The study was designed to explore the novel pharmacological interventions for experimental peripheral neuropathy. The chronic constriction injury (CCI) was induced in Wistar albino rats by placing four loose ligatures around the sciatic nerve, while vincristine (50 µg/kg i.p.) was administered for 10 days to induce chemotherapy-induced neuropathic pain. The pain related behavioral alterations such as cold allodynia, mechanical hyperalgesia, heat hyperalgesia and mechanical allodynia were evaluated on 1st day (before surgery/vincristine administration) and on 14th day by employing acetone, pin-prick, hot plate and von Frey tests, respectively. The spontaneous pain and postural index in terms of foot deformity were also assessed. The levels of TNF-α were measured in the sciatic nerve as an index of inflammation. Spironolactone (5, 10 and 20 mg/kg, p.o.), telmisartan (1, 2 and 5 mg/kg, p.o.) and pregabalin as standard (10 mg/kg, p.o.) were administered for 14 days in CCI and vincristine-injected rats to explore their attenuating potential in peripheral neuropathic pain. FTS, a novel Ras inhibitor, and GW5074, a selective c-Raf-1 inhibitor, were employed to explore their analgesic potential in CCI and vincristine-induced neuropathic pain in rats. A single dose of FTS (2.5, 5 and 10 µg), GW 5074 (1 µg, 2 µg and 4 µg) and pregabalin (100 µg) was administered intra-theccally in CCI subjected and vincristine injected rats on 14th day and pain related behavioral changes were assessed at 30 min, 60 min, 120 min and 180 min after drug administration. The following salient findings of the present study may be summarized:

1. The chronic constriction injury to the sciatic nerve and vincristine injection for 10 days led to significant development of cold allodynia, mechanical hyperalgesia, heat hyperalgesia and mechanical allodynia. The pain manifestations were significantly higher in CCI as compared to vincristine model.

2. The spontaneous pain, the foot deformity and rise in the levels of TNF-α in the sciatic nerve were observed in CCI subjected rats. However, these changes were not observed in vincristine injected rats.

3. Administration of spironolactone (10 and 20 mg/kg), telmisartan (2 and 5 mg/kg) and pregabalin (10 mg/kg) for 14 days in CCI subjected rats significantly
attenuated pain manifestations, foot deformity and increased TNF-α levels in the sciatic nerve.

4. However, administration of spironolactone (5, 10 and 20 mg/kg) and telmisartan (1, 2 and 5 mg/kg) for 14 days did not modulate pain related behavioral alterations in vincristine model. Administration of pregabalin (10 mg/kg) for 14 days attenuated pain manifestations in vincristine model.

5. Single intrathecal administration of FTS (5 µg and 10 µg), GW 5074 (2 µg and 4 µg) and pregabalin (100 µg) significantly attenuated CCI and vincristine-induced hyperalgesia and allodynia at 30 min, 60 min, 120 min and 180 min. The peak analgesic effects were observed at 60 min and the diminished anti-nociceptive effects were observed at 180 min after their administration.

The pain attenuating effect of spironolactone and telmisartan in CCI model may be due to their anti-inflammatory properties and ability to decrease pro-inflammatory cytokines, while involvement of non-inflammatory mechanisms in the pathogenesis of vincristine-induced pain may probably explain their lack of beneficial effects in chemotherapy associated pain. The analgesic effects of FTS and GW 5074 in CCI and vincristine-induced neuropathic pain suggest that Ras and c-Raf-1 may serve as potential therapeutic targets for inhibiting neuropathic pain. Based on these, it is concluded that spironolactone, telmisartan, FTS and GW 5074 may be potential novel therapeutic agents for neuropathic pain management.