SECTION 1

INTRODUCTION
Neuropathic pain is a common and severely disabling state affecting millions of people worldwide and is initiated after damage to the nociceptive pathway. It is characterized by the sensory abnormalities such as unpleasant abnormal sensation (dysesthesia); an increased response to painful stimuli (hyperalgesia); and pain in response to a stimulus that does not normally provoke pain i.e., allodynia (Woolf and Mannion, 1999; Dworkin, 2002). Furthermore, the neuropathic pain persists even after the resolution of the cause of initial injury. In contrast, similar sort of damage to other somatic senses has been associated with partial or total loss of the sensation. Peripheral neuropathic pain is observed in patients with cancer, AIDS, long standing diabetes, lumbar disc syndrome, herpes infection, traumatic spinal cord injury, multiple sclerosis and stroke (Werhagen et al., 2004). Moreover, post-thoracotomy, post-herniorrhaphy, post-mastectomy and post-sternotomy have also been associated with neuropathic pain (Perkins and Kehlet, 2000). Neuropathic pain responds poorly to many classical analgesics and is costly to manage (Harden and Cohen, 2003). Consequently, there is still a considerable need to explore novel treatment modalities for neuropathic pain management.

The chronic constriction injury (CCI) model is the most commonly used animal model of nerve damage-induced allodynia/hyperalgesia and has been shown to share the pathophysiology with a variety of neuropathic pain conditions in the patients (Bennett and Xie, 1988). The sciatic nerve is entrapped through four loose ligatures in this model and it shares the pathophysiology of carpal tunnel syndrome in humans due to entrapment of the median nerve in the narrowing carpal tunnel and tarsal tunnel syndrome due to entrapment of the tibial nerve. Furthermore, this model has also been suggested to share the pathophysiology of complex regional pain syndrome in humans (Bennet and Xie, 1988; Jin et al., 2008). Chemotherapeutic drugs such as vincristine, paclitaxel, oxaliplatin etc. are widely used in management of cancers especially non-Hodgkin lymphoma, Hodgkin lymphoma and leukemia. Unfortunately, these anticancer drugs are also associated with neurotoxicity and painful neuropathy (Bromberg, 2000). In recent years, rodent models of vincristine-induced neuropathy have been developed to unravel the mechanisms of toxicity and identify novel therapeutic agents (Jaggi et al., 2011).
Spironolactone is an aldosterone receptor antagonist and it has been clinically used to treat patients with hyperaldosteronism, edema associated with liver failure and nephrotic syndrome. It is reported to increase the survival rate of patients with cardiovascular diseases (Campana et al., 2008; Doggrell and Brown, 2001). In recent years, spironolactone has been shown to produce beneficial effects in number of diseases in which inflammation play a key role in the pathogenesis including diabetic nephropathy, rheumatoid arthritis associated endothelial dysfunction and retinal vasculopathy (Syngle et al., 2009; Kithas and Supiano, 2010; Lin et al., 2010). Its beneficial effects in different diseases have been attributed to its ability to inhibit the production of different pro-inflammatory cytokines (Miura et al., 2006). A large number of evidences document the prominent role of inflammation and pro-inflammatory cytokines in the pathobiology of different types of neuropathic pain (Thacker et al., 2007; Jain et al., 2009). Therefore, it may be possible that spironolactone, with potent anti-inflammatory actions, may modulate the pathobiology of neuropathic pain associated with inflammation. Recently, our own laboratory has reported anti-hyperalgesic effect of spironolactone in diabetic neuropathic pain (Khan et al., 2009). However, its potential in other types of neuropathic pain remains to be explored.

Renin-angiotensin system plays an important role in the body to maintain homeostasis and angiotensin II is the main final effector molecule of this system which in-turn produces majority of its effects through activation of angiotensin AT1 receptors. The studies have documented the presence of angiotensin AT1 receptors on inflammatory cells (Kitazono et al., 1995; Potter et al., 1998) and critical role of activation of renin-angiotensin system in different processes of inflammation including accumulation of neutrophils; differentiation of dendritic cells and production of inflammatory chemokines (Nahmod et al., 2003; Nabah et al., 2004). Telmisartan is reported to possess highest affinity for the angiotensin AT1 receptors (Kakuta et al., 2005) and stronger anti-inflammatory effects than other angiotensin AT1 receptor antagonists (Kurtz and Pravenec, 2004). The clinical studies have shown that efficacy of angiotensin AT1 receptor blockers including telmisartan in preventing the migraine attacks (Diener et al., 2009; Gales et al., 2010). Angiotensin AT1 receptor blockers-induced inhibition of neurogenic inflammation may probably be responsible for their beneficial effects in
migraine (Fusayasu et al., 2007; Ba'albaki and Rapoport, 2008). Furthermore, it has also been reported that repeated administration of angiotensin AT\textsubscript{1} receptor blockers and angiotensin converting enzyme inhibitors such as spirapril, trandolapril and losartan exhibit anti-nociceptive actions in mice (Takai et al., 1996). However, the ameliorative potential of telmisartan is not exploited in neuropathic pain models.

Neuropathic pain is associated with various changes in the expression of a variety of neurotransmitters, their receptors and other genes in the spinal cord and the dorsal root ganglia (DRG). The studies have shown the critical role of mitogen activated protein (MAP) kinase family including extracellular signal-regulated kinase (ERK), p38 kinase, and c-Jun N-terminal kinase (JNK) in various models of neuropathic pain (Tsuda et al., 2004). Ras, a small guanine-nucleotide (GTP/GDP) binding-protein kinase, and c-Raf, a cytosolic serine threonine protein kinase, constitute an important part of intracellular signal transduction pathway as Ras/Raf/MEK/ERK2 signaling cascade. Ras initiates intracellular signaling by binding to c-Raf which in-turn triggers the activation of kinase cascade through a MAPK family. Recent study has shown elevated mRNA levels of Ras homolog enriched in brain (Rheb) in the carrageenan model of inflammatory pain in rats (Norsted Gregory et al., 2010). Farnesyl thiosalicylic acid (FTS, Salirasib) is a novel Ras inhibitor which dislodges Ras proteins from the cell membrane and inhibits Ras-dependent signaling. FTS, with C15 farnesyl moiety, is structurally similar to the S-farnesyl cysteine of all Ras proteins and it interferes with anchorage sites recognizing the S-prenyl moiety of Ras (Marom et al., 1995). Furthermore, it exhibits significant selectivity towards Ras in its active i.e., in GTP-bound forms (Haklai et al., 1998). Apart from well documented anti-tumor effects of FTS through a combination of cytostatic and pro-apoptotic effects (Blum et al., 2008), it exerts neuroprotective effects in traumatic brain injury in rats (Shohami et al., 2003; Marciano et al., 2007) and attenuates experimental autoimmune encephalomyelitis, a model of multiple sclerosis in mice (Aizman et al., 2010). Furthermore, it has also been shown to attenuate the bovine myelin-induced experimental autoimmune neuritis in rats suggesting its potential use in the treatment of inflammatory neuropathies (Kafri et al., 2005).

Raf kinase plays an important role in the DRG neuron development including differentiation and axon growth (Zhong et al., 2007). Furthermore, its role in regulating
neuronal survival and senescence has also been documented (Echeverria et al., 2008). The key role of c-Raf1 in the development of morphine mediated hyperalgesia and development of tolerance is also defined (Tumati et al., 2008; 2010). The sustained morphine administration-mediated increase in pain sensitization is linked to augmentation of calcitonin gene-related peptide (CGRP) release from the primary nerve afferents in a c-Raf-1 dependent manner as selective c-Raf-1 inhibitor GW5074 is reported to attenuate morphine-mediated augmented CGRP release (Yue et al., 2008; Tumati et al., 2009). The studies have demonstrated an inter-relationship between development of morphine tolerance and induction of hyperalgesia in neuropathic pain at the level of receptor activation and subsequently, intracellular signal transduction cascade (Mao et al., 1995; Mayer et al., 1999). Accordingly, it is possible that pharmacological inhibition of c-Raf1 may also attenuate neuropathic pain. Pregabalin is an anti-convulsant agent that has been generally employed as first line treatment for neuropathic pain management (Kumar et al., 2010; Baidya et al., 2011). Therefore, pregabalin may be employed as standard drug (positive control) in peripheral neuropathic pain models.