Pharmacophore and QSAR Study of some novel selective COX-2 inhibitors as anticancer agents

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Introduction: Cancer represents a global health concern worldwide owing to absence of an efficient therapy with appropriate safety profile. Therefore, recent research is devoted to develop more safe and efficient anticancer agents. Cyclooxgenase-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 variety of cancer cell types; thus treatment with selective COX-2 inhibitors could relieve symptoms and limit side effects.

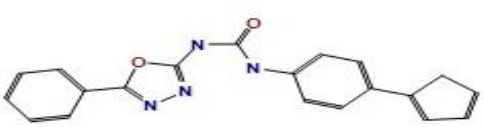
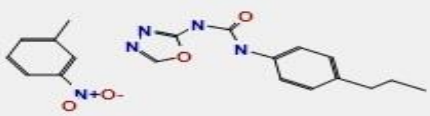
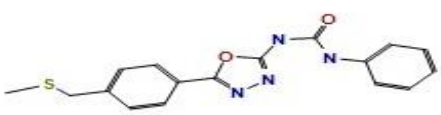
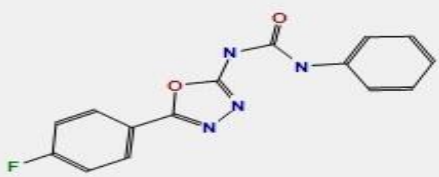
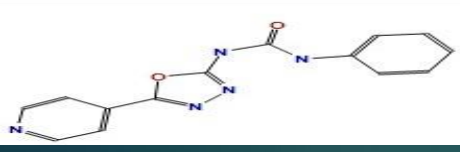
Aim of work: In the light of the above findings, design and synthesis of novel selective COX-2 inhibitors is the most proposed solution. Therefore, this study was directed at studying the structure activity relationship analysis of some heterocyclic oxadiazoles compounds via generating pharmacophore and QSAR models.

Methodology

- Generating a pharmacophore model using MOE software version 2014.0901. A database of eight oxadiazole molecules with selective COX-2 inhibitory activity was created followed by generating pharmacophore models. After that the best model was selected and run on zinc database. The number of hits generated was 114 hits. The pharmacophore model (RRRd_1) with cover 5, overlap 4.2140 and accuracy 1 was selected. Based on the selected pharmcophore model, some novel oxadiazole derivatives were designed.
- 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. Afterwards, the equation was used to predict the activity of novel potential mole ***molecules***

Results

Table showing QSAR analysis for proposed molecules

	mol	$PRED
1		10.3397
2		11.2574
3		9.7477
4		8.1482
5		7.8613

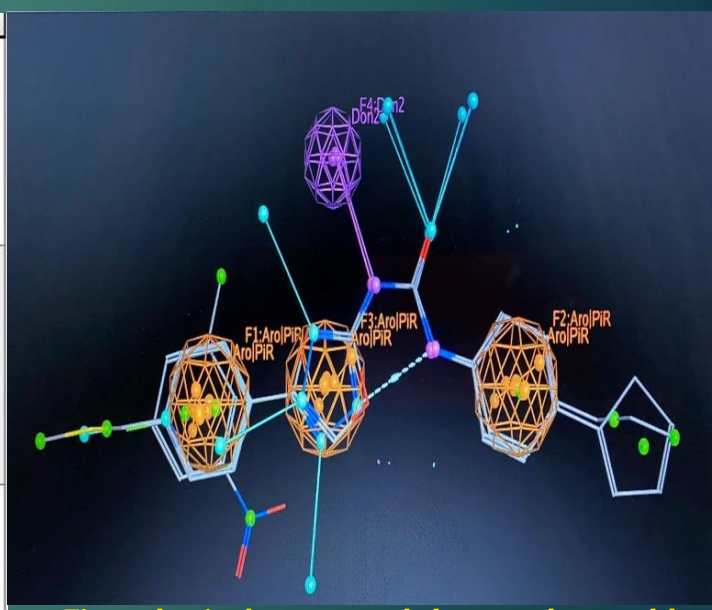


Figure showing best generated pharmacophore model

Conclusion: According to the obtained results, there was variance in the predicted activity of the adopted manipulations, some compounds have shown less activity than the reference set (i.e. compounds 1&2). Other compounds shown a slightly improve in the predicted activity (i.e. compounds 3, 4 & 5 in the given table).

References: Nehad A. El-Sayed , Mai S. Nour, M. Alaraby Salem Reem, K. Arafa; ***New oxadiazoles with selective-COX-2 and EGFR dual inhibitory activity: Design, synthesis, cytotoxicity evaluation and in silico studies:*** *European Journal of Medicinal Chemistry 183* **(2019).**