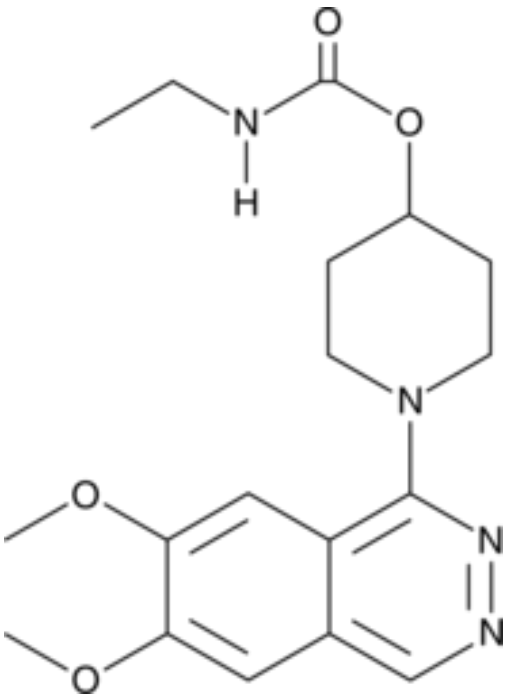
Product Data Sheet

Product Name: Carbazeran
Cat. No.: GC41449

Chemical Properties

Cas. No.	70724-25-3		
SMILES	COC1=C(OC)C=C(C=NN=C2N3CCC(OC(NCC)=O)CC3)C2=C1		
Formula	$C_{18}H_{24}N_4O_4$	M.Wt	360.4
Solubility	Chloroform: Slightly Soluble,Methanol: Slightly Soluble	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		

Structure



Protocol

Cell experiment [1]:

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Cell lines	MPCC hepatocytes
Preparation Method	MPCC hepatocytes were maintained in serum-free medium for 2h prior to compound treatment, then treated with Carbazeran at 10μM for 168h (0, 48 and 168h time points) in 400μL media (DMSO final concentration ≈0.03%), followed by protein precipitation with acetonitrile, centrifugation, evaporation and UHPLC-UV-MS analysis for metabolite profiling.
Reaction Conditions	10μM; 0-168h
Applications	Carbazeran underwent oxidative demethylation (m/z 333 and 347), aldehyde oxidase-mediated oxidation (m/z 377), direct conjugations (m/z 523b and 537) and secondary metabolism (m/z 349, 427 and 523a) in MPCC hepatocytes.
Animal experiment [2]:	
Animal models	chimeric TK-NOG mice transplanted with human hepatocytes (humanized-liver mice) and control TK-NOG mice
Preparation Method	Mice were orally administered a single dose of Carbazeran (10mg/kg) dissolved in corn oil containing 10%(v/v) DMSO; blood was collected at 0.5, 1, 2, 4, 7, 24, and 48h and urine/feces collected up to 72h for LC-MS/MS analysis of Carbazeran and metabolites.
Dosage form	10mg/kg; p.o.; single administration

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Applications	Carbazeran administration produced higher plasma levels of 4-oxo-carbazeran, N-desethyl-4-oxo-carbazeran, and 6,7-dimethoxy-1-[4-(hydroxy)-piperidino]-4-phthalazinone and greater urinary/fecal excretion of these 4-oxidation-derived human metabolites in humanized-liver mice, while O-desmethylcarbazeran levels were lower in humanized-liver mice than control mice.
References:[1] Ballard TE, Kratochwil N, Cox LM, et al. Simplifying the Execution of HepatoPac MetID Experiments: Metabolite Profile and Intrinsic Clearance Comparisons. Drug Metab Dispos. 2020 Jul 4.[2] Uehara S, Yoneda N, Higuchi Y, et al. Human Aldehyde Oxidase 1-mediated Carbazeran Oxidation in Chimeric TK-NOG Mice Transplanted with Human Hepatocytes. Drug Metab Dispos. 2020;48(7):533-542.	

Background

Carbazeran is a phosphodiesterase PDE2 and PDE3 dual inhibitor. Carbazeran inhibits cAMP and cGMP hydrolysis to enhance myocardial contraction and regulate heart rate. Carbazeran serves as an aldehyde oxidase AOX1 substrate for drug metabolism and clearance research. Carbazeran can be used for studies on heart failure, arrhythmia, cyclic nucleotide signaling, and metabolic diseases[1-4].

In vitro, treatment of MPCC cells with 10μM Carbazeran for 0-168h induced intracellular oxidative demethylation, aldehyde oxidase-mediated oxidation, direct conjugation reactions, and secondary metabolic transformations of Carbazeran[5].

In vivo, a single oral administration of 10mg/kg Carbazeran to TK-NOG mice transplanted with human hepatocytes increased the formation of 4-oxidation metabolites in plasma, including 4-oxo-carbazeran, N-desethyl-4-oxo-carbazeran, and 6,7-dimethoxy-1-[4-(hydroxy)-piperidino]-4-phthalazinone[6].

References:
[1] Critchley DJ, Rance DJ, Beedham C. Biotransformation of carbazeran in guinea pig: effect of hydralazine pretreatment. Xenobiotica. 1994 Jan;24(1):37-47.
[2] Kaye B, Rance DJ, Waring L. Oxidative metabolism of carbazeran in vitro by liver cytosol of

baboon and man. Xenobiotica. 1985 Mar;15(3):237-42.
[3] Shahid M, Rodger IW. Chronotropic and inotropic actions of amrinone, carbazeran and isobutylmethyl xanthine: role of phosphodiesterase inhibition. Br J Pharmacol. 1989 Sep;98(1):291-301.
[4] Hoey M, Houslay MD. Identification and selective inhibition of four distinct soluble forms of cyclic nucleotide phosphodiesterase activity from kidney. Biochem Pharmacol. 1990 Jul 15;40(2):193-202.
[5] Ballard TE, Kratochwil N, Cox LM, et al. Simplifying the Execution of HepatoPac MetID Experiments: Metabolite Profile and Intrinsic Clearance Comparisons. Drug Metab Dispos. 2020 Jul 4.
[6] Uehara S, Yoneda N, Higuchi Y, et al. Human Aldehyde Oxidase 1-mediated Carbazeran Oxidation in Chimeric TK-NOG Mice Transplanted with Human Hepatocytes. Drug Metab Dispos. 2020;48(7):533-542.