Suven Research Publications in 2013

1. Xenobiotica. 2013 Oct 24. [Epub ahead of print]

Identification of a suitable and selective inhibitor towards aldehyde oxidase catalyzed reactions.

Nirogi R, Kandikere V, Palacharla RC, Bhyrapuneni G, Kanamarlapudi VB, Ponnamaneni RK, Manoharan AK.

Source

Discovery Research, Suven Life Sciences Ltd., Hyderabad-500 055, Andhra Pradesh, India. Electronic address: nvsrk@suven.com.

Abstract

Abstract 1. Aldehyde oxidase (AO) is a liver cytosolic molybdoflavoprotein enzyme whose importance in drug metabolism is gaining in the recent. The objective of this work is to find a potent and selective inhibitor for Among AO activity using phthalazine oxidation as a marker reaction. 2. organic solvents tested, it was identified that methanol was not a suitable choice for AO activity even at concentrations less than 0.2% v/v. Acetonitrile and DMSO did not show any effect till 0.5% v/v but For selectivity, 23 compounds thereafter activites tend to decrease. 3. were selected and evaluated for their effects on AO and nine CYP450 enzymes. Among the tested compounds chlorpromazine, estradiol, hydralazine, quetiapine and raloxifene were selected based on their Raloxifene was found to be potency of inhibition towards AO activity. 4. a non-specific inhibitor of all major tested CYP450 enzymes and was excluded as a selective inhibitor for AO. Quetiapine also showed a degree of inhibition towards the major CYP450 tested. Hydralazine used as a specific inhibitor during the past for AO activity demonstrated a stimulation of AO activity at high and low concentrations respectively and the inhibition noted to be time dependent while inhibiting other Estradiol showed no inhibition enzymes like monoamine oxidase. 5. towards the tested CYP450 enzymes and thus proved to be a selective and specific inhibitor for AO activity with an uncompetitive mode of inhibition.

PMID: 24156774

2. Eur J Pharmacol. 2013 Oct 14. doi:10.1016/j.ejphar.2013.10.005. [Epub ahead of print]

Effect of olanzapine on scopolamine induced deficits in differential reinforcement of low rate 72s (DRL-72s) schedule in rats: Involvement of the serotonergic receptors in restoring the deficits.

Nirogi R, Jayarajan P, Shinde A.

Source

Discovery Research, Suven Life Sciences Ltd., Hyderabad-500 055, Andhra Pradesh, India. Electronic address: nvsrk@suven.com.

Abstract

Scopolamine, a non-selective muscarinic receptor antagonist has widespread central nervous system effects. Muscarinic receptors located in the central nervous system play a vital role in the modulation of impulsivity. The objective of the current study was to evaluate the effect of scopolamine on impulsivity using differential-reinforcement-of-low-rate 72-s schedule (DRL-72s) and to demonstrate the involvement of serotonergic receptors in mediating the effect of olanzapine (atypical antipsychotic) on scopolamine induced impulsivity. Scopolamine impaired the performance of the rats trained under DRL-72s schedule. Olanzapine reversed the deficits induced by scopolamine. We evaluated the effect of donepezil (cholinesterase inhibitor), SB-742457 (5-HT6 and 5-HT2a antagonist), and haloperidol (typical antipsychotic) in rats challenged with scopolamine in the DRL-72s schedule to identify the receptor(s) involved in reversing the deficits. SB-742457 partially reversed the deficits, but donepezil and haloperidol did not show any effects on the deficits induced by scopolamine. Olanzapine and SB-742457 shifted the peak location (PkL) towards longer IRT duration, indicating a decrease in motor impulsivity. Modulation of scopolamine-induced impulsivity by olanzapine could be partly due to its antagonistic action at 5-HT2a and 5-HT6 receptors, respectively. Superior effects of olanzapine on impulsivity in schizophrenic patients may be mediated through the antagonism of 5-HT2a and 5-HT6 receptors.

PMID: 24135200

3. Biomed Chromatogr. 2013 Jun 13. doi: 10.1002/bmc.2939. [Epub ahead of print]

LC-MS/MS method for the determination of pitolisant: application to rat pharmacokinetic and brain penetration studies.

Nirogi R, Ajjala DR, Kandikere V, Pantangi HR, Jonnala MR, Bhyrapuneni G, Muddana NR, Vurimindi H.

Source

Biopharmaceutical Research, Suven Life Sciences Ltd, Serene Chambers, Road 5, Avenue 7, Banjara Hills, Hyderabad, 500034, India.

Abstract

A simple and sensitive LC-MS/MS method was developed and validated for the quantitation of pitolisant, an H_3 receptor antagonist/inverse agonist. Acetonitrile protein precipitation technique was used to prepare rat blood and brain tissue homogenate samples by using aripiprazole as internal standard (IS). Chromatographic separation was performed by using Xbridge column (2.1×50 mm, 3.5 µm) with a gradient elution program. The mobile phase consists of ammonium formate (10 mm) with 0.2% formic acid and acetonitrile. Multiple reaction monitoring mode was used in positive polarity with a transition of m/z 296.3→98.2 for the pitolisant and m/z 448.2→285.3 for the IS. The calibration curves were linear in the range of 0.1-100 ng/mL in both the blood and brain homogenate samples. This method was applied to quantify samples obtained from the pharmacokinetic and brain penetration studies in male wistar rats. Mean maximum concentration, area under the curve from zero to infinity and half-life of the pitolisant were found to be 3.4±1.7 ng/mL, 5±4 ng h/mL and 1.9±0.3 h, respectively, after a 3 mg/kg oral dose. The mean calculated concentrations in the brain were found to be 38, 60 and 52 ng/g at 0.5, 1 and 2 h, respectively.

PMID: 23760876

4. J Pharm Biomed Anal. 2013 Jul-Aug; 81-82:160-7. Epub 2013 Apr 16.

LC-MS/MS method for the quantification of almotriptan in dialysates: application to rat brain and blood microdialysis study.

Nirogi R, Ajjala DR, Kandikere V, Aleti R, Pantangi HR, Srikakolapu SR, Benade V, Bhyrapuneni G, Vurimindi H.

Source

Biopharmaceutical Research, Suven Life Sciences Ltd, Serene Chambers, Road - 5, Avenue - 7, Banjara Hills, Hyderabad 500034, India. ramakrishna_nirogi@yahoo.co.in

Abstract

A sensitive LC-MS/MS method was developed and validated for the quantification of almotriptan in rat brain and blood dialysates. Almotriptan is a 5HT1B/1D receptor agonist used for the treatment of migraine pain. Method consists of rapid gradient elution program with 10mM ammonium formate (pH 3) and acetonitrile on a Xbridge column. The MRM transitions monitored were m/z 336.2-58.1 for almotriptan and m/z 448.2-285.3 for the IS. The assay was linear in the range of 0.1-20 ng/ml, with acceptable precision and accuracy along with adequate sensitivity. The between batch accuracy was in the range of 99.0-104.3% with precision in between 0.6% and 5.8%. Microdialysis is an important sampling technique, with the capability of capturing the concentrations of various analytes in different bio fluids, at a single time point. This method was applied to quantify brain and blood dialysate samples obtained from a microdialysis study of rats treated with almotriptan (10mg/kg, p.o.). In vivo recovery experiments were performed to correct the dialysate concentrations into extracellular concentrations. Mean peak dialysate concentrations of almotriptan were found to be 152 ± 78 and 7.4 ± 1.0 ng/ml in blood and prefrontal cortex, respectively. The brain penetration of almotriptan is characterized by the AUCbrain/AUCblood found to be 0.07 ± 0.05. The results revealed the importance of measuring the unbound almotriptan concentrations in the brain over the blood for understanding its PK/PD relationship.

PMID: 23666253

5. Eur J Pharmacol. 2013 Jul 15; 712(1-3):22-9. Epub 2013 May 7.

α4β2* neuronal nicotinic receptor ligands (agonist, partial agonist and positive allosteric modulators) as therapeutic prospects for pain.

Nirogi R, Goura V, Abraham R, Jayarajan P.

Source

In-Vivo Pharmacology, Discovery Research, Suven Life Sciences Ltd., Serene Chambers, Road No. 5, Avenue-7, Banjara Hills, Hyderabad 500034, India. nvsrk@suven.com

Abstract

α4β2* neuronal nicotinic acetylcholine receptor are ligand-gated ion channels and widely expressed throughout the central and peripheral nervous system. α4β2* neuronal nicotinic acetylcholine receptor play crucial role in pain signaling via modulation of multiple

neurotransmitters like acetylcholine, dopamine, γ-amino butyric acid (GABA) and norepinephrine. Both spinal and supraspinal pathways are involved in the mechanisms by which α4β2* neuronal nicotinic acetylcholine receptor ligands modulate the neuropathic and inflammatory pain. Selective α4β2* neuronal nicotinic acetylcholine receptor ligands are being developed for the treatment of neuropathic and inflammatory pain as they show considerable efficacy in a wide range of preclinical pain models. Agonists/partial agonists of α4β2* neuronal nicotinic acetylcholine receptor show efficacy in animal models of pain and their anti-nociceptive properties are blocked by nicotinic antagonists. Positive allosteric modulators are being developed with the aim to increase the potency or therapeutic window of agonists/partial agonists. Accumulating evidences suggest that anti-nociceptive effects of nicotinic acetylcholine receptor ligands may not be mediated solely by α4β2* neuronal nicotinic acetylcholine receptor. We have also reviewed the stage of clinical development of various α4β2* neuronal nicotinic acetylcholine receptor ligands.

PMID: 23660369

6. J Pharm Pharmacol. 2013 May; 65(5):704-12. Epub 2013 Jan 25.

In-vivo rat striatal 5-HT4 receptor occupancy using non-radiolabelled SB207145.

Nirogi R, Kandikere V, Bhyrapuneni G, Saralaya R, Ajjala DR, Aleti RR, Rasheed MA.

Source

Pharmacokinetics and Drug Metabolism, Suven Life Sciences Ltd, Hyderabad, India. nvsrk@suven.com

Abstract

OBJECTIVES:

The objective of the current investigation was to develop a simple, rapid method for determining in-vivo 5-hydroxytryptamine type 4 receptor (5-HT4 R) occupancy in rat brain using non-radiolabelled SB207145 as a tracer for accelerating the drug discovery process.

METHODS:

In-vivo tracer optimization studies for tracer dose, survival intervals and brain distribution profile were carried out in rats. The tracer was pharmacologically validated using potent well-characterized 5-HT4 R ligands. The brain regional concentrations of tracer (SB207145); plasma and brain concentrations of 5-HT4 R ligands were quantified using high-performance liquid chromatography coupled with a tandem mass spectrometric detector (LC-MS/MS).

KEY FINDINGS:

SB207145 showed a higher specific binding in striatum (1.96 ng/g) and lower binding in cerebellum (0.66 ng/g), which is consistent with findings of other published 5-HT4 R expression studies. Pretreatment with potent 5-HT4 ligands dose-dependently reduced striatal SB207145 concentration and the effective dose to achieve 50% receptor occupancy (ED50) values were

4.8, 2.0, 7.4, 9.9, 3.8 and 0.02 mg/kg for GR113808, piboserod, prucalopride, RS67333, TD8954 and PF04995274, respectively.

CONCLUSIONS:

Results from the mass spectrometry approach to determine 5-HT4 R occupancy in rat brain are comparable with those reported using radiolabelled scintillation spectroscopy methods. In conclusion, the LC-MS/MS characterization permits use of tracer at a preclinical stage in high-throughput fashion as well as characterization of target expression.

PMID: 23600388

7. Am J Drug Alcohol Abuse. 2013 Mar; 39(2):72-9.

Aripiprazole in an animal model of chronic alcohol consumption and dopamine D2 receptor occupancy in rats.

Nirogi R, Kandikere V, Jayarajan P, Bhyrapuneni G, Saralaya R, Muddana N, Abraham R.

Source

Department of ADME, Discovery Research, Suven Life Sciences Ltd ., Hyderabad - 500055, India. nvsrk@suven.com

Abstract

BACKGROUND:

Epidemiologic studies and clinical assessment of schizophrenic population have revealed a high incidence of overlap between schizophrenia and addictive disorders.

OBJECTIVE:

The aim of the present investigation was to study the effect of aripiprazole in a preclinical animal model of chronic alcohol self-administration (CASA) and also to evaluate the influence of CASA on plasma pharmacokinetics and dopamine D2 receptor (D2 R) occupancy in rats.

METHODS:

The effect of oral administration of aripiprazole (1, 3, and 10 mg/kg) on 4% alcohol intake in CASA was studied for a period of 45 min after a post-dosing interval of 60 min. Brain penetration, pharmacokinetics, and D2 R occupancy of aripiprazole were evaluated in normal and CASA rats.

RESULTS:

Aripiprazole reduced alcohol consumption in CASA rats by 13, 28, and 86% at 1, 3, and 10 mg/kg, respectively, and the effect reached statistical significance at 10 mg/kg ($p < .01$). At this behavioral effective dose, a decrease (75%) in total plasma apparent clearance and an increase in oral area under the concentration-time curve (3.98-fold) and bioavailability (3.50-fold) of aripiprazole was observed in CASA rats. Striatal D2 R occupancy and brain exposure of

aripiprazole were significantly higher (~twofold) in CASA rats when compared to normal rats ($p < .01$).

CONCLUSION:

Chronic alcohol intake results in a significant increase in exposure of aripiprazole in plasma and brain and striatal D2 R occupancy. Scientific significance: Chronic alcohol intake would increase aripiprazole exposure, thus aripiprazole dose might have to be decreased (assuming this same phenomenon occurs in humans).

PMID: 23421566

8. J Chromatogr B Analyt Technol Biomed Life Sci. 2013 Jan 15;913-914:41-7. Epub 2012 Sep 27.

A sensitive and selective quantification of catecholamine neurotransmitters in rat microdialysates by pre-column dansyl chloride derivatization using liquid chromatography-tandem mass spectrometry.

Nirogi R, Komarneni P, Kandikere V, Boggavarapu R, Bhyrapuneni G, Benade V, Gorentla S.

Source

Biopharmaceutical Research, Drug Discovery, Suven Life Sciences Ltd., Serene Chambers, Road - 5, Avenue - 7, Banjara Hills, Hyderabad 500 034, India. ramakrishna_nirogi@yahoo.co.in

Abstract

A rapid and sensitive liquid chromatography tandem mass spectrometry method for simultaneous quantification of catecholamine neurotransmitters in microdialysates was developed. The catecholamine neurotransmitters dopamine (DA) and norepinephrine (NE) were pre-column derivatized with dansyl chloride and analyzed. A gradient elution method was used to separate the analytes from the interferences on an Agilent Poroshell 120 EC-C18 outer porous micro particulate column. The method was robust and sensitive to determine with the lower limit of quantification value of 0.068pmol/mL and 0.059pmol/mL for DA and NE, respectively. It has acceptable precision and accuracy for concentrations over the standard curve range. The method was successfully applied for simultaneous quantitation of DA and NE in the prefrontal cortex (PFC) dialysates of rats obtained from a microdialysis study dosed with vehicle and atomoxetine through intra peritoneal (i.p.) route at a dose of 3mg/kg to monitor the change in extracellular concentrations. Thus, accomplishment of this method would facilitate the neurochemical monitoring for discovery of new chemical entities targeted for the treatment of attention deficit hyperactivity disorder (ADHD).

PMID: 23270937

9. J Pharm Biomed Anal. 2013 Feb 23; 74:227-34. Epub 2012 Oct 23.

LC-MS/MS method for the quantification of aldose reductase inhibitor-epalrestat and application to pharmacokinetic study.

Nirogi R, Kandikere V, Ajjala DR, Bhyrapuneni G, Muddana NR.

Source

Biopharmaceutical Research, Suven Life Sciences Ltd., Serene Chambers, Road - 5, Avenue - 7, Banjara Hills, Hyderabad 500034, India. ramakrishna_nirogi@yahoo.co.in

Abstract

A simple and rapid LC-MS/MS method was developed and validated for the quantification of epalrestat, an aldose reductase inhibitor for the treatment of diabetic neuropathy. Following protein precipitation epalrestat and IS were eluted with 10mM ammonium acetate and acetonitrile using a rapid gradient program on reverse phase column. Multiple reaction monitoring mode was used to monitor the transitions of m/z 318→58 for epalrestat and m/z 410→348 for the IS. The assay exhibited a linear dynamic range of 2-5,000 ng/mL for epalrestat in rat plasma. Acceptable precision and accuracy were obtained for concentrations over the standard curve range. The within batch accuracy was in the range of 101.3-108.0% with precision in the range of 3.0-12.3%. All the other validation parameters were within the acceptable limits. Validated method was applied to analyze rat plasma samples obtained from a pharmacokinetic study. After oral administration of epalrestat at 10mg/kg to wistar rats (n=3) mean C(max), AUC(0-24) (ngh/mL) and t(1/2) were found to be 4077 ± 1327 ng/mL, 8989 ± 1590 ngh/mL and 2.9 ± 1.4h, respectively. Bioavailability was found to be 90 ± 14% for epalrestat in male wistar rats.

PMID: 23245255