BNC210 is a novel, fast-acting compound with potential anxiolytic activity and no side effects.

O'Connor S.1, Andriambeloson E.2, Huyard B.2, Wagner S.2, Sleebs B.3, Bui C.3, Kremmidiotis G.1, Street I.3 and Flynn B.1

1. Bionomics Limited, 31 Dalge Street, Thebarton 5031, Australia.
3. Walter and Eliza Hall Institute Biotechnology Centre, Bundoora 3086, Australia.

ECNP Barcelona 2008

Introduction

Clinically significant anxiety disorders remain one of the most widespread health problems in the world. Generalized Anxiety Disorder (GAD) is characterized by excessive worry that interferes with the daily lives of those who suffer from it. The major pharmacological agents currently used to manage patients with GAD include benzodiazepines, SSRIs and SNRIs. The therapeutic benefits offered by these agents are counterbalanced by significant side effects.

There is a clear medical need for fast-acting anxiolytic agents that:

- Lack the side effects seen with current treatments and offer the same or greater therapeutic benefits

We have undertaken a targeted medicinal chemistry approach, directed towards improving the anxiolytic profile of select substrates known to exhibit central nervous system (CNS) effects, to discover novel agents that will satisfy this medical need. This effort has led to the identification of BNC210, a compound with a unique profile in which we suggest a novel mode of action.

BNC210 has an anxiolytic effect in the Mouse Light Dark Box

BNC210 has a significant effect on the performance of mice in this test, as demonstrated here with doses of 0.1–10mg/kg. We have previously shown that the minimum effective dose is 0.01mg/kg (PD0) for the Time and Distance parameters. At 0.1mg/kg, the magnitude of the anxiolytic response with BNC210 is not significantly different from diazepam. Data represent mean ±SEM, n=10 mice, p values calculated using Fisher's Protected Least Significant Difference test.

BNC210 does not sedate in the Open Field (Dark)

BNC210 does not affect spontaneous locomotor activity in the Open Field (dark) at doses of 20, 50 or 100mg/kg (PO). In contrast, the sedative side effect of diazepam is clearly observed at a dose of 5mg/kg (PO). Data represent mean ±SEM, n=10 mice, *p<0.01 (Fisher's Protected Least Significant Difference test).

BNC210 has no pharamacokinetic interactions in mice

BNC210 has no effect on the pharmacokinetics of the positive control drug, diazepam. This is important as it indicates that BNC210 can be used in combination with other anxiolytic drugs.

Safety Studies

Assessment of interactions with rERG:

A rERG binding assay was used to determine if BNC210 can interact with the rERG channel, which is important for pain sensation and drug safety. Data represent mean ±SEM, n=10 mice, p values calculated using Fisher's Protected Least Significant Difference test.

BNC210 is very safe

BNC210 has been evaluated in Acute and 7-Day Toxicology studies in rats and dogs. BNC210 is well tolerated at all dose levels.

Anxiolytic Behaviour in the Elevated Plus Maze

BNC210 was evaluated in the rat elevated plus maze at doses of 0.1 and 1mg/kg PD. The number of entries into each arm of the maze was significantly increased in the minimum effective dose at 0.1mg/kg. Data represent mean ±SEM, n=10 rats, p values calculated using Fisher's Protected Least Significant Difference test.

BNC210 reduces the duration of separation-induced vocalizations in a Guinea Pig Model of Anxiety

BNC210 significantly reduced total vocalization time by guinea pigs pups at 5mg/kg (IP). The anxiolytic profile of BNC210 in this model differs from other anxiolytic compounds and supports the concept that it has a novel mechanism of action.

Duration of the Anxiolytic Effect of BNC210 in the Mouse Light Dark Box After Administration of an Acute Dose

At a dose of 20mg/kg (PO), which is 20x the minimum therapeutic dose, BNC210 does not increase the time mice spend in the drug-poor compartment of the open-field preference test. This indicates that BNC210 offers long-lasting efficacy, which is desirable for the treatment of anxiety disorders.

BNC210 Summary

- Potent anxiolytic activity in multiple models and species with efficacy as low as 0.01mg/kg
- T<sub>D</sub> 10 < 1000mg/kg
- No sedation
- No effect on motor coordination
- No memory impairment
- No abuse liability
- No effect on CYP3A4 enzymes or rERG
- Good physicochemical properties 7.8K
- Good oral bioavailability and potential for 1 daily oral dosing
- Novel proprietary compound

Pharmacokinetics of BNC210 in Rat and Dog Studies

Rat Study Parameters:
- 5 day repeated dosing at 1, 10, 100, 300, 1000, 3000 mg/kg PO
- Food Consumption, Weight:
- Clinical Pathology:

Dog Study Parameters:
- Single-dose at 1000 and 3000 mg/kg PO
- Food Consumption, Weight:
- Clinical Pathology: