

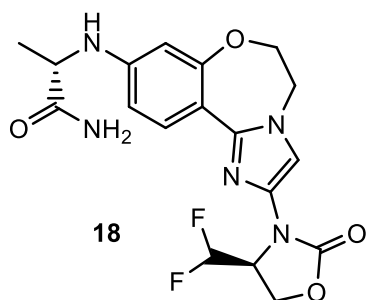
new selective inhibitors of mutant PI3K α isoforms.

GDC-0077, also known by the IUPAC name: (S)-2-((2-((S)-4-(difluoromethyl)-2-oxooxazolidin-3-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)amino)propanamide, has potent PI3K activity (WO 2017/001645, US 2017/0015678, Edgar K. et al, #156, "Preclinical characterization of GDC-0077, a specific PI3K alpha inhibitor in early clinical development", and Staben. S. #DDT02-0 "Discovery of GDC-0077, a highly isoform selective inhibitor of PI3K alpha that promotes selective loss of mutant-p110alpha", American Assoc. for Cancer Res. (AACR) annual meeting, April 2, 2017, Washington DC), and is being studied in patients with locally advanced or metastatic solid tumors. There remains a need for new processes for making benzoxazepin oxazolidinone compounds such as GDC-0077.

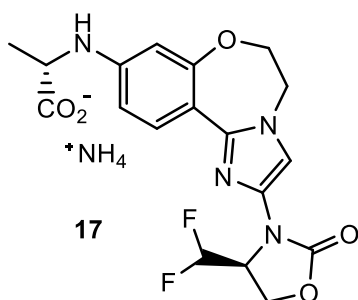
SUMMARY

The disclosure relates to methods of making benzoxazepin oxazolidinone compounds and intermediates thereof.

There is provided a process for the preparation of compound **18**, having the structure:

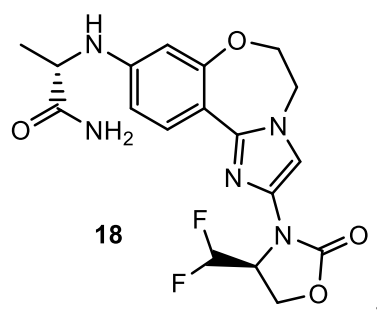


comprising reacting compound **17**, having the structure:

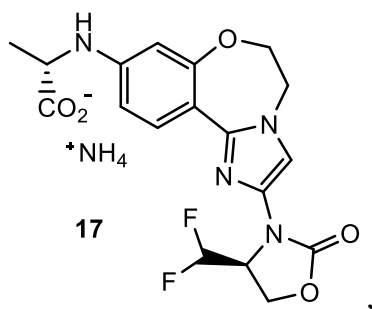


with ammonia (or an ammonia equivalent) and a peptide coupling reagent to form compound **18**.

In one aspect, provided is a process for the preparation of compound **18**, having the structure:



comprising reacting compound **17**, having the structure:

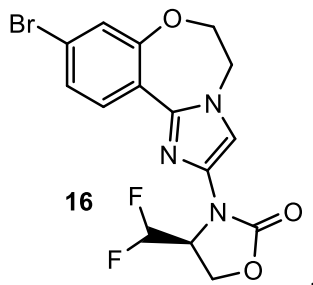


with ammonia or an ammonia equivalent selected from the group consisting of ammonium acetate, ammonium bicarbonate, ammonium carbamate, ammonium carbonate, ammonium chloride, ammonium hydroxide, and ammonium phosphate, and a peptide coupling reagent selected from the group consisting of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride/*N*-hydroxysuccinimide; *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride/1-hydroxybenzotriazole; and 1,1'-carbonyldiimidazole (CDI), to form compound **18**.

In some examples, the peptide coupling agent is selected from the group consisting of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC)/*N*-

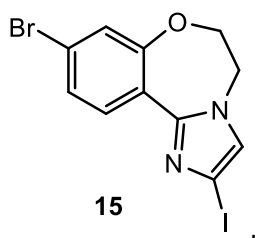
hydroxysuccinimide (HOSu), EDC/1-hydroxybenzotriazole (HOBT) and 1,1'-carbonyldiimidazole (CDI). In some examples, the peptide coupling reagent is EDC/HOSu.

In some examples, compound **17** is prepared by a process comprising reacting compound **16**, having the structure:

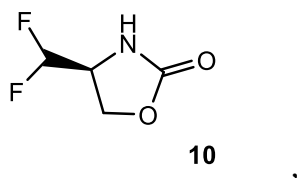


with (S)-2-aminopropanoic acid and a copper (I) catalyst (e.g., copper(I) oxide) to form compound **17**.

In some examples, compound **16** is prepared by a process comprising reacting compound **15**, having the structure:



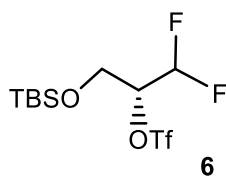
with compound **10**, having the structure:



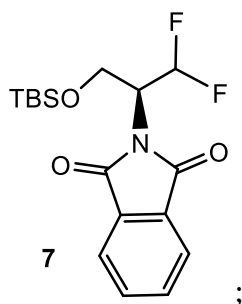
a copper salt (e.g., copper(II) acetate) and a ligand (e.g., *trans*-*N,N*-dimethylcyclohexane-1,2-diamine or 3,4,7,8-tetramethyl-1,10-phenanthroline) to form compound **16**.

In some examples, compound **10** is prepared by a process comprising:

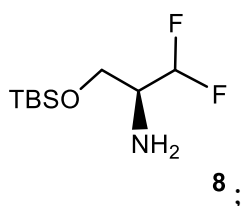
(a) reacting compound **6**, having the structure:



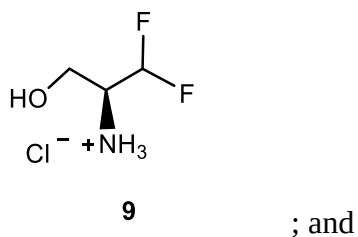
with potassium phthalimide to form compound **7**, having the structure:



(b) reacting compound **7** with hydrazine in water to form compound **8**, having the structure:



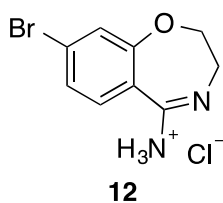
(c) reacting compound **8** with hydrochloric acid to form compound **9**, having the structure:



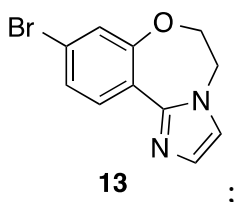
(d) reacting compound **9** with triphosgene to form compound **10**.

In some examples, compound **15** is prepared by a process comprising:

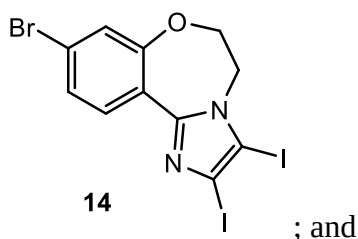
(a) reacting compound **12**, having the structure:



with chloroacetaldehyde to form compound **13**, having the structure:

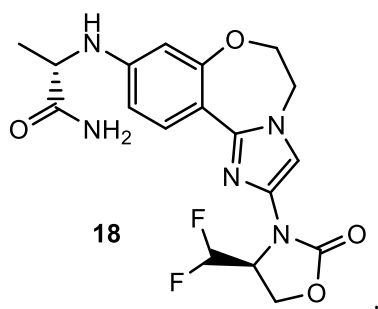


(b) reacting compound **13** with *N*-iodosuccinimide (NIS) to form compound **14**, having the structure:

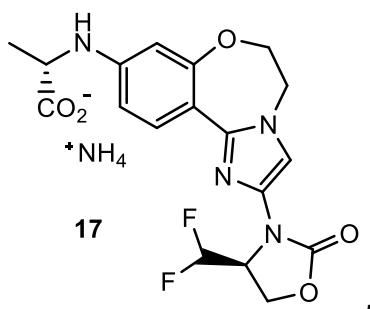


(c) reacting compound **14** with a ethylmagnesium bromide to form compound **15**.

In some examples, provided is a process for the preparation of compound **18**, having the structure:

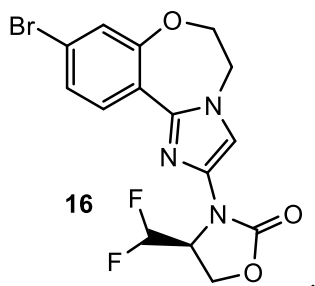


comprising reacting compound **17**, having the structure:



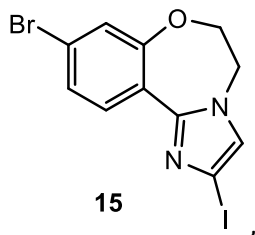
with N-hydroxysuccinimide, ammonia, and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride to form compound **18**.

In some examples, compound **17** is prepared by a process comprising reacting compound **16**, having the structure:

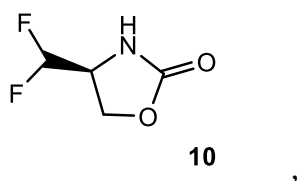


with (*S*)-2-aminopropanoic acid and copper (I) oxide to form compound **17**.

In some examples, compound **16** is prepared by a process comprising reacting compound **15**, having the structure:

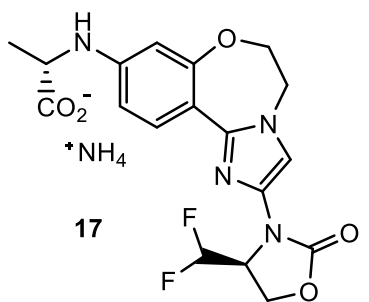


with compound **10**, having the structure:

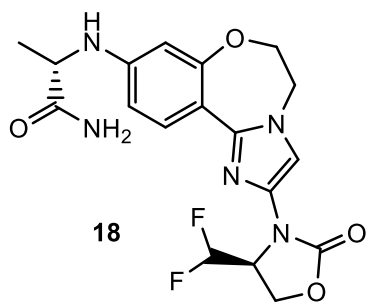


copper (II) acetate and *trans*-*N,N*-dimethylcyclohexane-1,2-diamine to form compound **16**.

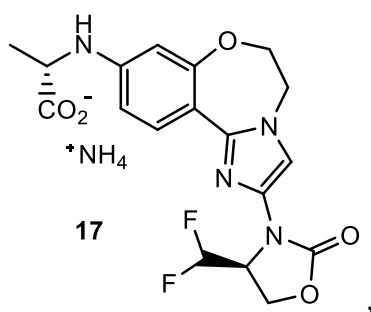
In another aspect, provided is a compound of ammonium (*S*)-2-((2-((*S*)-4-(difluoromethyl)-2-oxooxazolidin-3-yl)-5,6-dihydrobenzo[*f*]imidazo[1,2-*d*][1,4]oxazepin-9-yl)amino)propionate (compound **17**), having the structure:



In another aspect, provided is a process for the preparation of compound **18**, having the structure:

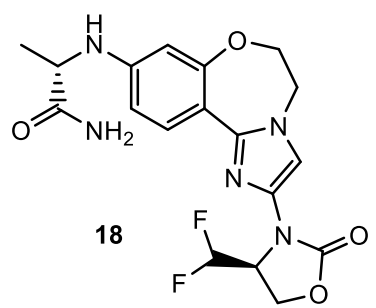


comprising reacting compound **17**, having the structure:

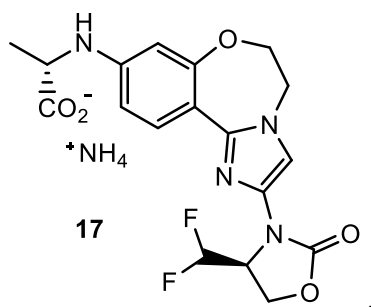


with ammonia and a peptide coupling reagent which is *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride/*N*-hydroxysuccinimide, to form compound **18**.

In another aspect, provided is a process for the preparation of compound **18**, having the structure:



comprising reacting compound **17**, having the structure:



with ammonia or an ammonia equivalent and a peptide coupling reagent, to form compound **18**.

DETAILED DESCRIPTIONS OF THE INVENTION

Definitions

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

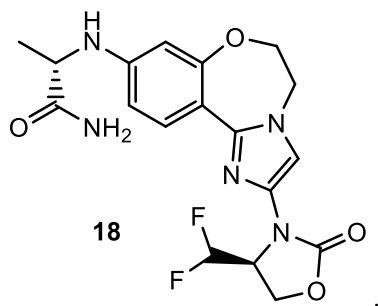
The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities.

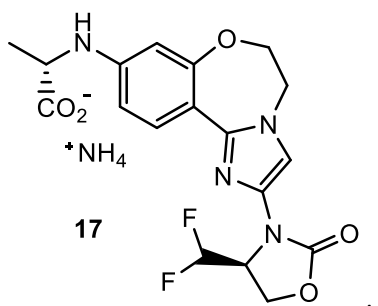
CLAIMS

What is claimed is:

1. A process for the preparation of compound **18**, having the structure:



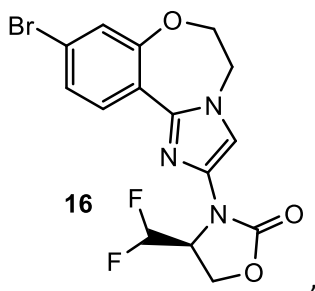
comprising reacting compound **17**, having the structure:



with ammonia or an ammonia equivalent selected from the group consisting of ammonium acetate, ammonium bicarbonate, ammonium carbamate, ammonium carbonate, ammonium chloride, ammonium hydroxide, and ammonium phosphate, and a peptide coupling reagent selected from the group consisting of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride/*N*-hydroxysuccinimide; *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride/1-hydroxybenzotriazole; and 1,1'-carbonyldiimidazole (CDI), to form compound **18**.

2. The process of claim 1, wherein the peptide coupling reagent is *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride/*N*-hydroxysuccinimide.

3. The process of claim 1 or 2 wherein compound **17** is prepared by a process comprising reacting compound **16**, having the structure:



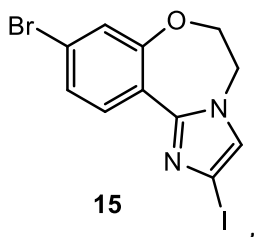
with (S)-2-aminopropanoic acid and a copper catalyst to form compound **17**.

4. The process of claim 3, wherein the copper catalyst is copper (I) catalyst.

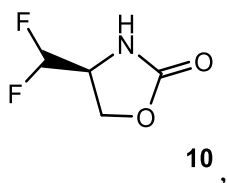
5. The process of claim 3, wherein the copper catalyst is selected from copper (I) oxide, copper (I) chloride, copper (I) bromide, copper (I) iodide, copper (I) trifluoromethanesulfonate, and copper (II) oxide.

6. The process of claim 5, wherein the copper (I) catalyst is copper (I) oxide.

7. The process of any one of claims 3 to 6, wherein compound **16** is prepared by a process comprising reacting compound **15**, having the structure:



with compound **10**, having the structure:



a copper salt and a ligand to form compound **16**.

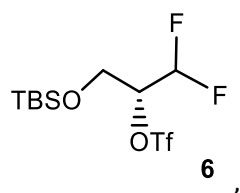
8. The process of claim 7, wherein the copper salt is copper(II) acetate.

9. The process of claim 7 or 8, wherein the ligand is *trans*-N,N-dimethylcyclohexane-1,2-diamine.

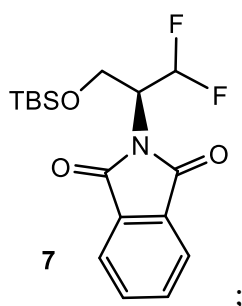
10. The process of claim 7 or 8, wherein the ligand is 3,4,7,8-tetramethyl-1,10-phenanthroline.

11. The process of any one of claims 7 to 10, wherein compound **10** is prepared by a process comprising:

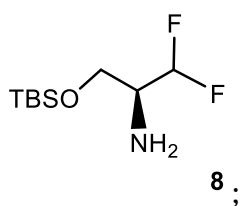
(a) reacting compound **6**, having the structure:



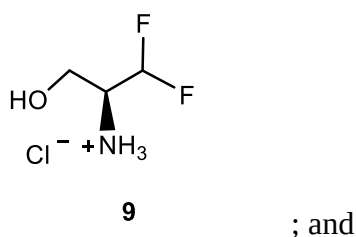
with potassium phthalimide to form compound **7**, having the structure:



(b) reacting compound **7** with hydrazine in water to form compound **8**, having the structure:



(c) reacting compound **8** with hydrochloric acid to form compound **9**, having the structure:

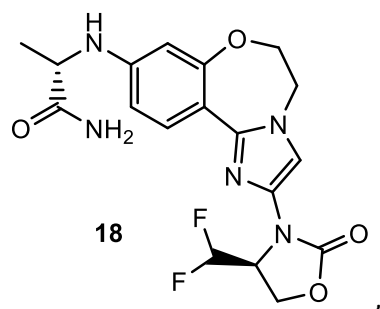


(d) reacting compound **9** with triphosgene to form compound **10**.

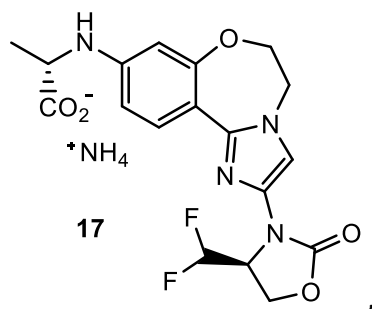
12. The process of any one of claims 7 to 11, wherein compound **15** is prepared by a process comprising:

(a) reacting compound **12**, having the structure:



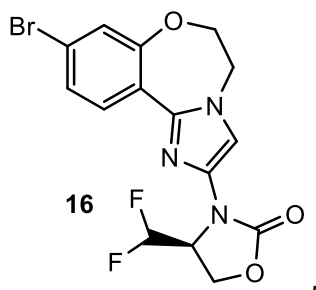


comprising reacting compound **17**, having the structure:



with ammonia and a peptide coupling reagent which is *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride/*N*-hydroxysuccinimide, to form compound **18**.

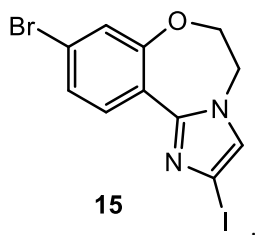
15. The process of claim 14, wherein compound **17** is prepared by a process comprising reacting compound **16**, having the structure:



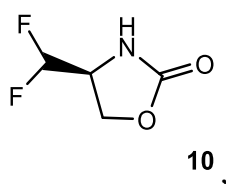
with (S)-2-aminopropanoic acid and a copper (I) catalyst to form compound **17**.

16. The process of claim 15, wherein the copper (I) catalyst is copper (I) oxide.

17. The process of claim 15 or 16, wherein compound **16** is prepared by a process comprising reacting compound **15**, having the structure:



with compound **10**, having the structure:



a copper salt and a ligand to form compound **16**.

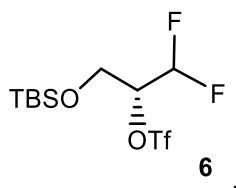
18. The process of claim 17, wherein the copper salt is copper(II) acetate.

19. The process of claim 17 or 18, wherein the ligand is *trans*-*N,N*-dimethylcyclohexane-1,2-diamine.

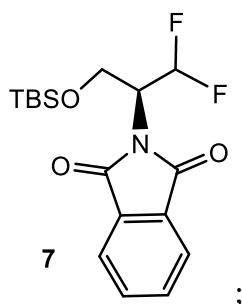
20. The process of claim 17 or 18, wherein the ligand is 3,4,7,8-tetramethyl-1,10-phenanthroline.

21. The process of any one of claims 17 to 20, wherein compound **10** is prepared by a process comprising:

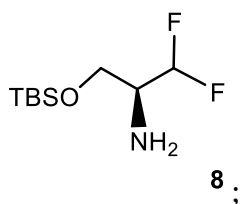
(a) reacting compound **6**, having the structure:



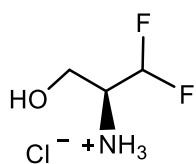
with potassium phthalimide to form compound **7**, having the structure:



(b) reacting compound **7** with hydrazine in water to form compound **8**, having the structure:



(c) reacting compound **8** with hydrochloric acid to form compound **9**, having the structure:

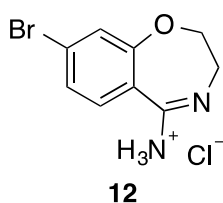


; and

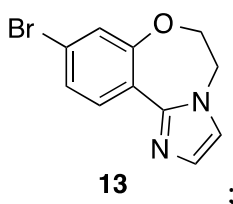
(d) reacting compound **9** with triphosgene to form compound **10**.

22. The process of any one of claims 17 to 21, wherein compound **15** is prepared by a process comprising:

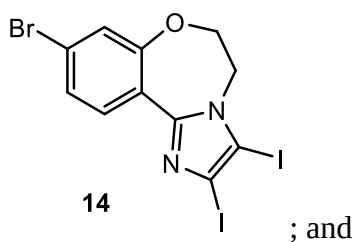
(a) reacting compound **12**, having the structure:



with chloroacetaldehyde to form compound **13**, having the structure:

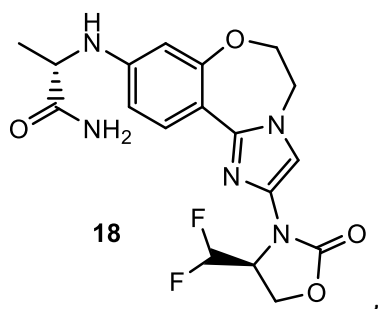


(b) reacting compound **13** with *N*-iodosuccinimide to form compound **14**, having the structure:

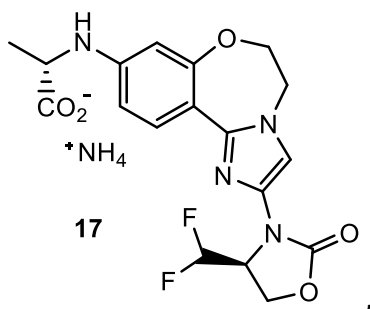


(c) reacting compound **14** with a ethylmagnesium bromide to form compound **15**.

23. A process for the preparation of compound **18**, having the structure:



comprising reacting compound **17**, having the structure:



with ammonia or an ammonia equivalent and a peptide coupling reagent, to form compound **18**.

24. The process of claim 23, wherein the peptide coupling reagent is a reagent or a combination of two reagents selected from *N*-hydroxysuccinimide (HOSu) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole (HOBt) and EDC, 1-hydroxy-7-azabenzotriazole (HOAt) and EDC, 2-hydroxypyridine-1-oxide and EDC, ethyl (hydroxyimino)cyanoacetate (Oxyma) and EDC, 3-[bis(dimethylamino)methylumyl]-3H-benzotriazol-1-oxide hexafluorophosphate (HBTU), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), and 1,1'-carbonyldiimidazole (CDI); and *N,N'*-diisopropylcarbodiimide (DIC) or *N,N'*-dicyclohexylcarbodiimide (DCC).

25. The process of claim 23 or 24, wherein the ammonia equivalent is selected from ammonium acetate, ammonium bicarbonate, ammonium carbamate, ammonium carbonate, ammonium chloride, ammonium hydroxide, and ammonium phosphate.