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Abstract

In Silico Fragment-Based Drug Design and Molecular Docking of Tranilast Analogues as Potential Inhibitors of Transforming Growth Factor- β Receptor Type 1 †

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Abstract: Transforming Growth Factor- β Receptor type 1 (TGF-βR1) is an important anticancer target involved in promoting cell proliferation, progression, and metastasis through the induction of angiogenesis and suppression of immunological responses during the late stage of malignancy. Tranilast was initially approved for the treatment of bronchial asthma and allergic conditions in 1982. Later, it was revealed that Tranilast had numerous effects on cancer hallmarks, including immune evasion and sustained proliferation via the inhibition of TGF-βR1. This research describes the design of a novel series of anthranilate derivatives having various modes of interactions with TGF-βR1 compared with Tranilast. A database of novel Tranilast analogues was generated using Molecular Operating Environment Software (MOE 2020.09, Chemical Computing Group CCG, Montréal, Canada) using fragment-based drug design. Representative compounds were selected from the database and docked in the identified binding site of TGF-βR1. Several compounds showed higher binding affinity for TGF-βR1 compared with the lead compound in this work, Tranilast. Compounds with high docking scores contained a positively charged amine group that interacted with Asp290 or a negatively charged carboxylate group with Lys 335 in the TGF-βR1 ATP binding site. Additionally, compounds containing an aromatic group showed high docking scores through interacting with Ser287, Lys337, or Ile 211. Compounds A11, A14, A16, and B5 which had the best poses in terms of binding interactions and docking scores to the binding site will be considered for further synthesis and biological evaluation.

Keywords: TGFβ-R1; Tranilast; FBDD; docking

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