

COMPOUNDS AND COMPOSITIONS USEFUL FOR TREATING DISORDERS RELATED TO NTRK

CLAIM OF PRIORITY

5 This application claims priority from U.S.S.N. 62/257,476 filed November 19, 2015, which is incorporated herein by reference in its entirety.

BACKGROUND

Neurotrophic Tyrosine Receptor Kinase (NTRK) 1, 2 and 3 are receptor tyrosine kinases (RTKs) that activate multiple downstream pathways involved in cell proliferation and survival.

10 Various genetic fusions, arising from aberrant chromosomal translocations of the genes coding for these RTKs, are implicated in the etiology of multiple cancers including high and low grade glioma, cholangiocarcinoma, papillary thyroid carcinoma, colon cancer and non-small cell lung cancer. A genomics analysis on the landscape of kinase fusions identified NTRK fusions in a wide array of additional cancer types including head and neck squamous cell carcinoma, pancreatic
15 adenocarcinoma, sarcoma and melanoma, thereby providing further therapeutic rationale for deploying inhibitors of these kinases to treat multiple oncologic indications.

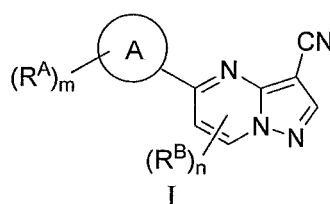
The identification of NTRK fusions as the underlying cause of certain cancers prompted the discovery and clinical development of several NTRK kinase inhibitors to treat tumors that harbor an NTRK fusion protein. Early clinical data support the viability of this approach in providing benefit
20 to patients with specific human malignancies. Ultimately however, despite clear signs of clinical activity, most patients' cancers will become resistant to kinase inhibitor therapy leading to relapse and progression of the disease. When resistance occurs, the patient's treatment options are often very limited. There is thus a need for compounds that inhibit NTRK, as well as its resistant mutants.

SUMMARY OF THE INVENTION

25 The present disclosure provides inhibitors of NTRK and NTRK mutants, *e.g.*, NTRK resistant mutants (as defined herein), for example, inhibitors of structural formula (I) and pharmaceutically acceptable salts and compositions thereof. The present disclosure further provides
30 methods of using the compounds of the invention, and pharmaceutically acceptable salts and

compositions thereof, to inhibit the activity of NTRK or its mutants in a cell or patient. The present disclosure further provides methods for using the compounds of the invention, and pharmaceutically acceptable salts and compositions thereof, to treat a subject suffering from a condition mediated by aberrant NTRK activity, *e.g.*, cancer.

- 5 In one aspect, the present disclosure features a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein:



- Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;
- 10 each R^A is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, - $N(R^1)(R^1)$, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2N(R^2)(R^2)$, $-(C_1-C_6$
- 15 alkylene)- $S(O)_2N(R^2)(R^2)$, $-C(O)-N(R^2)(R^2)$, $-N(R^2)(R^2)-C(O)R^1$, $-(C_1-C_6$ alkylene)- $N(R^2)-C(O)R^1$, $-NR^2S(O)_2R^1$, $-P(O)(R^1)(R^1)$, and $-OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of R^a ;
- each R^B is independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, and $-OR^1$;
- 20 each R^1 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently
- 25 substituted with 0-5 occurrences of R^b ;
- each R^2 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl; or 2 R^2 together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of R^b ;

each R^a and R^b is independently selected from halo, cyano, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -N(R'')(R''), -C(O)-N(R'')(R''), -N(R'')(R'')-C(O)R', and -(C₁-C₆ alkylene)-N(R'')-C(O)R';

each R' and R'' is independently selected from hydrogen and C₁-C₆ alkyl or C₁-C₆

5 hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2;

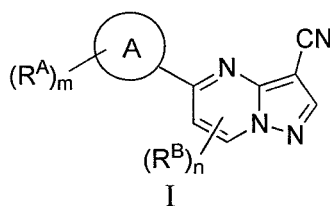
provided that the compound is not (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile.

10 In another aspect, the present disclosure provides pharmaceutical compositions comprising a compound of structural formula (I) as described herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present disclosure provides a method for inhibiting NTRK activity in a cell or in a patient. In some embodiments, said method comprises the step of contacting the cell or

15 administering to the patient a compound of structural formula (I) or a pharmaceutically acceptable salt or composition thereof.

In another aspect, the present disclosure provides a method for inhibiting NTRK activity in a cell, said method comprising the step of contacting the cell with a compound of structural Formula I or a pharmaceutically acceptable salt or composition thereof, wherein:



Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each R^A is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ hydroxyalkyl, C₁-C₆ heteroalkyl, -N(R¹)(R¹), nitro, cyano, -C(O)R¹, -OC(O)R¹, -C(O)OR¹, -SR¹, -S(O)₂R¹, -S(O)₂-N(R²)(R²), -(C₁-C₆

alkylene)-S(O)₂-N(R²)(R²), -C(O)-N(R²)(R²), -N(R²)(R²)-C(O)R¹, -(C₁-C₆ alkylene)-N(R²)-C(O)R¹, -NR²S(O)₂R¹, -P(O)(R¹)(R¹), and -OR¹; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of R^a;

each R^B is independently selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ hydroxyalkyl, C₁-C₆ heteroalkyl, -N(R¹)(R¹), nitro, cyano, and -OR¹;

each R¹ is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ hydroxyalkyl, C₁-C₆ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^b;

each R² is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ heteroalkyl; or 2 R² together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of R^b;

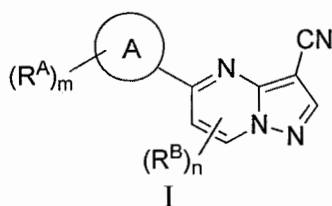
each R^a and R^b is independently selected from halo, cyano, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -N(R'')(R''), -C(O)-N(R'')(R''), -N(R'')(R'')-C(O)R', and -(C₁-C₆ alkylene)-N(R'')-C(O)R';

each R' and R'' is independently selected from hydrogen and C₁-C₆ alkyl or C₁-C₆ hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

In another aspect, the present disclosure provides a use of a compound of structural Formula I or a pharmaceutically acceptable salt or composition thereof in the manufacture of a medicament for inhibiting NTRK activity in a patient, wherein:



Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each R^A is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2N(R^2)(R^2)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2N(R^2)(R^2)$, $-C(O)-N(R^2)(R^2)$, $-N(R^2)(R^2)-C(O)R^1$, $-(C_1-C_6 \text{ alkylene})-N(R^2)-C(O)R^1$, $-NR^2S(O)_2R^1$, $-P(O)(R^1)(R^1)$, and $-OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of R^a ;

each R^B is independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, and $-OR^1$;

each R^1 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^b ;

each R^2 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl; or 2 R^2 together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of R^b ;

each R^a and R^b is independently selected from halo, cyano, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $-N(R'')(R'')$, $-C(O)-N(R'')(R'')$, $-N(R'')(R'')-C(O)R'$, and $-(C_1-C_6 \text{ alkylene})-N(R'')-C(O)R'$;

each R' and R'' is independently selected from hydrogen and C_1 - C_6 alkyl or C_1 - C_6 hydroxyalkyl;

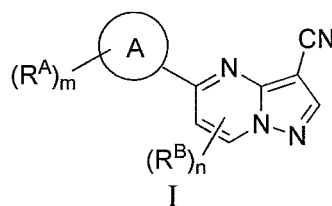
m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

The present disclosure also provides a method for treating a subject suffering from a condition mediated by aberrant NTRK activity. In some embodiments, said method comprises

administering to the subject a therapeutically effective amount of a compound of structural formula (I) or a pharmaceutically acceptable salt or composition thereof.

In another aspect, the present disclosure provides a use of a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament, for treating a subject suffering from a condition mediated by aberrant neurotrophic tyrosine receptor kinase (NTRK) activity, wherein:



Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each R^A is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2-N(R^2)(R^2)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2-N(R^2)(R^2)$, $-C(O)-N(R^2)(R^2)$, $-N(R^2)(R^2)-C(O)R^1$, $-(C_1-C_6 \text{ alkylene})-N(R^2)-C(O)R^1$, $-NR^2S(O)_2R^1$, $-P(O)(R^1)(R^1)$, and $-OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of R^a ;

each R^B is independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, and $-OR^1$;

each R^1 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^b ;

each R^2 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl; or 2 R^2 together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of R^b ;

each R^a and R^b is independently selected from halo, cyano, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $-N(R'')(R'')$, $-C(O)-N(R'')(R'')$, $-N(R'')(R'')-C(O)R'$, and $-(C_1-C_6 \text{ alkylene})-N(R'')-C(O)R'$;

each R' and R'' is independently selected from hydrogen and C_1 - C_6 alkyl or C_1 - C_6 hydroxyalkyl;

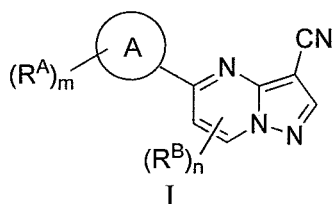
m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

The present disclosure further provides a method for treating a subject who has developed resistance to a cancer treatment. In some embodiments, said method comprises administering to the subject a therapeutically effective amount of a compound of structural formula (I) or a

5 pharmaceutically acceptable salt or composition thereof.

In another aspect, the present disclosure provides a use of a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a subject who has developed resistance to a cancer treatment, wherein:



Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each R^A is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2-N(R^2)(R^2)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2-N(R^2)(R^2)$, $-C(O)-N(R^2)(R^2)$, $-N(R^2)(R^2)-C(O)R^1$, $-(C_1-C_6 \text{ alkylene})-N(R^2)-C(O)R^1$, $-NR^2S(O)_2R^1$, $-P(O)(R^1)(R^1)$, and $-OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of R^a ;

each R^B is independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, and $-OR^1$;

each R^1 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^b ;

each R^2 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl; or 2 R^2 together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of R^b ;

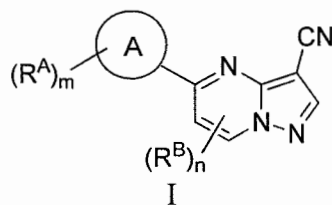
each R^a and R^b is independently selected from halo, cyano, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxyl, C_1 - C_6 haloalkoxyl, $-N(R'')(R'')$, $-C(O)-N(R'')(R'')$, $-N(R'')(R'')-C(O)R'$, and $-(C_1-C_6 \text{ alkylene})-N(R'')-C(O)R'$;

each R' and R'' is independently selected from hydrogen and C_1 - C_6 alkyl or C_1 - C_6 hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

In a further aspect, the present disclosure provides a compound of structural Formula I or a pharmaceutically acceptable salt or composition thereof for use in inhibiting NTRK activity in a cell or in a patient, wherein:



Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each R^A is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxyl, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2-N(R^2)(R^2)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2-N(R^2)(R^2)$, $-C(O)-N(R^2)(R^2)$, $-N(R^2)(R^2)-C(O)R^1$, $-(C_1-C_6 \text{ alkylene})-N(R^2)-C(O)R^1$,

$-\text{NR}^2\text{S}(\text{O})_2\text{R}^1$, $-\text{P}(\text{O})(\text{R}^1)(\text{R}^1)$, and $-\text{OR}^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of R^a ;

each R^b is independently selected from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, halo, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ haloalkoxy, $\text{C}_1\text{-C}_6$ hydroxyalkyl, $\text{C}_1\text{-C}_6$ heteroalkyl, $-\text{N}(\text{R}^1)(\text{R}^1)$, nitro, cyano, and $-\text{OR}^1$;

each R^1 is independently selected from hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ haloalkoxy, $\text{C}_1\text{-C}_6$ hydroxyalkyl, $\text{C}_1\text{-C}_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ hydroxyalkyl, $\text{C}_1\text{-C}_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^b ;

each R^2 is independently selected from hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ heteroalkyl; or 2 R^2 together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of R^b ;

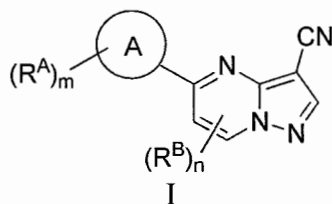
each R^a and R^b is independently selected from halo, cyano, hydroxyl, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkoxy, $-\text{N}(\text{R}'')(\text{R}'')$, $-\text{C}(\text{O})-\text{N}(\text{R}'')(\text{R}'')$, $-\text{N}(\text{R}'')(\text{R}'')-\text{C}(\text{O})\text{R}'$, and $-(\text{C}_1\text{-C}_6\text{ alkylene})-\text{N}(\text{R}'')-\text{C}(\text{O})\text{R}'$;

each R' and R'' is independently selected from hydrogen and $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_1\text{-C}_6$ hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

In yet another aspect, the present disclosure provides a compound of structural Formula I or a pharmaceutically acceptable salt or composition thereof for use in treating a subject suffering from a condition mediated by aberrant neurotrophic tyrosine receptor kinase (NTRK) activity, wherein:



Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each R^A is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2-N(R^2)(R^2)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2-N(R^2)(R^2)$, $-C(O)-N(R^2)(R^2)$, $-N(R^2)(R^2)-C(O)R^1$, $-(C_1-C_6 \text{ alkylene})-N(R^2)-C(O)R^1$, $-NR^2S(O)_2R^1$, $-P(O)(R^1)(R^1)$, and $-OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of R^a ;

each R^B is independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, and $-OR^1$;

each R^1 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^b ;

each R^2 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl; or 2 R^2 together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of R^b ;

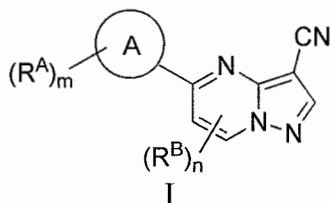
each R^a and R^b is independently selected from halo, cyano, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $-N(R'')(R'')$, $-C(O)-N(R'')(R'')$, $-N(R'')(R'')-C(O)R'$, and $-(C_1-C_6 \text{ alkylene})-N(R'')-C(O)R'$;

each R' and R'' is independently selected from hydrogen and C_1 - C_6 alkyl or C_1 - C_6 hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

In another aspect, the present disclosure provides a compound of structural Formula I or a pharmaceutically acceptable salt or composition thereof for use in treating a subject who has developed resistance to a cancer treatment, wherein:



Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each R^A is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2-N(R^2)(R^2)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2-N(R^2)(R^2)$, $-C(O)-N(R^2)(R^2)$, $-N(R^2)(R^2)-C(O)R^1$, $-(C_1-C_6 \text{ alkylene})-N(R^2)-C(O)R^1$, $-NR^2S(O)_2R^1$, $-P(O)(R^1)(R^1)$, and $-OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of R^a ;

each R^B is independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, and $-OR^1$;

each R^1 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^b ;

each R^2 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl; or 2 R^2 together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of R^b ;

each R^a and R^b is independently selected from halo, cyano, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $-N(R'')(R'')$, $-C(O)-N(R'')(R'')$, $-N(R'')(R'')-C(O)R'$, and $-(C_1-C_6 \text{ alkylene})-N(R'')-C(O)R'$;

each R' and R'' is independently selected from hydrogen and C_1 - C_6 alkyl or C_1 - C_6 hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

EMBODIMENTS OF THE INVENTION

- 5 In one aspect, the invention features a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein:

each R^1 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^b ;

each R^2 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl; or 2 R^2 together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of R^b ;

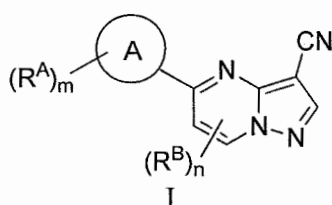
each R^a and R^b is independently selected from halo, cyano, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxyl, C_1 - C_6 haloalkoxyl, $-N(R'')(R'')$, $-C(O)-N(R'')(R'')$, $-N(R'')(R'')-C(O)R'$, and $-(C_1-C_6 \text{ alkylene})-N(R'')-C(O)R'$;

each R' and R'' is independently selected from hydrogen and C_1 - C_6 alkyl or C_1 - C_6 hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

11. A method for inhibiting NTRK activity in a cell, said method comprising the step of contacting the cell with a compound of structural Formula I or a pharmaceutically acceptable salt or composition thereof, wherein:



Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each R^A is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxyl, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2-N(R^2)(R^2)$, $-(C_1-C_6$

alkylene)-S(O)₂-N(R²)(R²), -C(O)-N(R²)(R²), -N(R²)(R²)-C(O)R¹, -(C₁-C₆ alkylene)-N(R²)-C(O)R¹, -NR²S(O)₂R¹, -P(O)(R¹)(R¹), and -OR¹; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxyl, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of R^a;

each R^B is independently selected from C₁-C₆ alkyl, C₁-C₆ alkoxyl, halo, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxyl, C₁-C₆ hydroxyalkyl, C₁-C₆ heteroalkyl, -N(R¹)(R¹), nitro, cyano, and -OR¹;

each R¹ is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxyl, C₁-C₆ hydroxyalkyl, C₁-C₆ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^b;

each R² is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ heteroalkyl; or 2 R² together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of R^b;

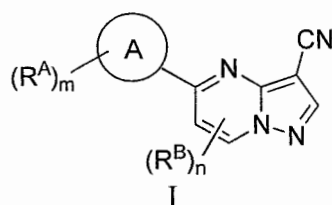
each R^a and R^b is independently selected from halo, cyano, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxyl, C₁-C₆ haloalkoxyl, -N(R'')(R''), -C(O)-N(R'')(R''), -N(R'')(R'')-C(O)R', and -(C₁-C₆ alkylene)-N(R'')-C(O)R';

each R' and R'' is independently selected from hydrogen and C₁-C₆ alkyl or C₁-C₆ hydroxyalkyl;

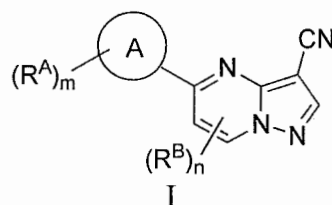
m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

12. Use of a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament, for treating a subject suffering from a condition mediated by aberrant neurotrophic tyrosine receptor kinase (NTRK) activity, wherein:



13. Use of a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a subject who has developed resistance to a cancer treatment, wherein:



Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each R^A is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2N(R^2)(R^2)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2N(R^2)(R^2)$, $-C(O)-N(R^2)(R^2)$, $-N(R^2)(R^2)-C(O)R^1$, $-(C_1-C_6 \text{ alkylene})-N(R^2)-C(O)R^1$, $-NR^2S(O)_2R^1$, $-P(O)(R^1)(R^1)$, and $-OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of R^a ;

each R^B is independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, and $-OR^1$;

each R^1 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^b ;

each R^2 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl; or 2 R^2 together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of R^b ;

each R^a and R^b is independently selected from halo, cyano, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $-N(R'')(R'')$, $-C(O)-N(R'')(R'')$, $-N(R'')(R'')-C(O)R'$, and $-(C_1-C_6 \text{ alkylene})-N(R'')-C(O)R'$;

$-\text{NR}^2\text{S}(\text{O})_2\text{R}^1$, $-\text{P}(\text{O})(\text{R}^1)(\text{R}^1)$, and $-\text{OR}^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of R^a ;

each R^b is independently selected from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, halo, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ haloalkoxy, $\text{C}_1\text{-C}_6$ hydroxyalkyl, $\text{C}_1\text{-C}_6$ heteroalkyl, $-\text{N}(\text{R}^1)(\text{R}^1)$, nitro, cyano, and $-\text{OR}^1$;

each R^1 is independently selected from hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ haloalkoxy, $\text{C}_1\text{-C}_6$ hydroxyalkyl, $\text{C}_1\text{-C}_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ hydroxyalkyl, $\text{C}_1\text{-C}_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^b ;

each R^2 is independently selected from hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ heteroalkyl; or 2 R^2 together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of R^b ;

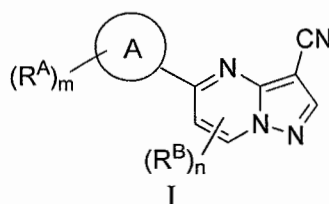
each R^a and R^b is independently selected from halo, cyano, hydroxyl, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkoxy, $-\text{N}(\text{R}'')(\text{R}'')$, $-\text{C}(\text{O})-\text{N}(\text{R}'')(\text{R}'')$, $-\text{N}(\text{R}'')(\text{R}'')-\text{C}(\text{O})\text{R}'$, and $-(\text{C}_1\text{-C}_6\text{ alkylene})-\text{N}(\text{R}'')-\text{C}(\text{O})\text{R}'$;

each R' and R'' is independently selected from hydrogen and $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_1\text{-C}_6$ hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

17. Use of a compound of structural Formula I or a pharmaceutically acceptable salt or composition thereof in the manufacture of a medicament for inhibiting NTRK activity in a patient, wherein:



Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each R^A is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2-N(R^2)(R^2)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2-N(R^2)(R^2)$, $-C(O)-N(R^2)(R^2)$, $-N(R^2)(R^2)-C(O)R^1$, $-(C_1-C_6 \text{ alkylene})-N(R^2)-C(O)R^1$, $-NR^2S(O)_2R^1$, $-P(O)(R^1)(R^1)$, and $-OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of R^a ;

each R^B is independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, and $-OR^1$;

each R^1 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^b ;

each R^2 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl; or 2 R^2 together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of R^b ;

each R^a and R^b is independently selected from halo, cyano, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $-N(R'')(R'')$, $-C(O)-N(R'')(R'')$, $-N(R'')(R'')-C(O)R'$, and $-(C_1-C_6 \text{ alkylene})-N(R'')-C(O)R'$;

each R' and R'' is independently selected from hydrogen and C_1 - C_6 alkyl or C_1 - C_6 hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.