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Ion channels & Transporters

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* Full Glass Equipment (glass equipment is used to avoid adherence of sticky compounds to plastic surfaces)

*** coming in 2009

Ion channels & Transporters

Organ system screening list

Indication - screening list

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Assay	Gene	Page
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GABA _A (α1β3γ2)	GABRA1 / GABRB3 / GABRG2	20
GABA _A (α2β2γ2)	GABRA2 / GABRB2 / GABRG2	21
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*** coming in 2009

Ion channels & Transporters hERG

hERG dose range finding

Gene: KCNH2

Standard throughput time	1 week
Source	human
Expression system	CHO or HEK 293, stable expression
Method	whole cell patch-clamping
Quality level	high quality functional assay
References	E-4031
References, further examples	Dofetilide, Terfenadine, Ketoconazole
Additional readouts	solubility check, stability check
+ should be used for quality characterization of hERG interaction	
+ I _{Kr} screen	

Zhou, Z. et al. (1998) Biohys. Journal, 74:230-241

Zhou, Z. et al. (1997) Biohys. Journal, 72:A225

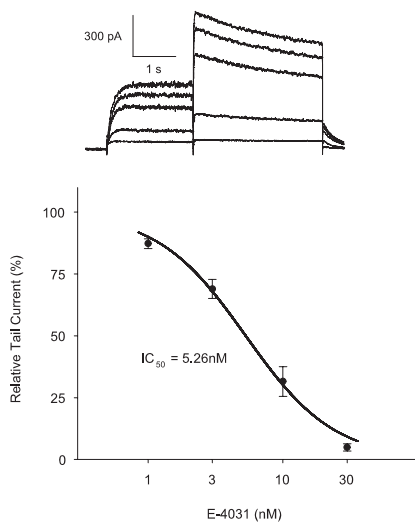
hERG (CHO)

Gene: KCNH2

Standard throughput time	2 weeks (0-100 compounds) (draft)
Source	human
Expression system	mammalian (CHO), stable expression
Method	whole cell patch-clamping
Quality level	high quality functional assay
References	E-4031 (IC ₅₀ : 5.3nM)
References, further examples	Dofetilide (IC ₅₀ : 8.3nM), Terfenadine (IC ₅₀ : 12.2nM) Ketoconazole (IC ₅₀ : 3.3μM)
Additional readouts	solubility check, stability check
+ should be used for quality characterization of hERG interaction	
+ I _{Kr} screen	

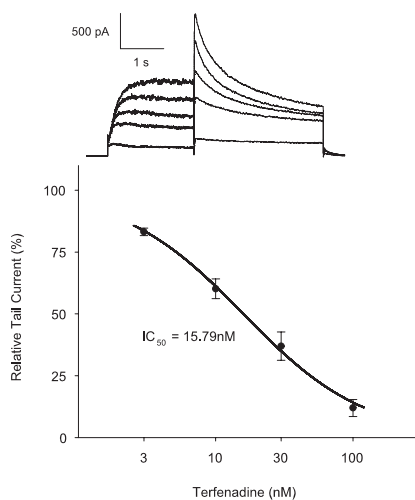
Zhou, Z. et al. (1998) Biohys. Journal, 74:230-241

Zhou, Z. et al. (1997) Biohys. Journal, 72:A225



Ion channels & Transporters hERG

hERG (HEK 239)



Gene: KCNH2

Standard throughput time	2 weeks (0-100 compounds) (draft)
Source	human
Expression system	human (HEK 293), stable expression
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	E-4031 (IC ₅₀ : 11.6nM)
References, further examples	Dofetilide (IC ₅₀ : 11.7nM), Terfenadine (IC ₅₀ : 15.8nM) Ketoconazole (IC ₅₀ : 5.5μM)

+ should be used for quality characterization of hERG interaction

+ I_{Kr} screen

Zhou, Z. et al. (1998) *Biochem. Biophys. Res. Commun.* 241:230-241

Zhou, Z. et al. (1997) *Biochem. Biophys. Res. Commun.* 225:225-230

hERG full glass equipment (CHO)

Gene: KCNH2

Standard throughput time	2 weeks (0-100 compounds), (draft)
Source	human
Expression system	mammalian (CHO), stable expression
Method	whole cell patch-clamping
Quality level	high quality functional assay full glass equipment
References	E-4031 (IC ₅₀ : 5.3nM)
References, further examples	Dofetilide (IC ₅₀ : 8.3nM), Terfenadine (IC ₅₀ : 12.2nM) Ketoconazole (IC ₅₀ : 3.3μM)

Additional readouts: solubility check, stability check

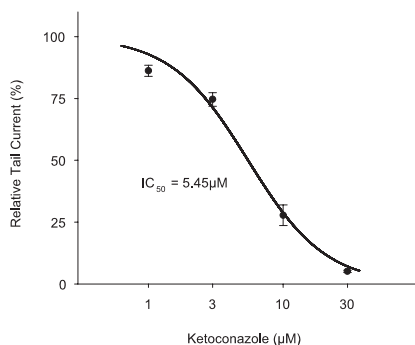
+ should be used for quality characterization of hERG interaction

+ full glass equipment avoids false results due to sticky compounds

Zhou, Z. et al. (1998) *Biochem. Biophys. Res. Commun.* 241:230-241

Zhou, Z. et al. (1997) *Biochem. Biophys. Res. Commun.* 225:225-230

Ion channels & Transporters hERG



hERG full glass equipment (HEK 293)

Gene: KCNH2

Standard throughput time	2 weeks (0-100 compounds), (draft)
Source	human
Expression system	human (HEK 293), stable expression
Method	whole cell patch-clamping
Quality level	high quality functional assay full glass equipment
Reference	E-4031 (IC ₅₀ :11.6nM)
References, further examples	Dofetilide (IC ₅₀ :11.7nM), Terfenadine (IC ₅₀ :15.8nM) Ketoconazole (IC ₅₀ : 5.5µM)

- + should be used for quality characterization of hERG interaction
- + full glass equipment avoids false results due to sticky compounds

Zhou, Z. et al. (1998) Biohys.Journal, 74:230-241
 Zhou, Z. et al. (1997) Biohys.Journal, 72:A225

hERG-GLP (HEK 293)

Gene: KCNH2

Standard throughput time	4 weeks (draft) final depending on sponsor's comments
Source	human
Expression system	human (HEK 293), stable expression
Method	whole cell patch-clamping
Quality level	highest quality functional GLP study
Reference	E-4031 (IC ₅₀ : 11.6nM)
References, further examples	Dofetilide (IC ₅₀ : 11.7nM), Terfenadine (IC ₅₀ : 15.8nM) Ketoconazole (IC ₅₀ : 5.5µM)

- + should be used as preclinical hERG assessment
- + modification to test design can be included
- + for analysis of dose solution, please inquire

Zhou, Z. et al. (1998) Biohys.Journal, 74:230-241
 Zhou, Z. et al. (1997) Biohys.Journal, 72:A225
 ICH S7A (2000) Safety pharmacology studies for human pharmaceuticals, issued as CPMP/ICH/539/00
 ICH S7B (2005) The nonclinical evaluation of the potential for QT interval prolongation issued as CHMP/ICH/423/02

hERG-GLP (CHO)

Gene: KCNH2

Standard throughput time	4 weeks (draft), final depending on sponsor's comments
Source	human
Expression system	mammalian (CHO), stable expression
Method	whole cell patch-clamping
Quality level	highest quality functional GLP study
Reference	E-4031 (IC ₅₀ : 5.3nM),
References, further examples	Dofetilide (IC ₅₀ : 8.3nM), Terfenadine (IC ₅₀ : 12.2nM) Ketonotazole (IC ₅₀ : 3.3μM)
+ should be used as preclinical hERG assessment	
+ modification to test design can be included	
+ for analysis of dose solution, please inquire	

Zhou, Z. et al. (1998) *Biochem. J.* 341:230-241

Zhou, Z. et al. (1997) *Biochem. J.* 322:A225

ICH S7A (2000) Safety pharmacology studies for human pharmaceuticals, issued as CPMP/ICH/539/00

ICH S7B (2005) The nonclinical evaluation of the potential for QT interval prolongation issued as CHMP/ICH/423/02

Ion channels & Transporters Serum protein incubation

hERG; Na_v1.5; KvLQT/minK; K_v1.5

Genes: **KCNH2** (hERG); **SCN5A** (Nav1.5), **KCNQ1/KCNE1** (KvLQT/minK), **KCNA5** (Kv1.5)

Standard throughput time	3 weeks (draft)
Source	human recombinant channels
Expression system	mammalian (CHO, HEK 293), stable expression
Method	patch-clamping in the presence of a physiological albumin or serum protein concentration.
Quality level	high quality functional assay
References	see respective ion channel
Further protein options	please inquire
Additional readouts	solubility check, stability check
+ to be used to anticipate physiological conditions / unbound fraction effects in presence of serum proteins	

ICH S7B (2005) The nonclinical evaluation of the potential for QT interval prolongation issued as CHMP/ICH/423/02

If serum proteins are present during ion channel testing, IC₅₀ values may be higher than previously measured for compounds due to a decrease in the unbound fraction of the test compound (ETPCfree). This reflects a more physiological situation.

Ion channels & Transporters K⁺ channel

K_v1.1

Gene: KCNA1

Standard throughput time	3 weeks (draft)
Source	human
Expression system	mammalian (CHO/HEK 293)
Method	whole cell patch-clamping and fluorescence (FlexStation/FLIPR)
Quality level	high quality functional assay and fluorescence assay

K_v1.2

Gene: KCNA2

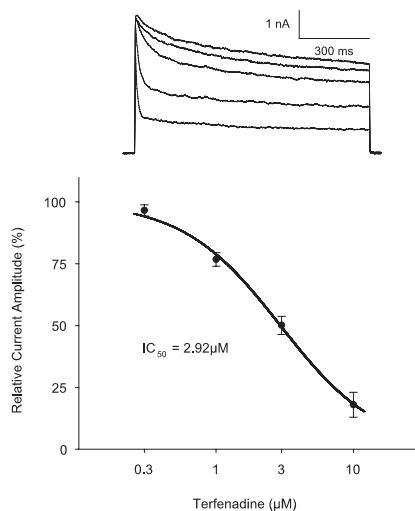
Standard throughput time	3 weeks (draft)
Source	human
Expression system	mammalian (CHO/HEK 293)
Method	whole cell patch-clamping and fluorescence (FlexStation/FLIPR)
Quality level	high quality functional assay and fluorescence assay

K_v1.3

Gene: KCNA3

Standard throughput time	3 weeks (draft)
Source	human
Expression system	mammalian (CHO/HEK 293)
Method	whole cell patch-clamping and fluorescence (FlexStation/FLIPR)
Quality level	high quality functional study and fluorescence
References, further examples	
+ Immunomodulatory ion channel	

Ion channels & Transporters K⁺ channel



K_v1.5

Gene: KCNA5

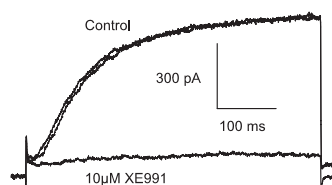
Standard throughput time	2 weeks (draft)
Source	human
Expression system	mammalian (CHO/HEK 293)
Method	whole cell patch-clamping and fluorescence (FlexStation/FLIPR)
Quality level	high quality functional study and fluorescence
Reference	Terfenadine (IC ₅₀ : 2.9 μM), Ibesartan, Amiodarone
References, further examples	Diclofenac, Meclofenamate
+ Cardiac toxicity/safety relevant ion channel test	
+ antiarrhythmic screening	

Tamargo J et al. (2004) Cardiovascular Research, 62: 9-33

K_v1.6

Gene: KCNA6

Standard throughput time	3 weeks (draft)
Source	human
Expression system	mammalian (CHO/HEK 293)
Method	whole cell patch-clamping and fluorescence (FlexStation/FLIPR)
Quality level	high quality functional assay and fluorescence assay



K_v7.2

Gene: KCNQ2

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (CHO/HEK 293)
Method	whole cell patch-clamping
Quality level	high quality functional study
Reference	XE991
References, further examples	Diclofenac, Meclofenamate
+ CNS Screening	
+ Antiepileptic	

Bievert C et al. (1998) Science, 279: 403-40

Otto JF et al. (2006) The Journal of Neuroscience 26: 2053-20596

Ion channels & Transporters K⁺ channel

KvLQT1/minK

Gene: KCNQ1/KCNE1

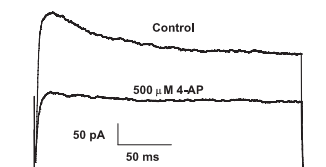
Standard throughput time	2 weeks (draft)
Source	human
Expression system	mammalian (HEK 293), stable expression
Method	whole cell patch-clamping
Quality level	high quality functional study
Reference	Chromanol 293B (IC ₅₀ : 6.2μM)
References, further examples	HMR1556 (IC ₅₀ : 0.1μM), Mefloquine (IC ₅₀ : 3.6μM)
+ cardiac toxicity/safety relevant ion channel test	
+ antiarrhythmic screening	

ICH S7B The nonclinical evaluation of the potential for QT interval prolongation issued as CHMP/ICH/423/02, adopted by CHMP in May 2005; Gerlach, U et al, (2001) J. Med. Chem. 44 (23) 3831-3837; Kang, G et al (2001) J. Pharmacol. Exp. Ther. 299(1) 290-296; Lo, CF and Numann, R (1998) A. Circ. Res. 83 995-1002; Dong, MQ et al, (2006) J. Membrane Biol., 210:183-192

Neuroblastoma whole potassium

Standard throughput time	4 weeks (draft)
Source	mouse
Expression system	mammalian N1E-115
Method	whole cell patch-clamping
Quality level	high quality functional study
References, further examples	4-AP

Im HK, et al. (1993) J Pharmacol Exp Ther 265: 529-535
Kimhi Y et al. (1976) Proc Natl Acad Sci USA 73: 462-466
Matsuki N et al. (1984) J Pharmacol Exp Ther 228: 523-530
Moolenaar WH et al. (1978) J Physiol 278: 265-286
Narahashi T et al. (1984) Neuroscience 13: 249-262
Narahashi T et al. (1987) J Physiol 383: 231-249.



Ion channels & Transporters Na⁺ channel

Na_v1.1

Gene: SCN1A

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (CHO/HEK 293)
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	TTX
+ neuronal sodium channel assay	
+ cns toxicity / safety relevant ion channel test	

Na_v1.2

Gene: SCN2A

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (CHO/HEK 293)
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	TTX
+ neuronal sodium channel assay	
+ cns toxicity / safety relevant ion channel test	

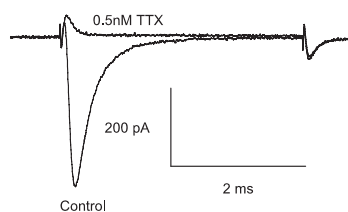
Ahmed CMI. et al. (1992) Proc Natl Acad Sci USA 98:8220-8224

Na_v1.3

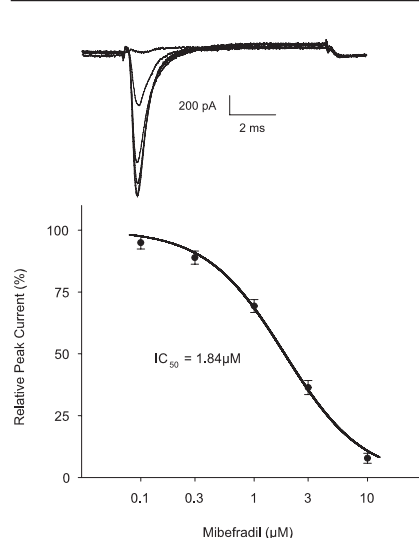
Gene: SCN3A

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (CHO/HEK 293)
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	TTX
+ neuronal sodium channel assay	
+ cns toxicity / safety relevant ion channel test	

Chen YH. et al. (2000) Europ J Neurosci, 12:4281-4289



Ion channels & Transporters Na⁺ channel



Na_v1.5

Gene: SCN5A

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (CHO), stable expression
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	carbamazepine (IC ₅₀ : 59.2 μM)
References, further examples	Mibefradil, Lidocaine, TTX
+ cardiac toxicity/safety relevant ion channel test	
+ antiarrhythmic screening	

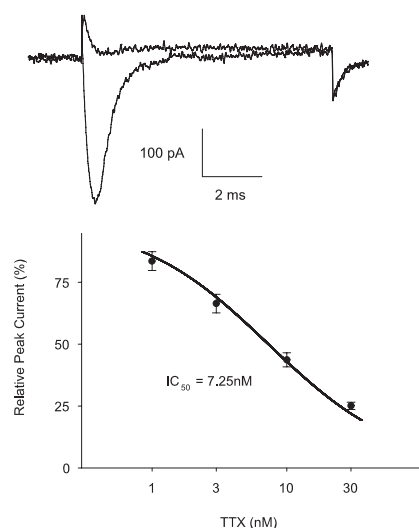
ICH S7B The nonclinical evaluation of the potential for QT interval prolongation issued as CHMP/ICH/423/02, adopted by CHMP in May 2005.

Na_v1.5 GLP

Gene: SCN5A

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (CHO), stable expression
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	carbamazepine (IC ₅₀ : 59.2 μM)
References, further examples	Mibefradil, Lidocaine, TTX, Propafenone, Quinidine
+ cardiac toxicity/safety relevant ion channel test	
+ antiarrhythmic screening	

ICH S7B The nonclinical evaluation of the potential for QT interval prolongation issued as CHMP/ICH/423/02, adopted by CHMP in May 2005.



Na_v1.6

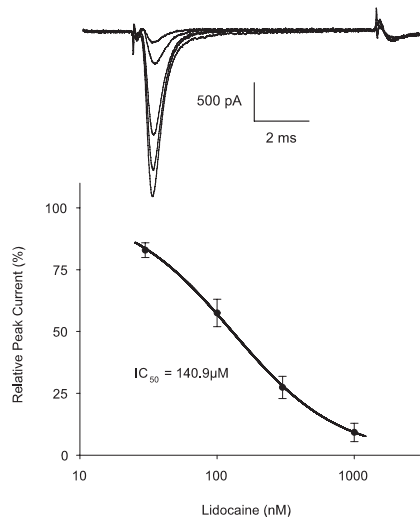
Gene: SCN8A

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (CHO/HEK 293)
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	TTX (IC ₅₀ : 7.3 nM)
References, further examples	Mibefradil, Lidocaine
+ neuronal sodium channel assay	
+ antinociceptive screening (CNS / dorsal root ganglion)	
+ cns toxicity / safety relevant ion channel test	

Wood JN. et al. (2004) Wiley InterScience DOI 10.1002/neu.20094
Rosker C. et al. (2007) Am J Physiol Cell Physiol 293: C783-C789

Ion channels & Transporters Na⁺ channel

Na_v1.7

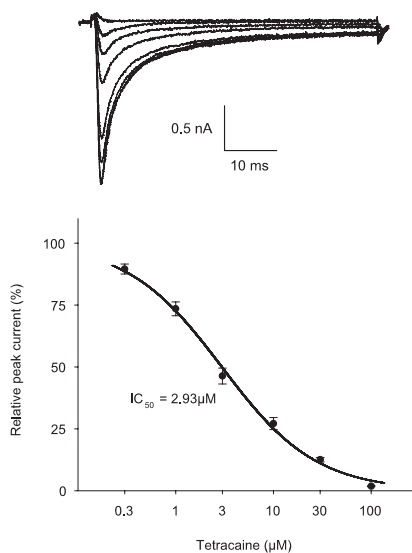


Gene: SCN9A

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (HEK/CHO)
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	TTX (IC ₅₀ : 54.8nM)
References, further examples	Mibefradil, Lidocaine (IC ₅₀ : 140.8 μM)
+ neuronal sodium channel assay: Dorsal root ganglion channel	
+ antinociceptive screening	
+ cns toxicity/safety relevant ion channel test	

Wood JN. et al. (2004) Wiley InterScience DOI 10.1002/neu.20094
Klugbauer N. et al. (1995) EMBO 14(6): 1084 – 1090
Chevrier P. et al. (2004) British Journal of Pharmacology 142: 576–584

Na_v1.8



Gene: SCN10A

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	Tetracaine (IC ₅₀ : 2.9 μM)
References, further examples	
+ neuronal sodium channel assay: Dorsal root ganglion channel	
+ antinociceptive screening	
+ cns toxicity/safety relevant ion channel test	

John VH. et al. (2003) Neuropharmacology 46: 425-438
Tate S. et al. (1998) 1:653-655
Chevrier P. et al. (2004) British Journal of Pharmacology 142: 576–584

Ion channels & Transporters Na⁺ channel

Neuroblastoma whole sodium (TTX sensitive sodium channels)

Standard throughput time 4 weeks (draft)

Source mouse

Expression system mammalian N1E-115

Method whole cell patch-clamping

Quality level high quality functional assay

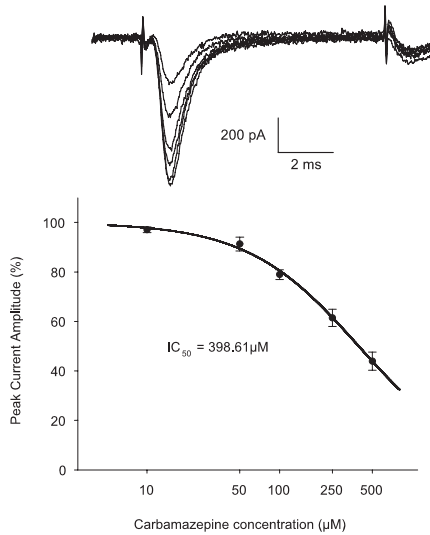
Reference Carbamazepine (IC₅₀: 398.6 μM)

References, further examples TTX

+ neuronal sodium channel assay: Dorsal root ganglion channel

+ useful for antinociceptive screening

Bonifacio MJ. et al. (2001) Epilepsia 42: 600-608



Ion channels & Transporters Ca²⁺ channel

Ca_v2.1

Gene: CACNA1A / CACNB3 / CACNA2D2 or CACNA2D4

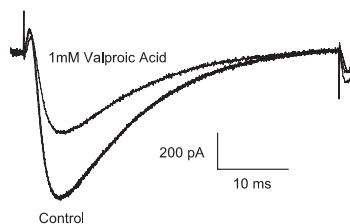
Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (HEK 293) semistable expression
Method	whole cell patch-clamping
Quality level	high quality functional assay

Torodovic SM and Lingle CJ (1998) Pharmacological Properties of T-Type Ca²⁺ Current in Adult Rat Sensory Neurons: Effects of Anticonvulsant and Anesthetic agents. *Journal of Neurophysiology* 79: 240-252

Ca_v3.2

Gene: CACNA1H

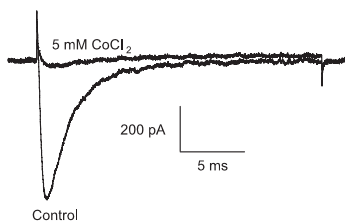
Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (HEK 293)
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	Valproic Acid sodium salt



Kubista H et al. (2007) *Neuropharmacology* 52: 1650-1662.
Torodovic SM et al. (1998) *Journal of Neurophysiology* 79: 240-252
Todorovic SM et al. (2001) *Molecular Pharmacology* 60: 603-610
Yamashita N et al. (2006) *Molecular Pharmacology* 69: 1684-1691

Neuroblastoma whole calcium

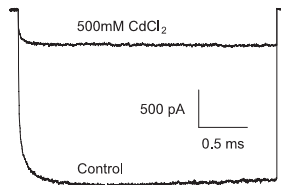
Standard throughput time	4 weeks (draft)
Source	mouse
Expression system	mammalian N1E-115
Method	whole cell patch-clamping
Quality level	high quality functional study
Reference	Cobalt Chloride



Im HK et al. (1993) *J Pharmacol Exp Ther* 265: 529-535
Kimhi Y et al. (1976) *Proc Natl Acad Sci USA* 73: 462-466
Matsuki N et al. (1984) *J Pharmacol Exp Ther* 228: 523-530
Moolenaar et al. (1978) *J Physiol* 278: 265-286.
Narahashi T et al. (1987) *J Physiol* 383: 231-249

Ion channels & Transporters Cl⁻ channel

ClC-2



Gene: CLCN2

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	Flufenamic acid, CdCl ₂

Ion channels & Transporters GABA_A-Receptor

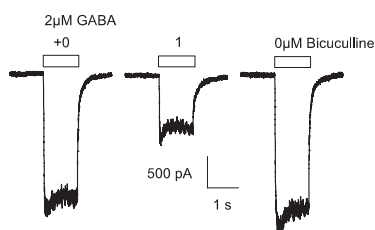
GABA_A ($\alpha_1\beta_2\gamma_2$) FLUORESCENCE – HTS

Gene: GABRA1 / GABRB2 / GABRG2

Standard throughput time	please inquire
Source	human
Expression system	mammalian (Ltk, HEK 293), stable expression
Method	Fluorescence assay (Flexstation/FLIPR)
Quality level	HTS-fluorescence assay
Reference	positive allosteric modulator: Diazepam
+ GABA _A profiling for pesticides	
+ antinociceptive screening	
+ profiling for anticonvulsive / sedative / anxiolytic / memory effects	

Joesch C. et al.: (2008) VH. et al. (2003) J Biomol Screen, ahead of print

GABA_A ($\alpha_1\beta_2\gamma_2$)



Gene: GABRA1 / GABRB2 / GABRG2

Standard throughput time	6 weeks (draft)
Source	human
Expression system	mammalian (Ltk, HEK 293), stable expression
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	positive allosteric modulator: Diazepam
+ GABA _A profiling for pesticides	
+ antinociceptive screening	
+ profiling for anticonvulsive / sedative / anxiolytic / memory effects	

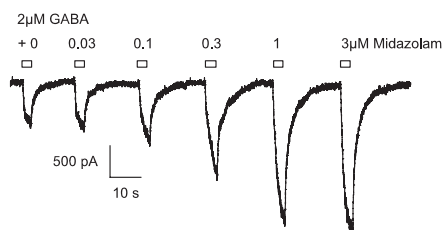
GABA_A ($\alpha_1\beta_3\gamma_2$)

Gene: GABRA1 / GABRB3 / GABRG2

Standard throughput time	6 weeks (draft)
Source	human
Expression system	mammalian (Ltk, HEK 293, CHO)
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	positive allosteric modulator: Diazepam

Ion channels & Transporters GABA_A-Receptor

GABA_A (α₂β₂γ₂)



Gene: GABRA2/GABRB2/GABRG2

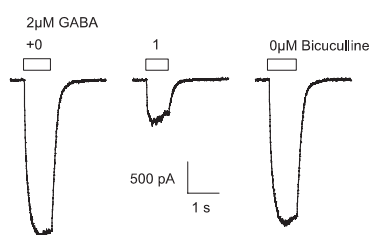
Standard throughput time	6 weeks (draft)
Source	human
Expression system	mammalian (Ltk, HEK 293), stable expression
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	positive allosteric modulator: Diazepam
References, further examples	Midazolam

+ GABA_A profiling for pesticides

+ antinociceptive screening

+ profiling for anticonvulsive / sedative / anxiolytic / memory effects

GABA_A (α₃β₂γ₂)



Gene: GABRA3/GABRB2/GABRG2

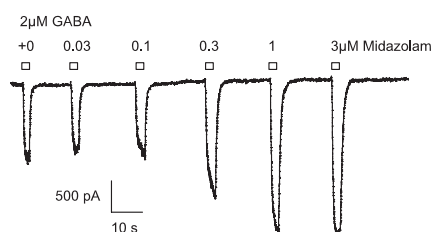
Standard throughput time	6 weeks (draft)
Source	human
Expression system	mammalian (Ltk, HEK 293), stable expression
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	positive allosteric modulator: Diazepam

+ GABA_A profiling for pesticides

+ antinociceptive screening

+ profiling for anticonvulsive / sedative / anxiolytic / memory effects

GABA_A (α₅β₂γ₂)



Gene: GABRA5/GABRB2/GABRG2

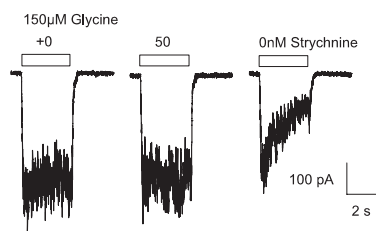
Standard throughput time	6 weeks (draft)
Source	human
Expression system	mammalian (Ltk, HEK 293), stable expression
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	positive allosteric modulator: Diazepam

+ GABA_A profiling for pesticides

+ antinociceptive screening

+ profiling for anticonvulsive / sedative / anxiolytic / memory effects

Ion channels & Transporters Glycine-Receptor



GlyR α_3

Gene: GLYRA3

Standard throughput time	6 weeks (draft)
Source	human
Expression system	mammalian (CHO), stable expression
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	Strychnine, Tropisetron

- + anitnociceptive profiling
- + antinociceptive screening

Heindl C et al. (2007) Neuroscience Letters 429: 59-63
Nikolic Z et al. (1998) JBC 273 (31): 19708-19714
Sobetzko D et al. (2001) Am J Med Genet.105(6):534-8
Harvey RJ et al. (2004) Science 304(5672):884-7

Ion channels & Transporters Glutamate-Receptor

AMPA

Gene: GRIA1

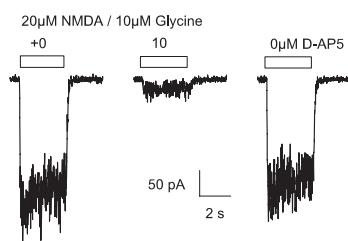
Standard throughput time	6 weeks (draft)
Source	human
Expression system	mammalian
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	(RS)-AMPA
+ antinociceptive, antidepressive, anxiolytic screening	
+ cns compound profiling	

Kew JN et al. (2005) *Psychopharmacology* 179(1): 4-29
Möykkynen T et al (2003) *Journal of Pharmacology And Experimental Therapeutics* 306(2): 546-55
Weiser T (2005) *CNS & Neurological Disorders* 4(2):153-9
Dinse A (2005) *British Journal of Anaesthesia* 94(4): 479-485

NMDA (NR1/2A)

Gene: GRIN1/GRIN2A

Standard throughput time	6 weeks (draft)
Source	human
Expression system	mammalian
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	D-(-)-2-Amino-5-phosphonopentanoic acid (AP 5)
+ antinociceptive, antidepressive, anxiolytic screening	
+ cns compound profiling	



NMDA (NR1/2B)

Gene: GRIN1/GRIN2B

Standard throughput time	6 weeks (draft)
Source	human
Expression system	mammalian
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	D-(-)-2-Amino-5-phosphonopentanoic acid (AP 5)
+ antinociceptive, antidepressive, anxiolytic screening	
+ cns compound profiling	

Cais O et al. (2008) *Neuroscience*, 151, 428-438
Kew JN, Kemp JA (2005) *Psychopharmacology*, 179(1): 4-29

Ion channels & Transporters

Acetylcholine-Receptor

Serotonin-Receptor

ATP-Receptor

nAChR (α_7)

Gene: CHRNA7/RIC-3

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (GH4), stable expression
Method	whole cell patch-clamping
Quality level	high quality functional assay

nAChR ($\alpha_4\beta_2$)

Gene: CHRNA4/CHRN2

Standard throughput time	6 weeks (draft)
Source	human
Expression system	mammalian (HEK 293/CHO), stable expression
Method	whole cell patch-clamping
Quality level	high quality functional assay

SEROTONIN 5HT3A

Gene: HTR3A

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (HEK 293)
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	Tubocurarine

P2X7

Gene: P2RX7

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian
Method	whole cell patch-clamping
Quality level	high quality functional assay

Ion channels & Transporters TRP

TRPV1

Gene: TRPV1 (VR1)

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (CHO/HEK 293)
Method	whole cell patch-clamping
Quality level	high quality functional assay
Reference	Capsazepine (IC ₅₀ : 1.6µM)
References, further examples	positive modulator: Capsaicin
+ antinociceptive research: safety screening	

Seabrook GR et al., (2002) J Pharmacol Exp Ther. 303(3):1052-60
Novakova-Tousova K et al., (2007) Neuroscience 149(1):144-54
Ohta T et al., (2007). Biochem Pharmacol 73(10):1646-56
Ohta T et al., (2005) Biochem Pharmacol 71(1-2):173-87

TRPV2

Gene: TRPV2

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (CHO/HEK 293)
Method	whole cell patch-clamping
Quality level	high quality functional assay

TRPV4

Gene: TRPV4

Standard throughput time	4 weeks (draft)
Source	human
Expression system	CHO
Method	whole cell patch-clamping and FlexStation
Quality level	high quality functional assay and fluorescence assay

TRPM8

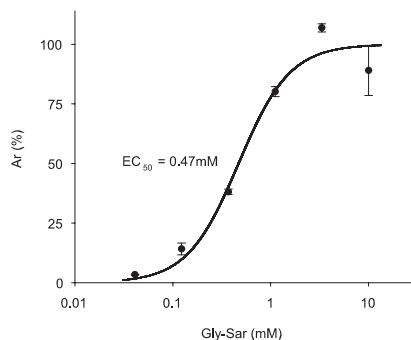
Gene: TRPM8

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (CHO/HEK 293)
Method	whole cell patch-clamping
Quality level	high quality functional assay

Ion channels & Transporters

Transporter

GPCR



PepT1

Gene: SLC15A1

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (MDCK), stable expression
Method	Fluorescence
Quality level	indirect (fluorescence) assay
Reference	Gly-Sar

Faria TN. et al. (2003) Molecular Pharmaceutics, 1:67-76

GlyT1/GlyT2 (Glycine transporters)

Gene: SLC6A9/SLC6A5

Standard throughput time	8 weeks (draft)
Source	human
Expression system	mammalian
Method	Fluorescence
Quality level	Indirect (fluorescence) assay
Reference	Doxepin, amitriptyline, nortriptyline, amoxapine
+ Epilepsy	
+ CNS compound profiling	

Benjamin E. et al. (2005) Journal of Biomolecular Screening, 10(4): 365-373

mGLUR1

Gene: GRM1

Standard throughput time	4 weeks (draft)
Source	human
Expression system	mammalian (HEK 293)
Method	Fluorescence
Quality level	Indirect (fluorescence) assay
Reference	Gly-Sar
+ Oligopeptide transporter assay	

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Assay	Gene	Page
Cardiac Screen		
hERG dose range finding	KCNH2	6
hERG (CHO)	KCNH2	6
hERG (HEK 293)	KCNH2	7
hERG full glass* (CHO)	KCNH2	7
hERG full glass* (HEK 293)	KCNH2	8
hERG-GLP (HEK 293)	KCNH2	8
hERG-GLP (CHO)	KCNH2	9
K _v 1.5	KCNA5	12
Na _v 1.5	SCN5A	15
Na _v 1.5-GLP	SCN5A	15
Ca _v 1.2	CACNA1C / CACNB2 / CACNA2D	–

Assay	Gene	Page
CNS Screen		
K _v 7.2	KCNQ2	12
Na _v 1.1	SCN1A	14
Na _v 1.2	SCN2A	14
Na _v 1.3	SCN3A	14
Na _v 1.6	SCN8A	15
Na _v 1.7	SCN9A	16
Na _v 1.8	SCN10A	16
Neuroblastoma whole sodium (TTX sensitive sodium channels)		17
Ca _v 2.1	CACNA1A / CACNB3 / CACNA2D2 or CACNA2D4	18
CIC-2	CLCN2	19
GABA _A (α ₁ β ₂ γ ₂)	GABRA1 / GABRB2 / GABRG2	20
GABA _A (α ₁ β ₃ γ ₂)	GABRA1 / GABRB3 / GABRG2	20
GABA _A (α ₂ β ₂ γ ₂)	GABRA2 / GABRB2 / GABRG2	21
GABA _A (α ₃ β ₂ γ ₂)	GABRA3 / GABRB2 / GABRG2	21
GABA _A (α ₅ β ₂ γ ₂)	GABRA5 / GABRB2 / GABRG2	21
Glycine (GlyRα ₃)	GLYRA3	22
nAChR (α ₇)	CHRNA7	24
nAChR (α ₄ β ₂)	CHRNA4 / CHRNB2	24
Serotonin 5HT _{3A}	HTR3A	24
P2X ₇	P2RX7	24
AMPA	GRIA1	23
NMDA (NR1/2A)	GRIN1/GRIN2A	23
NMDA (NR1/2B)	GRIN1/GRIN2B	23

* Full Glass Equipment (glass equipment is used to avoid adherence of sticky compounds to plastic surfaces)
 ** GLP
 *** coming in 2009

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Assay	Gene	Page
Antiarrhythmic		
hERG dose range finding	KCNH2	6
hERG (CHO)	KCNH2	6
hERG (HEK 293)	KCNH2	7
hERG full glass * (CHO)	KCNH2	7
hERG full glass * (HEK 293)	KCNH2	8
hERG-GLP (HEK 293)	KCNH2	8
hERG-GLP (CHO)	KCNH2	9
K _v 1.5	KCNA5	12
Na _v 1.5	SCN5A	15
Na _v 1.5-GLP	SCN5A	15
Ca _v 1.2	CACNA1C / CACNB2 / CACNA2D	–
Ca _v 3.2	CACNA1H	18

Assay	Gene	Page
Antiepileptic		
K _v 7.2	KCNQ2	12
Na _v 1.1	SCN1A	14
Na _v 1.2	SCN2A	14
Na _v 1.3	SCN3A	14
Na _v 1.6	SCN8A	15
Na _v 1.7	SCN9A	16
Na _v 1.8	SCN10A	16
Neuroblastoma whole sodium (TTX sensitive sodium channels)		17
Ca _v 2.1	CACNA1A / CACNB3 / CACNA2D2 or CACNA2D4	18
ClC-2	CLCN2	19
GABA _A (α1β2γ2)	GABRA1 / GABRB2 / GABRG2	20
GABA _A (α1β3γ2)	GABRA1 / GABRB3 / GABRG2	20
GABA _A (α2β2γ2)	GABRA2 / GABRB2 / GABRG2	21
GABA _A (α3β2γ2)	GABRA3 / GABRB2 / GABRG2	21
GABA _A (α5β2γ2)	GABRA5 / GABRB2 / GABRG2	21
GABA _A (α1β2γ2) Fluorescence	GABRA1 / GABRB2 / GABRG2	20
Glycine GlyRα ₃	GLRA3	22
AMPA	AMPA1	23
NMDA	NR1/2A	23
NMDA	NR1/2B	23

* Full Glass Equipment (glass equipment is used to avoid adherence of sticky compounds to plastic surfaces)
 ** GLP
 *** coming in 2009

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1 Request the assay type via e-mail and order and offer / confirmation of order.

Please indicate:

1. Your contact information (phone, fax number, e-mail)
2. GLP or non-GLP
3. Requested replicates
4. Requested concentrations
5. Number of compounds for each assay

You will receive our offer, order confirmation form and compound datasheets.
Please return the confirmation of order to B'SYS (by e-mail or fax).

2 Complete the provided order confirmation form and compound datasheets.

Required information for non-GLP studies

1. Compound designation
2. Molecular weight
3. Vehicle to be used
4. Solubility in vehicle
5. Storage conditions

Send the compound datasheet via:

e-mail: assay@bsys.ch
fax: +41 61 721 77 44

Or along with the compounds to:

B'SYS GmbH Laboratories
Benkenstrasse 254
CH-4108 Witterswil
Switzerland

3 You will receive our proposed study plan for review.

4 Compounds, format and amount required.

**Ship the compounds in safely closed vials or plates to the address above.
The amount of compound required depends on its molecular weight and nature:**

Stock solutions:

Your in house available stock solutions in e.g. 250 µL DMSO at 10 mM

Solid compound for non-GLP studies:

Pre-weighed 10 µmol (typically around 5 mg for drug molecular weights)

Solid compound for GLP studies:

20 mg (true for typical molecular weight)

Study start

Upon arrival an acknowledgement of compound receipt will be sent to you via e-mail.
The study is initiated

5 Study start.

Our assays usually require 1 to 6 weeks from compound arrival to completion of a draft report.

See specific assays for additional information.

Final completion of the report depends on when we receive your comments but is typically within two weeks of receipt of the comments.

6 Terms and conditions.

Our standard terms and conditions are outlined in the respective offer.

Calculation of prices and datapoints

One data point corresponds to testing one concentration of the test item at a single cell
The following examples illustrate the calculation:

Single point screen:

Single point screens use one concentration at $n = 2$ or 3 cells, resulting in 2 or 3 data points per compound

2 Point screens:

Two point screens use 2 concentrations at $n = 2$ or 3 cells, i.e. 4 or 6 data points per compound

IC₅₀ screens at $n = 3$:

The determination of an IC₅₀ at 4 to 7 concentrations results in 12 to 21 data points per compound

Prices

BSYS is delivering high quality at very moderate prices.

Calculation example:

If the IC₅₀ of a single compound is determined at 6 concentrations in triplicate 18 data points result.

If the price per data point is 70 €, a total price of 1.260 € is calculated.

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A		K		P	
AMPA	23	K _{ir} 2.1	–	PepT1	26
		K _v 1.1	11	P2X7	24
		K _v 1.2	11		
C		K _v 1.3	11	S	
Ca _v 1.2	–	K _v 1.4	–	Serotonin 5HT3A	24
Ca _v 2.1	18	K _v 1.5	12		
Ca _v 3.2	18	K _v 1.5 GLP	12	T	
CIC-2	19	K _v 1.6	12	TRPV1	25
		K _v 7.2	12	TRPV2	25
E		KvLQT/minK (K _v 7.1)	13	TRPV4	25
ENaC	–			TRPM8	25
G		M			
GABA _A (α ₁ β ₂ γ ₂)	20	mGLUR1	26		
GABA _A (α ₁ β ₂ γ ₂) Fluorescence HTS	20				
GABA _A (α ₁ β ₃ γ ₂)	20	N			
GABA _A (α ₂ β ₂ γ ₂)	21	nAChR (α ₇)	24		
GABA _A (α ₃ β ₂ γ ₂)	21	nAChR (α ₄ β ₂)	24		
GABA _A (α ₅ β ₂ γ ₂)	21	Na _v 1.1	14		
Glycine GlyRα ₃	22	Na _v 1.2	14		
GlyT1	26	Na _v 1.3	14		
GlyT2	26	Na _v 1.5	15		
		Na _v 1.5 GLP	15		
H		Na _v 1.6	15		
hERG	6–9	Na _v 1.7	16		
		Na _v 1.8	16		
		Neuroblastoma whole sodium (TTX sensitive sodium channels)	17		
		Neuroblastoma whole calcium	18		
		NMDA	23		

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