191. TREATMENT OF KRAS-VARIANT CANCERS

(Yale University)

Asset Overview

Product Type	small molecule
Disease Area	Oncology
Indication	Ovarian cancer
Current Stage	Lead Optimization
Target	The serotonin transporter (SERT) and the XRN2 nuclease
MoA	selectively inhibit KRAS-variant ovarian cancer
Brief Description	• The KRAS variant impacts responses to various cancer therapies. Ovarian tumors with the KRAS variant are resistant to treatment with standard chemotherapies including cisplatin. • EOC tumors harboring the KRAS-variant were found to be significantly more resistant to treatment with platinum than those without the KRAS-variant. There is currently no drug available to specifically treat KRA-variant ovarian cancer. • The method comprising administering to the subject an effective amount of a serotonin uptake inhibitor, wherein the subject comprises rs6176430 variant of the KRAS gene. • The serotonin uptake inhibitor is more effective in killing a cancer cell comprising the rs61764340 variant of the KRAS gene than killing a corresponding cancer cell that doe not comprise the rs61764370 variant of the KRAS gene. • The serotonin uptake inhibitor is more effective in inhibiting survival of a cancer cell comprising the re61764340 variant of the KRAS gene than in inhibiting survival of a corresponding cancer cell that does not comprise the rs61764970 variant of the KRAS gene. • The administration of the serotonin uptake inhibitor results in inhibition of the growth of a tumor of the cancer.
Intellectual Property	WO2021236498A1
Publication	-
Inventors	Joann SWEASY, Z Ping LIN, Elena Ratner

Highlights

- Ovarian tumors with KRAS variant are resistant to treatment with standard chemotherapies including cisplatin
- Yale inventors have discovered that serotonin transport inhibitors selectively inhibit KRAS-variant ovarian cancer.
- This method can also be used to specifically treat other cancer, such as breast cancer, with KRAS–variant.

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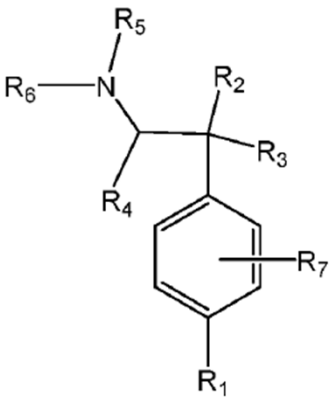
Key Data

The basic structure and examples of the serotonin inhibitor



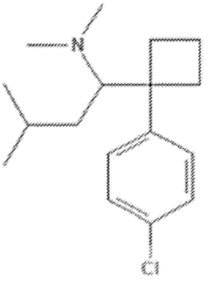
R_1 is -Cl;

R_2 and R_3 together form a 4-membered carbocycle;

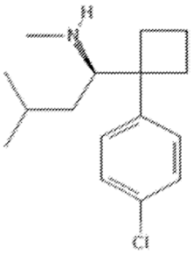
R_4 is a selected from n-propyl, isopropyl, n-butyl, isobutyl, and t-butyl;

R_5 and R_6 are independently selected from H and $-CH_3$;

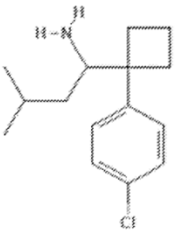
R_7 is absent. In various embodiments, a pharmaceutically acceptable salt of the compound is provided.



Sibutramine

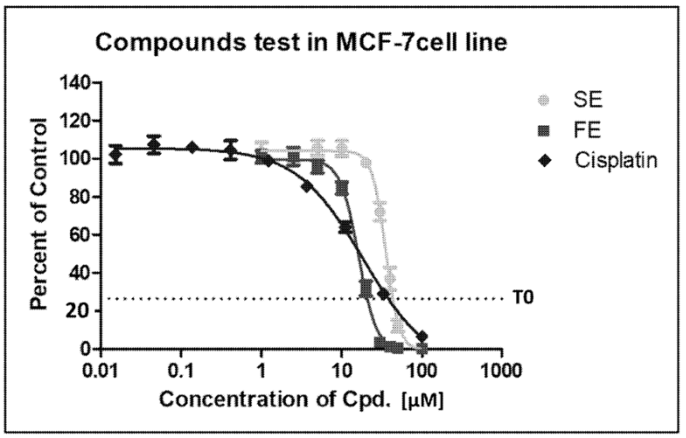


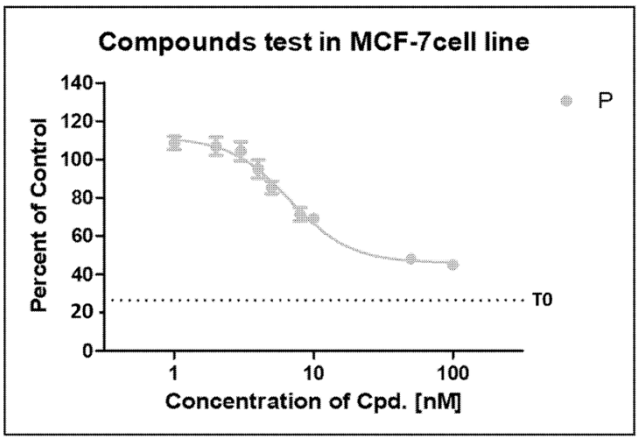
Desmethylsibutramine



Didesmethylsibutramine

inhibitory effects of fluoxetine (FE), sibutramine (SE), cisplatin (CisP), and paclitaxel (P) on the proliferation of MCF-7 cell line





FIGs. 6A-6B are graphs showing the inhibitory effects of fluoxetine (FE), sibutramine (SE), cisplatin (CisP) (FIG. 6A), and paclitaxel (P) (FIG. 6B) on the proliferation of MCF-7 cells, with cisplatin (CisP) and paclitaxel (P) used as the positive control