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QSAR Modeling for 1□ Phenoxy-2-Aminoindanes As oral Inhibitors of The Na+/H+ Exchanger Type 3 (Nhe3)

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Abstract:

In the present, an attempt has been made to develop a robust QSAR model for 1□ Phenoxy-2-aminoindanes as oral inhibitors of the Na+/H+ Exchanger Type 3 (NHE3). The moderate size dataset consists of sixty-seven derivatives of 1□ Phenoxy-2-aminoindane. The standard procedure recommended by OECD was used to develop the QSAR model and its validation. Thorough validation was performed to judge the QSAR model. The results are excellent and could be useful to medicinal chemists for future optimizations of 1□ Phenoxy-2-aminoindanes as oral inhibitors of the Na+/H+ Exchanger Type 3 (NHE3).

Keywords: QSAR, 1□ Phenoxy-2-aminoindanes, Na+/H+ Exchanger Type 3 (NHE3)

Introduction:

Sodium–hydrogen (Na+/H+) exchanger type 3, also known as NHE3, sodium–hydrogen antiporter 3, or solute carrier family 9 member 3 (SLC9A3), is mainly sited in the nephron of the kidney, apical membrane of intestinal enterocytes, and in the brain stem cell area. NHE3 inhibition results in augmented muscle tone of the upper airways. Therefore, its inhibitors can be used for curing obstructive sleep apneas and snoring [1-4].

Recently, Rackelmann et al [1] synthesized and tested 1□ Phenoxy-2-aminoindanes as oral inhibitors of the Na+/H+ Exchanger Type 3 (NHE3). The results indicate that 1□ Phenoxy-2-aminoindanes possess moderate to high activity, but further optimizations are required to achieve the goals. In this regard, an attempt was to develop a QSAR model to identify structural features having correlation with bioactivity. QSAR (quantitative Structure- Activity Relationship) is a thriving branch of CADD (Computer Aided Drug Designing) to identify important pharmacophore features and predict the bioactivity.

Experimental Methodology:

Selection of Dataset: The selected dataset is moderate in size with sixty-seven derivatives of 1□ Phenoxy-2-aminoindane, which were tested as oral inhibitors of the Na+/H+ Exchanger Type 3 (NHE3). The variation in substation pattern is eclectic enough to provide coverage of wide chemical space. The dataset with SMILES notation along with reported IC50 values has been presented in Table 1.

Sr. No.	CANONICAL_SMILES	IC50 (uM)	pIC50 (NME3)
1.	CC(=O)Nc1cccc(O[C@@H]2[C@H](Cc3ccccc23)N4CCCC4)c1	438	3.359
2.	CS(=O)(=O)c1ccc(O[C@@H]2[C@H](Cc3c(F)cc(Cl)cc23)N4CCCC4)cc1	737	3.133