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in silico studies of 1,4-disubstituted 1,2,3-triazole with amide functionality antimicrobial evaluation against Escherichia coli using 3D-QSAR, molecular docking, and ADMET properties

Y. Koubi[(a)], H. Hajji[(a)], Y. Moukhliss[(a)], K. El Khatabi[(a)], Y. El Masaoudy[(a)], H. aghat[(a)], M.A. Ajana[(a)], M. Bouachrine[(a,b)] and T. Lakhlifi[(a)*]

[(a)] MCNSL Molecular Chemistry and Natural Substances Laboratory Department of Chemistry, Faculty of Science. Moulay Ismail University, BP 298 Meknes, Morocco

[(b)] Higher School of Technology (HST), Sultan Moulay Sliman University, BP 23000 Beni-Mellal, Morocco.

** Corresponding author*
t.lakhlifi@umi.ac.ma
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Abstract

E. coli are microbes responsible for the development of urinary tract cancer in women, therefore, the discovery of new antimicrobial agents by computer chemistry allows to improve and provide the new compounds with antimicrobial activity, it is necessary to carry out a 3D-QSAR (quantitative three-dimensional structure-activity) study of antimicrobial analogues to study the validity of this study by statistical parameters. We established the 3D-QSAR model from the comparative analysis of the molecular field (CoMFA)and the comparative analysis of molecular similarity indices (CoMSIA), The most tabular modulus of which is obtained by the CoMFA model (Q^2=0,71; R^2=0.98; R=0.97) and the best comparative model of acceptor and hydrophobic molecular similarity indices (CoMSIA /AH) (Q^2=0.69; R^2 = 0.96; R =0.94). To test the validity of the two models, we need to compute the SEE, t-F and their y-randomization for the training set, and the parameters of k. Roy de A. Golbraikh, A. Tropsha for the test set. The CoMFA model analysis shows that the activity of the antimicrobial molecules in our study is influenced by the steric effect and by the acceptor effect of hydrogen for the CoMSIA/AH model, in particular the molecular docking results we show that the interest of amino acids has a direct influence on antimicrobial activity, based on this result we have proposed 4 molecules with antimicrobial activity. These molecules are tested by analyzing their ADMET properties and their drug similarity.

Keywords: *3D-QSAR, E. coli- y-randomization, molecular docking, ADMET, CoMFA, CoMSIA*

1. Introduction

The first isolation of the bacterium Escherichia coli was discovered by Dr. Theodor Eschechia [1]. E. Coli is lives in the gastrointestinal tract of animals and humans. they belong to the bacterial family of Enterobacteriaceae [2]. Usually, it lives with hosts in association and rarely causes disease. However, it has caused uncomplicated urinary tract infections in humans and animals [3]. women suffer from E. Coli infection due to the proximity of the urethra to the anus [4]. E. Coli is a multi-resistance microbe and therefore researchers are developing new drugs every time to control multi-resistance microbes. the QSAR method is a theoretical average that allows us to find the relation between the biological activity and the chemical structure in a quantitative way to develop new drugs [5],[6]. the nitrogenous heterocycle is frequently used as a basic structure in several drugs having different activities such as cancerous activity, antimicrobial [7]; Antiparasitic [8]; antibacterial [9]; Antioxidant [10]; antitubercular [11]. For this reason we have chosen a series of disubstituted 1,2,3-triazole molecules which are already tested as an inhibitor of E. Coli antimicrobial activity, we applied a 3D-QSAR study on 21 triazole compounds with antimicrobial activity, this activity is expressed by the minimal concentration of the inhibitor (MIC). We used comparative molecular similarity indices analysis (CoMSIA) [12] and Comparative molecular field analysis (CoMFA) [13], to predict new molecules with a biological activity using contour analysis of descriptors (hydrophobic, steric electrostatic donor-acceptor). in the present work we have chosen a basic molecule built by 1,2,3-triazole, the model obtained is analyzed by statistical validation parameters such as R^2, R, Q, F. SEE, and also a test of y -randomization to validate the test set by the criteria of A. Golbraikh, A. Tropsha. The study of the molecular interaction between the antimicrobial agent made by the molecular docking of the 4c molecules in the active lees and the most active 4p molecule with the protein (PDB 3G7B) [14] to predict the new antimicrobial agents, we determined the total pure scoring compares the stability of the proposed molecule. this study was carried out by the software Sybyl-X.2.00. An in-silico study was carried out in this study to complete the results obtained by the 4 molecules proposed, we examined a study of the pharmacokinetic properties, and toxicological ADMET and prediction of the drug-likeness against infection due to microbe E. Coli which causes cancer of the Urinary tract in the PC-3 cell line [15].

2. Materials and methods

2.1. Database and biological activity

We have selected a series of 21 (Table 1) derived from molecules of 1,2,3-triazole recently published in the literature [7], for our study of the 3D-QSAR method. we converted the biological activity against E. Coli of 1,2,3-triazole derivatives expressed by MIC (the minimum concentration of the inhibitor) d into pMIC (-Log (MIC)), solidity and reliability of 3D-QSAR model, we have divided the series of molecules into two sets, 16 molecules for the training set and 5 molecules for the test set.

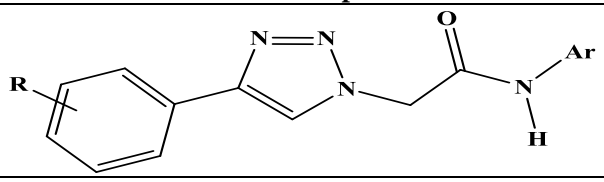
2.2. *Alignment and Molecular modeling*

The first obligatory step of the 3D-QSAR study is the structural alignment for this we have applied the method of the maximum comune structure (MCS) [16] for the 21 compounds of 1,2,3-triazole in this step we have chosen the Standard Tripos force champs with a Gasteiger-Huckel atomic partial charge with 0.005 kcal / (mol Å) [17] as the convergence character of the Powell gradient algorithm and a maximum of 10,000 iterations to obtain the stable conformation [18]. Visualization and calculation were carried out using Sybyl-x 2.0 software.

2.3. Generation of 3D-QSAR models

The CoMFA and CoMSIA approaches are the methods used in this study [19], for the predictivity of new antimicrobial agents apart from the study of 21 triazole compounds already tested as an effective antimicrobial agent. The predictivity of the new anti-microbial ligand by the CoMFA [20] method is based on the contour analysis of electrostatic and steric potential as a single Coulomb function in a three-dimensional potential and from this study we find the relationship between the three-dimensional chemical structure and biological activity, noting CoMFA is the first technique used for the 3D-QSAR study and also the most used technique by researchers. In addition, we have all studied compounds in a cubic grid of resolution 2A with an sp3 hybrid carbon with +1 as probe charge [21]. Kleber et al are developing another approach (CoMSIA) to study the relationship between structure and biological activity by analyzing similarity indices instead of fields on a grid. they have used a functional form adopted by a SEAL algorithm to calculate the indices obtained [22].

Table 1. ***Triazole compounds studied and their observed and predicted antimicrobial activities***



Compound	Ar	R	pMIC	CoMFA		CoMSIA HA	
4a	C_6H_5	H	7,047	7,034	0,013	7,025	0,022
4b	4-$CH_3OC_6H_4$	H	7,091	7,048	0,043	7,011	0,080
4c*	4-$NO_2C_6H_4$	H	6,676	6,679	-0,003	6,748	-0,072
4d	4-FC_6H_4	H	7,097	7,095	0,002	7,101	-0,004
4e	4-ClC_6H_4	H	7,419	7,391	0,028	7,364	0,055
4f	4-BrC_6H_4	H	7,110	7,167	-0,057	7,158	-0,048
4g	α-Naphthyl	4-CH_3	7,431	7,447	-0,016	7,432	-0,001
4h	C_6H_5	4-CH_3	7,472	7,465	0,007	7,418	0,054
4i*	4-$CH_3OC_6H_4$	4-CH_3	7,377	7,446	-0,069	7,518	-0,141
4j*	4-$NO_2C_6H_4$	4-CH_3	7,417	7,349	0,068	7,346	0,071
4k	4-FC_6H_4	4-CH_3	7,423	7,498	-0,075	7,513	-0,090
4l*	4-ClC_6H_4	4-CH_3	7,478	7,493	-0,016	7,509	-0,032
4m	4-BrC_6H_4	4-CH_3	7,757	7,79	-0,033	7,814	-0,057
4n	α-Naphthyl	4-CH_3	7,738	7,641	0,096	7,621	0,116
4o	C_6H_5	3-F	7,701	7,648	0,053	7,653	0,048
4p	4-$CH_3OC_6H_4$	3-F	7,772	7,481	-0,039	7,444	-0,002
4q	4-$NO_2C_6H_4$	3-F	7,412	6,934	0,478	6,899	0,513
4r*	4-FC_6H_4	3-F	7,094	7,365	-0,271	7,421	-0,327
4s	4-ClC_6H_4	3-F	6,815	7,476	-0,661	7,614	-0,799
4t	4-BrC_6H_4	3-F	6,836	7,422	-0,586	7,471	-0,635
4u	α-Naphthyl	3-F	7,068	7,629	-0,561	7,571	-0,503

* Compounds in the test set

2.4. Partial least squares (PLS) analysis

The partial least squares method is used and is frequently used in the QSAR study for the construction of predictive models [23]. The PLS statistical method is often used when the objective is to predict the model if we do not have the relationship between the variables [17]. Herman Wold was developed This method was the econometric technique [24]. In our study, we have evolved the relationship between the electrostatic, steric, hydrophobic, acceptor, donor descriptor and the biological activity present by pMIC; with the PLS method, we allow us to calculate the validation parameters between the biological activity and the descriptors. such as coefficient of determination R (must be greater than 0.5), and also an increasing validation value (LOO) greater than 0.5 [25], with a base value of the error estimate (must be less a 1), and we take into account the Fischer test (F) and an optimal value of the components (NOC) [26]. To give reliability and consistency of predictability we will calculate statistical parameters of internal and external validation using the PLS method [27].

2.5. Internal and External validation of CoMFA and CoMSIA models

To study a QSAR model it is necessary to make two validations, the first is the internal validation, this validation is characterized by a coefficient of determination R greater than 0.5, and a correlation coefficient and the coefficient R greater than 0.6, and cross-validation (LOO) Q greater than 0.5, and the Fisher test which must be a significant value and the validation by y-randomization and finally the EES which must be less than 1. the second validation is the external validation which is necessary to calculate the determinant of the tested coefficient R_{test} and correlation coefficient of the test R2test and to make our model reliable we must calculate the values of A. Golbraikh, A.Tropsha [28], using the following equation [29]:

$$r_m{}^2 = r^2\left(1 - \sqrt{r^2 - r_0{}^2}\right) \quad \text{(Eq.1)}$$

$$r_m{}'^2 = r^2\left(1 - \sqrt{r^2 - r_0{}'^2}\right) \quad \text{(Eq.2)}$$

$r_m{}^2$ and $r_m{}'^2$ are a validation metrics parameters and cross validation leave one-out predicted values with:

r^2: Squared correlation coefficient value between predicted and experimental activity values.

$r_0{}^2$: Squared correlation coefficient value between predicted versus and zero intercept.

$r_0{}^{2'}$: Squared correlation coefficient value between experimental versus and zero intercept.

to calculate r02and r02' we must use the following equations [30]:

$$r_0{}^2 = 1 - \frac{\sum(\tilde{y}_i - y_i{}^{r_0})^2}{\sum(\tilde{y}_i - \bar{\tilde{y}})^2} \quad \text{(Eq.3)}$$

$$r_0{}'^2 = 1 - \frac{\sum\left(y_i - \tilde{y}_i{}^{r_0}\right)^2}{\sum(y_i - \bar{y})^2} \quad \text{(Eq.4)}$$

The regression of $\tilde{y}$ versus y is equal to 1. A real QSAR model may have a great predictive ability if it is close to the ideal value [31]. This can imply that the correlation coefficient R between the actual y and predicted $\tilde{y}$ activities must be close to 1 and regressions of y against $\tilde{y}$ or $\tilde{y}$ against y through the origin, i.e. $y_i{}^{r_0} = K\tilde{y}_i$ and $\tilde{y}_i{}^{r_0} = k'y_i$, respectively [32]. But, should be characterized by at least either k or k' close to 1. Slopes k and k' are calculated as follows [28]:

$$k = \frac{\sum y_i \tilde{y}_i}{\sum \tilde{y}_i{}^2} \quad \text{(Eq.5)}$$

$$k' = \frac{\sum y_i \tilde{y}_i}{\sum y_i{}^2} \quad \text{(Eq.6)}$$

In the external validation, we calculated the coefficient of determination R, and also we applied the Toubsha and Glbraikh criteria on the set of tests to give rigidity and reliability for our model [33].

2.6. Docking validation protocol

Molecular docking is a study validation method that consists in studying the type of interactions between the ligand and the biological target and also studying the affinity and the stability of the ligand inside the target protein

recognition site [25] and also for validating the contour map results of the CoMFA and CoMSIA approaches, for this we have applied the Sybyl-X software 2.00 The stages of preparation of ligands and proteins for the docking protocol were carried out in the Sybyl-X tools. 2.00, with a Threshold of 0.50 and a Bloat of 1A, the bioactive conformations were simulated at pyMol [34]. The results were analyzed using Discovery studio 2016 software [35].

2.7. In silico pharmacokinetics ADMET and drug-likeness prediction

The procedure of new drug discovery with computer tools and drug similarity are important and necessary steps to evaluate proposed new drugs with computational chemistry [36,37].

ADMET and Drug Similarity is developed for the estimation of physicochemical and pharmaceutical parameters and drug similarity. This study does not only allow us to know the adsorption percentage. the distribution. but also, parameters related to metabolism and excretion in humans. as well as toxicity [38]. Its absorption in the human intestine. penetration of the blood-brain barrier and the central nervous system. metabolism refers to the chemical biotransformation of a drug by the body. total drug clearance and drug toxicity levels [39]. The prediction of drug-similarity of designed drugs was assessed by rules based on Lipinski, Ghose, Veber and Egan [40].

3. Materials and methods

3.1. Molecular alignment

Molecular alignment is an axial step in the 3D-QSAR study, we have chosen the 4p molecule which is the highest biological activity of the series studied, as a model structure to align our series of molecules and also to visualize the contours [41], and to help us visualize contour maps in 3D-QSAR studies (Figure 1). The model uses the alignment method based on the best-anchored conformation of the product 4p.

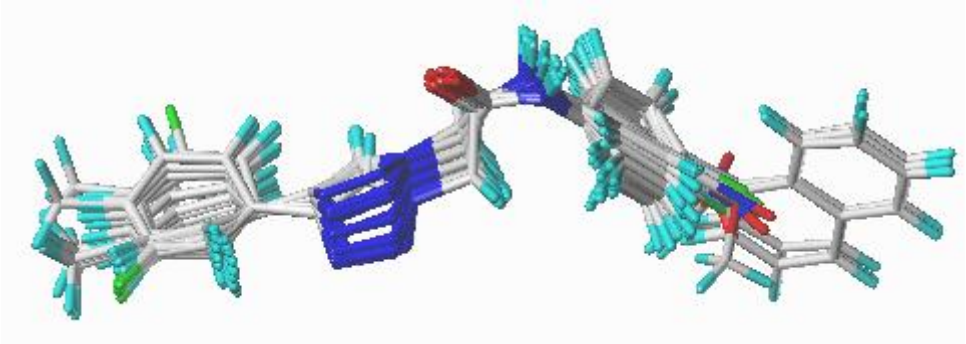


Figure 1. Superposition and alignment of studied compounds using compound 4p as a template

3.2. CoMFA and CoMSIA Result

We have developed 47 models using the PLS statistical method of the CoMFA and CoMSIA models (Table 3). According to the analysis of the CoMFA and CoMSIA results, we note that two models among the 47 models before the results, the first model is the CoMFA model which is the best model of the prediction of the antimicrobial activity of the molecules studied by the CoMFA model [42], because of the more predictive is carried out by a minimum number of compounds equal to 3 with a coefficient of determination equal to (R = 0.97) and a significant value of cross-validation (LOO) equal to (Q^2 = 0.71) and the Fisher test equal to (t-F131.82) with the contributions of the steric parameters 56.1% and electrostatic 43.9%. The second model, CoMSIA / HA shows very significant statistical results with a coefficient of determination and cross-validation values Q^2 (LOO) respectively of (R = 0.94), (Q^2 = 0.68), the hydrophobic contribution and acceptor being respectively 47.8%, 52.2% In addition, a large value of the test parameter File (t-F = 62.9) and a small value of SEE is (SEE = 0.07).

Table 3. ***The PLS statistical results of 47 models by CoMFA and CoMSIA***

	R^2	EES	F	Q^2	Ster	Wlect	Don	Acc	Hyd	NOC
CoMFA	0,971	0,055	131,82	0,712	0,561	0,439				3
CoMFA	0,922	0,086	76,377	0,562	0,564	0,436				2
DHSAE	0,904	0,099	37,47	0,619	0,093	0,24	0,095	0,288	0,284	3
DHSAE	0,852	0,118	37,522	0,608	0,089	0,251	0,097	0,297	2,66	2
DHSA	0,905	0,099	38,072	0,598	0,122		0,121	0,398	0,359	3
DHSA	0,837	0,124	33,387	0,598	0,117		0,133	4,1	0,34	2
DHSE	0,889	0,107	32,195	0,592	0,131	0,374	0,124		0,371	3
DHSE	0,827	0,128	30,971	0,592	0,124	0,379	0,139		0,358	2
DHAE	0,84	0,123	43,01	0,598		0,277	0,108	0,327	0,288	2
DHAE	0,906	0,098	38,651	0,598		0,261	0,108	0,314	0,317	3
DSAE	0,88	0,111	29,255	0,61	0,137	0,33	0,144	0,389		3
DSAE	0,811	0,134	27,923	0,587	0,118	0,341	0,146	0,396		2
HSAE	0,926	0,088	49,779	0,657	0,099	0,255		0,333	0,312	3
HSAE	0,895	0,1	55,249	0,649	0,102	0,27		0,312	0,317	2
DHS	0,866	0,117	25,834	0,565	0,22		0,218		0,563	3
DHS	0,787	0,142	24,02	0,565	0,189		0,283		0,527	2
DHA	0,908	0,097	39,412	0,584			0,143	0,445	0,412	3
DHA	0,822	0,13	29,956	0,584			0,159	0,464	0,377	2
DHE	0,892	0,106	32,961	0,573		0,425	0,145		0,43	3
DHE	0,81	0,134	27,683	0,573		0,432	0,171		0,397	2
HSA	0,937	0,08	59,936	0,661	0,125			0,488	0,387	3
HSA	0,896	0,1	55,862	0,65	0,138			0,445	0,417	2
HSE	0,912	0,095	41,583	0,675	0,15	0,449			0,401	3
HSE	0,87	0,111	43,369	0,675	0,141	0,436			0,423	2
SAE	0,91	0,096	20,31	0,688	0,185	0,37		0,445		3
SAE	0,865	0,113	41,533	0,637	0,156	0,393		0,451		2
DES	0,876	0,113	28,264	0,556	0,219	0,57	0,211			3
DES	0,784	0,143	23,606	0,554	0,182	0,563	0,255			2
DAE	0,873	0,114	27,442	0,578		0,378	0,177	0,446		3
DAE	0,791	0,141	24,626	0,571		0,382	0,177	0,441		2
DH	0,868	0,117	26,298	0,53			0,279		0,721	3
DH	0,762	0,15	20,794	0,53			0,371		0,629	2
DS	0,842	0,128	21,315	0,494	0,534		0,466			3
DE	0,874	0,114	27,87	0,517		0,718	0,282			3
HS	0,889	0,102	35,626	0,648	0,284				0,716	3
HS	0,844	0,122	35,216	0,648	0,263				0,737	2
HA	0,94	0,078	62,902	0,683				0,552	0,478	3
HA	0,898	0,098	57,496	0,649				0,509	0,491	2
HE	0,922	0,09	47,123	0,568		0,527			0,473	3
HE	0,874	0,109	45,188	0,568		0,449			0,501	2
SA	0,859	0,116	39,515	0,636	0,227			0,745		2
SA	0,901	0,101	36,283	0,7	0,305			0,695		3
SE	0,889	0,107	31,882	0,645	0,288	0,712				3
SE	0,859	0,116	39,668	0,645	0,263	0,737				2
DA	0,856	0,122	23,808	0,565			0,272	0,728		
DA	0,765	0,149	21,17	0,543			0,31	0,69		

R2: Non-cross-validated correlation coefficient; Q2: Cross-validated correlation coefficient.; rext2: External validation correlation coefficient; N: Optimum number of components; SEE: Standard error of the estimate

From Table 3, we can check the validation of the CoMFA and CoMSIA / H-A model. Thus, all the statistical parameters show a high estimate of the stability and favorable predictive quality of these models [42]. We have calculated the statistic parameters of the extern validation for the two models According to Golbatikh and Tropsha [43], the CoMSIA / HA and CoMFA models successfully verify all the statistical criteria of K. Roy, A. Golbatikh, and A. Tropsha [29] (Table 4).

Table4. ***Statistical parameters for the validation of the CoMSIA/H-A and CoMFA model.***

Parameters	Equations	Model score CoMFA	Model score CoMSIA/H-A	Threshold
R^2_{test}	$1-\frac{\sum(Y_{obs(test)}-Y_{(test)})^2}{\sum(Y_{obs(test)}-\overline{Y_{obs(test)}})^2}$	0.96	O.87	>0.50
$\overline{r_m}\ test$	$\frac{\lvert r_m^2-r_m'^2\rvert}{2}$	0.771	0.58	>0.50
$\Delta\ r^2_{test}$	$\lvert r_m^2-r_m'^2\rvert$	0.097	0.10	<0.20
$\Delta\ r^2_{0\ test}$	$\lvert r_0^2-r_0'^2\rvert$	0.074	0.22	<0.30
$(r^2-r^2_0)/\ r^2$	$\frac{\lvert r^2-r_0^2\rvert}{r^2}$	-0.007	-0.098	<0.10
$(r^2-r'^2_0)/\ r^2$	$\frac{\lvert r^2-r_0'^2\rvert}{r^2}$	0.04	0.88	<0.10
K	$\frac{\sum Y_{obs}Y_{calc}}{\sum Y_{calc}^2}$	0.957	0.99	O.85≤K≤1.15
K’	$\frac{\sum Y_{obs}Y_{calc}}{\sum Y_{obs}^2}$	1.044	1.00	O.85≤ K’≤1.15

3.3. y-randomization test

As a supplement to the validation of our CoMFA reliability models. we calculated the y-randomization test [44]. The latter consists in randomly mixing the descriptors and the activities between the compounds and in redoing the calculations of the statistical parameters. And if these static randomization parameters are equal to or greater than that of the chosen model. then the model is unacceptable. We have applied this technique 10 times on our model (Table 5.6). we have used the following online tool http://dtclab.webs.com/software-tools and no test exceeds our table of statistical parameters and therefore the model chosen is a (Table 5, 6).

Table 5. ***Results of the y-randomization test.***

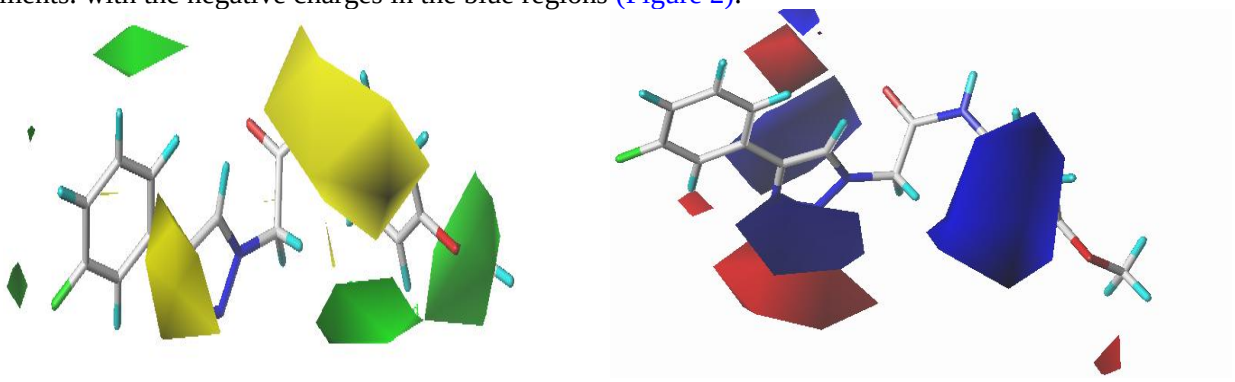
Model	R	R^2	Q^2
Original	0,951	0,974	0,68
Random 1	0,334	0,111	-0,052
Random 2	0,204	0,041	-0,133
Random 3	0,242	0,058	-0,142
Random 4	0,265	0,070	-0,08
Random 5	0,243	0,059	-0,131
Random 6	0,245	0,060	-0,114
Random 7	0,356	0,127	-0,033
Random 8	0,264	0,069	-0,084
Random 9	0,246	0,060	-0,128
Random 10	0,186	0,034	-0,145

Table 6. ***Random Models Parameters***

Average r :	0,259
Average r^2:	0,069
Average Q^2:	-0,105
cRp^2:	0,519

3.4. Graphical interpretation of CoMSIA/H-A and CoMFA models

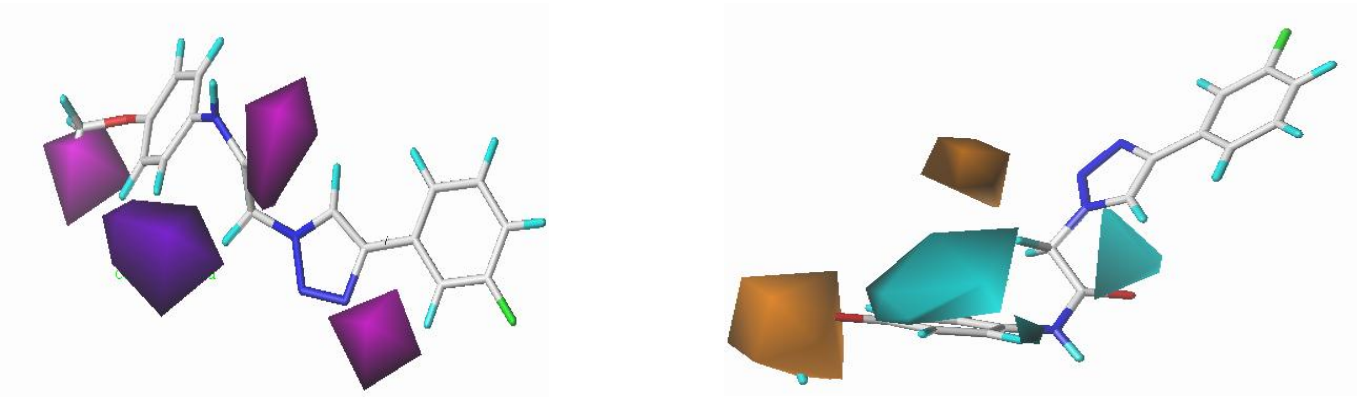
The contours of blue color are representing the favorable electrostatic interactions with a contribution of 80% and the green color presents the favorable steric interactions with a contribution of 80% of CoMFA while the adverse interactions for the steric and electrostatic interactions are represented by regions green and yellow respectively. The blue contours indicate that the biological activity augments with the positive charges in the blue regions and also augments. with the negative charges in the blue regions (Figure 2).



a b

Figure 2. (a) Steric and (b) Electrostatic Contour maps of CoMFA analysis with 2 Å grid spacing in combination with compound 4p.

Figure 3 shows the magenta contours which represent the favorable acceptor interactions with a contribution of 80% therefore the biological activity increases by the increase of the hydrogen acceptor molecules. the cyan color presents the favorable hydrophobic interactions with a contribution of 80% of CoMSIA therefore the increase of the biological activity is done by the hydrophobic group. while the unfavorable interactions for the acceptor and the hydrophobic interactions are represented by the regions respectively colored purple and orange.



(C) (d)

Figure 3. (c) acceptor and (d) hydrophobic Contour maps of CoMSIA/H-A analysis with 2 Å grid spacing in combination with compound 4p.

3.5. Molecular docking

Molecular docking analysis is used in this work to analyze the stability of the ligand within the active site (PDB: 3G7B) of the PC-3 cell line of the agent proteins. has been identified with residues such as Asn54; Asp81; Arg84; Gly85; Ile86; Pro87; Ile102; Arg144; Thr173 in previous studies and the X-ray crystallographic structure [14]. Figure

4 shows the interactions between the active site and the most active compound, while Figure 5 shows the interactions between the least active compound and the active site of proteins.

In the docking analysis, it was found that the most active compound 4p of the series studied interacts with the active site with hydrogen bond-like interactions with amino acid Gly85 and Arg144 with hydrogen group N of the triazole ring (Table 7) the ligand 4p has a very high total score value by addition to the least active ligand 4c (Table 7), we also observe Van der Waals type interactions with Asp81 and Thr173 and two Pi-sigma interactions with Ile102 and Cys44. The less active ligand 4c exhibits a Pi-donor Hydrogen-Bond interaction Thr173 and the Amide Pi-stacked interaction with Gly85. and a classical Pi-sigma interaction with Ile85 (Table 7).

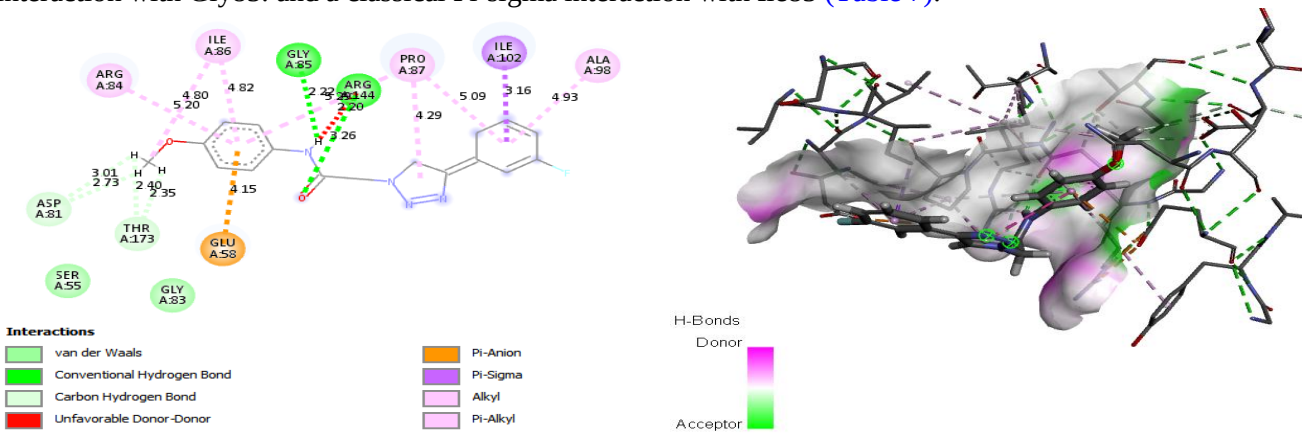


Figure 4. Types of interactions between the PC-3 cell receptor (PDB: 3G7B) and the most active derivative active 4p (pMIC=7.77).

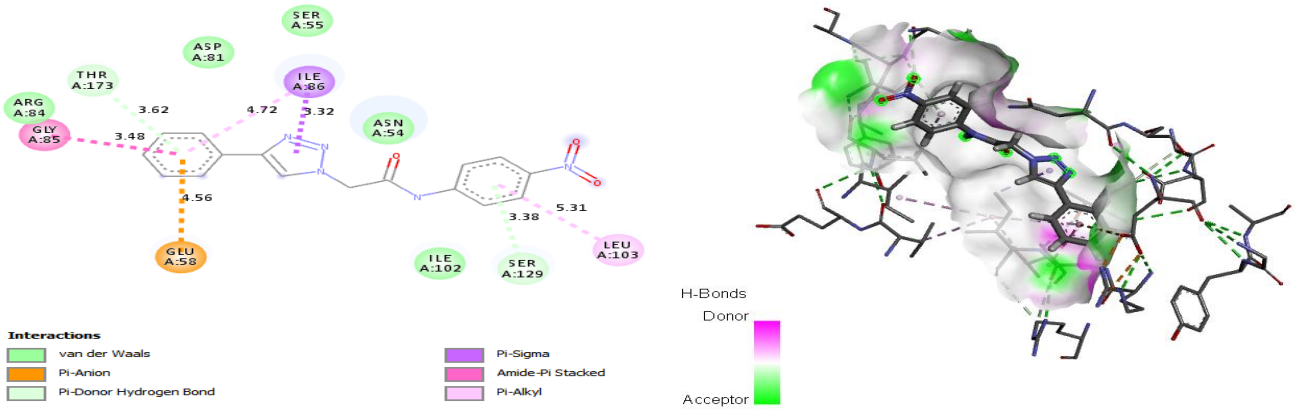


Figure 5. Types of interactions between the PC-3 cell receptor (PDB: 3G7B) and the lower derivative active 4c(pMIC=6.67).

Table 7. ***type of interaction and total score of the most active derivative 4p and the most lower active derivative 4c***

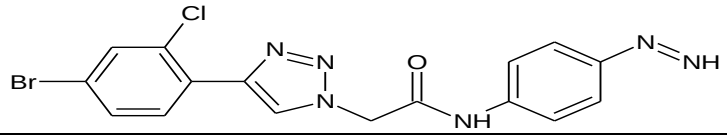
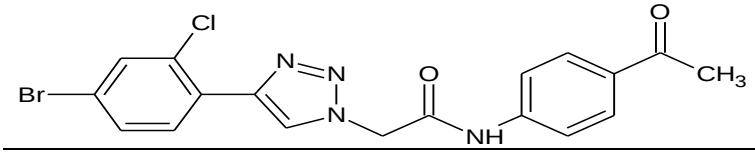
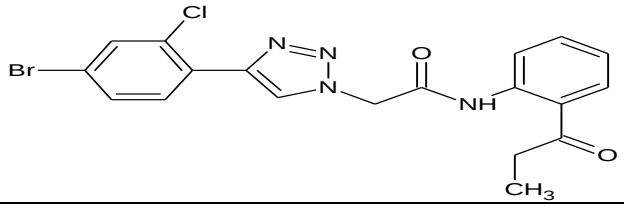
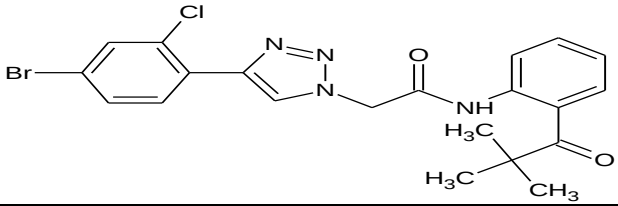
	4p		4c	
active site amino acid	**type of interaction**	**Total Score**	**type of interaction**	**Total Score**
Asn54	No	2.674	Van der Waals	2.544
Asp81	Van der Waals		No	
Arg84	Pi-alkyl		No	
Gly85	Conventional Hydrogen Bond		Amide-Pi stacked	
Ile86	Pi-alkyl		Pi-sigma	
Pro87	Pi-alkyl		No	
Ile102	Pi-sigma		Pi-sigma	

Arg144	Conventional Hydrogen Bond	No
Thr173	Van der Waals	Pi-Donor Hydrogen Bond

3.5. Design of new compounds

The objective of this work is to propose new anticancer agents for the PC-3 cells responsible for Urinary tract cancer. following the analysis of the results of the study of the electrostatic and steric CoMFA QSAR contours and the Docking study of the as the most active ligand 4p, we have proposed 4 novel agents for cancer inhibition of Urinary tract cancer. In this study. 4 compounds of 1.2.3-triazole derivatives were proposed as novel anti-microbial agents responsible for cancer of the Urinary tract. These compounds are aligned in Sybyl-X. and we have chosen compound 4p as structure common. we studied the activity of the 4 compounds proposed by the predictivity of the CoMFA model (Table 8).

Table 8. ***predicted pMIC based on CoMFA model for newly designed compounds***

Compound	pMIC
X1 	8,30
X2 	8,17
X3 	7.91
X4 	7,88

3.7 ADMET prediction and drug-likeness

In this study, we calculated the pharmacokinetic parameters ADMET (Absorption, Distribution, Metabolization, Excretion, and Toxicity) and drug similarity for the 4 proposed compounds and the 4p reference molecule. For in-silico calculators of the proposed molecules, the online tool SuissADME [45] was used to predict drug similarity properties, and the online pKCMS [46] was chosen to predict ADMET parameters [47].

The value of the volume of distribution and the blood-brain barrier (BBB), the LogBB are compared with the literature. The central nervous system (CNS) is characterized by the parameter of LogPS. If this value must be between -3 and 2, for LogPS values greater than 2 the molecules are considered to penetrate the CNS, as well as

LogPS values less than -3 the molecules are difficult to move inside the CNS. central nervous system [48,49]. Cytochrome P450 (CYP450) is an enzymatic metabolism that can catalyze the chemical biotransformation of drugs therefore it is very important in drug metabolism as it is the essential liver enzyme system involved in phase 1 metabolism (oxidation). There are 57 CYP genes from 17 families that have been identified in humans, but only the CYP1, CYP2, CYP3, and CYP4 families are involved in drug metabolism, CYP (1A2, 2C9, 2C19, 2D6, and 3A4) being responsible for the biotransformation of more than 90% of drugs in phase I metabolism[50,51]. However, among these families, CYP3A4 is the most important inhibition in this study [52]. All of the newly designed compounds are CYP3A4 substrates and inhibitors.

Table 9. ***Prediction of drug similarity of the 21 compounds based on Lipinski, Veber, Veber, and Egan, and their synthetic accessibility***

Compound	Lipinski	Veber	Egan	Muegge	Synthetic accessibility
4f	Yes	Yes	Yes	Yes	2.70
X1	Yes	Yes	Yes	Yes	3.01
X2	Yes	Yes	Yes	Yes	2.97
X3	Yes	Yes	Yes	Yes	3.11
X4	Yes	Yes	Yes	No	3.33

Table 10. ***In silico ADMET prediction of newly designed compounds***

	Absorption		Distribution		Metabolism							Excretion	Toxicity
					substrate			Inhibitor					
					Cyp	Categorical (Yes/No)							
Compound	Intestinal absorption (human) Numeric (% Absorbed)	VDSS (human) Numeric (Log L/kg)	BBB permeability Numeric (Log BB)	CNS Permeability Numeric (Log PS)	2D6	3A4	1A2	2C19	2C9	2D6	3A4	Total clearance Numeric (Log ml/min/kg)	AMES Toxicity Categorical (Yes/No)
4f	92%	-0.469	0.788	-2.023	No	Yes	Yes	Yes	No	No	Yes	0.052	No
X1	88.19%	-0.319	-0.833	-1.991	No	Yes	Yes	Yes	Yes	No	Yes	0.091	No
X2	91.12%	-0.532	-0.747	-2.029	No	Yes	Yes	Yes	Yes	No	No	-0.081	No
X3	91.5%	-0.37	-0.648	-1.991	No	Yes	No	Yes	Yes	No	Yes	0.228	No
X4	92.44%	-0.363	-0.494	-1.667	No	Yes	No	Yes	Yes	No	Yes	0.179	No

Conclusion

To design new antimicrobial inhibitors, 3D-QSAR technique was performed to statistically study the relationship between structure and activity of reported 1,2,3-triazole inhibitors. Using a set of tests, we performed a 3D-QSAR and Molecular Docking, and ADMET study. In this study, we calculated 43 predictive models of antimicrobial activity, among them we chose a CoMFA model, this choice of model was tested by several types of validation such as internal validation (R^2, R, Q^2, SEE, t-F), external validation (R_{test}, R^2_{test}, the criteria of A. Golbraikh, A. Tropsha,) and the y randomization technique, which indicates good predictability. The results of the molecular docking between the most active molecule (4p) and the least active molecule (4c) showed that the 1,2,3-triazole derivatives act on the active site of PC-3. with interactions of the type (Van der Waals, Conventional Hydrogen Bond, Carbon Hydrogen Bond) of the ligands and the active site of PC-3, which were in good agreement with the chemical characteristics of 1,2,3-triazole revealed by the contour map analysis. These results also showed that the type of interaction attached is a very important role in the validation of antimicrobial agents. Moreover, the analysis of Molecular Docking and CoMFA

contour results allows us to propose 4 new inhibitors with very high pMIC, these results can be used as antimicrobial inhibitors. In addition, each engineered compound was subjected to ADMET standard pharmacokinetic parameter calculations to assess drug-like capability. These new compounds show high reliability in terms of antimicrobial biological activity and also meet most of the parameters of the in silico ADMET and Drug-likeness methods. Finally, these new antimicrobial agents proposed in this research could be good drug candidates for the treatment of urinary tract cancer due to the microbial effect of E. Coli.

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