The present study has been planned to investigate the effect of various test articles like SU-6656, Ro 32-0432 hydrochloride, ammonium pyrrolidine dithiocarbamate (APD), RS 102895 and FTI-276 trifluoroacetate on the development of nicotine withdrawal syndrome in vivo in mice. Sub-acute nicotine (2.5 mg/kg, s.c) administration followed by a single injection of mecamylamine hydrochloride (3 mg kg⁻¹, i.p.), was used to precipitate nicotine withdrawal syndrome in dependent mice. Behavioral interpretations were made immediately after mecamylamine hydrochloride treatment. Withdrawal syndrome was quantitatively assessed in terms of composite withdrawal severity score, frequency of jumping, tremor and piloerection.

On the basis of results obtained in the present study, the following salient findings may be summarized.

1. Nicotine dependence was induced by repeated s.c. injections, four times a day, at an time interval of 4 h starting at 08:00 am, for 7 days (2.5 mg/kg, s.c). The control groups were treated with saline or DMSO following the same protocol as above. On the 8th day (test day), mice received one nicotine injection. In an effort to precipitate nicotine abstinence, mice were given mecamylamine hydrochloride [A nicotinic receptor antagonist] at a dose of 3 mg kg⁻¹, (i. p.), 1 h after the last nicotine injection. Precipitated withdrawal syndrome in mice as reflected by a statistical substantial results in increased stereotyped jumping behaviour, withdrawal severity score, frequencies of tremor and piloerection, along with anxiety and hyperalgesia in nicotine/ mecamylamine hydrochloride group, when compared to that of the vehicle treated control groups.

2. Co administration of test compounds like SU-6656 or Ro 32-0432 hydrochloride or ammonium pyrrolidine dithiocarbamate (APD) or RS 102895 or FTI-276 trifluoroacetate significantly and dose dependently attenuated mecamylamine hydrochloride induced withdrawal syndrome in nicotine dependent mice.
3. Administration of four doses of nicotine (2.5 mg/kg, s.c) for a period of 7 days, followed by a single injection of mecamylamine hydrochloride (3 mg/kg, i.p.) precipitated withdrawal syndrome in mice as reflected by a statistical substantial increase in anxiety like behaviour as measured in terms of average time spent in the open arm and head dipping frequency particularly in the nicotine-mecamylamine group, when compared to that of the vehicle treated control groups. Co administration of test compounds like SU-6656 or Ro 32-0432 hydrochloride or ammonium pyrrolidine dithiocarbamate (APD) or RS 102895 or FTI-276 trifluoroacetate significantly and dose dependently attenuated mecamylamine hydrochloride induced anxiety like behaviour as measured in terms of the average time spent in the open arm and head dipping frequency.

4. After chronic intermittent administration of nicotine (2.5 mg kg−1, 7 days, four injections/day) produced significant hyperalgesia, as indicated by decreased tail-flick latencies, when compared to vehicle control group. Co administration of test compounds like SU-6656 or Ro 32-0432 hydrochloride or ammonium pyrrolidine dithiocarbamate (APD) or RS 102895 or FTI-276 trifluoroacetate significantly and dose dependently attenuated nicotine-mecamylamine induced hyperalgesia measured in terms reversal of withdrawal induced decrease in the tail flick latency.

3. It may be concluded that the selective inhibition of nuclear factor kappa B; Src-kinase; chemokine CCR-2 receptor; G-protein couple receptor kinase-5 and Farnesyltransferase-I attenuates the development of nicotine dependence as observed in the mecamylamine hydrochloride induced precipitation of withdrawal symptoms in nicotine dependent mice. Therefore, inhibitors of these targets may be considered as novel pharmacological interventions for the management of nicotine withdrawal syndrome.
CONCLUSION:
Nicotine treatment followed by mecamylamine challenge precipitated withdrawal syndrome in mice as reflected by a significant increase (p<0.01) in withdrawal severity score, jumping frequency, tremor, piloerection, hyperalgesia and anxiety like behaviour in mice as reported earlier (Damaj et al., 2003; Biala and Weglinska, 2005; Stoker et al., 2008). In the present investigations, administration of SU-6656, a selective src-kinase inhibitor (Blake et al., 2000), Ro 32-0432 hydrochloride: A selective GRK-5 receptor (G protein-coupled receptor kinase-5 enzyme) Inhibitor, Ammonium pyrrolidine dithiocarbamate (APD), a selective nuclear factor kappa-B (NF-κB) inhibitor (Schreck et al., 1992), RS 102895, a selective CCR-2 chemokine receptor antagonist (Mirzadegan et al., 2000; Onuffer and Horuk, 2002), FTI-276 trifluoroacetate, a selective inhibitor of farnesyltransferase subtype I (Lerner et al., 1995) produced a significant dose dependent attenuation of the development of nicotine dependence as observed in the mecamylamine induced withdrawal syndrome in nicotine dependent mice, particularly in terms of stereotyped jumping behaviour, composite withdrawal severity score, tremor, piloerection, anxiety and hyperalgesia test.