



hydrochloride up-regulates expression of the cholesterol transporter gene ABCA1 and the E3 ubiquitin ligase IDOL and reduces LDLR levels<sup>[2]</sup>. LXR ligands inhibits platelet aggregation and calcium mobilization stimulated by collagen or CRP. GW3965 hydrochloride (1 or 5  $\mu$ M) displays a minor inhibitory effect on fibrinogen binding and P-selectin exposure, when platelets are stimulated with 1  $\mu$ g/mL CRP. But using higher concentrations of GW3965 hydrochloride (10  $\mu$ M) or T0901317 (40  $\mu$ M), the levels of fibrinogen and P-selectin on the platelet surface are reduced<sup>[3]</sup>.  
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

#### In Vivo

GW3965 hydrochloride induces an increase of neuroactive steroids in the spinal cord, the cerebellum and the cerebral cortex of STZ-rats, but not in the CNS of non-pathological animals. GW3965 hydrochloride treatment induces an increase of dihydroprogesterone in the spinal cord of diabetic animals in association with an increase of myelin basic protein expression<sup>[1]</sup>. GW3965 hydrochloride (40 mg/kg, p.o.) strongly induces ABCA1 expression and reduces LDLR expression, and this is accompanied by 59% inhibition of tumor growth, and a 25-fold increase in GBM cell apoptosis in vivo<sup>[2]</sup>. GW3965 hydrochloride (2 mg/kg, i.v.) increases bleeding time and modulated platelet thrombus formation in vivo<sup>[3]</sup>.  
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

## PROTOCOL

#### Cell Assay <sup>[2]</sup>

Cells are seeded in 96 wells and are treated after 24 hours with different drugs indicated in each experiment in medium containing 1% FBS or lipoprotein deficient serum. Relative proliferation is determined using Cell Proliferation Assay Kit. Cells are incubated 1.5 hrs after adding tetrazolium salt WST-1 [2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfo-phenyl)-2H-tetrazolium, monosodium salt] at 5% CO<sub>2</sub>, 37°C and the absorbance of the treated and untreated cells are measured using a microplate reader at 420 to 480 nm. Cells seeded in 12 well plates are counted using a hemocytometer, and dead cells are assessed using trypan blue exclusion assays.  
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#### Animal Administration <sup>[1]</sup>

Diabetes is induced in two-month-old male rats by a single i.p. injection of freshly prepared STZ (65 mg/kg) in 0.09 M citrate buffer, pH 4.8. Control animals are injected with 0.09 mol/L citrate buffer at pH 4.8. Hyperglycemia is confirmed 48 h after streptozotocin injection by measuring tail vein blood glucose levels using a glucometer OneTouch Ultra2. Only animals with mean plasma glucose levels over 300 mg/mL are classified as diabetic. Glycemia is also assessed before treatment with Ro5-4864 or GW3965 hydrochloride and before death. Two months after STZ injection, diabetic animals are treated once a week with Ro5-4864 (3 mg/kg) or GW3965 hydrochloride (50 mg/kg). Thus, they receive four subcutaneous injections in a month. Control diabetic rats receive 200  $\mu$ L of vehicle (sesame oil). Four-month-old non-diabetic male rats are injected, following the same experimental schedule, with Ro5-4864, GW3965 hydrochloride or vehicle. Rats are killed 24 h after the last treatment.  
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

## CUSTOMER VALIDATION

- Sci Adv. 15 Jul 2022.
- Cell Death Differ. 2020 Aug;27(8):2433-2450.
- Theranostics. 2020 Jul 11;10(19):8834-8850.
- J Am Heart Assoc. 2021 May 8;e018455.
- Bioconjug Chem. 2015 Nov 18;26(11):2216-22.

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## REFERENCES

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[2]. Guo, Deliang., et al. An LXR Agonist Promotes Glioblastoma Cell Death through Inhibition of an EGFR/AKT/SREBP-1/LDLR-Dependent Pathway. *Cancer Discovery* (2011), 1(5), 442-456.

[3]. Spyridon, Michael., et al. LXR as a novel antithrombotic target. *Blood* (2011), 117(21), 5751-5761.

[4]. Collins JL, et al. Identification of a nonsteroidal liver X receptor agonist through parallel array synthesis of tertiary amines. *J Med Chem.* 2002 May 9;45(10):1963-6.

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