In silico Fragment-Based Drug Design & Molecular Docking of Tranilast Analogues as Potential Inhibitors of Transforming Growth Factor- β Receptor type 1

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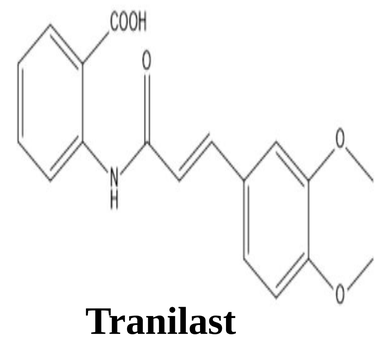
Abstract

Transforming Growth Factor- β Receptor type 1 (TGF-βR1) is an important anticancer target involved in promoting cell proliferation, progression and metastasis through 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 has numerous effects on cancer hallmarks, including immune evasion and sustained proliferation via 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 MOE software 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. Also, 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: TGF-βR1; Tranilast; FBDD



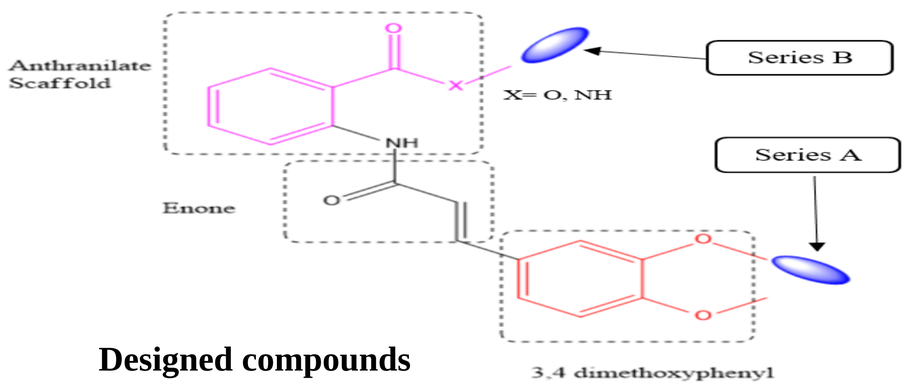
Tranilast

Introduction

Transforming Growth Factor- β Receptor type 1 (TGF-βR1) is an important anticancer target involved in promoting cell proliferation, progression and metastasis through induction of angiogenesis and suppression of immunological responses during the late stage of malignancy [(1,2)]. **Tranilast** was initially approved for the treatment of bronchial asthma and allergic conditions in 1982. Later, it was revealed that Tranilast has numerous effects on cancer hallmarks, including immune evasion and sustained proliferation via inhibition of TGF-βR1 [(3)].

Objective

This study aims to design two novel series of Tranilast analogues having various modes of interactions with TGFβR1 compared with Tranilast. Besides, the biological evaluation will be conducted to evaluate the newly designed compounds' anticancer activity. The compounds with promising results could be used as anticancer agents.



Designed compounds

Method

- MOE software was used to generate a database composed of two series of Tranilast analogues utilizing Fragment-Based Drug Design technique. Series A contained compounds generated through the addition of new fragments in 3,4 dimethoxyphenol position. While series B was generated via esterification and amidation of the Anthranilate Scaffold.
- Compounds of series A and B were docked in the identified and validated ATP binding pocket of TGF-βR1. The binding energy difference (S) was the method of predicting the binding affinity of the designed compounds.

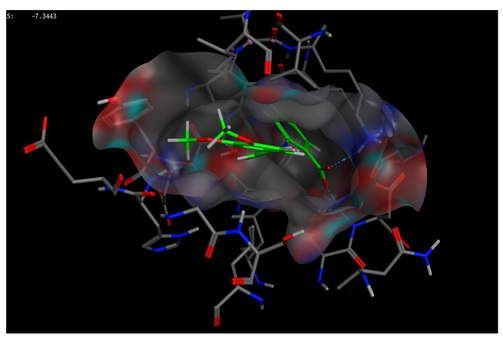


Figure 1: ATP binding pocket of TGF-βR1 docked with Tranilast which is shown as green sticks (S = -7.3443).

Results

Compounds of series A that had high docking scores, their fragments made ionic interactions with Asp290 or Lys 335. Additionally, compounds containing a fragment possessing aromatic ring also showed high docking scores through interacting with Ser287, Lys337 or Ile 211.

Table 1: Docking scores of series A. Entry 1 is Tranilast.

	mol	mseq	S	rmsd_refine	E_conf
1	Tranilast	1	-7.3443	1.1520	-77.9529
2	A11	11	-9.0141	2.0814	-40.3897
3	A14	14	-9.0100	2.0812	-40.3895
4	A16	16	-8.9631	1.4396	-44.6193
5	A2	2	-8.8573	1.5145	-27.8976
6	A20	20	-8.8416	1.9310	-101.3558

Compounds of Series B that had high docking scores, their fragments made ionic interactions with Glu 209 or Asp 351or hydrogen bonding with His 283, Lys 337, Ile 211 or Gly 214.

Table 2: Docking scores of series B. entry 1 is Tranilast.

	Mol	mseq	S	rmsd_refine	E_conf
1	Tranilast	1	-7.3443	1.1861	-94.8551
2	B5	5	-8.9228	1.3230	-42.3915
3	B7	7	-8.8806	1.2363	-17.5674
4	B6	6	-8.8505	2.0372	-12.9925
5	B4	4	-8.5615	1.3513	-44.7362

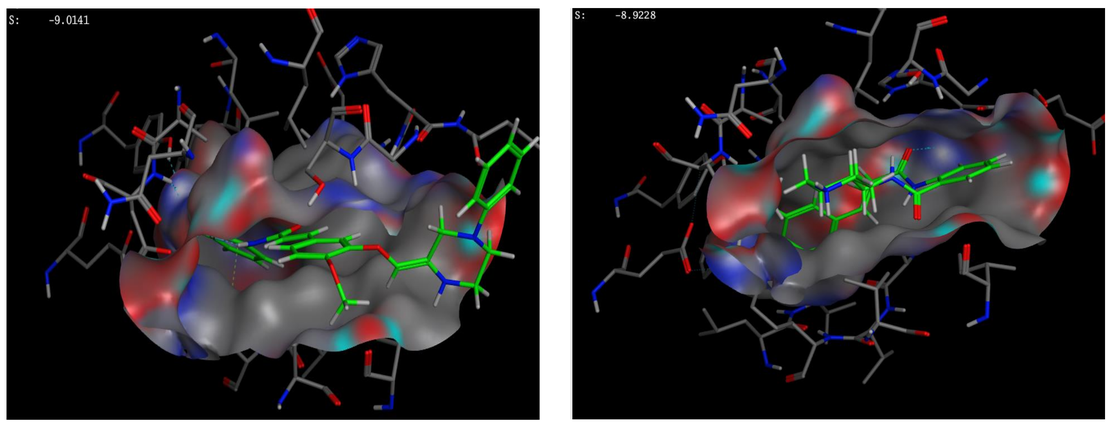


Figure 3: ATP binding pocket of TGF-βR1 docked with A11 and B5.

Conclusion and Future Plan

- Compounds A11, A14, A16, and B5 had the best poses in terms of binding interactions and docking scores to the ATP binding pocket of TGFβR1.
- Compounds A11, A14, A16, and B5 will be synthesized according to different synthesis schemes, followed by structural validation of the synthesized compounds by different spectroscopic techniques (NMR, IR, mass spectrometry and elemental analysis).
- Synthesized compounds will be evaluated for anticancer activity using, Determination of TGF-βR1 activity, Cell cycle analysis and Annexin V-FITC apoptosis assay.

References

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