

Suven Research Publications in 2011

1. Drug Chem Toxicol. 2011 Dec 19. [Epub ahead of print]

Mutagenicity and clastogenicity evaluation of tacrine by Ames and micronucleus assays.

Mulla MS, Vedamurthy RB, Jana S, Pandey SK, Goyal VK, Nirogi R.

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Abstract

Tacrine was evaluated for its mutagenic and clastogenic activities using the Ames bacterial reverse-mutation assay and the rodent bone marrow micronucleus assay. Tacrine was tested for mutagenic potential at six different concentrations, with 1,250 µg/plate as the highest concentration, followed by five lower concentrations with 2-fold spacing. In clastogenic evaluation, tacrine was administered orally to Wistar rats for 2 days at 5, 10, and 20mg/kg body weights to assess micronucleus induction in bone marrow erythrocytes. In the Ames assay, tacrine showed nonmutagenicity in four tester strains of Salmonella typhimurium viz. TA98, TA100, TA102, and TA1535, but it was found to be mutagenic in the TA1537 tester strain, both in the presence and absence of a metabolic activation system. Tacrine was found to be nonclastogenic on bone marrow cells of rats at all doses tested and was found to be mutagenic in only the TA1537 strain of Salmonella.

PMID: 22182316 [PubMed - as supplied by publisher]

2. Drug Metab Dispos. 2011, Nov; 39(11):2162-4. Epub 2011 Aug 8.

Effect of Dimethyl Sulfoxide on In Vitro Cytochrome P450 1A2 Mediated Phenacetin-o-deethylation IN Human Liver Microsomes.

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

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Abstract

In this study, we report the effect of dimethyl sulfoxide (DMSO), acetonitrile, and methanol on the cytochrome P4501A2 (CYP1A2) mediated metabolism of phenacetin in human liver microsomes (HLM). Phenacetin O-deethylation is the preferred probe reaction for CYP1A2 where the metabolite, acetaminophen, is quantified using liquid chromatography tandem mass spectrometry (LC-MS/MS). DMSO was found to inhibit CYP1A2 mediated phenacetin O-deethylation even at low concentrations (0.1%). Acetonitrile did not significantly change the phenacetin O-deethylation activity at concentrations up to 2%. There was no effect on the phenacetin O-deethylation when methanol was present at levels up to 2%. It was found that the DMSO level should be kept lower than 0.05% because, a concentration of 0.1% strongly affected the metabolism of phenacetin. These findings should be taken into consideration when designing in vitro metabolism studies,

especially studies where metabolism of the investigational compound need to be evaluated, which would confound the results. The findings from this study indicate that methanol is the suitable solvent with no significant effects on CYP1A2 mediated phenacetin O-deethylation.

PMID: 21825116 [PubMed - as supplied by publisher]

3. J Enzyme Inhib Med Chem. 2011 Jul 21. [Epub ahead of print]

Synthesis and structure-activity relationship of novel conformationally restricted analogues of serotonin as 5-HT(6) receptor ligands.

Nirogi RV, Kambhampati R, Kothmirkar P, Konda J, Bandyala TR, Gudla P, Arepalli S, Gangadasari NP, Shinde AK, Deshpande AD, Dwarampudi A, Chindhe AK, Dubey PK.

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Abstract

5-Hydroxytryptamine 6 receptors (5-HT(6)R) are being perceived as the possible target for treatment of cognitive disorders as well as obesity. The present article deals with the design, synthesis, in vitro binding and structure-activity relationship of a novel series of tetracyclic tryptamines with the rigidized N-arylsulphonyl, N-arylcarbonyl and N-benzyl substituents as 5-HT(6) receptor ligands. The chiral sulphonyl derivatives 15a and 17a showed high affinity at 5-HT(6)R with the K(i) of 23.4 and 20.5nM, respectively. The lead compound from the series 15a has acceptable ADME properties, adequate brain penetration and is active in animal models of cognition like Novel Object Recognition Task (NORT) and water maze.

PMID: 21774748[PubMed - as supplied by publisher]

4. Eur J Pharmacol. 2011 Jul 3. [Epub ahead of print]

Antinociceptive activity of $\alpha 4\beta 2^*$ neuronal nicotinic receptor agonist A-366833 in experimental models of neuropathic and inflammatory pain.

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Abstract

Nerve injury, diabetes and cancer therapies are often associated with painful neuropathy. The mechanism underlying neuropathic pain remains poorly understood. The current therapies have limited efficacy and are associated with dose-limiting side effects. Compounds which act at nicotinic acetylcholine receptors have also been reported to show antinociceptive activity. Among those, tebanicline (ABT-594) a potent nicotinic acetylcholine receptor agonist demonstrated analgesic effects across a broad range of preclinical models of nociceptive and neuropathic pain. Another nicotinic acetylcholine receptor agonist, 5-[(1R,5S)-3,6-Diazabicyclo[3.2.0]heptan-6-yl]nicotinonitrile (A-366833) from the same group produced significant antinociceptive effects in

writhing pain (abdominal constriction), acute thermal pain (hot box), persistent chemical pain (formalin induced) and neuropathic pain. In the present study, we have demonstrated the efficacy of A-366833 in rat models of chronic constriction injury, partial sciatic nerve ligation, spinal nerve ligation, diabetes, chemotherapy induced neuropathic pain and complete Freund's adjuvant induced inflammatory pain. A-366833 (1, 3 and 6mg/kg) produced significant antihyperalgesic effects in partial sciatic nerve ligation, chronic constriction injury and spinal nerve ligation models. In the diabetic and chemotherapy induced neuropathic models compound exerted antinociceptive activity and reduction in the mechanical hyperalgesia was observed. A-366833 dose dependently attenuated mechanical hyperalgesia in complete Freund's adjuvant induced inflammatory pain model. These results demonstrated broad-spectrum antinociceptive properties of A-366833 in both neuropathic and inflammatory pain models.

PMID: 21756895 [PubMed - as supplied by publisher]

5. Arzneimittelforschung. 2011;61(5):301-11.

Simultaneous extraction of acetylsalicylic acid and salicylic acid from human plasma and simultaneous estimation by liquid chromatography and atmospheric pressure chemical ionization/tandem mass spectrometry detection. Application to a pharmacokinetic study.

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Abstract

A simple analytical method using liquid chromatography-tandem mass spectrometry (LC-MS/MS) in atmospheric chemical ionization mode (APCI) for the simultaneous estimation of acetylsalicylic acid (ASA, CAS 50-78-2) and its active metabolite salicylic acid (SA, CAS 69-72-7) in human plasma has been developed and validated. ASA and SA were analyzed simultaneously despite differences in plasma concentration ranges of ASA and SA after oral administration of ASA. In spite of having different chemical, ionization and chromatographic properties, ASA and SA were extracted simultaneously from the plasma sample using acetonitrile protein precipitation followed by liquid-liquid extraction. The analytes were separated on a reversed phase column with rapid gradient program using mobile phase consisting of ammonium acetate buffer and methanol. The structural analogue diclofenac was used as an internal standard. The multiple reaction monitoring (MRM) transitions m/z 179 \rightarrow 137 for ASA, m/z 137 \rightarrow 65 for SA and m/z 294 \rightarrow 250 for IS were used. The assay exhibited a linear dynamic range of 0.02-10 microg/mL for ASA and 0.1-50 microg/mL for SA. The between-batch precision (%CV) ranged from 2.1 to 7.9% for ASA and from 0.2 to 5.2% for SA. The between-batch accuracy ranged from 95.4 to 96.7% for ASA and from 94.6 to 111.3% for SA. The validated method was successfully applied for the evaluation of pharmacokinetics of ASA after single oral administration of 650 mg test formulation versus two 325 mg reference formulations of ASA in human subjects.

PMID: 21755814 [PubMed - indexed for MEDLINE]

6. Bioorg Med Chem Lett. 2011 Aug 1;21(15):4577-80. Epub 2011 Jun 6.

Rigidized 1-aryl sulfonyl tryptamines: Synthesis and pharmacological evaluation as 5-HT(6) receptor ligands.

Nirogi R, Dwarampudi A, Kambhampati R, Bhatta V, Kota L, Shinde A, Badange R, Jayarajan P, Bhyrapuneni G, Dubey PK.

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Abstract

A series of N(1)-arylsulfonyl-3-(pyrrolidin-3-yl)-1H-indole and N(1)-arylsulfonyl-3-(4-chloro-2,5-dihydro-1H-pyrrol-3-yl)-1H-indole derivatives (tryptamine derivatives with rigidized side chain) have been prepared and tested for their binding affinity to 5-HT(6) receptor. Several compounds displayed potent binding affinity for the 5-HT(6) receptor when tested in in vitro binding assay. The primary SAR indicates that rigidification of dimethylamino alkyl chain at C(3) of indole carbon maintains the binding affinity to 5-HT(6)R. The lead compound N(1)-benzenesulfonyl-3-(4-chloro-1-methyl-2,5-dihydro-1H-pyrrol-3-yl)-1H-indole, 10a ($K(b)=0.1\text{nM}$) has shown excellent in vitro affinity and was active in animal models of cognition like NORT and water maze.
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PMID: 21724392 [PubMed - in process]

7. J Pharm Biomed Anal. 2011 Sep 10;56(2):373-81. Epub 2011 May 27.

Quantification of cinacalcet by LC-MS/MS using liquid-liquid extraction from 50 μ L of plasma.

Nirogi R, Kandikere V, Komarneni P, Aleti R, Padala N, Kalaikadiban I.

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Abstract

A simple and economical high-performance liquid chromatography-positive ion electrospray tandem mass spectrometry method was developed and validated for the quantification of cinacalcet in plasma. Following liquid-liquid extraction, the analyte was separated using an isocratic mobile phase on a reversed-phase column and analyzed by MS/MS in the multiple reaction monitoring mode using the respective $[M+H]^+$ ions, m/z 358-155 for cinacalcet and m/z 310-148 for the internal standard. The assay exhibited a linear dynamic range of 0.1-200ng/mL for cinacalcet in plasma. Acceptable precision ($<10\%$) and accuracy ($100\pm 5\%$) were obtained for concentrations over the standard curve range. A run time of 3.5min for each sample made it possible to analyze more than 250 samples per day. The method was successfully applied to quantify cinacalcet concentrations in a preclinical pharmacokinetic study after a single oral administration of cinacalcet at 10mg/kg to rats. Following oral administration the maximum mean concentration in plasma ($C(\text{max})$; $160\pm 56\text{ng/mL}$) was achieved at 1.0h ($T(\text{max})$), area under the curve (AUC) and half-life ($t(1/2)$) were $949\pm 257\text{ng}\cdot\text{h/mL}$ and $3.58\pm 0.4\text{h}$, respectively.
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PMID: 21696904 [PubMed - in process]

8. J Enzyme Inhib Med Chem. 2011 Jun; 26(3):341-9.

Design, synthesis and pharmacological evaluation of conformationally restricted N-arylsulfonyl-3-aminoalkoxy indoles as a potential 5-HT6 receptor ligands.

Nirogi RV, Kambhampati R, Daulatabad AV, Gudla P, Shaikh M, Achanta PK, Shinde AK, Dubey PK.

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Abstract

A series of novel conformationally restricted N(1)-arylsulfonyl-3-aminoalkoxy indoles were designed and synthesized as 5-HT(6) receptor (5-HT(6)R) ligands. Many of the synthesized compounds have moderate in vitro-binding affinities at 5-HT(6)R. The lead compound 8b (% inhibition=97.2 at 1 μ M) from this series has good pharmacokinetic profile in male Wister rats and is active in animal model of cognition like Morris water maze. The details of chemistry, SAR, pharmacokinetics and pharmacological data constitute the subject matter of this report.

PMID: 21524149 [PubMed - in process]

9. Biomed Chromatogr. 2011 Feb 18. doi: 10.1002/bmc.1603. [Epub ahead of print]

Quantification of methyllycaconitine, selective $\alpha(7)$ nicotinic receptor antagonist, in rodent plasma and brain tissue by liquid chromatography tandem mass spectrometry - application to neuropharmacokinetics of methyllycaconitine in rats.

Nirogi R, Kandikere V, Komarneni P, Aleti R, Boggavarapu R, Bhyrapuneni G, Muddana N, Mukkanti K.

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Abstract

A sensitive high-performance liquid chromatography-positive ion electrospray tandem mass spectrometry (LC-MS/MS) method was developed and validated for the quantification of methyllycaconitine (MLA) in rat plasma and brain tissue. Following acetonitrile protein precipitation, the analyte was separated using a gradient mobile phase on a reversed-phase column and analyzed by MS/MS in the multiple reaction monitoring mode using the respective $[M + H]^+$ ions, m/z 683-216 for MLA and m/z 260-116 for the internal standard. The assay exhibited a linear dynamic range of 0.5-250 ng/mL for MLA in rat plasma and brain tissue. The lower limit of quantification was 0.5 ng/mL. Acceptable precision (<12%) and accuracy (100 \pm 6%) were obtained for concentrations over the standard curve range. The method was successfully applied to quantify MLA concentrations in a rodent pharmacokinetic and brain penetration study. Copyright © 2011 John Wiley & Sons, Ltd.

PMID: 21337354 [PubMed - as supplied by publisher]

10. Biomed Chromatogr. 2011 Feb 10. doi: 10.1002/bmc.1604. [Epub ahead of print]

Quantification of urapidil, α -1-adrenoreceptor antagonist, in plasma by LC-MS/MS: validation and application to pharmacokinetic studies.

Nirogi R, Kandikere V, Komarneni P, Aleti R, Boggavarapu R, Madala P.

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Abstract

A sensitive high-performance liquid chromatography-positive ion electrospray tandem mass spectrometry method was developed and validated for the quantification of urapidil in plasma. Following liquid-liquid extraction, the analyte was separated using an isocratic mobile phase on a reverse-phase column and analyzed by MS/MS in the multiple reaction monitoring mode using the respective $[M+H]^+$ ions, m/z 388 to 205 for urapidil and m/z 452 to 344 for the internal standard. The assay exhibited a linear dynamic range of 0.1-500 ng/mL for urapidil in plasma. Acceptable precision (<7%) and accuracy (100±8%) were obtained for concentrations over the standard curve range. The method was successfully applied to quantify urapidil concentrations in a preclinical pharmacokinetic study after a single oral administration of urapidil at 3 mg/kg to rats. Following oral administration the maximum mean concentration in plasma (C_{max}); 616 ± 73 ng/mL) was achieved at 0.5 h (T_{max}) and area under curve (AUC(0-24)) was 1841 ± 308 ng h/mL. The half-life ($t_{1/2}$) and clearance (Cl) were 2.47 ± 0.4 h and 1660 ± 276 mL/h/kg, respectively. Moreover, it is plausible that the assay method in rat plasma would facilitate the adaptability of urapidil quantification in human plasma for clinical trials. Copyright © 2011 John Wiley & Sons, Ltd.

PMID: 21308707 [PubMed - as supplied by publisher]

11. Beilstein J Org Chem. 2011 Jan 4;7:9-12.

Thermal rearrangement of tert-butylsulfonamide.

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Abstract

tert-Butylsulfonamides are unstable above room temperature, and in chlorinated solvents they undergo rearrangement to form the more stable N-(tert-butylthio)-tert-butylsulfonamide.

PMCID: PMC3028921

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PMID: 21286388 [PubMed]

12. Bioorg Med Chem Lett. 2011 Jan 1;21(1):346-9. Epub 2010 Nov 5.

Indole-3-piperazinyl derivatives: novel chemical class of 5-HT(6) receptor antagonists.

Nirogi RV, Deshpande AD, Kambhampati R, Badange RK, Kota L, Daulatabad AV, Shinde AK, Ahmad I, Kandikere V, Jayarajan P, Dubey PK.

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Abstract

N(1)-Arylsulfonyl-3-piperazinyl indole derivatives were designed and identified as a novel class of 5-HT(6) receptors ligands. All the compounds have high affinity and antagonist activity towards 5-HT(6) receptor. The compound 7a ($K(i) = 3.4$ nM, functional assay $IC(50) = 310$ nM) shows enhanced cognitive effect when tested in NORT and Morris water maze models. Synthesis, SAR and PK profile of these novel compounds constitute the subject matter of this Letter.

PMID: 21134749 [PubMed - indexed for MEDLINE]