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“Development of novel, small molecular TrkB agonists as potential therapeutic in treatment of central nervous system disorders.”

ABSTRACT

Effective treatment of neuropsychiatric diseases without exposing patients to adverse effects is the main challenge for contemporary neuropsychopharmacology. Brain-derived neurotrophic factor (BDNF) through interaction with the TrkB receptor is re-sponsible for the development and correct functioning of the nervous system. Due to the well-documented role of BDNF in the pathophysiology of central nervous system diseases, it is postulated that modulation of the BDNF-TrkB signalling pathway using low molecular weight TrkB agonists may offer therapeutic effects.

This study aimed to identify small-molecular compounds that act as a TrkB recep-tor agonists. The screening platform development in this work consisted of the use of appropriate screening techniques and functional assays to identify potential TrkB ago-nist molecules from a library of compounds with diverse chemotypes. Molecules with different chemotypes were selected using a screening platform developed within this project. The screening included examination of binding and interaction with the TrkB receptor, determination of orthosteric TrkB and downstream signalling pathway acti-vation, as well as assessment of their neuroprotective properties. Despite efforts and conducted research, it was impossible to identify molecules with desired properties for a TrkB agonist.

This work also presents a detailed characterization of compounds with the postu-lated or documented activity against TrkB. The obtained results showed that tested compounds do not exhibit TrkB agonist properties, both in terms of interaction with receptor and functional properties. Moreover, in vitro selectivity and in vivo pharma-cological studies were conducted for the 7,8-dihydroxyflavone (7,8-DHF) which is a best-studied compound postulated to be a TrkB agonist. The results demonstrated the unfavourable pharmacokinetic profile of 7,8-DHF, the lack of activity against TrkB and downstream molecular pathways in the murine brain. Moreover, 7,8-DHF interact-ed with multiple molecular targets proving to have poor selectivity.

The results of this study indicate that the tested reference compounds, including 7,8-DHF, do not activate the TrkB receptor; therefore the reported pharmacological activity of these

molecules should be interpreted carefully in a broad functional con-text. Nevertheless, the screening platform developed in this work can be successfully used in future projects related to the search for drug candidates.