. The use according to claim 1 or 2, wherein the amount of the biguanide compound is about 1500 mg, and wherein the delayed-release formulation minimizes the circulating plasma concentration of the biguanide compound in the patient below about 3 μg/mL, 2 μg/mL or 1 μg/mL.

14. The use according to claim 1 or 2, wherein the delayed-release formulation minimizes the plasma C_{max} level of the biguanide compound.

15. The use according to claim 14, wherein the amount of the biguanide compound is about 1000 mg, and wherein the biguanide compound plasma C_{max} in the patient resulting from administration of the delayed-release formulation is less than about 1000 ng/mL.

16. The use according to claim 1 or 2, wherein the daily dose of the biguanide compound is between about 50 mg and about 1000 mg.

17. The use according to claim 1 or 2, wherein the daily dose of the biguanide compound is between about 100 mg and about 500 mg.

18. The use according to claim 1 or 2, wherein the daily dose of the biguanide compound is about 500 mg.

19. The use according to claim 1 or 2, wherein the daily dose of the biguanide compound is about 600 mg.

20. The use according to claim 1 or 2, wherein the daily dose of the biguanide compound is about 1000 mg.

21. The use according to claim 1 or 2, wherein the biguanide compound is enterically-coated.

22. The use according to claim 1 or 2, wherein the biguanide compound is metformin hydrochloride.

23. The use according to claim 1 or 2, wherein the delayed-release formulation further comprises an antidiabetic agent selected from: thiazolidinediones, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, DPP-IV inhibitors, incretin mimetics, and SGLT inhibitors.

24. The use according to claim 23, wherein the antidiabetic agent is an SGLT inhibitor.

25. The use according to claim 1 or 2, wherein the delayed-release formulation further comprises an antiobesity agent.

26. The use according to claim 25, wherein the antiobesity agent is lorcaserin.

27. The use according to claim 25, wherein the antiobesity agent is phentermine.

28. The use according to claim 25, wherein the antiobesity agent is a combination of lorcaserin and phentermine.

29. The use according to claim 25, wherein the antiobesity agent is a combination of topiramate and phentermine.

30. The use according to claim 25, wherein the antiobesity agent is a combination of bupropion and naltrexone.

31. The use according to claim 1 or 2, wherein the patient has diabetes.