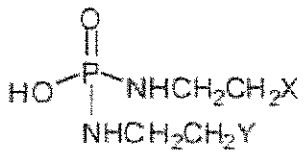
cytotoxic/cytostatic effects of the nitrogen mustards are mainly responsible for the antitumor activity of CPA and IFOS and, by preventing the proliferative expansion of autoreactive lymphocytes, also for the immunosuppressant activity of CPA in autoimmune disease. However, cross-linking of DNA in normal tissues by the nitrogen mustards also causes cytotoxic, mechanism-based collateral damage, particularly myelosuppression resulting in leucocytopenia, which is the principal dose-limiting hematological toxicity (Zhang *et al.*, Current Drug Therapy 1: 55-84 (2006)).

Although phosphoramide mustard and isophosphoramide are chemically similar, isophosphoramide mustard interacts with DNA with a higher affinity than phosphoramide mustard (Boal *et al.*, J. Med. Chem. 32: 1768-1773; 1989). Structural differences involving the intramolecular distance between the chloroethyl groups and their orientation appear to be responsible for the different affinities of the two mustards (Springer *et al.*, J. Org. Chem. 63: 7218-7222 (1998)).

By administering cytotoxic nitrogen mustards directly to cancer patients, the "off-target" toxicities and the drug resistance associated with the prodrugs may be reduced. IPM has been synthesized and preliminary biological evaluations of the compound have been conducted; but, unfortunately, IPM itself is unstable and difficult to use directly for human treatment. Stabilized formulations of IPM might further reduce toxicity and allow metronomic administration of doses that are sufficient for both direct cytotoxicity against the tumor and antiangiogenic activity. Improved methods for formulation and manufacture of IPM and analogues and salts thereof are needed.

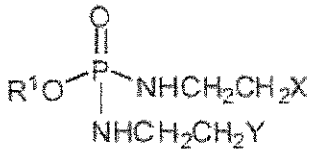
SUMMARY

In one aspect, there is provided a method for the preparation of a compound of formula (D):



(D);

comprising treating a compound of formula (C):



(C);

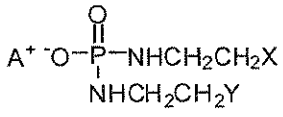
under hydrogenolysis conditions, wherein as valence and stability permit,

X and Y independently represent leaving groups; and

R^1 is benzyl optionally substituted with one or more substituents selected from halogen, $-R^2$, $-OR^2$ and $-NR^2_2$ wherein R^2 is selected in each occurrence from H and lower alkyl; and

the hydrogenolysis condition comprises a solvent system comprising one or more aprotic organic solvents.

The present disclosure~~invention~~ discloses pharmaceutical formulations of isophosphoramide mustard (IPM) salts and analogues thereof as well as methods for synthesizing IPM and salts and analogues thereof. IPM salts and analogues of the disclosure~~invention~~ include compounds of formula (E):



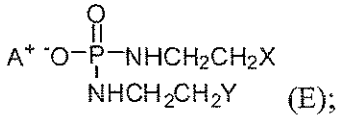
(E)

wherein X and Y independently represent leaving groups; and A^+ is an ammonium cation.

In certain embodiments, the disclosure~~invention~~ relates to pharmaceutical formulations comprising a compound of formula (E) and one or more pharmaceutically acceptable carriers. Methods of preparing such compounds and formulations are also described.

DETAILED DESCRIPTION

The disclosure concerns pharmaceutical formulations of isophosphoramide mustard (IPM) salts and analogues thereof as well as methods for synthesizing IPM and salts and analogues thereof. IPM salts and analogues of the invention include compounds of formula (E):



(E);

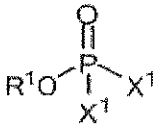
wherein X and Y independently represent leaving groups such as Cl, Br, I, or a sulfonate, e.g., toluenesulfonate, methanesulfonate, 2,4,6-triisopropylbenzenesulfonate, or 2,4,6-trimethylbenzenesulfonate; and A^+ is an ammonium cation. Compounds disclosed in U.S. Application No. 11/257,766, filed October 25, 2005 are useful in the compositions and methods of the invention and are herein incorporated by reference. Formulations of the invention include IPM salts and analogues together with a lubricant, a diluent and a disintegrant. Formulations of the invention may further comprise additional excipients such as a binder and a compression filler. The disclosure further concerns the synthetic preparation of IPM salts and analogues thereof.

I. Salts of IPM and IPM analogs

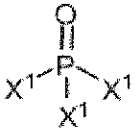
The formulations disclosed herein include IPM and IPM analogs that are formulated with one or more equivalents of base. In certain embodiments, the disclosed compounds are salts of isophosphoramide mustard or isophosphoramide mustard analogs including one or more cations. In one embodiment, the cations can be a conjugate acid of an amine base or can be a quaternary ammonium cation. Suitable counterions for isophosphoramide and its analogs include the conjugate acids (as used herein, terms that refer to amines should be understood to include their conjugate acids unless the context indicates that the free amine is intended) of bases including basic amino acids, aliphatic amines, heterocyclic amines, aromatic amines, pyridines, guanidines, and amidines.

In certain embodiments, group A of formula (E):

1. A method for the preparation of a compound of formula (B):


(B);

comprising treating a compound of formula (A):


(A);

with an alcohol R^1-OH under condensation conditions, wherein, as valence and stability permit,

X^1 independently for each occurrence, is selected from Cl, I, and Br,

R^1 is benzyl optionally substituted with one or more substituents selected from halogen, $-R^2$, $-OR^2$ and $-NR^2_2$ wherein R^2 is selected in each occurrence from H and lower alkyl.

2. The method of claim 1, wherein the condensation conditions comprise an amine base.

3. The method of claim 2, wherein the amine base is triethylamine.

4. The method of any of claims 1-3, wherein the compound of formula (A) is $P(O)Cl_3$.

5. The method of any of claims 1-4, wherein R^1 is unsubstituted benzyl.

6. The method of any of claims 1-5, wherein the condensation conditions comprise an aprotic organic solvent.

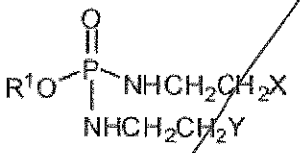
7. — The method of claim 6, wherein ~~the organic solvent comprises acetonitrile.~~

8. The method of any of claims 1-7, wherein the condensation conditions comprise approximately equimolar amounts of the compound of formula (A) and substitution reagent R^1-OH.

9. The method of any of claims 1-8, wherein the condensation conditions comprise maintaining a temperature between -35 to -25 °C.

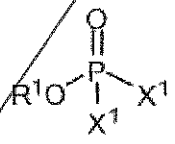
10. The method of claim 9, wherein the condensation conditions comprise maintaining a temperature of about -30 °C.

11. A method for the preparation of a compound of formula (C):



(C);

comprising treating a compound of formula (B):



(B);

with amines $XCH_2CH_2NH_2$ and $YCH_2CH_2NH_2$ or salts thereof under condensation conditions, wherein, as valence and stability permit,

X and Y independently represent leaving groups which may be the same or different; and

R^1 is benzyl optionally substituted with one or more substituents selected from halogen, $-R^2$, $-OR^2$ and $-NR^2_2$ wherein R^2 is selected in each occurrence from H and lower alkyl.

12. The method of claim 11, wherein the condensation conditions comprise approximately equimolar amounts of amines $XCH_2CH_2NH_2$ and $YCH_2CH_2NH_2$ or salts thereof.

13. The method of claim 11, wherein the condensation conditions comprise approximately two equivalents of amine or salts thereof per equivalent of the compound of formula (B).

14. The method of claim 11, wherein the condensation conditions comprise sequential addition of amines $XCH_2CH_2NH_2$ and $YCH_2CH_2NH_2$ or salts thereof to a compound of formula (B).

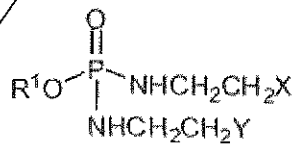
15. The method of claim 11, wherein X and Y are both halogen.

16. The method of claim 15, wherein X and Y are both Cl.

17. The method of claim 11, wherein the condensation conditions comprise an amine base.

18. The method of claim 17, wherein the amine base is triethylamine.

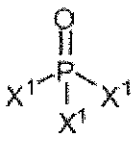
19. A method for the preparation of a compound of formula (C):



(C);

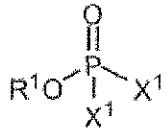
comprising

a. treating a compound of formula (A):



(A);

~~with an alcohol R^1-OH under condensation conditions to generate a compound of formula~~ (B):


(B) ; and

b. treating a compound of formula (B) with amines $XCH_2CH_2NH_2$ and $YCH_2CH_2NH_2$ or a salt thereof under condensation conditions, wherein, independently for each occurrence and as valence and stability permit,

X and Y independently represent leaving groups;

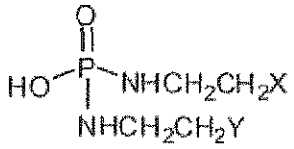
X^1 independently for each occurrence, is selected from Cl, I, and Br,

R^1 is benzyl optionally substituted with one or more substituents selected from halogen, $-R^2$, $-OR^2$ and $-NR^2_2$ wherein R^2 is selected in each occurrence from H and lower alkyl.

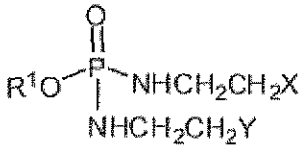
20. The method of claim 11, wherein the condensation conditions comprise maintaining a temperature between -35 to -25 °C.

21. The method of claim 20, wherein the condensation conditions comprise maintaining a temperature of about -30 °C.

22. A method for the preparation of a compound of formula (D):


(D);

comprising treating a compound of formula (C):


(C);

with a reducing agent under hydrogenolysis conditions, wherein as valence and stability permit,

X and Y independently represent leaving groups; and

R^1 is benzyl optionally substituted with one or more substituents selected from halogen, $-R^2$, $-OR^2$ and $-NR^2_2$ wherein R^2 is selected in each occurrence from H and lower alkyl.

23. The method of claim 22, wherein X and Y are both halogen.

24. The method of claim 23, wherein X and Y are both Cl.

25. The method of claim 22, wherein R^1 is unsubstituted benzyl.

26. The method of claim 22, wherein the hydrogenolysis conditions comprise hydrogen gas and a hydrogenolysis catalyst.

27. The method of claim 26, wherein the hydrogenolysis catalyst comprises Pd.

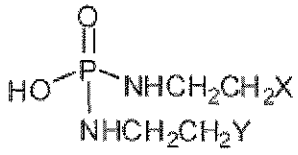
28. The method of claim 26, wherein the hydrogenolysis catalyst comprises Pd/carbon.

29. The method of claim 22, wherein the reducing conditions comprise hydrogen pressure greater than 1 atm.

30. The method of claim 29, wherein the pressure is less than or equal to 50 psi.

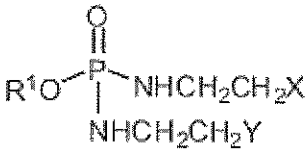
Claims

1. A method for the preparation of a compound of formula (D):



(D);

comprising treating a compound of formula (C):



(C);

under hydrogenolysis conditions, wherein as valence and stability permit,

X and Y independently represent leaving groups; and

R^1 is benzyl optionally substituted with one or more substituents selected from halogen, $-R^2$, $-OR^2$ and $-NR^2_2$ wherein R^2 is selected in each occurrence from H and lower alkyl; and

the hydrogenolysis condition comprises a solvent system comprising one or more aprotic organic solvents.

2. The method of claim 1, wherein X and Y are both halogen.

3. The method of claim 2, wherein X and Y are both Cl.

4. The method of claim 1, wherein R^1 is unsubstituted benzyl.

5. The method of claim 1, wherein the hydrogenolysis conditions comprise hydrogen gas and a hydrogenolysis catalyst.

6. The method of claim 5, wherein the hydrogenolysis catalyst comprises Pd.

7. The method of claim 5, wherein the hydrogenolysis catalyst comprises Pd/carbon.

8. The method of claim 1, wherein the hydrogenolysis conditions comprise hydrogen pressure greater than 1 atm.

9. The method of claim 8, wherein the pressure is less than or equal to 50 psi.

10. The method of claim 1, wherein the aprotic organic solvent is selected from the group consisting of acetone, 2-butanone, butyl acetate, ethyl acetate, acetonitrile, toluene, THF, dioxane, N,N-DMF, DMSO, 1,2-dichloroethane, and methylene chloride.

11. The method of claim 10, wherein the aprotic solvent is acetonitrile.

12. The method of claim 11, wherein acetonitrile represents more than about 10, 20, 30, 50, 70, 90, or 95% of the solvent system.

13. The method of claim 8, wherein the hydrogen pressure is between 20 psi and 75 psi.

14. The method of claim 13, wherein the hydrogen pressure is between 20 psi and 50 psi.

15. The method of claim 13, wherein the hydrogen pressure is between 50 psi and 75 psi.