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Molecular Modeling and Biological Activities of New Potent Antimicrobial, Anti-Inflammatory and Anti-Nociceptive of 5-Nitro Indoline-2-One Derivatives

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Abstract

In recent years, molecular modeling has become an important technique for drug discovery and pharmaceutical science. The objective of this study is to determine the molecular modeling of the antibacterial, anti-inflammatory and anti-nociceptive activities of a new series of pyrazoles, oxadiazoles and sugar hydrazines of 5-nitroindolin-2-one derivatives. The molecular modeling protocol was applied using the MOE (Molecular Operating Environment) software. Synthetic compounds 1, 3, 8, 9, 10 and 12 were the most active compounds, as antibacterial, anti-inflammatory and anti-nociceptive activities were studied for the binding affinity of the cyclooxygenase1 (COX1), The glucocorticoid receptor (GR), the cytochrome P450 receptor of 14alfa-sterol demethylases (CYP51) and the dihydroprotease synthase receptor. Molecular modeling studies revealed that the [(methylbenzyl)-5-nitro-2-oxoindolin-3-ylideneamino-benzohydrazide derivative (3) gave a score of (-15.8587 kcal/mol), while 1,3,4-oxadiazol-2-yl) phenylimino)-1-(methylbenzyl)-5-nitroindolin-2-one derivative (9) gave a higher score (-16.8038 kcal/mol) than flucanazole Co-crystallized gave a score of (-10.2837 kcal/mol). However, the compound (12), D-Arabinose-(methylbenzyl)-5-nitro-2-oxoindolin-(3-ylideneamino) hydrazone derivative gave a score of (-24.6577 kcal/mol) greater than the co-crystallized ligand which gave a score of (-16.6717 kcal/mol).

Keywords: Molecular modeling; Co-crystallized ligand; Scoring functions; Optimization; Molecular Operating Environment MOE; Drug design

Introduction

The application of molecular modeling approaches for drug discovery is provided for novel therapeutic targets for drug discovery. Molecular modeling is a technique providing the energy of interaction between two molecules; this approach has several recent methods used recently in pharmaceutical applications and drug discovery [1]. It is used to allow the binding affinity of small molecule candidate drugs to their protein targets in order to improve the affinity and activity of small molecules. Molecular modeling techniques are powerful in elucidating the different physical, chemical and biological properties of large molecules and interactions [2,3]. In recent years, new drugs are developed from a process of trial phases in the procedure, including several computer systems developed depend on the design based on the structure of the protein and the targets are used to discover new candidates for therapeutic applications [4-9].

In addition, the physical and chemical properties of the synthesized compounds are derived from oxadiazole as antibacterial, anti-*Trypanosoma cruzi* and antifungal using the molecular modeling techniques that leads to more biological activity [10]. On the other hand, the quantitative structure-activity relationship (3D-QSAR) based on both the pharmacophore and the docking alignments. This method has been used successfully to assist in the design of new small molecule candidates and to investigate the mechanism of ligand-protein interaction [11,12].

Materials and Methods

In the present study the tested compounds 1, 3, 8, 9, 10 and 12 were allowed; 3D conformations and reduction of the energy to be minimized were determined using ChemBioOffice V12 and Merifom Merck Molecular Force Field function, with a maximum number of iterations of 500 and a minimum of 0.1 RMS gradients [13]. The PharmMapper service was used to predict targets based on the Pharmaparget db database containing 7000 pharmacophores based on a set of 1500 drug targets [14]. The procedure was followed using the standard protocol set on SurFlex-dock and the geometry of the result was studied using the SurFlex-dock Pose Viewer installation.

This study aims to model the optimization of the tested compounds for more potent inhibitors using the protocol steps that was developed by the MOE operating environment software [15] and to reducing the minimum energy of the tested compounds in the field of the fmmf-Hamiltonian-Force94x, followed by systematic conformational research (RMS gradient 0.01), the best 30 were stored in the database format (PDB2Oye) [16].

Active site Finder tool of MOE was used to identify and calculate active sites in the receptor molecule from the 3D atomic coordinates of the receptor. By default, all calculated sites were appeared as selected. Before the docking a database of these ligands was prepared using MOE.. These sites were refined with the help of the global handheld from the preliminary docking of the tested compounds,

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where the pocket that gave the largest installed group of docked was chosen as a pose in a pocket. Combined with a function score can be used to screen a large database of potential drugs *in silico* to identify molecules to bind to the target protein involved. This information can then be used to design more selective and potent analogues [16-19].

Results

In the present work, the most active compounds are ethyl 4-(5-nitro-2-oxoindolin-3-ylideneamino) benzoate derivative (**1**), [(methylbenzyl)-5-nitro-2-oxoindolin-3- ylideneamino)] benzohydrazide derivative (**3**), (5-oxo-4,5-dihydro-1H-pyrazole-1-carbonyl) phenylimino)-1-(methylbenzyl)-5-nitroindolin- 2-one derivative (**8**), (1,3,4-oxadiazol-2-yl)phenylimino)- 1-(p-methylbenzyl)-5-nitroindolin-2-one derivative (**9**), D-Glucose-(methylbenzyl)-5-nitro-2-(oxoindolin-3-ylideneamino) hydrazone derivative (**10**) and D-Arabinose-(methylbenzyl-5-nitro-2-oxoindolin-3-ylideneamino) hydrazone derivative (**12**) which were published in part I and II in *EPJ* [20,21] were docked using a rigid receptor/fexible ligand approach adopting five energy maps which are: hydrophobicity, electrostatics, formation of the hydrogen bonding and Van der Waal parameters. The docking scores were illustrated in negative energy terms; the lower part of the energy binding and the best binding affinity. The results depend on a statistical evaluation function according to which the interaction energy in numerical values as docking scores. The 3D pose of the ligand installation can be visualized using different visualization tools that could help visualize the best fit of the ligand. The protein-ligand interactions demonstrate the active site of the protein molecule and provide all available information on the target (receptor) and ligands.

In addition, the results are also analyzed by a statistical function score that converts energy into interaction and then into numerical values called docking scores; and also the interaction energy is calculated. The 3D pose of the bound ligand can be visualized using different visualization tools that could aid in interaction of ligands. The prediction of the protein-ligand interaction mode can take into account the active site of the protein and further help the protein – ligand of the molecules.

To validate the precision of the program used the docking of the native co-crystallized IM8 ligand which is done in its site of fixing of cyclooxygenase (COX1). The ligand docked set was superimposed at the native co-crystallized with 0, 6697 RMSD Å and the binding energy (-16.0084 kcal/mol). The hydrogen bonds between the ligand and the docked of amino acids are the same as those between the ligand and the amino acids.

Discussion

The structure-based design begins by identifying a potential ligand binding site on the target molecule. The target site is a pocket with a variety of potential hydrogen bond donors and acceptors, hydrophobic characteristics and molecular surface sizes.

The docking process involves several basic steps for the prediction of ligand conformation as well as its position and orientation in its site called pose and the evaluation of binding affinity. These steps are related to the synthesized compounds tested, scoring and to the rating and optimization process.

Docking by the MOE program provides a correct conformation of the ligand in order to obtain a minimum energy structure. After docking, the S score was considered the criteria for selecting the best

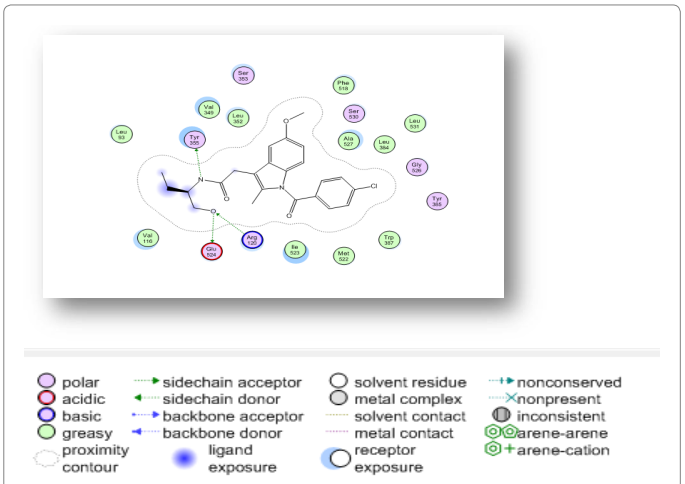

Figure 1: The interaction of the ligand and the binding to the mode of the native ligand IM8 (2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-1-(HYDROXYMETHYL)-PROPYL]-ACETAMIDE) with Cyclooxygenase 1, two donor H- donors were shown with TYR 355 at distance 1.93, GLU 524 at distance 1.94 and H-bonding acceptor with Arg 120 at The distance 2.76 and showed the green color as hatched line and gave a score of (-16.6717).

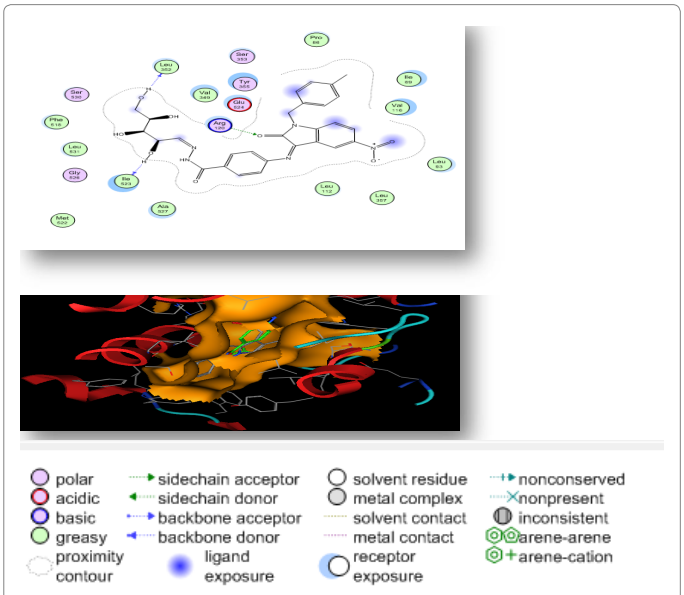

Figure 2: The superimposed compound 12 as a green color with the co-crystallized ligand IM8 as a gray color. Docking of the compound 12 with the cyclooxygenase 1 receptor showed an H-binding donor with LEU 352 at distance 2.12, a H-binding donor with ILE 523 at distance 3.22, an acceptor of Hydrogen bond with ARG 120 at the distance 3.10, formed hydrogen bonds as blue color and showed as hatched line, compound 12 gave a score of (-24.6577) greater than the co-crystallized ligand.

conformation and these were then studied to analyze the hydrogen / π-π bond interactions through the MOE tool.

Firstly, for the anti-inflammatory activity, the synthesis compounds were tested for the binding affinity of cyclooxgenase 1 (pdb 2oye) [22]. The optimization of the process duo to the interaction between compounds 1, 3, 8, 9 and 12 and the COX1 receptor was shown in Figures 1-3.

Prostaglandin endoperoxide synthase (PTGS) is the key to the

enzyme in prostaglandins biosynthesis. It converts the free arachidonic acid, released by membrane phospholipids, to the ester binding sn-2 site by the enzymatic activity of the phospholipase A2 to prostaglandin (PG) H2. The tested compounds were at least one hydrophobic aryl (R), an electron donor and a hydrogen acceptor/donor unit (HAD). The bond angles and lengths are close to the optimum value, and the proposed structures of the tested compounds are acceptable. The docking results were first evaluated on the basis of energy and the structure with the lowest total binding energy was chosen from the simulated models presented for each compound tested.

The structure with the lowest total binding energy was chosen from the simulated models presented for each compound. Each ligand has different potential energy, and the total binding energy of the complex cannot be used to compare the stability of the compounds with different ligands.

Secondly, for the anti-inflammatory activity, the glucocorticoid receptor (GR, or GCR) known as NR3C1 (sub-family of nuclear receptors 3, Group C, Member 1) was investigated. This receptor is used between cortisol and other glucocorticoids for binding. Dexamethasone acts as an agonist for the receptor which provides analgesic activity. The optimization and interaction between compounds 1, 8, 10, 12 and the receptor glucocorticoid were performed (pdb1p93) [23] and the docking protocol is present (Figures 4-6).

In addition, the docking of the precision of the program used to insert the native co-crystallized ligand was performed in its glycocorticoid receptor site binding. The ligand set was superimposed at the native co-crystallized with 0, 5993 RMSD Å and the energy of binding (-29.0660 kcal/mol). The hydrogen bonds between the ligand and the amino acids were the same as those between the ligand and the original amino acids.

Thirdly, for the antifungal activity, docking was performed against the cytochrome P450 14alpha- demethylases sterols (CYP51). These enzymes are fundamental in the biosynthesis of sterols in eukaryotes. CYP51 removes precursors of the 14alpha-methyl sterols from the group such as lanosterol, obtusifoliol, dihydrolanosterol and 24 (28)-methylene-dihydrolanosterol, Inhibitors of CYP51 include triazole derivatives as antifungal agents, fluconazole and itraconazole drugs were used in the treatment of the systemic mycoses for optimization to give the interaction between the compounds **3, 9** and the cytochrome P450 system 14alpha-sterol PDB demethylases PDB code: 1EA1 [24], the docking was compared

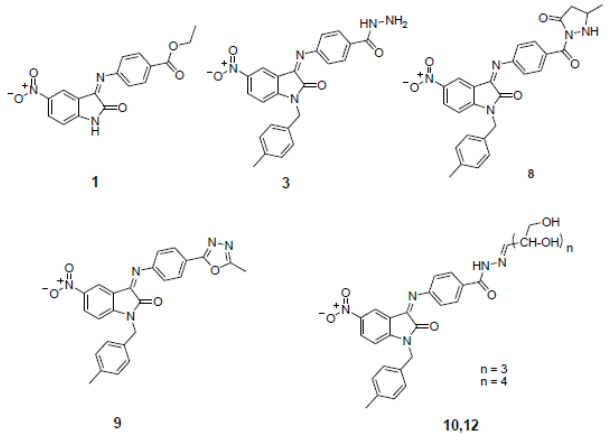

Figure 3: The structures of the activated compounds **1, 3, 8, 9, 10 and 12**.

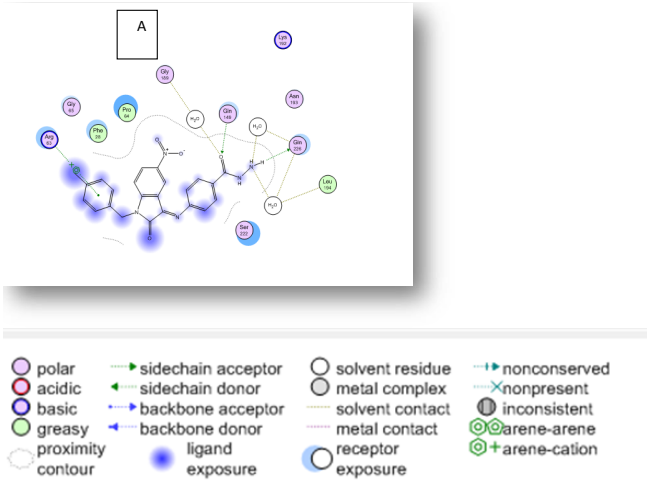

Figure 4: The interaction of the ligand and the mode of binding of the native sulphamethaxazole ligand (O8D), it showed an H-binding donor with HOH 333 at distance 2.76 and was shown in black color, showed H bond with SER 222 at a distance of 2.9 as a blue color and it was bound with the acceptor of an H bond with HOH 289 as a black color and was shown as a hatched line as a co-crystallized ligand.

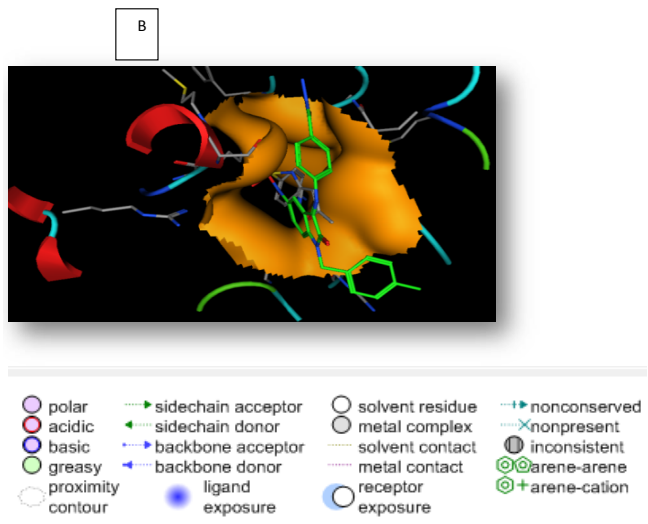

Figure 5: The superposition of the compound 3 as a green color with the co-crystallized sulphametazole ligand (O8D) as a gray color. Docking of compound 3 with the receptor, it was shown that a GLN 226 binding with H-donor at a distance of 2.89 and an H-binding donor with HOH 300 at the distance 2.86 and a donor of H bond with HOH 322 at the distance 2.53 and an H-acceptor HNL 149 at distance 2.56 and an H-bond acceptor with HOH 300 and at distance 2.53 and an H-binding acceptor with HOH 333 at distance 2.82 was shown as a green color and a hatched line as a co-crystallized ligand and gave a score of (-14.9855) greater than the co-crystallized ligand.

with the co- crystalized ligand which was shown in Figures 7-9 and all the results are shown in Tables 1-4.

Fourthly, for the anti-bacterial activity, the docking against the dihydropteroate synthase was carried out. The Antibiotics sulfonamide drugs inhibit the dihydropteroate synthase (DHPS), a key enzyme in the folate pathway of bacteria and eukaryotes. However, the resistance mutations have compromise these drugs, the synthesized of compounds 3 and 9 was studied for receptor affinity for dihydropteroate synthase (pdb 3TZF) [25].

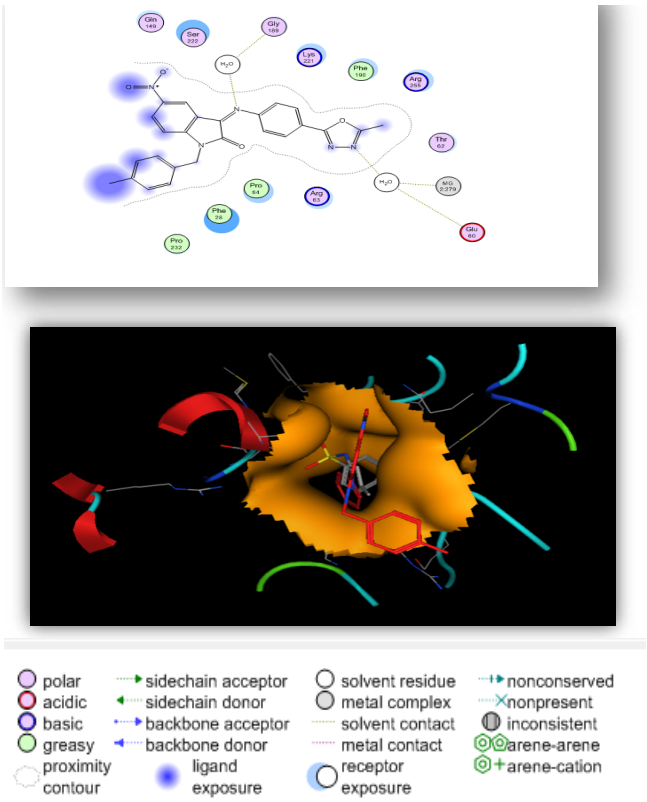

Figure 6: The superposition of compound 9 in red with the co-crystallized sulphametazole ligand (O8D) as a gray color. Docking of compound 9 with the receptor, it has been demonstrated to form an H-binding acceptor with HOH 298 at the distance 2.73 and an H-binding acceptor with HOH 333 at the distance 2.93 and has been shown as a black color and a hatched line as a co-crystallized ligand and received a score of (-14.8474) higher than the co-crystallized ligand.

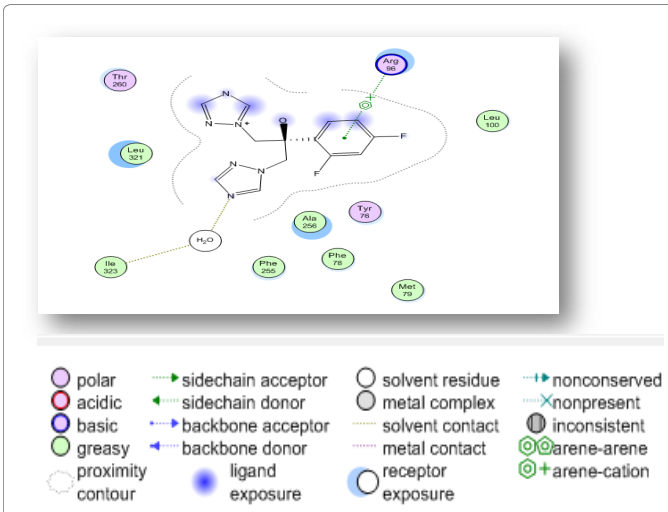

Figure 7: The interaction of the ligand and binding to the native ligand (TPF) mode showed an H-binding donor with HOH 2174 at distance 2.67, which appeared as a black color and as a hatched line.

The flexibility of the protein-ligand program, AutoDock4, has been used to be very useful in determining the binding modes of protein-ligand interactions and has proved very useful in determining the precise binding modes of protein-ligand interactions. The new tested compounds were docked into the binding sites in the proteins, the binding affinity of the tested compounds were calculated. The binding between proteins and ligand were characterized and form good interactions between the binding sites of proteins targets.

This information can in turn be used to design more powerful and selective analogues, docking combined with a scoring function can be used to quickly screen to large databases of potential drugs to identify molecules that can bind to a protein target of interest.

Advances in the fields of biochemistry and molecular biology have been facilitated by developments in the production of a large number of new target biological compounds that can be therapeutically applied to facilitate the discovery of novel therapeutic agents, these rational drug design methods are in combination with structural biology offers great potential activities for new candidates.

The most active compounds **1**, **3**, **8**, **9**, **10** and **12** (Figure 6) were chosen as lead to determine the structural modification in order to obtain new active ligands with an excellent binding ability. The results of docking showed that the importance of the 5-nitro-indoline-2-one derivatives which are connected to the side chain for strong interactions with the active site of the groups.

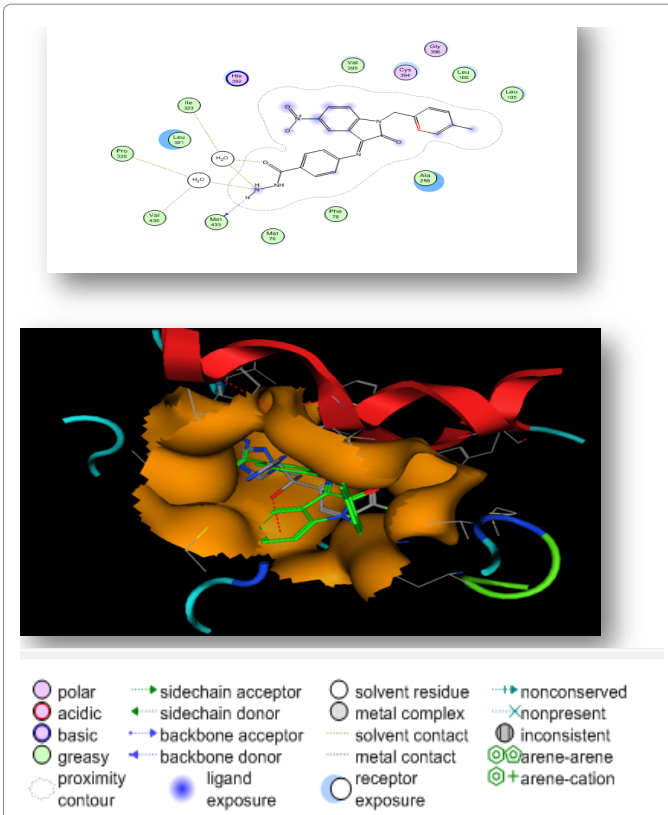

Figure 8: The superposition of compound 3 as a green color and the co-crystallized flucanazole ligand as a gray color and it was associated with HOH 2174 as a co-crystallized ligand. Docking of compound 3 with the receptor showed an H-binding donor with HOH 2174 at the distance 2.78 and the 2H-bond acceptor with HOH 2174 at the distance 2.66, 2.78 and a donor of H-bond with MET 433 at distance 2.19 and HOH 2122 with H-Donor at distance 3.28, it showed as blue and hatched line that the ligand co-crystallized and gave a score of (-15.8587).

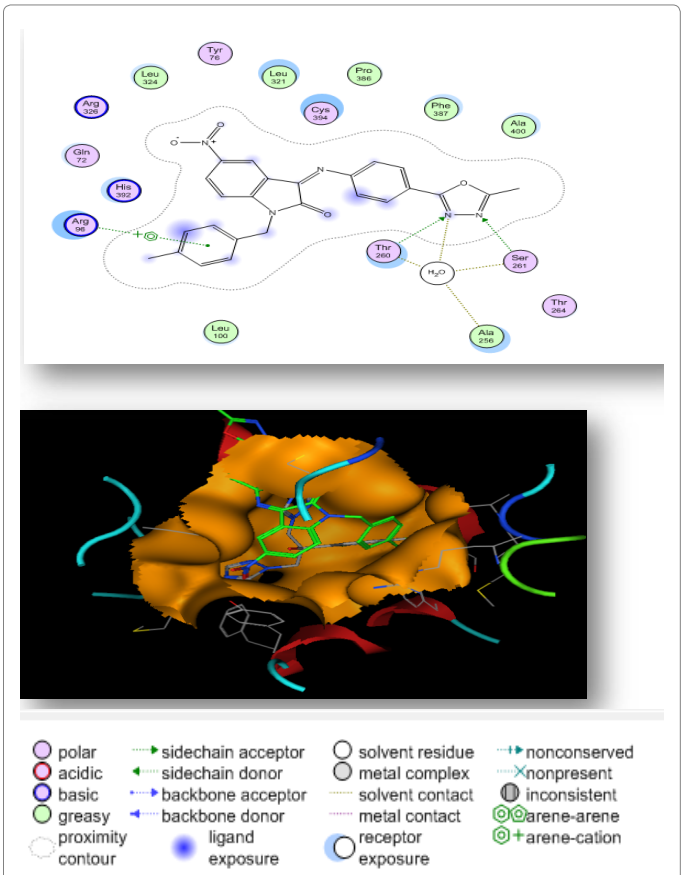

Figure 9: The superposition of the compound **9** as green color and co-crystallized ligand flucanazole as gray color. Docking of compound **9** with receptor, showed one H-bond acceptor with THR 260 at distance 2.76 and one H-bond acceptor with SER 261 at distance 3.06 and one H-bond acceptor with HOH 2090 at distance 3.06 with H-donor, it shown as green color and hatched line as co-crystallized ligand and gave a score of (-16.8038).

Compounds	Docking score	No of H-bond	Residue involved
Ligand	-16.6717	4	TYR 355, GLU 524, Arg 120
1	-12.1638	1	TYR 355
8	-13.2236	1	GLU 120
10	-21.0353	3	MET 522, ILE 523
12	-24.6577	3	LEU 352, ILE 52, ARG 120

Table 1: The docking scores and the interactions of the compounds **1, 8, 10** and **12** to the proposed target receptor Prostaglandine-endoperoxidase synthase (PTGS).

Compounds	Docking score	No. of H-bond	Residue involved
Ligand	-12.288	1	ASN 564
1	-11.914	1	ASN 546
8	-11.3219	1	THR 739
10	-9.31	5	ASP638, THR 73, GLN 642, TYR 735
12	-10.3308	3	TYR 735, ASP 638 ,TYR 735

Table 2: The docking scores and the interactions of the compounds **1, 8, 10** and **12** to the proposed target receptor glucocorticoid.

Compounds	Docking score	No. of H-bond	Residue involved
Ligand	-10.2837	1	HOH 2174
3	-15.8587	5	HOH 2174, MET 433, HOH 2122
9	-16.8038	3	THR 260, SER 261, HOH 2090

Table 3: The docking scores of and the interactions of the compounds **3** and **9** to the proposed target receptor CYP51.

Structure	Docking score	No. of H-bond	Residue involved
Ligand	-14.7560	3	HOH 333, SER, HOH 289
3	-14.9885	6	GLN 226, HOH 300, HOH 322, GLN 149, HOH 300, HOH 333
9	-14.8474	2	HOH 298, HOH 333

Table 4: The docking scores and the interactions of the compounds 3 and 9 to the proposed target receptor dihydropteroate synthase.

In addition, the substituents on the ring also appear to play a role for activity. As well as the position five of substituents at the 5-nitro-indoline-2-one ring were important, other substitutions to the other positions such as p-méthylbenzyle and benzohydrazide groups were investigated.

However, the 5-methyl-1,3,4 oxadiazol and 1H-pyrazole derivatives provided the best activity that due to the terminal aromatic ring, but we believe that the hydrophobic substituents on this ring can have a positive effect on the activity inhibitory. This information can be used in the role of design more selective and powerful design of analogues, combined with scoring function can be used to screen a large databases of drugs to distinguish the molecules that are bind to the protein target of interest. These results are important in the future for the development of new drugs. Recent advances include predicting the relative potency of different forms of innovation drugs.

From the molecular modeling and analysis of the docked results, the binding free energy was used to classify the binding affinity of the synthesis compounds **1**, **3**, **8**, **9**, **10** and **12**. In addition, the hydrogen bonds between the ligands and proteins have been used in the classification of the compounds. The hydrogen bonds have been done by measuring the length of hydrogen bonding. RMSD of the docking pose compared to the co-crystalline ligand position has been used in their classification. The mode of the interaction of the native ligand co-crystallized IM8, sulfamethaxazole, flucanazole in the structure of the cyclo-oxagenase 1 (COX 1), glucocorticoid receptor (GR), Cytochrome P450 14alpha-sterol demethylases receptor (CYP51) and dihydropteroate synthase receptor were used as a model of standard docked as well as for the calculation RMSD. The target molecule should be able to be inhibited by binding a small molecule. Enzymes are also often excellent drug targets because compounds can be designed to fit within the active site pocket.

Conclusion

Drug design is an important part of most industrial drug discovery programs and is the main important research topic for many academic laboratories. Drug design is more powerful when it is part of a complete drug discovery process. Among the discussions in this study, it is mentioned that a different docking score is very useful for determining the binding sites and the different binding modes for a type of ligand-proteins. The objective of the study of molecular modeling is to achieve an optimized conformation for both the protein and the ligand and the relative orientation between the proteins and the ligand and the free energy of the system is reduced to minimzed. Docking was performed on COX 1 for anti-inflammatory activity, glucocorticoid receptor for analgesic, cytochrome P450 for fungi and finally dihydroproterite synthase for antibacterial activity gave the highest activity comparable to the interaction scores and the reference drug that co-crystallized with the receptors. Based on the molecular modeling of compound 3, a score of (-15.8587 kcal / mol) was given, whereas compound 9 gave a (-16.8038 kcal/mol) score higher than that of the co-crystallized allowing a score of (-10.2837 kcal/mol). In addition, docking of compound 12

with cyclooxygenase 1 receptor provided a (-24.6577 kcal/mol) score greater than the co-crystallized ligand which gave a score of (-16.6717 kcal/mol). Concluding remarks would suggest that antibacterial, anti-inflammatory and anti-nociceptive activities of a new series of pyrazoles, oxadiazoles and sugar hydrazines of 5-nitroindoline-2-one derivatives are of great interest in successful chemotherapy.

Conflict of Interest

The authors confirm that the content of the article has no conflict of interest.

Acknowledgement

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