Research Article

QSAR, molecular docking approach on the estrogenic activities of persistent organic pollutants using quantum chemical disruptors

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Abstract
Quantitative structure–activity relationship (QSAR), for predicting estrogenic activity of persistent organic pollutants (POPS) activity of different compounds used as dataset. Density functional theory using B3LYP/6-31G* quantum chemical calculation method was used to find the optimized geometry of the studied chemical disruptor compounds. Fourteen types of molecular descriptors were used to find out the relation between POPS activity and structural properties. Relevant molecular descriptors were selected by genetic function algorithms. The best model obtained was given a distinct validated, good and robust statistical parameters which include; Square correlation coefficient R^2 value of (0.9289), Adjusted determination coefficient, R^2_{adj} value of (0.9284), leave one out cross validation determination coefficient Q^2 value of (0.9548) and external validation as predicted determination coefficient R value of R^2 (0.819335). Molecular docking analysis find out, the best lead-compound with the higher negative value score of (– 11.8 kcal/mol) were formed hydrophobic interaction and H-bonding with amino acid residue between the disruptor compounds with their $1 \times 7j$ as receptor. The result obtained from the study is expected to be significant and predict estrogenic activities disruptors of the POPS.

Keywords Pops · QSAR · GFA · DFT and molecular docking

1 Introduction

During the Second World War, scientists have identified some certain chemicals contaminants that exhibit toxic features and are persistent in the environment, bioaccumulative, prone to have long-range atmospheric transboundary migration, deposition, and expected to impose serious health effects on humans, wildlife, and marine biota adjacent to and distant from their origin of discharge. These chemical pollutants are referred to as persistent organic pollutants (POPs) [1]. POPs are usually hydrophobic (water-hating) and lipophilic (fat-loving) chemicals. In marine and terrestrial systems, they come strong to solids, particularly organic matter, evading the aqueous segment. Certainly pops enter the lipids of organisms more easily than the inside of the aqueous medium of cells territory and are stockpiled in fatty tissue. This stockpiling in fatty tissue allows the compounds to persevere in biota, where the metabolism rate is low. Persistent organic pollutants (pops) simultaneously to exist in the surrounding environment for several years, leading serious complications such as learning disabilities, birth defects, cancer, behavioral, neurological issue, reproductive, and immunological disorders in wildlife species and humans [2].

Chemicals are essential component of our daily lives. But some chemicals known as endocrine disruptors, can have harmful and dangerous effect on the body's endocrine (harmony) system. Hormones act in very small quantity and at precise moment in time to regulate the body's development, growth, production, metabolism, immunity

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and behaviors. Endocrine disruptors interfere with natural hormone system and the health effects can be felt long after exposure has stopped. Exposure to endocrine descriptors can have life-long effect and can even have consequences for the next generation to come. Endocrine disruptors chemical (EDCs) and potentials EDC are mostly man-made found, in various material such as pesticide DDT, dioxin and plasticizers such as metals, additives or contaminant in food, and personal care products. EDCs have been subjected to be associated with altered reproductive function in males and females. Increased incidence of breast cancer, abnormality of growth and neurodevelopmental delays in children as well as change in immune system. Human exposure to EDCs occurs via ingestion of food, dust and water inhalation of gases and particle in the air and via the skin. Such Diethystilbestrol (DES) was the first synthetic non-steroidal estrogen which was given between 1940 and 1971 to pregnant women with wrong idea [3]. In 1971, DES was shown [4], to cause clear cell carcinoma a rare vaginal tumor problem occurring in girl and women, therefore USA withdrew used of DES and France withdrew in 1977. A recently research shows that, DES also has a potential to cause a variety of significant adverse medical complication and infertility among DES daughters (Individuals were exposed to DES during their mothers' pregnancies) [5].

1.1 Action of endocrine discruptors

An endocrine disruptors may mimic or partly mimic natural hormone in the body like estrogen or androgen and also thyroid hormone, if may strict the interaction of natural hormones with their receptors by altering their metabolism in vivo [6], it may also bind to a receptor within a cell and block the endogenous hormone from binding. These chemicals that block or antagonize hormones are antiestrogens and anti-androgens. By snooping with the body's endocrine system, it give the chance for adverse developmental, reproductive, neurological, an immune effects in both humans. The data set (pops) of this research have divided into natural product, medicine & food additive, PCBS, Phenol, Phthalates, BPA, Polybrominated diphenyl ethers (PBDEs) etc. BPA is an industrial chemical that has been used to make certain plastics and resins since the 1960s. It is found in polycarbonate plastics and are often used in containers that store food and beverages, such as water bottles, and in other consumer goods. Under European legislation (UEL), it has been prohibited use of polycarbonate baby bottles since 2011. Then during a first phase of France's, BPA was banned in food contact materials effective from January 1, 2013. On January 1, 2015 the second phase of France's ban on bisphenol A (BPA) became effective. However a recent and systematic review [7] with meta-analysis has found to be, there is a consistent increase in risk of abnormal sperm quality with phthalate, ester group as well as with organochlorine (pops). Early phthalate exposure in pregnant women and also associated [8] with alterations in thyroid hormones leading to autism spectrum disorders and developmental delay. Parabens are esters of p-hydroxybenzoic acid which are widely used as preservatives in cosmetics as well as in foods and drugs. Animal experiments have shown that parabens weakening the estrogenic activity [9]. The use of QSAR approaches in chemical disrupting tests (toxicity) is expected to increase in a variety of applications and to report a number of regulatory tasks [10, 11]. In silico methods can be used to upkeep, prioritization, read-across and screening. Among various in silico approaches, molecular docking, where estrogenic activities disruptors' (pops) is predicted based on the ligand-receptor complex structure and binding energy, is a promising tool for persistent organic pollutants (disruptor chemicals) screening [12, 13]. Molecular docking strategy is a computational ligand-target docking approach that has been used to evaluate structural complexes of a target receptor with its ligand to realize the chemical and structural basis of a ligand's target specificity. Molecular docking approach has the potential to be applied for discovering molecular initiating events (MIEs) in the Adverse Outcome Pathway (AOP) framework [14]. Direct binding to nuclear receptor (NRs) is one of the main mechanisms by which EDCs can affect the endocrine system [15]. The interaction between a receptor and its ligand is one of the first reactions in the estrogenic activities disruptors (pops) pathway of chemicals in the AOP framework concept [16].

2 Materials and methods

2.1 Optimization approach and calculations of molecular descriptors

All the molecular structure of estrogenic disruptor compounds were drawn using ChemDraw ultra [17] version 12.02 software and subsequently imported into Spartan 14 wave function software [18] for structural minimization. All the 55 molecules geometry structure of pops were optimized using density functional theory (DFT) method at the B3LYP level of theory and 6-31G* accordingly.

2.2 Model generation

All the structures of 55 Pops compounds were studied by statistical methods based on the Genetic Function Algorithm technique to develop all the models. Number of descriptors in the regression equation is 5, the population

and maximum generation are 500 and 1000 correspondingly. The number of scaled LOF smoothness parameter is 0.5, maximum equation length number is 5, and mutation probability is 0.1. GFA algorithm selecting the basic function generally developed good and promising models than those made using stepwise regression approach, the model was assessed using LOF and measured using a slight variation of the unique Friedman formula, this come to chance, the best fitness score can be received. The revised formula of LOF [19] follow

$$\mathrm{LOF} = \mathrm{SSE}/\left(1 - \frac{C + dp}{M}\right)^2. \quad (1)$$

SSE is the sum of square errors, *c* is the number of terms in the model, other than the constant terms, *d* is a user defined smoothing parameter, *p* is the total number of descriptors enclosed in all model terms (ignoring the constant term) and *M* is the number of sample in the training set unlike the commonly used least squares measure (LSM), LOF measure cannot constantly be reduced by adding more terms to the regression model (Table 1).

2.3 Quality validations

Internal and external validation parameters were used to develop the consistency and predicted ability of the QSAR model. The QSAR models remained developed using the training set pops compound (optimized by Q_2), and then the developed novel compound were validated (externally) using the test set compounds. Multiple linear regression (MLR) was used to display the relationship between the dependent variable Y (ED_{50}) and independent variable X (atomic descriptors). The genetic algorithm-multiple linear regression (GA-MLR) investigation led to the selection of five descriptors that were used to collect a linear model for calculating predictive activity on the persistent organic pollutants (pops). The validation parameters have compared with the minimum recommended values for a generally acceptable QSAR model as shown in Table 2.

2.4 Square of the correlation coefficient (R^2)

Describes the friction of the total variation recommended to the model. The closer the value of R^2 is to 1.0, the better the regression equation explains in Y variable. R^2 is the most normally used internal validation and express as the following:

$$R^2 = 1 - \frac{\sum (Yobserved - Ypredicted)^2}{\sum (Yobserved - Ytraining)^2} \quad (2)$$

3 Applicability Domain

Applicability domain (AD) of a QSAR model is the physico-chemical, data on which the training set of the model has been developed and for which it is applicable to make prediction for new lead candidate. The model was authenticated using Williams's graph, and it's presented as standardized residuals by the leverages Fig. 1. This method exploited to visualize the applicability domain (AD). Leverage indicates a molecules distance from the centroid of X. [21]. The leverage of molecule in the original space is defined as;

$$h_i = X_i^T \left(X^T X\right)^{-1} X_i. \quad (3)$$

where *xi* is the descriptor vector of the considered molecule X the descriptor matrix derived from the training set descriptor values.

The leverage (h^*) is defined as:

$$h^* = \frac{3(p+1)}{n} \quad (4)$$

where n = Number of training set, P = Number of descriptors in a test set.

The above graph (Williams plot, Fig. 1) shows that all the molecules of training set fall within the domain of GFA model (Leverages of $h^* = 0.43$) and five molecules of test set are found to be out of warning leverages, so any molecule found beyond warning leverages are outliers not be consider as novel model. The Williams plot shows blue dot indicating training set molecules while the light-brown dot indicate test set molecules, the graph express high residual model, regular model, bad leverages model and good leverages model but four test set molecules found structural outliers.

4 Results and discussion

4.1 QSAR approach

Five developed QSAR models were obtained and recoded, one out of five models found and marked to be the best model (Model 3) due to statistics significance parameters. The developed model 3 shown (Table 3), both names and symbol descriptors used in the optimization model. And also shown the second (Table 4) for the validation result of the Genetic Function Algorithm of model 3 which was generated from the material studio software. The best QSAR model 3 developed has fulfilled the minimum recommendation value of validation measures for acceptable QSAR model [22].

Table 1 structure of the compound with their experimental value

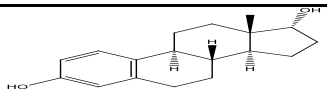
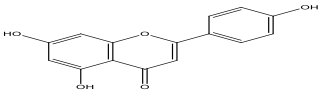
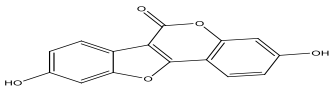
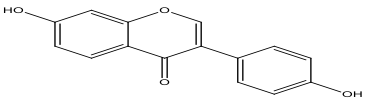
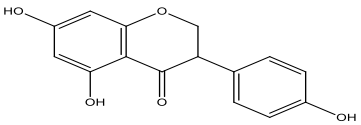
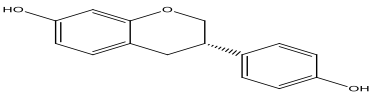
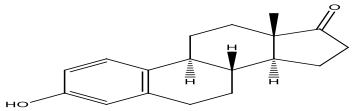
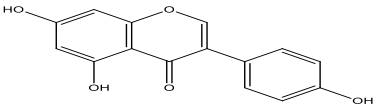
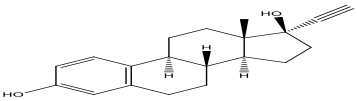
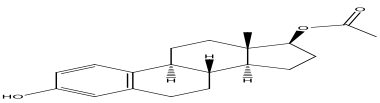
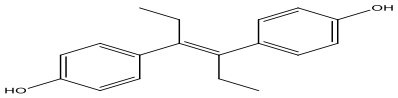
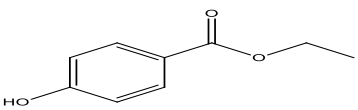
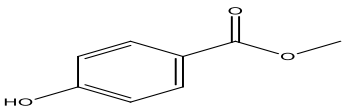
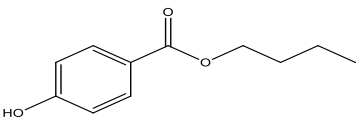
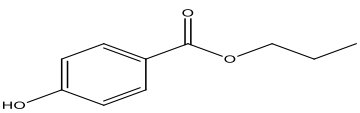
S/NO	STRUCTURES	EXPERIMENTAL ED_{50}	PREDICTED ED_{50}	RESIDUE
1		3.13	3.8	6.7
2		6.52	6.52	0
3		6.52	6.52	0
4		5	5.2	-0.2
5		5	3.82	1.18
6		6.52	6.52	0
7		2	2.1	-0.1
8		4.52	4.55	-0.03
9		1.82	2.24	-0.42
10		5.22	5.54	-0.32
11		1.82	1.83	0
12		7.52	7.52	0
13		8.13	8.1	0.03
14		2	6	-4
15		6.527	6	0.52

Table 1 (continued)

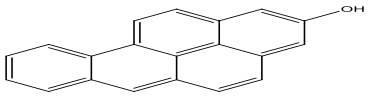
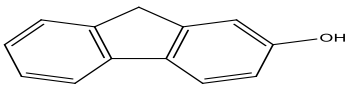
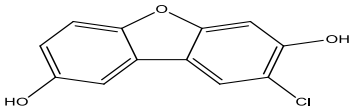
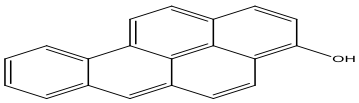
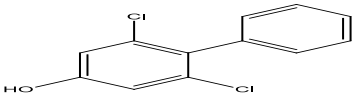
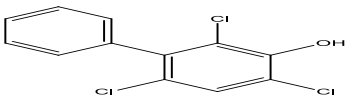
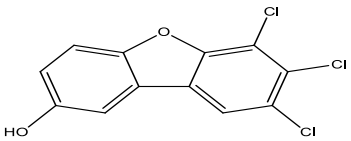
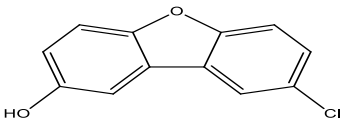
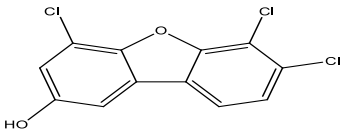
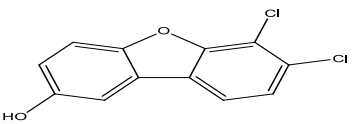
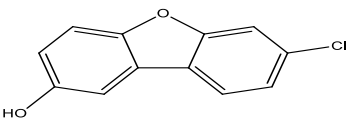
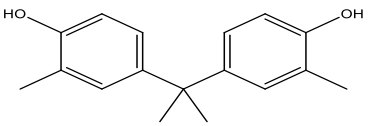
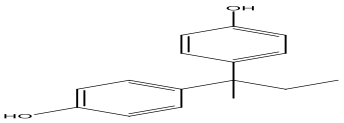
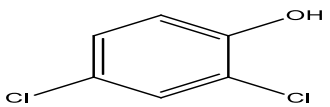
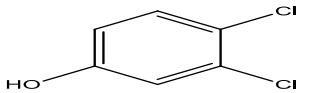
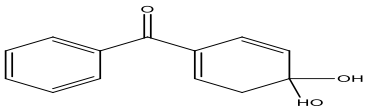
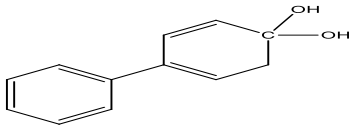
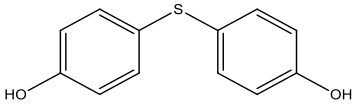
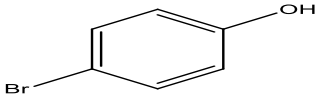
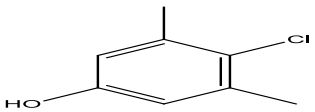
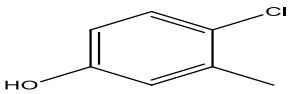
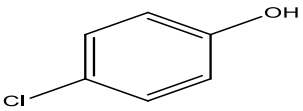
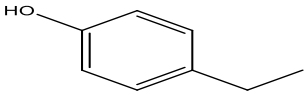
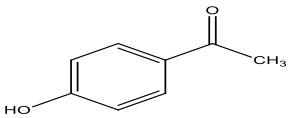
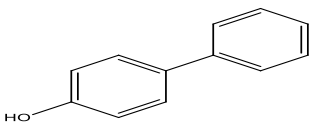
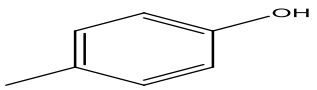
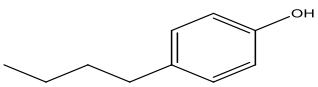
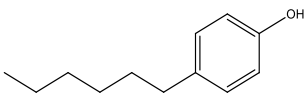
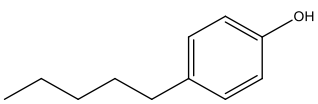
16		7.2	7.22	0.02
17		7.52	6.84	0.68
18		5.43	5.43	0
19		6.52	6.54	-0.02
20		5.13	5.14	-0.01
21		6.3	6.54	-0.24
22		6.52	6.51	0.01
23		6.52	6.51	0.01
24		6.52	6.52	0
25		6.22	6.69	-0.47
26		6.37	6.39	-0.02
27		6	6.1	-0.01
28		6	6.1	-0.01
29		7.13	7.71	-0.58

Table 1 (continued)

30		6.82	6.83	-0.01
31		8	8.1	-0.01
32		6.22	6.23	-0.01
33		6	6.81	-0.81
34		7.43	7.43	0
35		7.52	7.53	-0.01
36		7.52	7.51	0.01
37		7.82	7.34	0.48
38		7	7.1	-0.1
39		7.82	7.83	-0.01
40		7	7.1	-0.1
41		8	7.89	0.11
42		6.52	6.54	0.02
43		6.52	6.52	0
44		6	6.2	-0.2

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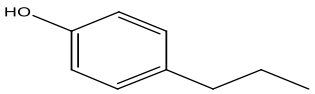
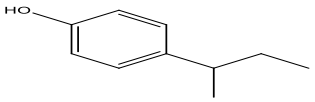
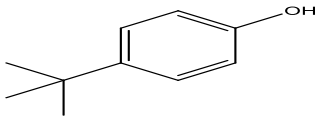
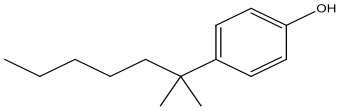
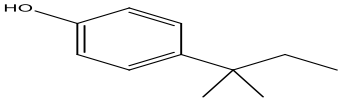
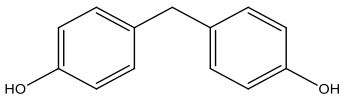
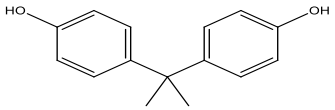
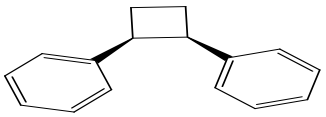
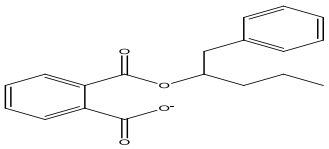
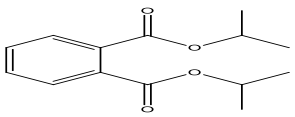
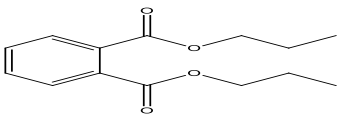
45		7.37	6.03	1.34
46		6.52	6.54	-0.02
47		7	7.41	-0.41
48		4.82	4.83	-0.01
49		5.52	6.48	-0.96
50		6.82	6.82	0
51		6	6.2	-0.2
52		8	8.20	-0.2
53		8.22	8.31	-0.09
54		8.82	8.81	0.01
55		8.52	8.53	-0.01

Model 1

IC50 = − 0.001955194 * **ATSC3v** + 2.361765161 * **GATS2c** + 3.856551375 * **SpMax3_Bhi** + 2.141975073* **TICi** − 0.407294756 * **TIC1** + 3.388758, $N = 41$ $R^2 = (0.9989)$, $R^2_{ADJ} = 0.928372$, $Q^2 = 0.944818$ and $R^2_{PRED} = 0.819335$, $LOF = 0.005644$, Significance-of-regression F-value = 3.34514.

Model 2

IC50 = − 0.001891673 * **ATSC3v** - + 2.260622850 * **ATSC2e** + 3.868519768 * **GATS2c** - + 2.387952229 * **SpMin3_Bhp** - + 2.387952229* **TIC1** + 5.376981, $N = 41$ $R^2 = (0.912891)$, $R^2_{ADJ} = 0.938365$, $Q^2 = 0.924845$ and $R^2_{PRED} = 0.80948$, $LOF = 0.005667$, Significance-of-regression F-value = 1.83E+03.

Table 2 Minimum recommended value for the evaluation of the quantitative QSAR model

S/N	Symbol	Name	Value
1	R^2	Coefficient of determination	≥ 0.6
2	Q^2	Cross validation coefficient	> 0.5
3	R^2_{pred}	Coefficient of determination for external set	≥ 0.6
4	R^2_{adj}	Adjusted square correlation coefficient	≤ 0.5
5	P (95%)	Confidence interval at 95%	≤ 0.05
6	Next test set	Minimum number of extend test set	≥ 5
7	$R^2 - Q^2$	Difference between R^2 and Q^2	≤ 0.3

Ravinchandran et al. [20]

Model 3

$IC50 = -0.001839735 * \mathbf{ATSC3v} + 2.189448988 * \mathbf{ATSC2e} + 4.153651066 * \mathbf{GATS2c} + 2.208946411 * \mathbf{SpMin3\_Bhv} - 0.070039733 * \mathbf{TIC1} + 5.314197$, $N = 41$ $R^2 = (0.923891)$, $R^2_{ADJ} = 0.938365$, $Q^2 = 0.9973$ and $R^2_{PRED} = 0.80348$, $LOF = 0.005669$, Significance-of-regression F-value = 1.83E+03.

These are the best three equations obtained from material studio software, which generated by training set of the persistent organic pollutant compounds, but equation one (Model 1) found to be the best equation and contribute more than the other descriptors (Table 3) with high value descriptor of (GATS2c + 3.856551375) among the five model generated from the software as internal validation. The descriptor GATS2c in Table 3, described as autocorrelation descriptor lag 2/weighted by charges in the descriptor java class, this explain the contribution of the compound that contains hydrogen oxygen, carbon and nitrogen respectively (Table 5).

4.2 Computational docking study

4.2.1 Docking materials

Docking preparation and energy calculation give as (kcal/mol) unit of active pops compound and receptor 1 × 7j were executed by MGL tool and AutoDock Vina of PyRx virtual screening software [23]. Autogrid pre-calculation of the docking estrogenic disruptor molecules was achieved by Autodock Vina of Pyrx by explaining the target point 1 × 7j receptor protein. Energy grid was enrolled based on Lamarckian Genetic Algorithm [24]. Chimera, discovery studio 3.5, Ligplot and PyMol visualization software

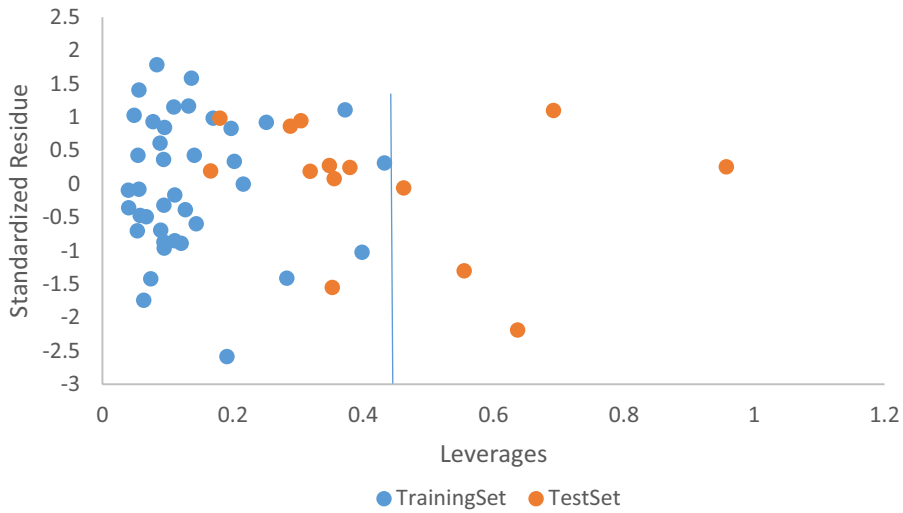


Fig. 1 Plot of standard versus leverages

Table 3 Physicochemical list of descriptors used in the best model

S/No	Symbol	Name of descriptors	
1	ATSC3v	Centered Broto-Moreau autocorrelation – lag 3/weighted by van der Waals volumes	2D
2	ATSC2e	Centered Broto-Moreau autocorrelation – lag 2/weighted by Sanderson electronegativities	2D
3	GATS2c	Geary autocorrelation – lag 2/weighted by charges	2D
4	SpMax3_Bhi	Smallest absolute eigenvalue of Burden modified matrix – n 3/weighted by relative first ionization potential	2D
5	TIC1	Total information content index (neighborhood symmetry of 1-order)	2D

Table 4 Validation of the genetic function approximation (GFA) from material studio

Equations	Equation 1	Equation 2	Equation 3	Equation 4	Equation 5
Friedman LOF	0.002853	0.005418	0.005644	0.005667	0.005669
R-squared	0.928922	0.918958	0.918915	0.912891	0.923891
Adjusted R-squared	0.928402	0.920437	0.928372	0.938365	0.938365
Cross validated R-squared	0.954858	0.956993	0.944818	0.924845	0.935023
Significant Regression	Yes	Yes	Yes	Yes	Yes
Significance-of-regression F-value	3.64E+03	1.92E+03	1.84E+03	1.83E+03	1.83E+03
Critical SOR F-value (95%)	3.345145	3.345145	3.345145	3.345145	3.345145
Replicate points	1	1	1	1	1
Computed experimental error	0.064031	0.064031	0.064031	0.064031	0.064031
Lack-of-fit points	9	9	9	9	9
Min expt. error for non-significant LOF (95%)	0.623698	0.624029	0.633336	0.635343	0.635548

Table 5 Best three docking interactions with the estrogenic activities disruptor's compound, docking scores and active site residues involved

Ligand	Binding energy	Residual interaction	Hydrogen bond interaction	Hydrogen bond distance
19	− 11.8	MET336, PHE356, LEU298, ALA302, LEU339, LEU343, LEU298, LEU298, ILE373, ILE376, LEU298, MET336	HIS475	2.16714
16	− 11.7	MET336, PHE356, PHE356, LEU339, LEU343, LEU298, LEU298, LEU476, LEU298, ALA302	BIS407	2.1940
7	− 11.0	MET340, PHE356, LEU298, ALA302, MET336, LEU298, ILE373, PHE356, PHE377, LEU339, LEU343	GLY472	3.46533

were used to perform the virtual analysis of (interaction between the molecules and the enzyme) docking site.

4.3 Preparation of the target receptor

The structure of 1 × 7j receptor protein inform of 3D was extracted from the protein data bank in PDB format. All hetero-atomic molecules were excluded from the file using Discovery Studio 3.5 software, hydrogen was added to the receptor and removed water from it by using discovery studio software, the 3D structure of 1 × 7j receptor protein was minimized, protonated and saved in pdbqt file format in all polar residues.

The above 3D and 2D shown the interactions between the ligands and receptor "a and b" (ligand 19-receptor interaction: best docking score), follow by "c and d" and "e and f" both the three ligands and receptor interactions shown the binding site pocket cavity by having H-bond interactions and hydrophobic residue interactions, this result revealed that all the fifty-five persistent organic pollutants (pops) compounds play a significant role as estrogenic activities disruptors compound.

5 Conclusion

The statistically significant model of GFA analysis obtained from material studio software ($R^2 = (0.923891)$, $R^2_{ADJ} = 0.938365$, $Q^2 = 0.9973$, Friedman LOF = 0.005669) are in good agreement with parameters reported in Table 2, this shows the goodness and reliability of the candidate. A comparison of the predicted toxicities with the experimental log ($1/ED_{50}$) reported in Table 1 indicated high predictability of the novel candidate evidenced by low residual values observed in the Table, estrogenic disruptor compounds of 55, 36, 26 and 23 are the best predicted in the series evident by its lowest positive residual values. The predicted toxicities of the

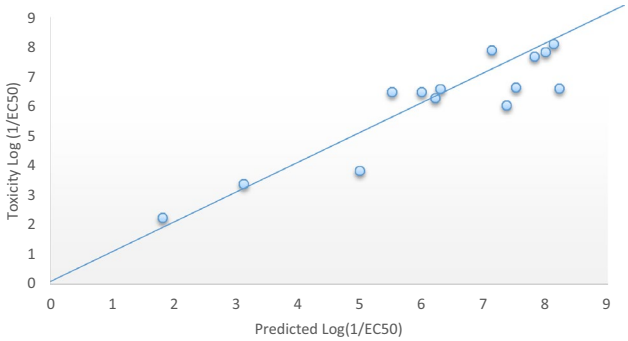


Fig. 2 Plot Log1/ED_{50} of toxicity versus predicted activity

Fig. 3 3D protein receptor 1 × 7j after prepared

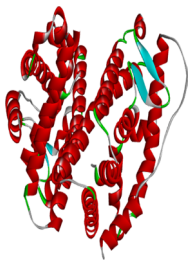


Fig. 4 3D prepared best 19 ligand

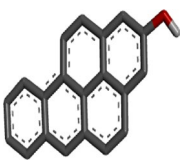
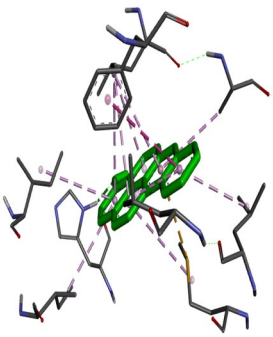


Fig. 5 3D interaction between receptor 1 × 7j



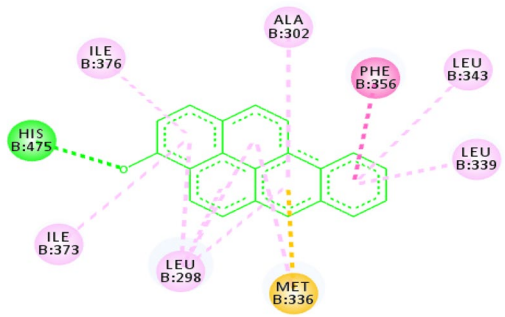


Fig. 6 2D visualization structure between receptor and Ligand 19 best 1 × 7j and Ligand 19

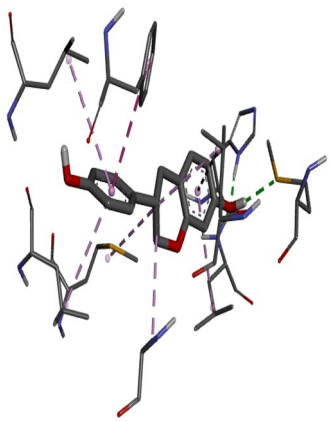


Fig. 7 3D interaction between receptor 1 × 7j and Ligand 16

disruptors compound in log (1/ED_{50}) in Table 1. Shows the promising results with the experimental values (R^2_{PRED} = 0.8348). The plot of experimental toxicities versus predicted log (I/ED_{50}) is shown in Fig. 1 for the test set and Fig. 2 for the training set with the R^2_{PRED} = 0.8848 also confirm the goodness reliability of the model. The Williams plotted standardized residual versus leverages in the Fig. 2 shows that exploited to visualized the applicability domain AD [25] of training and test set molecule five molecules from test set and two molecules from training set are found to be structural outliers the warning leverages found to be h* = 0.43 in the Fig. 1 Five descriptors **ATSC3v**, **ATSC2e**, **GATS2c, SpMin3_Bhp** and **TIC1** generated from the material studio software which are found to be responsible for the estrogenic activities disruptors, similarly GATS2c (Table 3) descriptor found to be more contributor in the estrogenic activities disrupting. Multistep framework of computational docking approach were performed to explore the estrogenic activity disruptors (toxicity) influence of structure features on the estrogenic activities of persistent organic pollutants and investigate the molecular mechanism of receptor (1 × 7js)—ligand (estrogenic activities disruptor compounds) interactions. The detailed binding affinity docking score of estrogenic activity disruptor molecule (Ligand 19. best docking score) were obtained as -11.8 kcal/mol, hydrogen bond distance of 2.16714Å

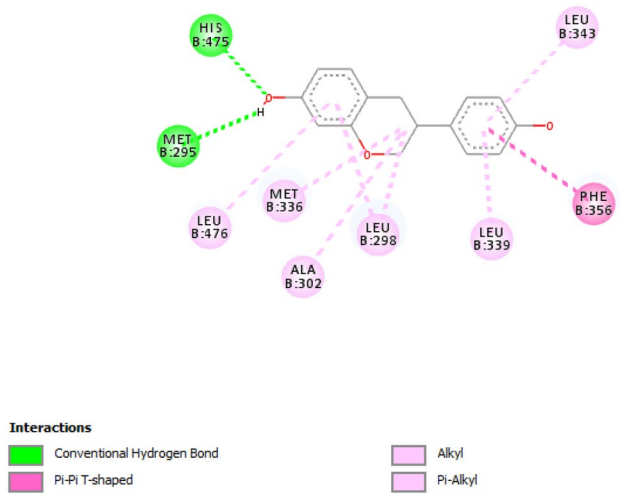


Fig. 8 2D visualization structure between 1 × 7j receptor and ligand 16 interactions

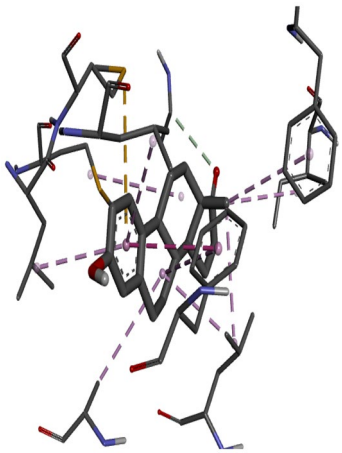


Fig. 9 3D Interactions between 1 × 7j receptor and ligand 7

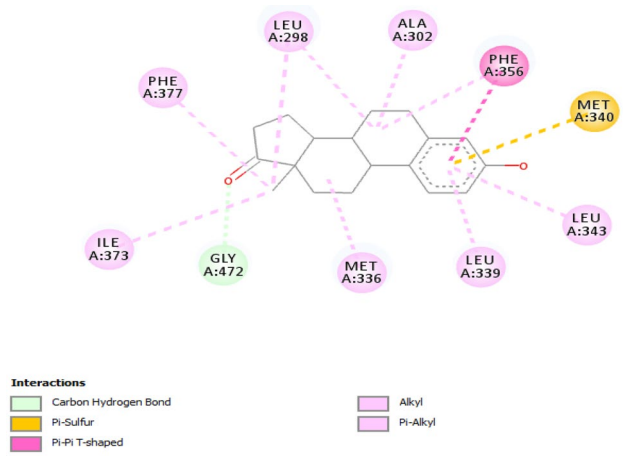


Fig. 10 2D visualization interactions between 1 × 7j receptor and ligand 7

and enclosed by amino acid residues (hydrophobic interactions) of MET336, PHE356, LEU298, ALA302, LEU339, LEU343, ILE373, ILE376, this indicated an acceptable reliability of the parameters specified in the docking approach results (Figs. 3, 4, 5, 6, 7, 8, 9, 10).

6 Summary

The topic title as "Qsar, molecular docking approach on the estrogenic activities of persistent organic pollutants using quantum chemical disruptors" stated the fifty-five compounds which are persistent organic pollutants against the estrogenic activity, the research paper found out the predicting of the persistent organic pollutants (disruptors of estrogenic activities), based on predicting by using *quantum chemical descriptors techniques*. The first method quantitative structure activity relationship (QSAR) generate a model among the disruptor compounds of estrogen hormone activities after optimized the whole persistent organic pollutants and generate the descriptors by PaDEL software, this enable to generate the model after dividing the descriptors into training-set and test-set and used a material studio software to generate the model. Similarly second method approach ***Molecular docking*** shows the interactions between the receptor enzyme and estrogenic activities disruptor compounds (Pops) using different software of Discovery studio, PyRx software, Ligplus and PyMol software for reviewing the graphics image of ligands and receptor inform of 2D and 3D structure.

Compliance with ethical standard

Conflict of interest The Authors declared that they have no conflict of interest.

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