Proceedings International
Platinum Open Access Journal (ISSN 2668-6384)

Proceedings, Abstract
Volume 4, Issue 1, 2022, 57
https://doi.org/10.33263/Proceedings41.057

Pharmacophore and QSAR Study of Some Novel Selective COX-2 Inhibitors as Anticancer Agents †

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† Presented at 1st OncoHub Conference – Connecting Scientists for Next Generation Cancer Management (13-15 October 2021, virtual)

Received: 25.10.2021; Accepted: 5.02.2022; Published: 14.02.2022

Abstract: Cancer represents a global health concern worldwide owing to the absence of an efficient therapy with an appropriate safety profile. Therefore, recent research is devoted to developing more safe and efficient anti-cancer agents. Cyclooxygenase-2 (COX-2) is a key enzyme in inducing an anti-cancer activity as it is involved in cancer survival, evasion of immunity, cancer cell repopulation during therapy, and eventually reduces resistance to chemo- and radiotherapy. COX-2 enzyme is overexpressed in various cancer cell types; thus, treatment with selective COX-2 inhibitors could relieve symptoms and limit side effects. In this regard, the design and synthesis of novel selective COX-2 inhibitors have always been of scientific attraction in treating cancerous cells. In the light of the above findings, this study was directed at studying the structure-activity relationship analysis of some heterocyclic oxadiazoles compounds via generating pharmacophore and QSAR models. Generating pharmacophore model; in an attempt to understand and determine the essential scaffolds for potential molecules with selective COX-2 inhibition, a pharmacophore model was generated using MOE software version 2014.0901. A database of five oxadiazole molecules with selective COX-2 inhibitory was created, then pharmacophore models were generated. Then the best model was selected and run-on the zinc database. The number of hits was 114. The second step was performing QSAR analysis using MOE software version 2014.0901. Some crucial descriptors as E, E_sol, ASA, apol, density, logP (o/w), mr, dipole, and vdw_vol were used to create a mathematical equation aiming at correlating different physicochemical properties of some reported oxadiazole candidates. Then the equation was used to predict the activity of novel potential molecules. The pharmacophore model (RRRd_1) with cover 5, overlap 4.2140, and accuracy 1 was selected. Based on the selected pharmacophore model, some novel oxadiazole derivatives were designed. The adopted molecular manipulations were: the addition of different functional groups i.e., the addition of fluorine atom, the addition of 5 membered rings, the addition of the nitro group, and sulfur atom with different side chains on different positions. The QSAR analysis includes using the generated QSAR equation to predict the activity of the novel candidates. It was observed that the adopted structural modifications affect the COX-2 inhibitory activity, where the activity was slightly improved in some of the novel oxadiazole derivatives.

Keywords: QSAR; COX-2 inhibition; pharmacophore models.

Funding

This research received no external funding.

Acknowledgments

This research has no acknowledgment.

Conflicts of Interest

The authors declare no conflict of interest.