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Technical Information about ESI-05

Membrane-permeant selective inhibitor of Epac 2

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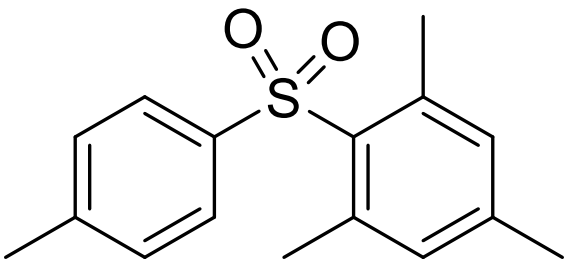


Abbreviation: **ESI-05**

Formula	CAS No.	Molecular Weight	UV	BIOLOG Cat. No.
$C_{16}H_{18}O_2S$	[5148-64-5]	274.4	λ_{max} 244 nm / ε 19000 / pH 7	M 092

Name: 4- Methylphenyl- 2, 4, 6- trimethylphenylsulfone

Description / Properties: According to Tsalkova et al. ESI-05 is a membrane-permeant and isozyme-selective inhibitor of Epac 2, the exchange protein activated directly by cyclic AMP, isoform 2. ESI-05 displays an *in vitro* IC_{50} value of 0.43 µM for Epac 2 with 25 µM cAMP as competing activator. It displays an at least 100-fold selectivity for Epac 2 compared to Epac 1 and compared to cyclic AMP-dependent protein kinase I and II at 25 µM concentration in *in vitro* assays. Pretreatment with 5 - 25 µM ESI-05 selectively inhibits Epac 2 activation with 10 µM 8-pCPT-2'-O-Me-cAMP-AM (our Cat. No. C 051) in intact cells (Tsalkova et al. 2012).

Specification: Crystallized or lyophilized solid. **Please keep in mind that equal concentrations of the compound may look different in volume due to sensitivity of the lyophilized form to humidity. The compound can even contract to small droplets.** Normally the product is located in the conical bottom of the tube. Micro molar quantities are determined by weight.

Purity: Typical analysis is better than 95% (HPLC / UV / 270 nm). The product is not sterile and has not been tested for endotoxins.

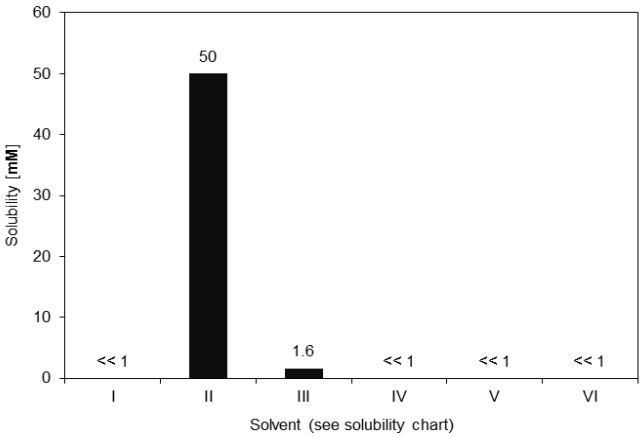
Stability and Storage: ESI-05 is chemically rather stable and does not need special care during handling or shipment. Nevertheless, we recommend that the compound should be stored in the freezer (-20° Celsius necessary, -80° recommended), for longer storage periods preferably in freeze-dried form.

Toxicity and Safety: Please keep in mind, that the *in vivo* properties of this compound are not sufficiently characterized up to now. Avoid skin contact or ingestion and allow only trained personnel to handle the product.
Our products are designed, developed and sold for research purposes only! They are intended for *in vitro* and nonhuman *in vivo* laboratory applications. Any other use requires approval of health authorities.
Not for drug, household or related uses!

BIOLOG Life Science Institute, Bremen, Germany Phone: 49 (0) 421 591355 Fax: 49 (0) 421 5979713 e-mail: service@biolog.de

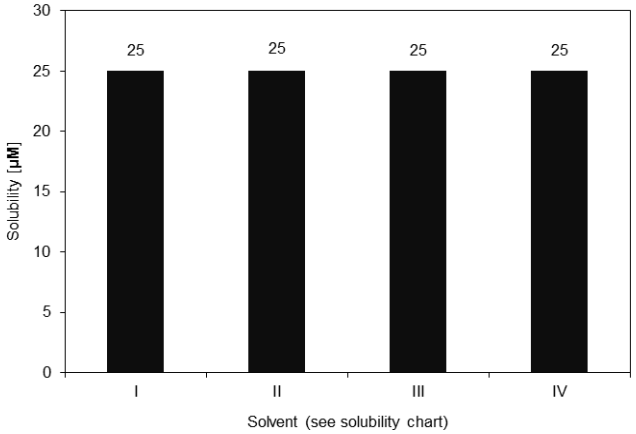
Solubility: Detailed information on the solubility of ESI-05 in water and various buffers are listed in the solubility chart below. Concentrations have been determined at ambient temperature and can be considered as concentrations usually obtainable, however, slight batch-to-batch variations cannot be ruled out.

No.	Solvent	Solubility [mM]
I	H_2O	<< 1
II	DMSO	50
III	Ethanol 96%	1.6
IV	PBS, pH 7.4	<< 1
V	25 mM Hepes/NaOH, pH 7.2	<< 1
VI	25 mM Tris/HCl, pH 7.4	<< 1



Due to its rather high lipophilicity, the solubility of ESI-05 in water or buffers is limited. We suggest to first use a small amount of DMSO for dissolution, and to dilute with DMSO and water or buffer down to the final concentration to be used in the biological assay (see below for a corresponding protocol). Please rinse tube walls carefully and preferably use ultrasonic or vortex to achieve total and uniform mixing. When opening the tube please make sure that no substance is lost within the cap.

No.	Solvent	Solubility [µM]
I	H_2O (1% DMSO)	25
II	PBS, pH 7.4 (1% DMSO)	25
III	25 mM Hepes/NaOH, pH 7.2 (1% DMSO)	25
IV	25 mM Tris/HCl, pH 7.4 (1% DMSO)	25



Preparation of a 25 µM solution in water or various buffers (1% DMSO):

Add 100 µL DMSO to a 5 µmol vial of ESI-05 to achieve a 50 mM solution. Use 5 µL of this solution and dilute with 95 µL DMSO to get a 2.5 mM solution. Addition of 990 µL water or buffer (PBS, Hepes, Tris) to 10 µL of this 2.5 mM DMSO solution will result in a 25 µM solution (1% DMSO).

Selected References for ESI-05:

Parnell, E.; Palmer, T.M.; Yarwood, S.J., *Trends Pharmacol. Sci*., **36**, 203 - 214 (2015): "The Future of EPAC-targeted Therapies: Agonism versus Antagonism"

Henquin, J.-C., Nenquin, M., *Endocrinology,* **155**, 3274 - 3287 (2014): "Activators of PKA and Epac Distinctly Influence Insulin Secretion and Cytosolic $Ca2^+$ in Female Mouse Islets Stimulated by Glucose and Tolbutamide"

Rehmann, H., *Sci. Rep.*, 3:3032 (2013): "Epac-Inhibitors: Facts and Artefacts"

Chen, H.; Tsalkova, T.; Chepurny, O.G.; Mei, F.C.; Holz, G.G.; Cheng, X.; Zhou, J., *J. Med. Chem.*, **56**, 952 - 962 (2013): "Identification and Characterization of Small Molecules as Potent and Specific EPAC2 Antagonists"

Tsalkova, T.; Mei, F.C.; Li, S.; Chepurny, O.G.; Leech, C.A.; Liu, T.; Holz, G.G.; Woods, V.L.; Cheng, X., *Proc. Natl. Acad. Sci. USA*, **109**, 18613 - 18618 (2012): "Isoform-Specific Antagonists of Exchange Proteins Directly Activated by cAMP"

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