

for aneuploidy since it can lead to multipolar mitosis (*See Shi and King, Nature, 2005; 437:1038-1042*).

[12] While loss of function due to APC may be partially correct, there are reports showing that a large fraction of colon cancer patients have at least one APC gene product that is truncated, and that this has a gain of function. Thus truncated APC proteins may play an active role in colon cancer initiation and progression as opposed to being recessive; for example, truncated APC, but not full-length APC may activate Asef and promote cell migration.

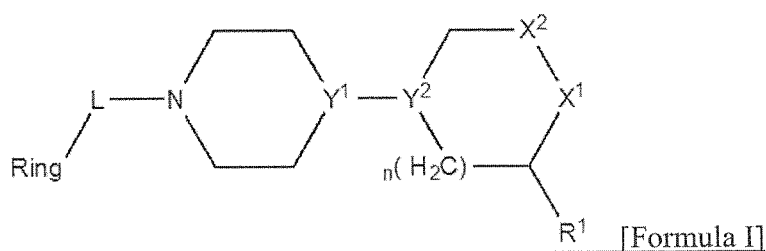
[13] Although defects in APC occur in a high fraction of colon cancer cases, there are currently no therapeutics targeting vulnerabilities resulting from these defects. The described invention provides small molecule inhibitor compounds that selectively target truncated APC in immortalized Human Colonic Epithelial Cells (HCECs) for treating colon cancer.

SUMMARY OF THE INVENTION

[14] According to one aspect ~~embodiment~~, the ~~described invention~~ disclosure provides a series of small molecule compounds that selectively inhibit the growth of human cancer cells that contain a truncated Adenomatous Polyposis Coli (APC) protein.

[15] According to one embodiment, the small molecule anti-cancer compound is a compound of Formula I.

In an aspect, there is provided a compound according to Formula I:



wherein

Y¹ and Y² are each independently CH or N;

L is SO₂, CO, CH₂, or CHMe;

X² is selected from the group consisting of CH₂, CHR², NR³, O, and S;

X¹ is selected from the group consisting of CH₂, CHR⁴, NR⁵, O, and S;

n = 0, 1, 2

R¹ and R² are each independently selected from the group consisting of H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, CH₂aryl, and CH₂heteroaryl;

R³, R⁴ and R⁵ are each independently selected from the group consisting of C₁₋₆ alkyl; C₁₋₆ cycloalkyl, C₁₋₆ alkenyl, C₁₋₆ alkynyl, aryl, heteroaryl, CH₂aryl, and CH₂heteroaryl;

R³ can form a methylene or ethylene bridge to one of the other ring atoms, thus providing a bicyclic ring structure;

and the Ring connected to L is aryl, heteroaryl, heterocyclyl, fused cycloalkylaryl, fused heterocyclylaryl, fused arylheterocyclyl, fused cycloalkylheteroaryl, fused heterocyclylheteroaryl, or fused heteroarylheterocyclyl;

such that all possible stereoisomers, including optically active isomers, are included whenever stereogenic centers are present;

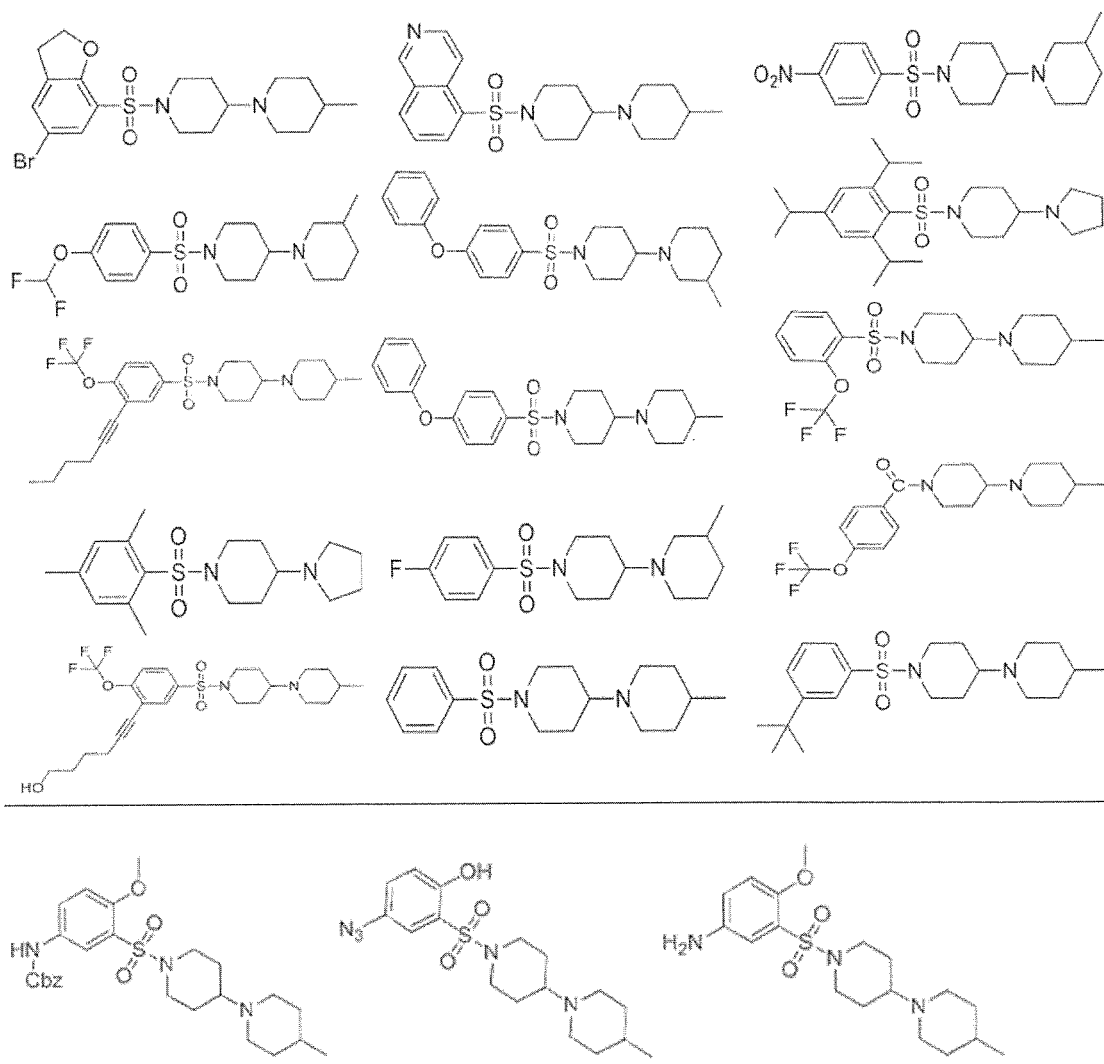
or a pharmaceutically acceptable salt, prodrug, active metabolite, or solvate thereof.

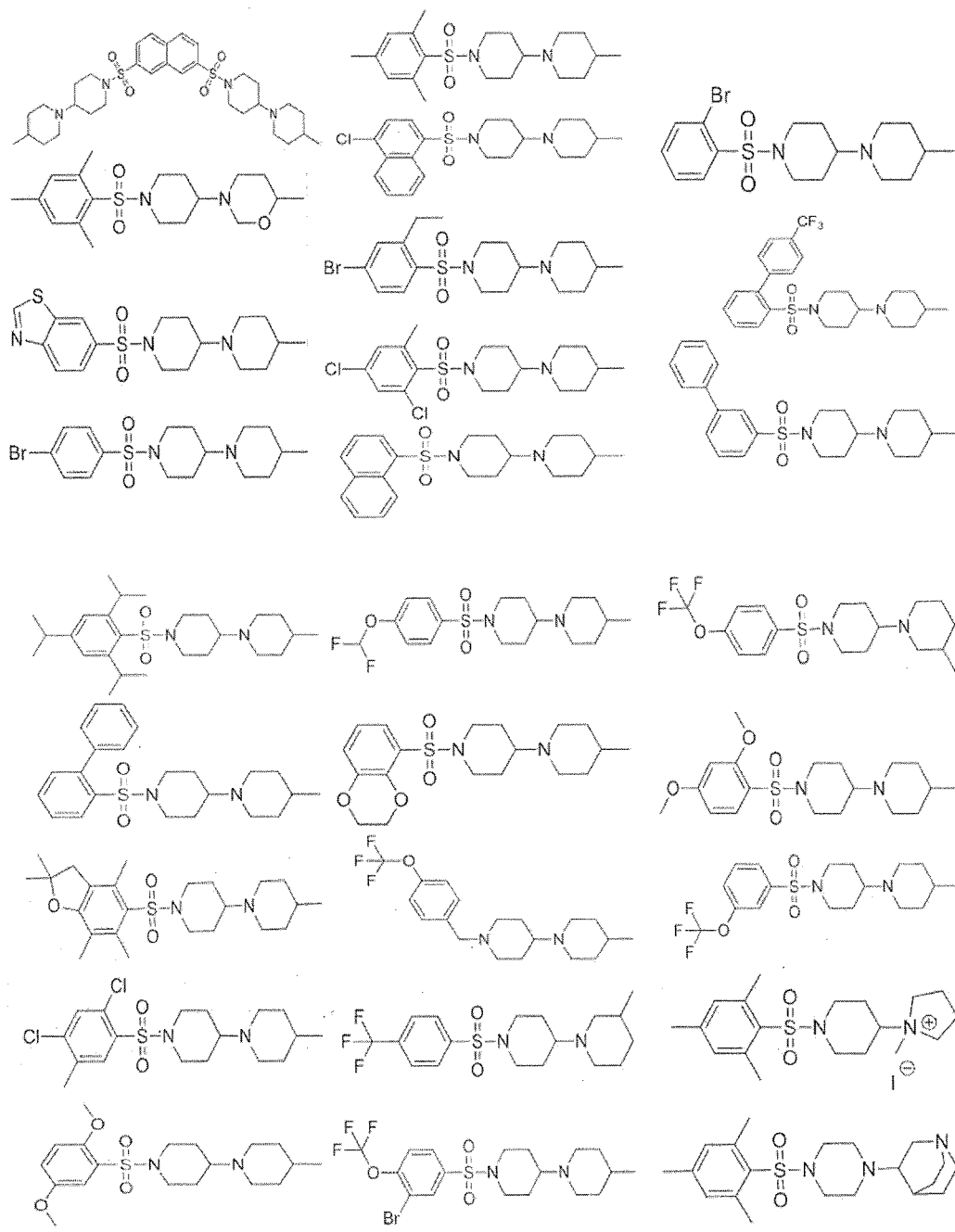
According to another embodiment, the small molecule anti-cancer compound is a compound of Formula I-a. According to another embodiment, the small molecule anti-cancer compound is a compound of Formula I-b. According to another embodiment, the small molecule anti-cancer compound is a compound of Formula I-c. According to another embodiment, the small molecule anti-cancer compound is a compound of Formula I-d. According to another embodiment, the small molecule anti-cancer compound is a

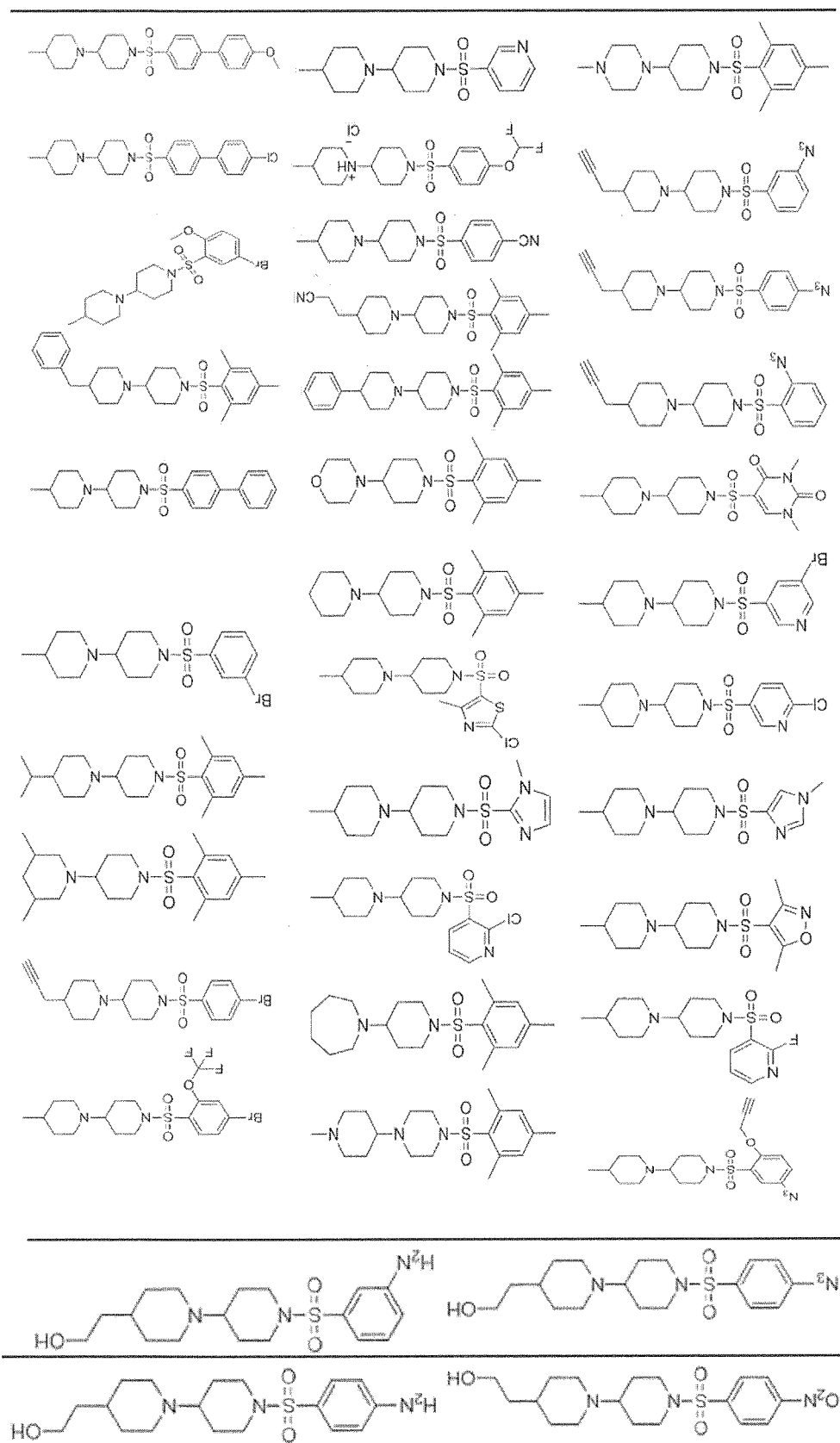
compound selected from the group consisting of the 43 structures disclosed in claim 3.

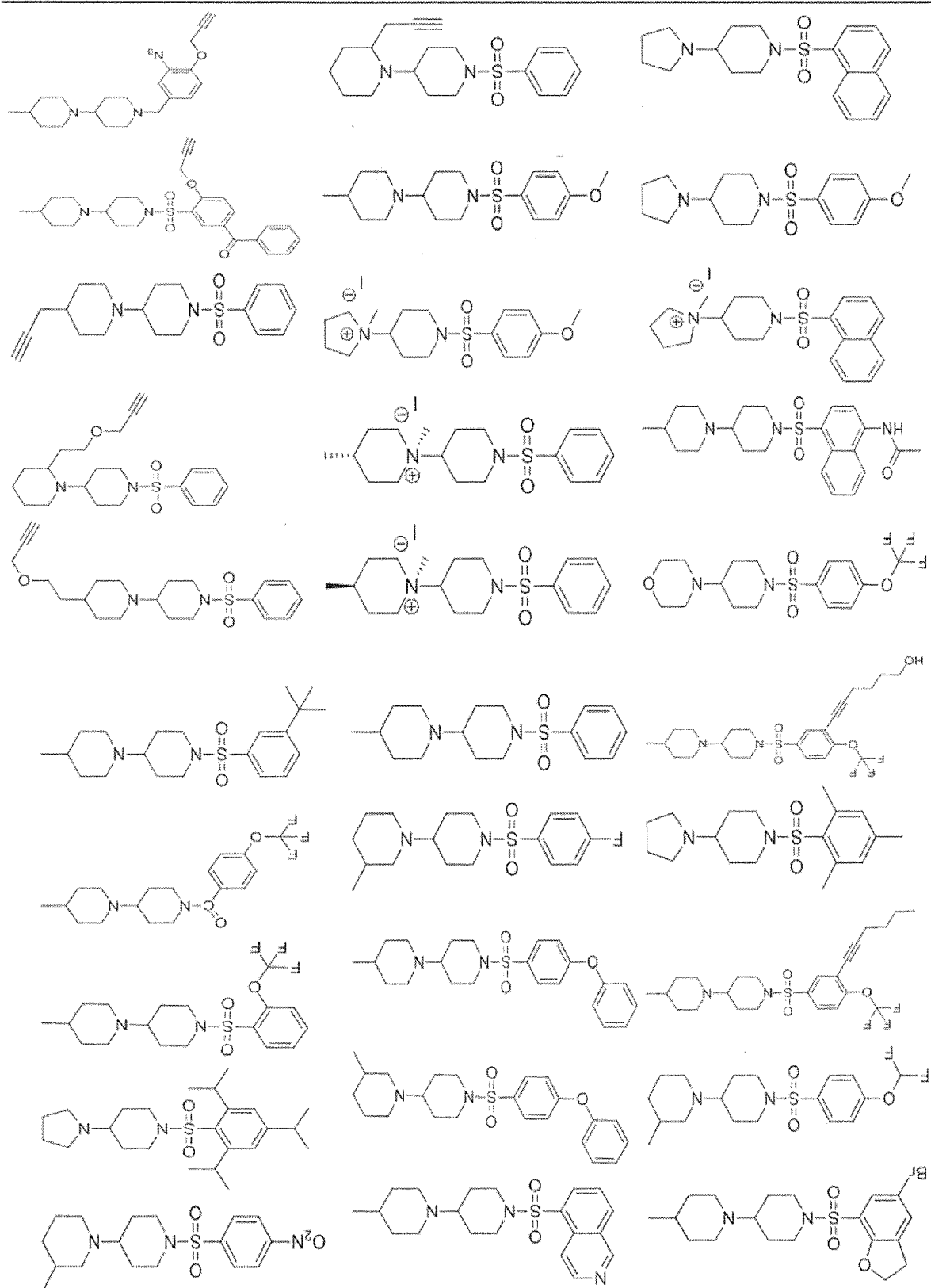
According to another embodiment, the small molecule anti-cancer compound is a compound of the structural formula disclosed in claim 5. According to another embodiment, the small molecule anti-cancer compound is selected from the group consisting of the 5 structures disclosed in claim 7. According to another embodiment, the small molecule anti-cancer compound is a compound of the structural formula disclosed in claim 9.

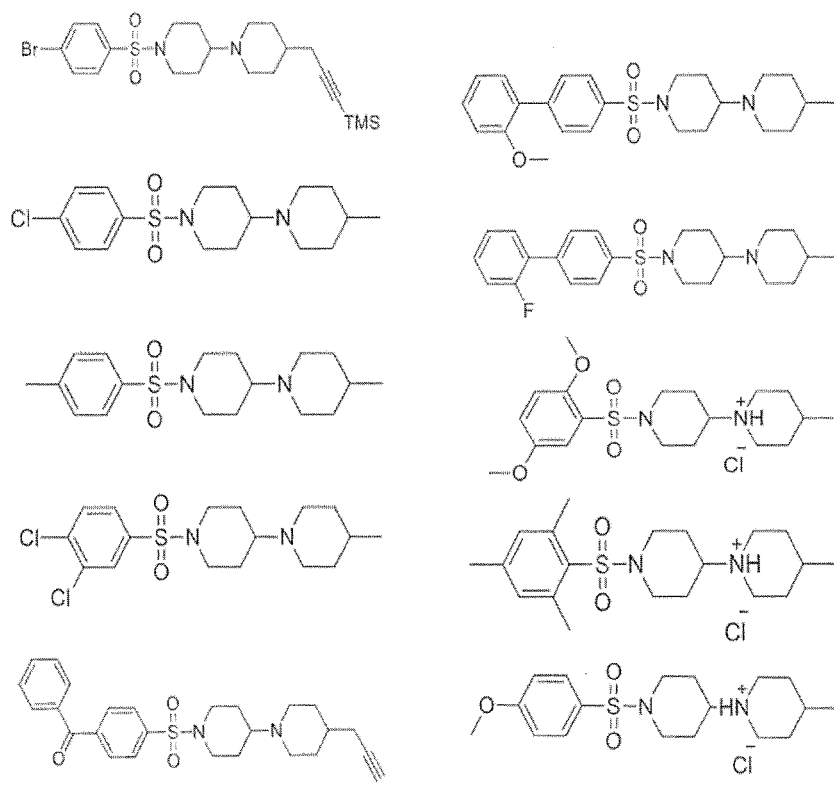
In another aspect, there is provided a compound selected from the group consisting of:











or a pharmaceutically acceptable salt thereof.

According to another embodiment, the IC_{50} of the small molecule anti-cancer compound is from 0.01nM to 5 μ M. According to another embodiment, the small molecule anti-cancer compound is in the form of a pharmaceutical composition comprising a therapeutic amount of the compound and a pharmaceutically acceptable carrier. According to another embodiment, the therapeutic amount of the small molecule anti-cancer compound is effective to inhibit tumor growth, inhibit tumor proliferation, induce cell death or a combination thereof.

[16] According to another aspect ~~embodiment~~, the ~~disclosure described invention~~ provides a method of treating colorectal cancer in a subject whose colonic epithelial cells express at least one truncated APC protein, comprising administering to the subject a pharmaceutical composition comprising a therapeutic amount of at least one small molecule anti-cancer compound of any one of claims 1 through 19 and a pharmaceutically acceptable carrier,

wherein the therapeutic amount is effective to inhibit tumor growth, inhibit tumor proliferation, induce cell death, or a combination thereof. In an aspect, there is provided the use of a pharmaceutical composition comprising a therapeutic amount of at least one small molecule compound as disclosed herein and a pharmaceutically acceptable carrier in the manufacture of a medicament for treating colorectal cancer in a subject whose colonic epithelial cells express at least one truncated APC protein, wherein the therapeutic amount is effective to inhibit tumor growth, inhibit tumor proliferation, induce cell death, or a combination thereof.

[17] According to another aspect, the ~~described invention~~disclosure provides an immortalized human colonic epithelial cell (HCEC) comprising a full length, wild type APC gene, wherein the cell comprises at least one of the following: an ectopically expressed vector containing Kirsten rat sarcoma viral oncogene homolog (*Krasv¹²*), a small hairpin RNA against tumor protein p53

21. The compound according to claim 1, wherein the compound is in form of a pharmaceutical composition comprising a therapeutic amount of the compound and a pharmaceutically acceptable carrier.
22. The compound according to claim 21, wherein the therapeutic amount is effective to inhibit tumor growth, inhibit tumor proliferation, induce cell death or a combination thereof.
23. ~~A method of treating colorectal cancer in a subject whose colonic epithelial cells express at least one truncated APC protein, comprising administering to the subject~~ Use of a pharmaceutical composition comprising a therapeutic amount of at least one small molecule compound of claims 1 through 19 and a pharmaceutically acceptable carrier in the manufacture of a medicament for treating colorectal cancer in a subject whose colonic epithelial cells express at least one truncated APC protein, wherein the therapeutic amount is effective to inhibit tumor growth, inhibit tumor proliferation, induce cell death, or a combination thereof.
24. An immortalized human colonic epithelial cell (HCEC) comprising a full length, wild type APC gene, wherein the cell comprises at least one of the following: an ectopically expressed vector containing Kirsten rat sarcoma viral oncogene homolog (*Kras*^{v12}), a small hairpin RNA against tumor protein p53 (shp53), and a small hairpin RNA against APC (shAPC).
25. The cell of claim 24, wherein the APC gene contains a somatic mutation at codon 1450.
26. The cell of claim 24, wherein the APC gene contains a somatic mutation at codon 1309.
27. The cell of claim 24, wherein a LacZ protein is expressed.
28. The cell of claim 24, wherein the Kirsten rat sarcoma viral oncogene homolog (*Kras*^{v12}) and the small hairpin RNA against APC (shAPC) are expressed.
29. The cell of claim 24, wherein the cell comprises a retroviral cyclin-dependent kinase 4 (*Cdk4*) and a catalytic component of human telomerase (*hTERT*).