

# The Novel Anxiolytic Compound BNC210 Reverses the Effects of Anxiogenic Compounds in the Rat Elevated Plus Maze

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## INTRODUCTION:

BNC210 is a novel CNS-acting small molecule that exhibits anxiolytic and antidepressant activity in a number of preclinical animal models while lacking the side effects associated with medications currently used in the clinic to treat anxiety and depression.

The anxiolytic activity of BNC210 has been demonstrated in rodent models of ethological anxiety (Light Dark Box, Elevated Plus Maze (EPM), Marble Burying Test) under conditions of basal and induced stress.

We have now sought to demonstrate the ability of BNC210 to overcome pharmacologically induced anxiety states in rats on the EPM. For this purpose, three compounds were selected, all of which are known to induce anxiogenic behaviour in rats on the EPM: the mGlu2/3 receptor antagonist LY341495 (Linden et al, 2005), the CCKB receptor agonist CCK-4 (Chopin & Briley, 1993) and the 5-HT1B receptor agonist CP-94,253 (Lin & Parsons, 2002).

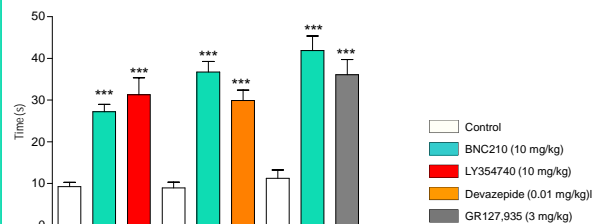
## METHODS

At the beginning of each trial on the EPM, the animal was placed on the central platform of the apparatus facing a closed arm. The number of entries and the time spent in the open arms was recorded during a 5 minute period (Pellow et al, 1985).

BNC210 was prepared in aqueous vehicle and administered *per os* 60' prior to testing. All other test compounds were administered intra-peritoneally 30' before testing.

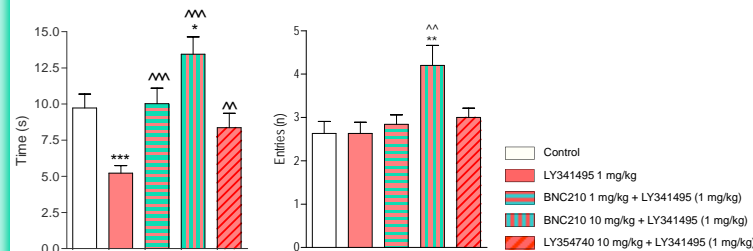
Data was analysed using the unpaired t-test in GraphPad Prism 4.

## BNC210, LY354740, DEVAZEPIDE & GR-127,953



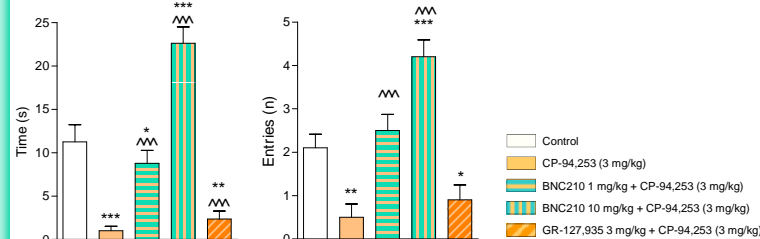
**FIGURE 1:** The anxiolytic activity of BNC210 in the rat EPM was compared to three other known anxiolytic compounds, LY354740 (mGlu2/3 receptor agonist), GR-127,935 (5-HT1B/1D receptor antagonist) and Devazepide (CCKA/B receptor antagonist). Changes in rat exploratory behaviour that reflected anxiolysis were seen as increased amount of time spent on the open arms of the EPM. All four compounds produced a significant anxiolytic effect (\*\*\*  $p \leq 0.0001$ ) in comparison to vehicle treated animals.  $n=10-20$  rats.

## BNC210 : mGluR2/3 Antagonist LY341495



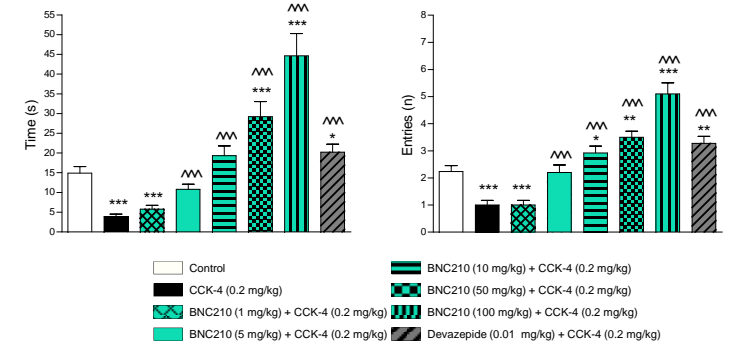
**FIGURE 2:** The mGlu2/3 receptor antagonist LY341495 (1 mg/kg) produced an anxiogenic effect. Animals dosed with this compound spent less time in the open arms of the EPM compared to control animals. The anxiogenic effects of LY341495 were ameliorated with administration of the mGlu2/3 receptor agonist LY354740. BNC210 (1 and 10 mg/kg) was effective in reducing the anxiogenesis caused by LY341495. Interestingly, the 10 mg/kg BNC210 dose also produced a significant anxiolytic response compared to vehicle treated rats. \*  $p \leq 0.05$ ; \*\*  $p \leq 0.001$ ; \*\*\*  $p \leq 0.0001$  denotes significant differences in comparison to vehicle treated animals. ^^  $p \leq 0.001$ ; ^^ $p \leq 0.0001$  denotes significant differences in comparison to animals pre-treated with LY341495.  $n=20$  rats.

## BNC210 : 5-HT1B Agonist CP94,253



**FIGURE 3:** The 5-HT1B agonist CP-94,253 (3 mg/kg) had a pronounced anxiogenic effect on exploratory behaviour and dose-dependently decreased the time spent on the open arms of the maze and the number of entries into the open arms when compared to vehicle treated animals. In rats pre-treated with CP-94,253, BNC210 at 1 and 10 mg/kg, produced a significant increase in exploratory behaviour on both the Time and Entries parameters. 10 mg/kg of BNC210 also produced significant anxiolytic behaviour compared to the vehicle treated rats. The 5-HT1B agonist GR-127,935 (3 mg/kg) offered some reduction of the CP-94,253-induced anxiety but did not restore behaviour to the level of vehicle treated rats. \*  $p \leq 0.05$ ; \*\*  $p \leq 0.001$ ; \*\*\*  $p \leq 0.0001$  denotes significant differences in comparison to vehicle treated animals. ^^ $p \leq 0.0001$  denotes significant differences in comparison to animals treated only with CP-94,253.  $n=10$  rats.

## BNC210 and CCK4



**FIGURE 4:** Administration of the CCKB receptor agonist CCK-4 (0.2 mg/kg) led to an anxiogenic response in the EPM. Administration of the CCK receptor antagonist, Devazepide (0.01 mg/kg) significantly reduced the anxious behaviour in CCK-4 treated rats and produced a potent anxiolytic effect as demonstrated by increased time spent in the open arms and increased number of entries into the open arms. The potential for BNC210 to reverse CCK-4-induced anxiety was evaluated over a broad dose range of 1-100 mg/kg. BNC210 treatment blocked the anxiogenic effect of CCK-4 at doses  $\geq 5$  mg/kg. Doses  $>10$  mg/kg produced a potent anxiolytic response. \*  $p \leq 0.05$ ; \*\*  $p \leq 0.001$ ; \*\*\*  $p \leq 0.0001$  denotes significant differences in comparison to vehicle treated animals. ^^ $p \leq 0.0001$  denotes significant differences in comparison to animals treated only with CCK-4.  $n=10-25$  rats.

## CONCLUSIONS

BNC210 demonstrates potent anxiolytic activity in animal models of basal, elevated and pharmacologically-induced anxiety.

BNC210 overcomes anxiety generated by agonism or antagonism of three neurotransmitter systems which are known to influence anxiety states: serotonin (5-HT1B receptor), glutamate (Group 2 metabotropic glutamate receptor) and cholecystokinin (CCKB receptor).

BNC210 offers significant protection against CCK-4 challenge in the rat model and may have potential as a treatment for panic disorder. Evaluation of BNC210 in the CCK-4 induced panic model in healthy volunteers is in progress.

## REFERENCES

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