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# Characterization of positive allosteric modulators of TrkB for the treatment of depression

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## Introduction

Major depression is one of the leading causes of disability worldwide, with more than 264 million people affected. In the US, recent estimates show 16 million adults had an episode of major depression in the course of a year. The most commonly prescribed drugs are the SSRI's, SNRI's, MAOI's and TCA's. Even though there are several drugs on the market, side-effects and slow time-to-onset are factors that limit their use. Moreover, subgroups, e.g. treatment-resistant depression, show little effect with available therapies and indicate the need for novel drugs with a different MoA on the market.

A potential novel mechanism involves enhancing the signaling of the neurotrophin brain-derived neurotrophic factor (BDNF) through its receptor TrkB. BDNF plays a key role in neuronal plasticity events in the brain such as long-term potentiation and the formation of memory. Given its role and expression BDNF has also been linked to depression and there is an accumulating body of evidence indicating a role of BDNF in this disorder. Recent data suggest that the different classes of antidepressants all bind directly to the TrkB-receptor and mediate, at least partially, their effects through this signaling pathway (1). Targeting the TrkB receptor directly with a positive allosteric modulator (PAM) could offer an even more selective way of enhancing the BDNF signaling, thus avoiding the side effects observed with the classical antidepressants.

The aim of these studies was to identify and characterize compounds that potently stimulate TrkB mediated signaling in various preclinical models.

## Methods

Screening of compound libraries identified several compounds as positive modulators of NGF and BDNF signalling. Hits and analogues thereof were characterized in different in vitro assays, and in vivo models assessing cognitive function and antidepressant-like effects in mice and rats. Moreover, microdialysis was performed in hippocampus of rats to assess neurotransmitter release.

## Results

The screening and optimization activities led to identification of multiple leads, which was subsequently characterized further. The compounds, here exemplified by ACD856, enhanced BDNF/TrkB signalling in a cell-based assay, some with both modulatory as well as agonistic properties (Fig 1A). Another compound from the same chemical series, ACD855, was shown to potentiate BDNF signalling and enhance ERK 1/2 phosphorylation in vivo (mice) in an activity-dependent manner, i.e. after exposure to the forced swim test (FST) (Fig. 1B). Ex vivo LTP experiments in rat hippocampal slices showed that ACD855 was able to potentiate theta-burst induced LTP in a similar fashion as BDNF itself (data not shown).

At the neurotransmitter level in vivo, subcutaneous administration of ACD856 in rats resulted in increased levels of serotonin (5-hydroxytrypatmine (5-HT)), noradrenalin (NA) and dopamine (DA) in the ventral part of hippocampus as measured by microdialysis (Fig. 2). There was a significant increase in the amount of serotonin after administration of ACD856 as compared to vehicle and a clear trend of increased levels of both noradrenalin and dopamine.

In vivo behavioural experiments demonstrated that ACD856 was able to significantly reduce immobility time in the Forced swim test in mice, with a similar effect to that of 20 mg/kg fluoxetine (Fig. 3). When tested in the same model using the Flinders sensitive line of rats, ACD856 was again able to significantly reduce the immobility time.

Assessing the effects on cognitive function, ACD856 could significantly and dose-dependently reverse scopolamine-induced memory impairment in mice in the passive avoidance (PA) model (fig 4). The attenuating effect of ACD856 could be blocked by the selective TrkB-antagonist ANA-12, suggesting that the effects were indeed mediated by TrkB. Interestingly, ACD856 was also able to significantly attenuate the effects of MK-801 in the same model.

*References*

*1. Casarotto P.C., Girych M., Fred S.M., Kovaleva V., Moliner R., Enkavi G., Biojone C., Cannarozzo C., Sahu M.P., Kaurinkoski K., Brunello C.A., Steinzeig A., Winkel F., Patil S., Vestring S., Serchov T., Diniz C.R.A.F., Laukkanen L., Cardon I., Antila H., Rog T., Piepponen T.P., Bramham C.R., Normann C., Lauri S.E., Saarma M., Vattulainen I., Castrén E., 2021. Antidepressant drugs act by directly binding to TRKB neurotrophin receptors. Cell. Mar 4;184(5):1299-1313.*

**Figure 1. Dose-response effects of compound ACD856 on TrkB-signaling at different concentrations of BDNF (A) and effect of ACD 855 on ERK1/2 phosphorylation in vivo (B)**

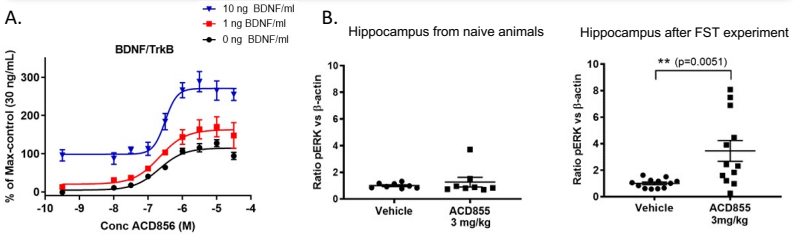



**Figure 2. Effects of ACD856 on the levels of neurotransmitters in rat ventral hippocampus**

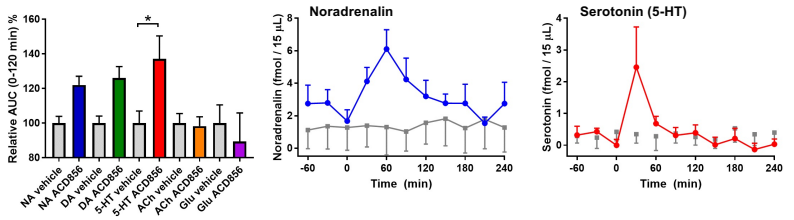



**Figure 3. Effects of ACD856 in the Forced swim test (FST) in FSL rats and C57Bl/6J mice**

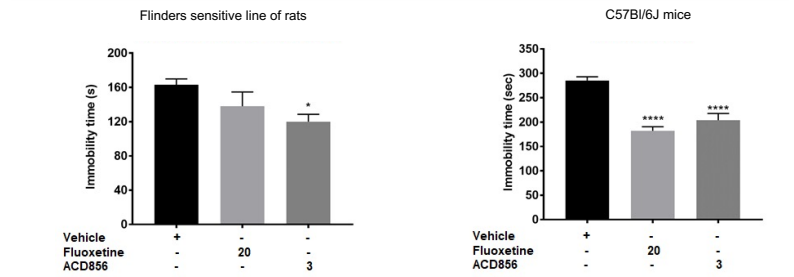
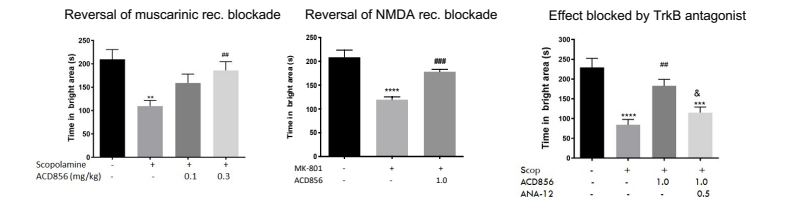



**Figure 4. Effects of ACD856 on long-term associative memory in C57Bl/6J mice**




## Conclusion

The BDNF/TrkB pathway is a promising alternative for new antidepressants, indicating that this mechanism potentially could be a new tool for antidepressant treatment. We have in our lead optimization program identified compounds with a unique mechanism of action that potently stimulates TrkB-signaling and which demonstrate antidepressant-like as well as cognitive enhancing effects in vivo. ACD856 is the lead compound from this chemical series and is currently in clinical development.

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