**BNC210: A Novel Compound with Potent Anxiolytic Activity**

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**Introduction**

Anxiety is the most widespread of all mental disorders, and current treatments are still limited by the presence of clinically undesirable side-effects of anxiolytic drugs. So, the discovery of novel, fast-acting anxiolytic, which is without significant side-effects (particularly sedation), would be welcomed. By applying a targeted medicinal chemistry strategy beginning from a compound cited in the literature, Bionomics has developed BNC210. This novel compound has potent anxiolytic activity (0.1mg/kg) in a range of rodent models and has no effect on short term memory at doses up to 20mg/kg or on spontaneous motor activity at doses up to 100 mg/kg thus realising a therapeutic index of over 1,000. BNC210 is readily absorbed and has good bioavailability in rats (69%) with a half life of 6.2 hours. The molecular mechanism of BNC210 has not been fully elucidated. Early safety assessment indicates that BNC210 will be safe and well tolerated.

**Methods**

- BNC210 was developed in a targeted medicinal chemistry program beginning from a compound cited in the literature with newly described anxiolytic activity.
- The aim of the program was to produce compounds with improved solubility, metabolic stability, and efficacy.
- A small focused library of 42 compounds was synthesized and evaluated according to the scheme in the adjacent figure.

**Physicochemical and Pharmacokinetic Properties**

Early ADME-T Studies are encouraging:

- Good Plasma stability: PK (rat)
  \[ T_{1/2} = 60 \text{ min} \]
  \[ T_{1/2} = 60 \% \]
- Protein Binding: 77.42 %
- HERG – no binding at 10 μM
- No Genotoxicity (micronucleus)
- Microsome Metabolism
  \[ \text{Low to intermediate metabolism rates} \]
- No significant species difference
- No inhibition of 5 CYP450 isoforms
  \[ \text{EC}50 > 30 \text{ μM} \]

**BNC210 has physicochemical properties that are consistent with good “drug like” profile:**

- MW: = 418
- PSA: 75 Å²
- BR: 4
- logD pH 7.4 = 2.71
- Solubility: pH 2.0 > 100 mg/mL
- pH 7.4 > 100 mg/mL
- Number of steps in synthesis: 8
- Number of Chiral Centres: 0

**Adapted tested:**
- CRFR1
- MCHR1
- BZD (central) – diazepam
- Cholinergic (nicotinic – pirenzepine)
- GABA-binding site – muscimol
- GABAtransporter – r-epiasectric
- GABA receptor – CGP

**BNC210 has a unique Pharmacology:**

- Potent anxiolytic
- No addictive potential
- No development of tolerance
- Not addictive
- No memory impairment

**Results**

BNC210 demonstrates a potent anxiolytic activity in 3 anxiety tests:

**BNC210 shows an outstanding performance in the Light Dark Box. A dose of as low as 0.01mg/kg significantly increases the amount of time that mice spend in, and the distance walked in, the brightly lit chamber.**

Data represent mean ± SEM. n=10 mice, *p<0.05, **p<0.01 (Fisher’s Protected Least Significant Difference test).

**BNC210 has a significant effect on Marble Burying behavior in mice, reducing their innate tendency for marble burying by more than 50% at a dose of 10mg/kg and a clear dose response was seen in the experiment.**

Data represent mean ± SEM. n=10 mice, **p<0.01 (Fisher’s Protected Least Significant Difference test).

**BNC210 does not have addictive properties and does not increase the time mice spend in the drug-paired compartment (ttest) of the Conditioned Place Preference Test when allowed to freely explore an apparatus containing a saline-paired compartment (ttest) and a drug-paired compartment. In contrast, 5mg/kg of diazepam reduces the time mice spend in the drug-paired compartment by almost 45%. Data represent mean ± SEM. n=10 mice.**

**No side effects**

**BNC210 is not sedating in mice in the Open Field Test.**

Data represent mean ± SEM. n=10 male, **p<0.05, ***p<0.001 (Fisher’s Protected Least Significant Difference test).

**BNC210 does not impair memory in rats in the Object Recognition Test.**

Data represent mean ± SEM. n=10 rats, **p<0.01 (Fisher’s Protected Least Significant Difference test).

**BNC210 does not cause sedation in mice.**

Data represent mean ± SEM. n=10 mice, data not presented (Fisher’s Protected Least Significant Difference test).

**Chronic Administration (14-days) of BNC210 does not cause tolerance to its anxiolytic activity in MICE.**

Main Swiss Mice were dosed daily by oral gavage with 5mg/kg of BNC210 for a period of 14 days. The mice were then evaluated in the Light Dark Model of anxiety. BNC210 had a clear anxiolytic effect and there was no evidence for the development of tolerance to the drug after chronic treatment. Data represent mean ± SEM of 10 mice and is analysed by Fisher’s Protected Least Significant Difference test. \( p<0.05, p<0.01 \)

**Chronic Administration (14-days) of BNC210 does not cause sedation in MICE.**

Main Swiss Mice were dosed daily by oral gavage with 5mg/kg of BNC210 for a period of 14 days. The mice were then evaluated in the Open Field Test and did not show any sedation after chronic administration with BNC210. Data represent mean ± SEM of 10 mice and is analysed by Fisher’s Protected Least Significant Difference test. \( p<0.05, p<0.01 \)

**BNC210 has potent activity in three rodent models of anxiety at 0.1mg/kg:**

- Shows no memory impairment in rats - is not sedating in mice or rats up to 100mg/kg
- Does not affect motor coordination in mice - is not addictive in mice
- Has good physicochemical & PK properties
- Current therapeutic window is >1000 in mice and rats