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A predictive study of titanocene dichloride derivatives activity inside DFT

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ABSTRACT

*A **QSAR** (Quantitative Structure- Activity Relationship) study was performed to evaluate the relative toxicity of 25 of titanocene dichloride derivatives. The quantum chemical descriptor molecular was calculated using DFT methods. The validations indicated that the QSAR model built was robust and satisfactory (R^2=77.71; Q^2_{LOO}=68.96; RMSE=0.27; F=18.59; Q^2ext =68.75). This validation afforded good predictive performance as assumed from internal and external confirmation. We have therefore apply this model to predict the biological activity of Bis-methyl titanocene dichloride, the value obtained for the IC50 72.3E-5M is widely better than tamoxifen substituted with titanocene.*

Key words: QSAR model, DFT, titanocene dichloride, inhibitory concentrations, molecular descriptor

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INTRODUCTION

Cancer is one of the leading causes of death; there is no chemotherapy available for the treatment of many varieties of this disease. The use of organometallic compounds against cancer is one of the field of chemistry known as bio-organometallic [1-3]. In 1985 the term bio-organometallic chemistry was first applied to the synthesis and study of organometallic species of biological and medical interest.

In recent years, a large number of antitumor agents have been discovered at different levels [4] and which have higher efficacy and lower toxicity than existing treatments. Metal-based drugs, for example metallocene dichloride (CP_2MCl_2) (e.g., Fig. 1) with M=Ti, Fe, V, Nb and Mo show remarkable antitumor activity. Titanium in particular is showing promising results [5-10]. The tamoxifen is the most commonly sold treatment for advanced-stages breast cancer, it is commercialized under the brand nolvadex and his activity is enhanced during the titanocene dichloride fixation [11]. QSAR analysis correlates the chemical structural characteristics with biological activity; the model can serve as screening tools to predict the biological activity of the untested compounds [12]. This technique should be remarked as titanium dichloride derivatives have been widely used to predict anticancer activity taking into account different molecular descriptors and statistical techniques. With the method quantitative structure–activity relationship in our knowledge does not have was made, the main idea behind the research presented in this paper has focused on the studies of derivatives titanocene dichloride synthesized and evaluated against **LLC-PK** (long-lasting cells-pig kidney) in term of the **IC50** (inhibitory concentration 50%) values were determined from the drug concentration that induced a 50 % reduction in light absorbance.

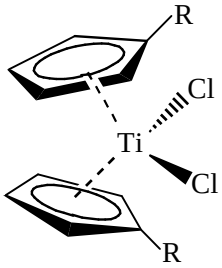


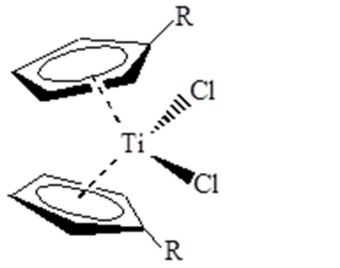
Fig1: Titanocene dichloride derivatives

MATERIALS AND METHODS

Compounds studied

The set of 25 compounds presented in (e.g., table 1) with known biological activity analyzed in this study. The anti-tumor activity expressed as log IC50 were **IC50** (inhibitory concentration 50%) values represents the concentration that induced a 50 % reduction in light absorbance.

R=H, A, B, C, D, E, F, G and K



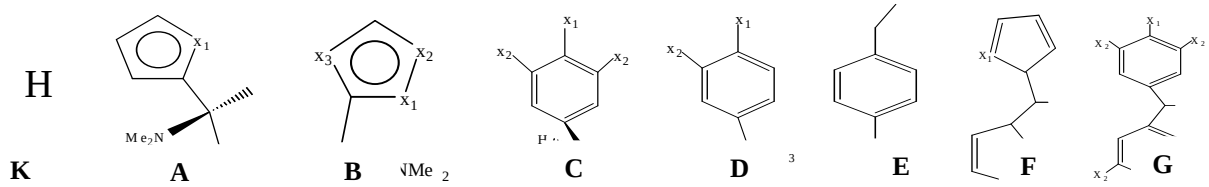


Table 1: Inhibitory concentration of Substituted titanocene dichloride Derivatives

R		X1	X2	X3	Nomenclature
K	b46	/	/	/	Titanocene dichloride
A	b1	O	/	/	N, N-dimethylamino-2-thiophenylmethyl
	b15	S	/	/	N,N-dimethylamino-2-(N-methylpyrrolyl) methyl
B	b4	N(Me)	/	C	N,N-dimethylamino-5-(N-methyl) pyrazolylmethyl
	b5	S	/	N	N,N-dimethylamino-2-thiazolylmethyl
	b6	$N(N(Me)_2)$	N	N	N, N-dimethylamino 2(N, N-dimethylamino) methylimidraz-olyl) methyl
C	b18	$N(Me)_2$	C	/	1,2-di(p-N,N-dimethylaminophenyl)ethanediyl
	b22	H	C	/	1,2-bis(m-dimethoxy-phenyl-ethanediyl
D	b2	$N(Me)_2$	H	H	p-dimethylaminobenzyl
	b8	H	OMe	H	3-metoxy-benzyl
	b9	OMe	OMe	H	3,4-bismethoxy-benzyl
	b44	$N(Me)_2HCL$	H	H	Dihydrochlorid derivative of P-dimethylaminobenzyl
	b41	OMe	H	$N(Me)_2$	N, N-dimethulamino-p-N, N-dimithylanylmethyl
	b42	$N(Me)_2$	H	$N(Me)_2$	p-anisyl-N,N-dimethylaminomethyl
E	b32	OMe	/	/	4-methoxymrthyl-benzyl
	b33	OEt	/	/	4-ethoxymethyl-benzyl
	b36	$N((CH_2)CH_3)_2$	/	/	4-di-iso-propylamonomethyl-benzyl
	b37	$N(CH_2CH_2)_2$	/	/	4-pyrollidin-1-ylmethyl-benzyl
	b38	$N(CH_2CH_2)_2O$	/	/	4-morpholinomrthyl-benzyl
F	b26	O		/	Di-(2-furyl) methyl
	b27	S	/	/	Di-(2-thiophenyl)methyl
G	b29	N(Me)2	H	/	Di-(p-N, N dimethylaminomethyl)-methyl
	b31	H	OMe	/	di-(3,5 dimetoxyphenyl) methyl
	b30	OMe	H	/	Di-(p-metoxyphenyl)-methyl
	b48	H	OMe	/	di-(3,5 dimetoxyphenyl)methyl

DFT calculations

The first step, the structures of the 25 compounds were synthesized by Matthias tacke et all [13-22]. All calculations for the optimization of the geometries of molecules were performed at the density functional theory DFT using the **ADF** (Amsterdam density function) software [23]. The most stable structure for each compound was generated and used for calculating various quantum chemical descriptors and polarizability. The optimized geometries were loaded in HyperChem, software which is used to calculate partition coefficient LogP (e.g., table 2).

Table 2: calculated logIC50 and Values of three selected descriptors of 25 titanocene dichloride derivatives

N°	code	logIC50	logP	HOMO(Kcal)	logα
1	b1	-4.55284	0.4200	-113.3530	4.01085
2	b4	-4.27572	-0.8100	-116.5820	4.06217
3	b5	-4.21467	0.6800	-117.5530	4.05174
4	b6	-5.26761	-1.0800	-99.6360	4.38617
5	b8	-3.7986	2.0600	-122.5460	3.97225
6	b9	-4.05552	1.9200	-111.4570	4.12283
7	b15	-3.61979	1.1100	-114.8650	4.06317
8	b22	-3.67778	0.5600	-120.0460	4.11256
9	b26	-3.85387	1.9500	-112.0900	3.96503
10	b27	-3.61979	3.3300	-119.3500	4.00089
11	b29	-4.42022	7.2300	-95.8840	4.52471
12	b32	-3.73518	2.4200	-125.7530	4.15918
13	b33	-3.52288	3.6300	-126.0920	4.26421
14	b38	-4.4437	2.5500	-113.1510	4.41055
15	b37	-4.61979	3.3600	-113.6290	4.37779
16	b41	-4.34679	3.0500	-99.4630	4.03226
17	b42	-4.26761	2.0200	-95.5040	4.04838
18	b46	-2.69897	-0.6000	-130.0660	3.20018
19	b48	-4.10791	4.1500	-113.5260	4.54043
20	b44	-4.04576	2.3400	-124.5040	3.94695
21	b2*	-3.92082	3.4600	-111.7830	3.88565
22	b18*	-3.56864	2.9700	-104.2070	4.03504
23	b30*	-4.34679	5.1600	-112.5840	4.4471
24	b31*	-4.10791	3.3400	-121.2270	4.43962
25	b36*	-4.36653	5.7300	-109.6320	4.51499

****** *Test set compound* ***P*** *Coefficient of division* ***α*** *polarisability*

QSAR method

The **QSAR** (quantitative structure–activity relationship) equations were obtained by the stepwise **MLR** (multiple linear regression) analysis using the QSARINS software [24] and the **GA-VSS** (genetic algorithm-variable subset selection). We applied the rule QUICK (Q under Influence of K) [25] is only the models with the K_{XY} correlation among the [X+Y]–variables greater than the K_X correlation among the [X]–variables can be accepted. In general, the best predictive models were selected by maximizing the Δ K ($K_{XY} - K_X$) values; in any case, negative threshold values are not allowed, being theoretically unacceptable models with negative differences. The robustness of the models and their predictive were evaluated by the coefficient of determination (R^2), standard deviation (s), Fisher's value (F) and both cross-validation techniques (Q^2_{LMO}; bootstrap), and (Q^2_{LOO}) [26]. A value Q^2>0.5 is generally regarded as a good result and Q^2> 0.9 as excellent [27-28].In fact, if a large value of Q^2_{LOO} is a prerequisite for a possible high predictive ability of a model, this condition alone is not sufficient. To avoid an over estimation of the predictive ability of the model, the procedure **LMO** (leave-more-out) was also applied, repeated 8000 times, excluding 30% of the objects at each stage (Q^2_{LOM} 30%). The real predictive capability of each model developed on the training set is verified on an external validation parameter Q^2_{EXT}. The application domain has been discussed with the Williams diagram treated in [28]; representing residues standardized in terms of the prediction values of hi levers. In this diagram the horizontal and vertical straight lines indicate the limits of normal values: the first for the Y outliers (i.e. compounds with cross-validated standardized residuals greater than 3.0 standard deviation units, ±3.0r.

RESULTS AND DISCUSSION

The correlation matrices between biological activities, logIC50, the descriptors, logP, logα and HOMO are given in (e.g., Table 3). The relationship between the structural descriptors and the activities log IC50 for 25compounds is modeled by equation (1).

Table 3: Correlation matrix between biological activities, logIC50, and physicochemical descriptors

LogIC50=-6.462420.08651*LogP+-0.02906*HOMO+-0.01763*Logα (1)

	logIC50	LogP	HOMO(Kcal)
LogP	-0.09		
HOMO(Kcal)	-0.61	0.25	
Logα	-0.66	0.56	0.37

α polarizability

This model exhibits a good coefficient of determination squared correlation coefficient (R^2), R^2=77.71explains a 77.71% variance in biological activity, with an F-value of 18.59. The cross-validated square correlation coefficient of the model is Q^2_{LOO} = 68.96%, which showed good correlation between predicted activity and actual activity, and this value reflects the accuracy of the models. The similarity SDEP and SDEC means that internal capacity prediction models are not too dissimilar from their adjustment authority. The very small differences between Q^2_{LOO} (68.96%) and Q30% (67.84%) show good stability in internal validation, the validation by the bootstrap (Q^2boot = 57.01%) at the same time confirms the ability of the stability and internal prediction model. the quality of Q^2_{ext} (68.75%) and the small (RMSE =0.27) values confirm the good predictivity of this model (e.g., Table 4). The plot of values predicted and experimental of log IC50, shown in (e.g., Fig. 2) suggests that the 20 compounds from the training set and 05 from the test set fit a straight line. The predicted radical scavenging activities given by Equation (1) are shown in (e.g., Table 2). The Williams plot of the standardized residual in terms of the leverages illustrated in (e.g., Fig. 2) shows that most compounds lie within the AD of equation (1) were calculated correctly. The values of all the compounds of calibration and testing are below the critical value (h* = 0.602) and none of these compounds is not influential. The difference between $R^2$and Q^2_{LOO} is not large. In view of these observations, we conclude that the QSAR model of equation is fairly robust. Experimental versus calculated and predicted logIC50 values of titanocene dichloride derivatives are presented graphically in (e.g., Fig. 3), they show a dispersion characteristic of a good fit, also confirmed by the value of Q^2_{LOO} (68.96%). The biological activity data listed in (e.g., Table 4) are the IC50 of titanocene dichloride derivatives. QSAR demonstrated a significant correlation of logP, HOMO and logα with IC50 and provided predictions in good agreement with experimental values.

Table 4: Diagnostic statistics for the Selected Model

R^2	Q^2_{LOO}	Q^2_{ext}	R^2_{adj}	SDEP	N_{TR}	F	Q_{LMO} 30 %
77.71	68.96	68.75	73.53	0.28	20	18.59	67.84
$SDEP_{ext}$	**SDEC**	**K_{xy}**	**RMSE**	**PRESS**	**N_{TEST}**	**K_x**	**$Q2_{boot}$**
0.29	0.24	47.2	0.27	1.66	5	42.1	57.01

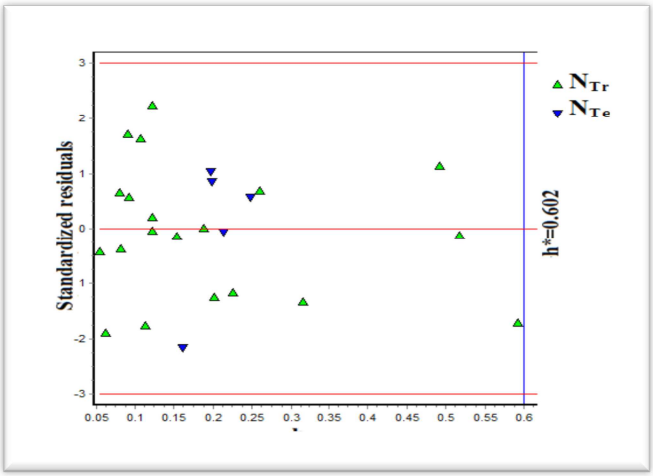


Fig 2: Plot of standardized residuals versus leverages, dash lines represent ± 3 standardized residual, dotted line represents warning leverage (h*=0.602)

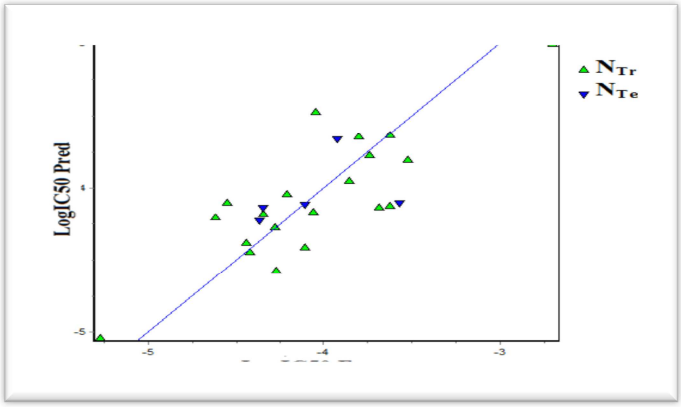


Fig 3: Regression line of the experimental and predicted values of Log IC50 for QSAR model generated by MLR

Testing

The predicted IC50 made by our model of bis-methyl titanocene dichloride is equal to 72.3E-5, this value concurrency those of drugs such as Tamoxifen. The QSAR model was tested on molecule with two metals[29]. The result obtained for IC50 is in agreement with the experimental value (see Table 5).

Table 5: predictive model

Compound	logP	log*α*	HOMO(Kcal)	$IC50_{(M)}$
[(η6-p-cymene)[(η5-C5H5)(μ-η5:κ1-C5H4-(CH2)4PPh2)TiCl2]RuCl2]	2.54	4.307	-103.49	2.69E-5
Bis-methyl titanocene dichloride	-0.44	3.33	-125.65	72.3E-5

CONCLUSION

The LogIC50 was correlated with three descriptors, quantum chemical descriptor HOMO and physicochemical descriptors polarizability(**α**) and Coefficient of division LOGP.

The found QSAR model is robust, with good internal and external predictive power and good quality of fit. This model is capable of accounting for the inhibitory activity (IC50) and could be utilized in predicting this property for novel compounds.

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