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ORIGINAL ARTICLE / ÖZGÜN MAKALE

DRUG REPOSITIONING APPROACH FOR THE TREATMENT OF ANKYLOSING SPONDYLITIS

ANKİLOZAN SPONDİLİT TEDAVİSİNDE İLAÇ YENİDEN YERLEŞTİRME YAKLAŞIMI

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ABSTRACT

Objective: *In this study, it was aimed to determine an FDA-approved molecule that inhibits the IL-17 receptor, which is an important target for the prevention of inflammation in Ankylosing Spondylitis (AS), using the drug repositioning approach.*

Material and Method: *Using the Drug-Gene Interaction database, 18 molecules specific to the active HLA-B gene were identified in AS. Then, the 3D structure of IL-17 was obtained from the RSCB database. I) Blind docking II) Computed Atlas of Surface Topography of Proteins web tool was used to determine the binding package. The interaction between the known inhibitor of IL-17, rhodomyrtone, and IL-17, was determined by molecular docking using grid boxes around the determined binding packages. Accordingly, configuration files were prepared with the selected grid box features, and docking was performed for 18 molecules with the AutoDock Vina program.*

Result and Discussion: *The carbamazepine molecule shows the best binding affinity and binding profile with IL-17. It was also revealed that minocycline, sulfasalazine, and thalidomide are tightly packed in the active site. It has been demonstrated that these molecules may be lead molecules for the treatment of AS disease.*

Keywords: *Ankylosing spondylitis, blind docking, drug repositioning, IL-17, molecular docking*

ÖZ

Amaç: *Bu çalışmada, AS'de inflamasyonun önlenmesinde önemli bir hedef olan IL-17 reseptörünü inhibe eden FDA onaylı bir molekülün ilaç yeniden konumlandırma yaklaşımı kullanılarak belirlenmesi amaçlanmıştır.*

Gereç ve Yöntem: "*Drug-Gene Interaction" veritabanı kullanılarak AS'de etkin HLA-B genine özgü 18 molekül belirlenmiştir. Ardından IL-17'nin 3D yapısına RSCB veri tabanından ulaşılmıştır. Bağlanma paketinin belirlenmesi için I) Kör kenetlenme II) "Computed Atlas of Surface Topography of Proteins" web aracı kullanılmıştır. Belirlenen bağlanma paketleri çevresindeki grid kutuları kullanılarak IL-17'nin bilinen*

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inhibitörü rhodomyrtone ile IL-17 arasındaki etkileşim moleküler doking ile belirlenmiştir. Buna göre seçilen grid kutusu özellikleri ile konfigürasyon dosyaları hazırlanarak 18 molekül için de AutoDock Vina programı ile doking gerçekleştirilmiştir.

Sonuç ve Tartışma: *Karbamazepin molekülü, IL-17 ile en iyi bağlanma afinitesini ve bağlanma profilini göstermiştir. Ayrıca minosiklin, sülfasalazin ve talidomidin moleküllerinin de aktif bölgede sıkıca paketlendiği ortaya çıkmıştır. Bu moleküllerin AS hastalığının tedavisi için bir öncü molekül olabileceği gösterilmiştir.*

Anahtar Kelimeler: *Ankilozan spondilit, IL-17, ilaç yeniden konumlandırma, kör kenetlenme, moleküler kenetlenme*

INTRODUCTION

Ankylosing Spondylitis (AS), which usually occurs at a young age; is a painful, inflammatory type of autoimmune disease that affects the spine and the joint between the spine and hipbone [1-3]. Although the exact cause of ankylosing spondylitis is unknown, hereditary factors are known to play an important role. People who carry the HLA-B27 gene have a higher risk of developing the disease [4-6].

As a result of inflammation, these two bones combine to form a single bone. Inflammation and then ossification occurs in all edges of the disc and ligaments from the lower part of the spine to the neck. As a result, an anterior curvature occurs in the upper part of the spine. Although most patients can go on with their lives, the spinal motion may be restricted in a group of patients with advanced disease [7-10]. Although the course of the disease generally continues with periods of remission, it is sometimes exacerbated by periods of attacks. During these attacks, the disease also affects the lungs, heart, kidneys, eyes, and also affects hip joints. Most often, eye involvement occurs with uveitis, and if left untreated, this leads to loss of vision in the patient. Therefore, the treatment of the disease is of great importance [11-13].

There is no known cure for AS. The drugs used clinically for AS are mostly aimed at relieving symptoms. Non-steroidal anti-inflammatory drugs (NSAIDs) are used specifically for pain relief. In addition, specific drugs such as sulfasalazine (CVS) and methotrexate (MTX), and TNF-alpha inhibitor immunosuppressants are used to relieve seizures [4, 14, 15]. The biggest problem with these drugs is their side effects. Therefore, the identification of more specific drugs is of great importance.

As with neurological diseases such as Alzheimer's Disease and central nervous system diseases such as Multiple Sclerosis, the biggest problem in AS is inflammation [16-18]. Therefore, prevention of inflammation is the main goal. TNF-α is the primary target in the prevention of inflammation and many signaling pathways are activated through it. This signaling releases several cytokines and initiates the apoptotic pathway, resulting in target cell activation, resulting in an inflammatory and immune response [19]. Currently, five tumor necrosis factor-alpha (TNF-α) inhibitors (Infliximab, Etanercept, Adalimumab, Certolizumab, and Golimumab) are available in the treatment of AS [20]. However, these structures, which are monoclonal antibodies, are known for their intense side effects [20, 21]. For this

reason, researchers turned to studies on the development of IL-17 inhibitors, which is another target in inflammation [22]. Another important pathway for inflammation in the pathogenesis of AS is IL-23/IL-17 pathway. T-helper 17 cells are one of the largest immunological flows that are expressed in AS patients and are involved in the immune response. Both animal models and clinical studies use IL-17 cytokines in this response of T-helper 17 cells [22]. Therefore, it is possible to stop inflammation in AS by inhibiting IL-17. Although Phase 2 and Phase 3 studies are ongoing for different anti-IL-17 agents (Secukinumab, Ixekizumab, Bimekizumab, Brodalumab) for rheumatological and inflammatory diseases, there is no specific IL-17 inhibitor used clinically [22-24].

Drug repositioning, in other words, drug repurposing, is a set of methods that enable us to investigate the use of drug molecules that have been clinically approved or whose phase studies are in progress, outside of their medical indications. It provides a great advantage in terms of both time and cost compared to the detection of a completely new drug molecule, since it works with molecules that have been clinically and preclinically determined to be safe [25-27].

Within the scope of the study, which is the subject of this article, FDA-approved drug molecules suitable for the active HLA-B gene family in AS were determined and their IL-17 cytokine inhibitory properties were examined by web tools and molecular docking methods.

MATERIAL AND METHOD

Drug-Gene Interaction Research

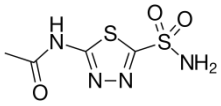
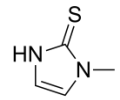
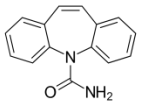
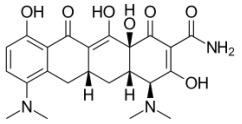
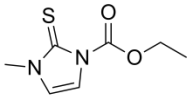
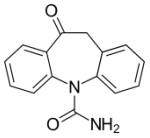
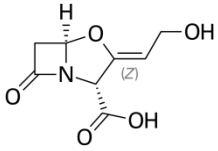
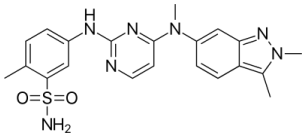
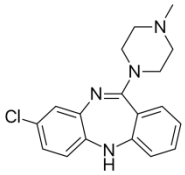
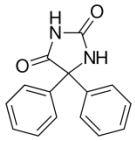
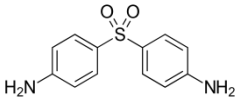
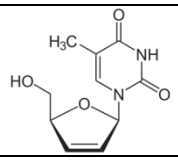
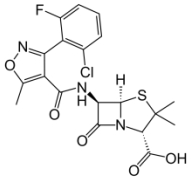
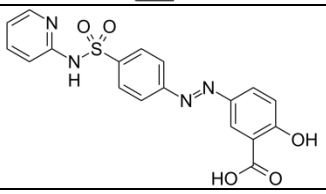
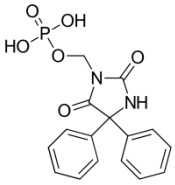
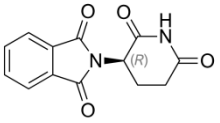
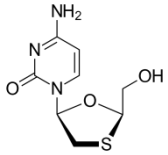
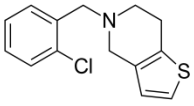
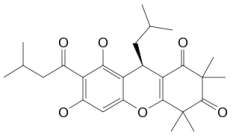
Using the Drug-Gene Interaction database (DGIdb) [28], a database containing drug molecules for genetic sources of diseases, 25 molecules associated with the HLA-B gene were identified. Eighteen of these molecules (Table 1) were downloaded from the PubChem database [29] for use in this study.

Molecular Docking

The interaction between the IL-17 receptor and 19 molecules (18 molecules from DGIdb and reference molecule, Rhodomyrtone, a known IL-17 inhibitor) was investigated by molecular docking. Molecular docking was performed using the AutoDock Vina program [30]. These 18 molecules determined were prepared by the “Ligand” module of the AutoDock Tools (ADT) [31] package, and gasteiger loads and TORSDOF parameters were also regulated by this module. The receptor structure (PDB ID: 4HR9 [32]) was downloaded from the RSCB database [33], and polar hydrogens and gasteiger charges were added to the ADT to obtain the 3D structure used in docking. However, since the receptor cannot crystallize with an inhibitor molecule, it is not possible to have a definite judgment about the binding pocket. For this reason, to determine the dimensions of the grid box be used in docking, firstly, the determination of the docking package was studied. All binding affinity values given in the article

are taken for conformations where the RMSD value is 0 Angstrom.

Table 1. Features of selected compounds for molecular docking

Compound	2D Structure	Compound	2D Structure
Acetazoleamide		Methimazole	
Carbamazepine		Minocycline	
Carbimazole		Oxcarbazepine	
Clavulanic Acid		Pazopanib	
Clozapine		Phenytoin	
Dapsone		Stavudine	
Floxacillin		Sulfasalazine	
Fosphenytoin		Thalidomide	
Lamivudine		Ticlopidine	
Rhodomyrtone (Reference)			

Binding Pocket Prediction of IL-17 Receptor

Computed Atlas of Surface Topography of Proteins (CASTp) [34], a web tool that scans for regions where molecules can interact within the receptor by examining receptor cavities and solvent access points, has been used to predict the receptor binding package. Predictions of the binding pocket are given in Table 2.

Blind Docking

Blind docking is performed when the target site containing the binding pocket at which receptor-ligand interaction will occur is unknown. The results of this process are combined by dividing the grid box into several pieces or repeating the process several times for the different pieces [35]. Another blind docking method is to specify a grid box containing all the receptors used in this study. Thus, it is predicted that the region where the greatest number of structures interact from different conformations of the molecule is the active site of the receptor. Blind docking was carried out using the AutoDock Vina program, and the dimensions of the grid box containing the whole receptor were determined by the "Grid" module of ADT (Table 2).

Grid Box Properties

Grid box parameters created by CASTp and blind docking are given in Table 2. In both methods, amino acid residues estimated to be in the active site were determined. While determining the grid box, the coordinates and dimensions of the box containing these amino acids were taken as a basis.

Table 2. Grid parameters used for molecular docking

Method	Pocket	X center	Y center	Z center	Grid Point	Dimensions
Blind Docking	-	11.572	28.93	48.65	0.375 Å	100 Å × 100 Å × 100 Å
	1	7.034	31.898	42.638	0.375 Å	40 Å × 40 Å × 40 Å
	2	21.505	23.063	49.071	0.375 Å	40 Å × 40 Å × 40 Å
	3	-7.205	28.536	65.44	0.375 Å	40 Å × 40 Å × 40 Å
CASTp Web server	1	-2.998	35.541	53.645	0.375 Å	40 Å × 40 Å × 40 Å
	2	16.385	28.426	48.287	0.375 Å	50 Å × 70 Å × 70 Å
	3	-3.586	28.31	63.124	0.375 Å	40 Å × 40 Å × 40 Å

RESULT AND DISCUSSION

Binding Pocket Prediction with CASTp

20 binding pockets were identified via the CASTp database. Among these packages, the properties of the 5 with the highest areas and the amino acid residues in the package are given in Table 3.

Table 3. Properties of pockets obtained from CASTp

Pocket	Area (SA)	Volume (SA)	Aminoacid Residues
1	434.832	256.325	LEU 53,TYR 62, PRO 63,VAL 65, ILE 66, TRP 67, ALA 69, GLN 94, GLU 95, ILE 96, LEU 97, VAL 98, LEU 99, LEU 112, LYS 114, VAL 117, SER 118, VAL 119
2	208.076	189.577	ARG 46, SER 47, THR 48, CYS 76, ILE 77, ASN 78, ALA 79, ASP 84, MET 87, CYS 123, THR 125
3	59.868	29.344	TYR 44, ASP 45, PRO 50, TRP 51, ASN 52, LEU 53, ARG 72
4	8.462	2.933	ARG 100, ARG 101, GLU 102, PRO 104, ARG 111
5	5.401	0.998	ASN 56, ARG 61, ILE 66, GLU 68, ILE 115, VAL 117

Configuration files were created with the first 3 packages for molecular docking work. The positions and sequences of the first 3 packages in the receptor are given in Figure 1.

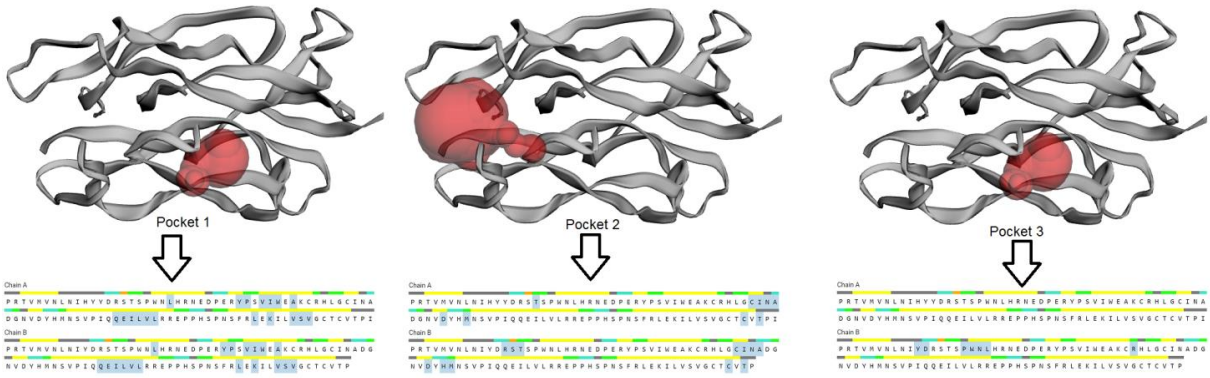


Figure 1. In the receptor shown in Cartoon style on the upper part of the figure, the parts areshown in CPK style (red balls) constitute the active regions. In the receptor sequence given at the bottom of the figure, the areas shaded in gray are the predicted binding packages.

Blind Docking

Blind docking was performed with the known inhibitor of IL-17, rhodomyrtone. The conformation of molecule 20 and its positions on the receptor was given in Figure 2. Accordingly, the 3 binding sites where the highest number of conformations is docked are given in the figure. The features of the Grid Box created by centering these regions are given in Table 2.

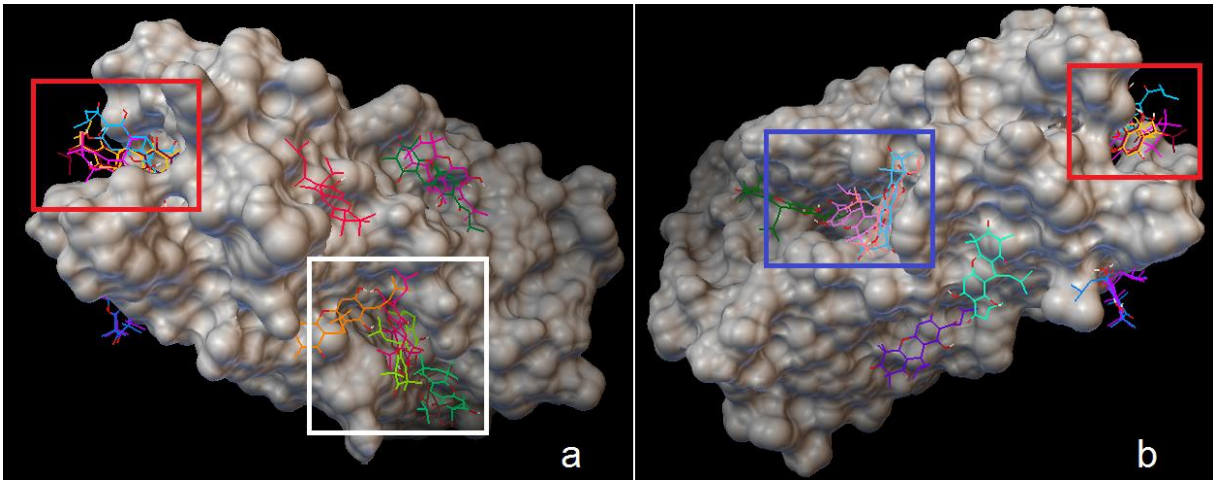


Figure 2. Blind docking conformations of rhodomyrtone. a) Front view of the surface representation of the receptor b) Back view of the surface representation of the receptor. The white rectangle represents binding pocket 1, the blue rectangle the binding pocket 2, and the red rectangle the binding pocket 3.

Molecular Docking

To determine the required docking protocol for examining the interaction of the molecules given in Table 1 and the IL-17 receptor, the interaction of rhodomyrtone was examined by using all the Grid Box features given in Table 2. Accordingly, when the obtained binding affinities are examined, it is seen that the second package obtained by blind docking and the second package obtained through the CASTp web tool give the same binding affinity (-7.6 kcal/mol) (Table 4).

Table 4. Properties of pockets obtained from CASTp

Method	Pocket	Affinity (kcal/mol)
Blind Docking	1	-6.9
	2	-7.6
	3	-5.9
CASTp Web server	1	-6.8
	2	-7.6
	3	-5.8

At the same time, it is understood from Table 2 that these 2 packages also show the same region on the receptor. For this reason, it was determined that the active site of the receptor was expressed by package 2, and other molecules were docked with the configuration file of package 2. In Figure 3, the interaction properties of rhodomyrtone in the binding package are given. Accordingly, it was determined that rhodomyrtone interacted with TRP 67 in accordance with the literature [36].

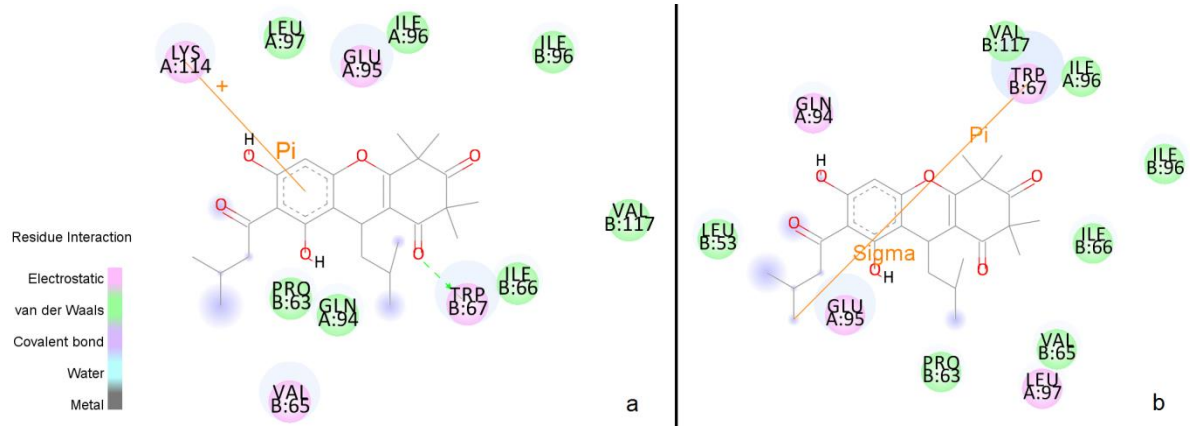


Figure 2. Analysis of interactions detected as a result of docking via Discovery Studio Visualizer program [37]. a) Interaction profile in binding packet 2 obtained via the CASTp web tool b) Interaction profile in bind pack 2 obtained with blind docking

The binding affinities of the molecules given in Table 1 with the binding package 2 are given in Table 5. Accordingly, it was determined that the highest binding affinity was obtained with carbamazepine (-7.8 kcal/mol). It was also observed that minocycline, sulfasalazine, and thalidomide gave a higher binding affinity (-7.7 kcal/mol) than rhodomyrtone (-7.6 kcal/mol).

Table 5. Molecular docking results between selected ligands and IL-17 receptor

Ligand	Affinity (kcal/mol)	Ligand	Affinity (kcal/mol)
Acetazoleamide	-5.0	Minocycline	-7.7
Carbamazepine	-7.8	Oxcarbazepine	-5.5
Carbimazole	-4.4	Pazopanib	-6.8
Clavulanic Acid	-5.5	Phenytoin	-6.8
Clozapine	-7.4	Stavudine	--5.9
Dapsone	-6.2	Sulfasalazine	-7.7
Floxacillin	-6.5	Thalidomide	-7.7
Fosphenytoin	-5.8	Ticlopidine	-4.9
Lamivudine	-5.0	Rhodomyrtone	-7.6
Methimazole	-3.2		

Figure 3 shows the interaction between carbamazepine and the receptor. Accordingly, it is observed that the molecule is in the binding package of the receptor and exhibits a similar interaction profile with rhodomyrtone and also shows a π-cation interaction with LYS 114.

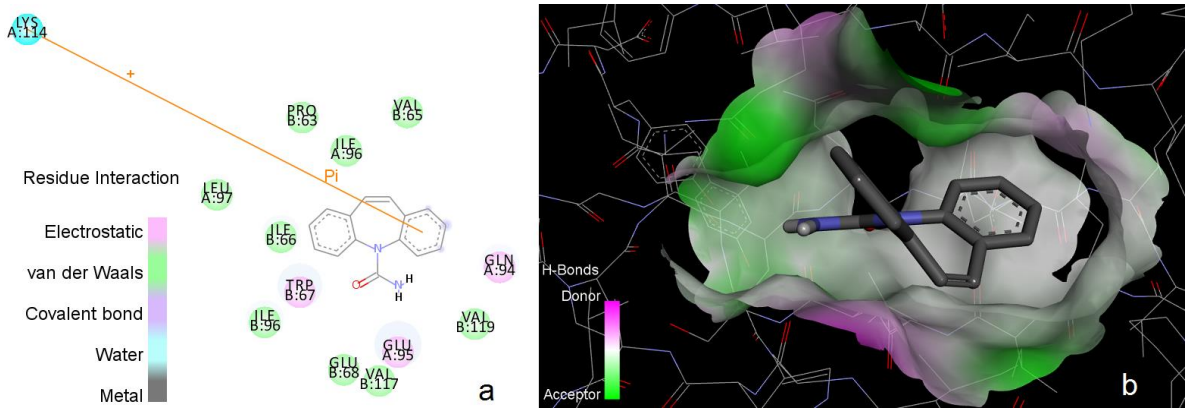


Figure 3. Binding profiles of the carbamazepine. a) 2D structure view. The orange line demonstrates *π-cation* interaction. b) 3D structure view

In Figure 4, it is observed that minocycline, sulfasalazine, and thalidomide are included in the binding package. Although minocycline does not show a similar interaction profile to the literature, it has been shown that sulfasalazine and thalidomide exhibit a similar profile to rhodomyrtone. Accordingly, it was determined that sulfasalazine made *π-cation* interaction and hydrogen bond with LYS 114, while thalidomide made hydrogen bonds with TRP 67.

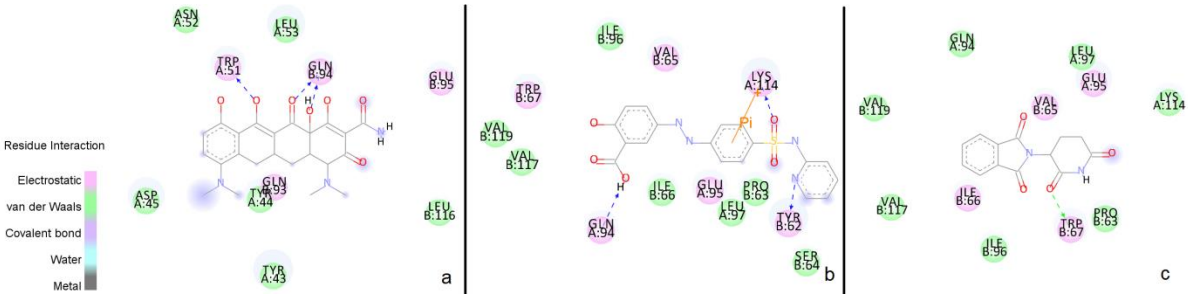


Figure 4. Binding profiles of compounds. a) minocycline b) sulfasalazine c) thalidomide. The orange line demonstrates *π-cation* interaction, blue and green discreet lines demonstrate the hydrogen bond.

In conclusion, the carbamazepine molecule shows the best binding affinity and binding profile with IL-17. It was also revealed that minocycline, sulfasalazine, and thalidomide are tightly packed in the active site. It has been demonstrated that these molecules may be lead molecules for the treatment of AS disease.

ACKNOWLEDGEMENTS

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AUTHOR CONTRIBUTIONS

Concept: *G.Y.O.*; Design: *G.Y.O.;* Control: *G.Y.O.;* Sources: *G.Y.O.;* Materials: *G.Y.O.;* Data Collection and/or processing: *G.Y.O.;* Analysis and/or interpretation: *G.Y.O.;* Literature review: *G.Y.O.;* Manuscript writing: *G.Y.O.;* Critical review: *G.Y.O.;* Other: *G.Y.O.*.

CONFLICT OF INTEREST

The author declares that there are no apparent financial or personal conflicts of interest that may affect the work in this article.

ETHICS COMMITTEE APPROVAL

The author declares that the ethics committee approval is not required for this study.

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