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Synthesis of 1,4-Biphenyl-triazole Derivatives as Possible 17β-HSD1 Inhibitors: An *in Silico* Study

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Cite This: *ACS Omega* 2020, 5, 14061−14068

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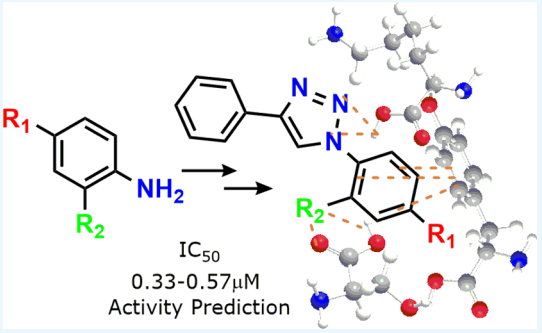
ABSTRACT: Triazoles occupy an important position in medicinal chemistry because of their various biological activities. The structural features of 1,2,3-triazoles enable them to act as a bioisostere of different functional groups such as amide, ester, carboxylic acid, and heterocycle, being capable of forming hydrogen bonds and $\pi-\pi$ interactions or coordinate metal ions with biological targets. In this work, the synthesis of 1,2,3-triazole derivatives via copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC) is reported. Overexpression of 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) is often found in breast cancer cells. Molecular similarity and docking analysis were used to evaluate the potential inhibitory activity of 1,2,3-triazoles synthesized over 17β-HSD1 for the treatment of mammary tumors. Our *in silico* analysis shows that compounds **4c**, **4d**, **4f**, **4g**, and **4j** are good molecular scaffold candidates as 17β-HSD1 inhibitors.



INTRODUCTION

In search of new breast cancer treatment strategies, a few endocrine therapies have been developed. Hormone therapy is based on selective estrogen receptor modulators or anti-estrogens that cause several undesired effects.[1,2] The activation of 17β-estradiol (E2) responsible for the growth of estrogen-dependent breast cancer is regulated by the enzyme 17β-HSD1. The inhibition of this enzyme that is expressed in different organs but mainly in many breast cancer tissues[3] is a better therapy with probably fewer side effects.

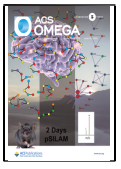
For this reason, several steroidal and nonsteroidal inhibitors of 17β-HSD1 have been developed. However, recently, nonsteroidal derivatives that act as inhibitors of 17β-HSD1 enzyme, having derivatives of thienopyrimidinones, biphenyl ethanones, 6-(hydroxyphenyl)naphthols, and bis-(hydroxyphenyl)azoles, have been researched intensively, with the last one being the most promising compound.[4] Biphenyltriazoles, as a bioisostere of azoles, open possibilities for evaluating several candidates as new inhibitors of the enzyme, having a platform with a straightforward methodology of synthesis that generates a library of compounds via CuAAC reaction. Besides, in conjunction with the computational study, it will be possible to evaluate better candidates for enzyme inhibition with extensive molecular screening.

Many triazole-based derivatives are available as medicines;[5] however, they also have a wide range of important applications in the agrochemical,[6] dendrimer,[7] supramolecular,[8] electrochemical,[9] corrosion retardant,[10] optical brightener,[11] metal chelator,[12] and material fields.[13] Their important biological activities include anticancer,[14] antitumor,[15] anti-HSV-1,[16] antimalarial,[17] antitubercular,[18] antileishmanial,[19] antifungal,[20] antibacterial,[21] antimicrobial,[22] antidiabetic,[23] antihypertensive,[24] anti-inflammatory,[25] anti-Alzheimer,[26] antiepileptic,[27] and anticonvulsant.[28]

Their importance in the field of medicinal chemistry is due to high dipole moment, rigidity, and capability to bind with various kinds of enzymes and receptors via weak interactions such as hydrogen bonds, coordination bonds, ion−dipole, dipole−dipole, and cation−π and π stacking interactions when they bind with the biological target.[29] Thus, 1,2,3-triazole scaffolds are of interest for drug development because these systems act as a bioisostere of different functional groups such as amide, ester, carboxylic acid, and heterocycle,[30] and they also are highly stable under basic, acidic, reductive, oxidative, and enzymatic conditions due to high aromatization.[31,32]

The 1,2,3-triazole ring system can be easily built via Huisgen's 1,3-dipolar cycloaddition of azides and alkynes by copper-catalyzed click reaction (CuAAC), allowing the production of a large number of 1,4-disubstituted-1,2,3-

Received: April 3, 2020
Accepted: May 15, 2020
Published: June 1, 2020



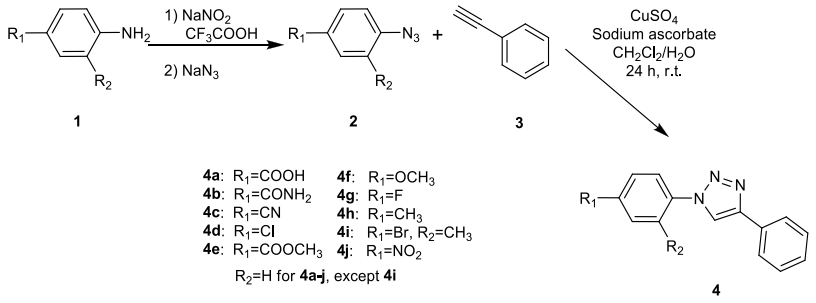


Figure 1. Synthesis of the 1,2,3-triazole ring system (**4a** to **4j**).

triazoles in high regioselectivity, broad substrate scope, favorable kinetic, excellent yield, insensitivity toward oxygen and water, and pure product isolation. This reaction can be performed in the presence of a wide variety of functional groups, facile and gentle conditions, wide pH range tolerance, and compatibility with a variety of solvents.

The click conjugation includes direct utilization of copper(I) salts, either added directly or generated by reduction of copper(II) or oxidation of Cu(0) and copper complexes.[33] There are also examples of CuAAC reactions by the heterogeneous catalyst using materials such as alumina, silica, polymers, zeolites, or activated carbon as supports.[34−36] Other catalytic systems used are Ru-, Zn-, Ag-, Ni-, Pt-, and Pd-catalyzed click.[37−39] The efficiency of the azide/alkyne click reaction was improved by the use of microwave irradiation and ultrasonication.[37,40,41]

1,2,3-triazole is a building block with many attributes for the development of new anticancer agents,[14] such as an inhibitor of human methionine aminopeptidase type 2 (hMetAP2),[42] inhibition of human cancer cell lines such as breast adenocarcinoma (MCF-7) and human hepatocellular carcinoma (HepG2),[43] cytotoxic activity against several cancer cell lines,[44,45] antiproliferative activity,[46] and so on.[47] To further enrich the structure−activity relationship of triazole in the enzyme inhibition, herein, the generation of a diverse library de triazole analogues using the CuAAC reaction is reported, as well as their inhibitory potency over 17β-HSD1.

Ten new triazole derivatives have been synthesized with good yields and evaluated as nonsteroidal inhibitors of 17β-HS1 for the treatment of estrogen-dependent diseases. The desired derivatives of triazoles were generated by click reaction with different functional precursors. Current research efforts are mainly focused on the optimization of the side chain attached to the pharmacophore in order to develop new compounds with better pharmacological activities.

RESULTS AND DISCUSSION

Chemistry. Aromatic azides were synthesized by the formation of benzenediazonium salt from substituted anilines with sodium nitrite in acid media, and then, sodium azide was added, having a range from good to excellent yields of reaction (Figure 1).[48,49] Anilines with electron-withdrawing groups allowed to obtain 94−97% yield of aromatic azide while electron-donor groups allowed to obtain 80−87% yields. The change of aniline to aromatic azide was confirmed by the presence of N_3 vibration at 2111 and 2069 cm^{-1} with very strong intensity and the absence of primary amine vibration at 3500 and 3300 cm^{-1}.

The formation of the 1,2,3-triazole ring was made by copper-catalyzed 1,3-dipolar cycloaddition between an aromatic azide and terminal alkyne having 65−88% yield (Figure 1).[48,49] The nature of functional groups in the aromatic azide was not a determinant factor for the formation of the triazole ring.[50] 1,2,3-triazole was confirmed for increasing the number of vibrations in the aromatic region between 1600 and 1400 cm^{-1} due to C=C and the absence of N_3 vibration.

In ^{1}H NMR, a singlet signal of around 9.3 ppm was observed for triazoles. This chemical shift at downfield is due to the magnetic anisotropy effect from triazole itself and the electronegative effect of the nitrogen atoms attached at the triazole ring by the electron-withdrawing effect reducing the valence electron density around the proton. In the same way, ^{13}C NMR showed one signal in the range 148.67−130.37 ppm corresponding to the carbon of triazole. The substituted aromatic carbon cannot be distinguished by its decreased peak height.

All compounds analyzed by mass spectrometry did not show the molecular ion, and the easy liberation of phenyl acetylene (m/z = 102.05) resulted in the production of the aromatic azide,[51,52] which can act as a nucleophile or an electrophile agent at the same time generating azo or hydrazine molecules by intramolecular cyclization.

On the other hand, in UV−vis spectroscopy, the transformation of substituted anilines to azide and then to triazole molecule showed a hypsochromic shift. The most characteristic transitions of the triazolinic ring were $\pi \rightarrow \pi^*$ and $\eta \rightarrow \pi^*$ at 250−244 and 290 nm, respectively. The displacement of $\pi \rightarrow \pi^*$ band transition of aromatic is showed as a weak conjugation with each aromatic ring, changing the space arrangement to nonplanar rings, and this result is congruent with optimal conformation by computational calculations made below.

Computational Details. *Ligand Preparation and MEP.* The optimized structures of all the compounds are shown in Figure S1. All the structures were in a minimum in the potential energy surface because all the vibrational frequencies were positive. From Figure 2, it can be observed that all the

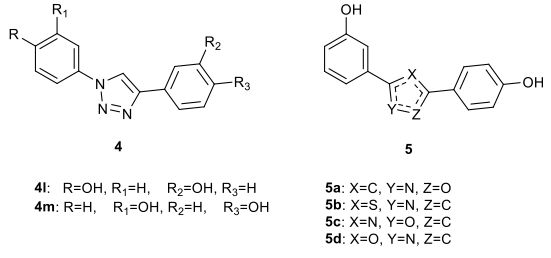


Figure 2. Template structure used for the MSA. **4l**, **4m**, and **5a** to **5d** are inhibitors of 17β-HSD1.

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ACS Omega 2020, 5, 14061−14068

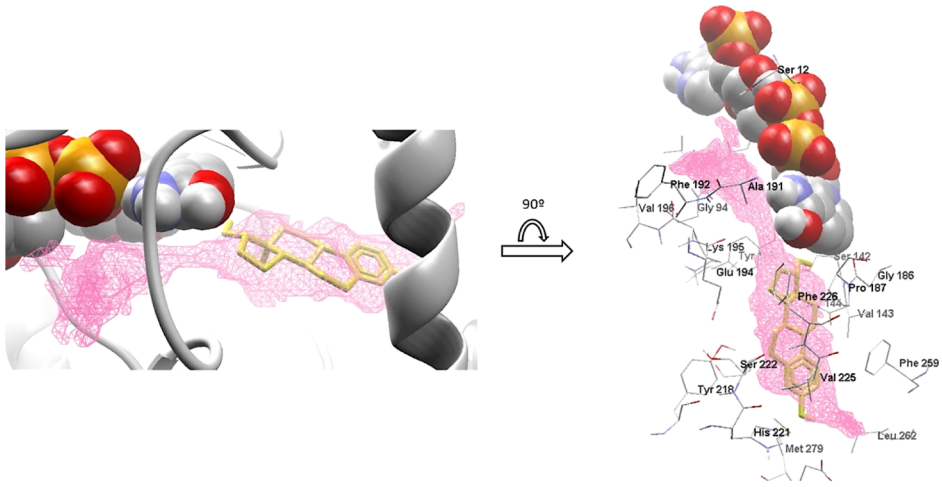

Figure 3. Catalytic cavity (pink color) of 17β-HSD1 in a mesh representation with estradiol (yellow sticks). The $NADP^+$ cofactor is displayed in a sphere representation.

compounds possess a planar molecular shape with a hydrogen bond acceptor in the para position of the phenyl ring 1. Employing these structures as a starting point, we performed a molecular docking calculation to evaluate these compounds as potential inhibitors of 17β-HSD1.

To evaluate how the interaction of these molecules with their biological receptor may occur (neutral, positive, and negative electrostatic regions), we obtained the molecular electrostatic potential mapped over a surface of electronic iso-density value (0.002 $e^-/Å^3$). Also, from these molecular graphics, we can visualize the shape of the compounds, an important feature for the protein interaction process. The molecular electrostatic potential of all the reference molecules (Figure S2) and our triazole derivatives (Figure S3) is displayed.

In Figure S2, it can be seen how for all the reference molecules, their aliphatic part (phenyl rings) is a neutral MEP zone and that they share a similar molecular shape. Also, we can observe the negative MEP zones located over the nitrogen atoms of the triazole ring and the oxygen atoms of the OH moiety. The positive MEP zones are located over the hydrogen atom of the OH group, which are important in order to bind similarly to estradiol.

On the other hand, in our triazole derivatives, the positive zones of MEP in the corner of the molecules are lacking; instead they present a positive MEP zone over the hydrogen of the triazole ring. They possess the same negative MEP zone over the triazole ring as the reference molecules and the neutral zone over the phenyl rings. Besides, they possess a highly similar molecular shape with the reference molecules. These electronic characteristics of our molecules suggest that they will interact in the same binding site (lock−key principle) but with different binding residues. To corroborate this assumption, a molecular docking study was carried out.

Molecular Docking Analysis. All the compounds were docked in the catalytic site of 17β-HSD1. In Figures S4 and 4, the interaction of each compound with 17β-HSD1, according to the docking calculations, is displayed. All the compounds bind in the lipophilic pocket near the $NADP^+$ cofactor (Figure 3) by embedding their unsubstituted phenyl ring. This lipophilic pocket is formed by Gly92, Leu93, Gly94, Ala291, Phe192, and Val196; it is located after a hydrophilic "bottle neck" type composed by Ser142, Tyr155, Glu194, and Lys195. This hydrophilic zone is crucial for the catalytic reaction of the estradiol, forming two HBs with Ser142 and Tyr 155.

These regions of the catalytic cavity help us to explain the binding mode of the triazole derivatives because of the planar and cylindrical shape of our molecules, and the most hydrophobic part of these molecules (unsubstituted phenyl ring) fits in a perfectly good manner in the lipophilic pocket; meanwhile, the triazole ring forms a high number of strong HBs with the residues of the hydrophilic zone. According to our docking results, besides the similarity between the triazoles synthesized by Bey et al.[4] and the estradiol, these compounds bind in the lipophilic pocket with their phenyl group with more hydrophobic character-forming HB with Gly92. Similarly, all our triazole derivatives bind in the lipophilic pocket by the phenyl ring with less electronic density, in our case, the unsubstituted ring, increasing the hydrophobic interactions and decreasing the steric repulsions. At the same time, the triazole ring strongly interacts with 17β-HSD1 by many HBs with Lys195 (HBs and cation−π interactions), Ser 142, and Tyr 155.

In Table 1, all the interaction energy values of the triazoles studied in this work are displayed. According to these results, it can be noted that two of our compounds (**4a** and **4e**) possess a more negative interaction energy value (better binding) with 17β-HSD1 than that of the triazoles of Bey et al.,[4] and other two of our compounds (**4b** and **4i**) possess a similar interaction energy value to that of the reference triazoles (around −148 kcal/mol). We can explain these results by the aforementioned energy interaction involved in the two regions of the catalytic domain. It can be noted that our compounds with the best interaction energy are those which have an electron-withdrawing group (halogen or carbonyl group). This structural feature of these molecules enhances the interaction by HB with the residues located before the hydrophilic bottleneck, especially with Arg258.

From this analysis, we can conclude that one of the phenyl rings must be unsubstituted, and the other needs to have an electron-withdrawing group to facilitate the binding in the lipophilic group of the catalytic site and the electrostatic interactions and HB formation with the residues of the catalytic hydrophilic zones.

Prediction of IC_{50} Values. From the results of molecular docking, a mathematical model was generated for the

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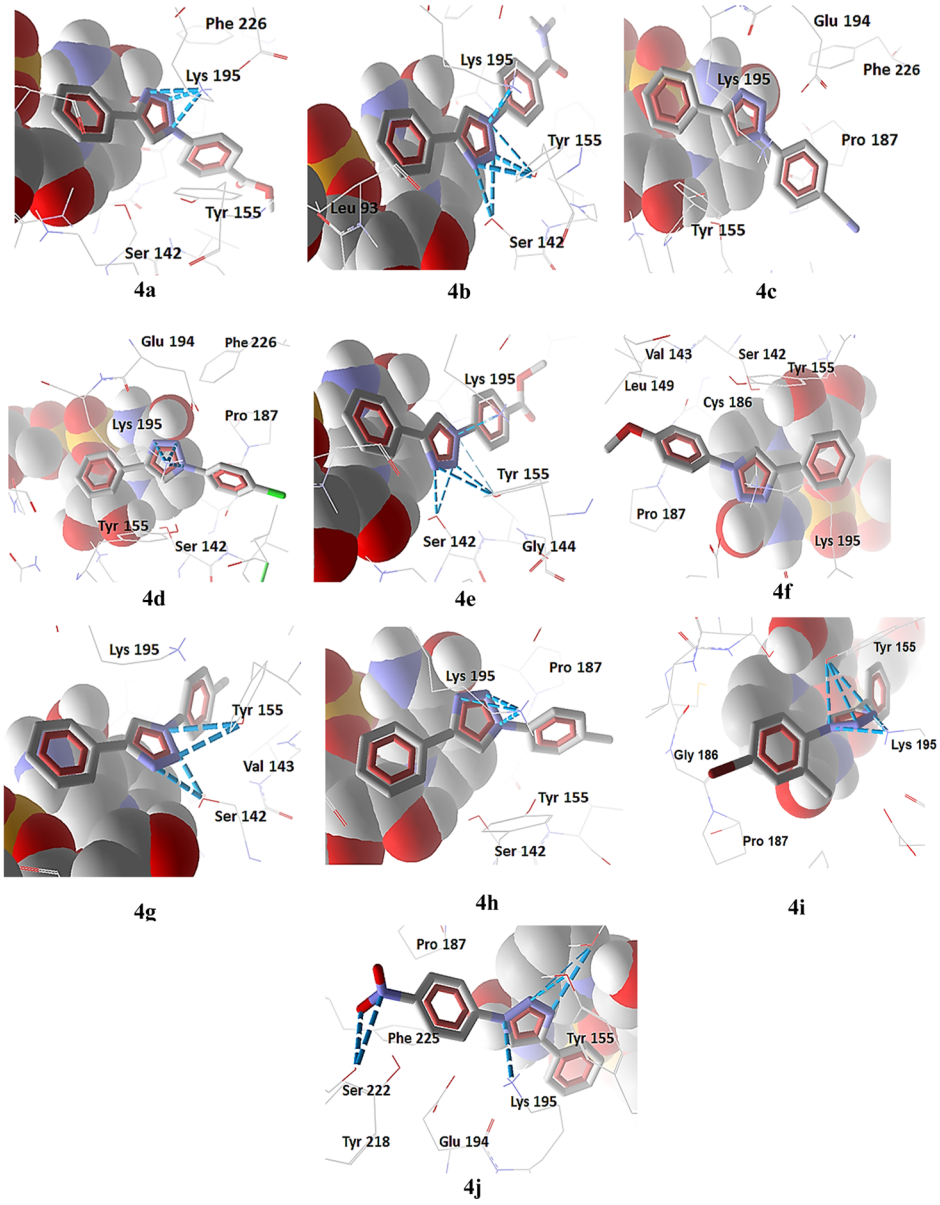

Figure 4. Molecular docking results of the synthetized triazole derivatives. $NADP^+$ is represented as colored spheres. Hydrogen bonds are displayed as blue dashed lines.

prediction of the IC_{50} values of the proposed compounds (**4a** to **4j**) based on the interaction energies. For the generation of the mathematical model, the transformation of IC_{50} to logarithm was used to normalize the data and resulted in eq 1 (see below).

$$\log IC_{50} = -0.06844E_{inter} - 7.08916 \quad (1)$$

This model has produced high statistical quality ($R^2 = 93.52$, $Q^2 = 86.96$, $s = 0.196$), which was obtained by relating interaction energies and log IC_{50} (log Y) values (Figure S5).

All the log IC_{50} (Y_{exp}) experimental, calculated (Y_{calc}), and predicted (Y_{pred}) activity values by our model are presented in Table 2. Also, the absolute value of the differences between Y_{exp} and both Y_{calc} and Y_{pred} is represented by $error_{calc}$ and $error_{pred}$ term, respectively. Y_{exp} versus Y_{pred} activity plots are shown in Figure S6. The predicted calculation of the IC_{50} values of the proposed compounds (**1** to **10**) was realized using the mathematical model and the interaction energy values (Table 1). Table 3 shows the predicted IC_{50} values, and the values are represented in μM.

The compounds that obtained better IC_{50} values were the triazole derivatives **4c**, **4d**, **4f**, **4g**, and **4j**, with values from 0.33 to 0.57. Comparing these results with the interaction energy values, the triazole derivatives **4a**, **4b**, **4e**, and **4i** showed better interaction energy values with the 17β-HSD1 protein and would be expected to obtain better activity (low IC_{50} values); however, these compounds predicted high IC_{50} values. These results should consider that there is no direct relation between highly negative interaction energy (binding affinity) and better IC_{50} values; the IC_{50} estimates the effect on the target activity, which does not necessarily reflect the affinity. The interaction energy values of the compounds **4c**, **4d**, **4f**, **4g**, and **4j** are similar to those of the reference triazoles. From the docking and mathematical model results, we can conclude that these triazole derivatives can be used as molecular scaffolds for the design of new inhibitors of 17β-HSD1.

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Table 1. Interaction Energy (kcal/mol) Values of the Triazole Derivatives

Molecule	MolDock score (kcal/mol)	Hbond (kcal/mol)
4a	−154.93	−7.5
4b	−148.98	−11.09
4c	−142.18	−7.74
4d	−142.85	−6.58
4e	−160.25	−10.78
4f	−143.89	−5.23
4g	−140.84	−7.05
4h	−144.34	−4.44
4i	−141.05	−3.18
4j	−140.44	−13.58
4l	−145.92	−6.35
4m	−147.12	−7.41
5a	−143.29	−1.81
5b	−128.11	−7.73
5c	−143.29	−5.00
5d	−150.28	−3.21

CONCLUSIONS

In summary, 1,2,3-triazole derivatives were successfully synthesized through the optimized Cu(I) click conditions. They were obtained in moderate to high yield and purity without chromatographic purification. Most of them showed high activity. Structures of the prepared compounds were elucidated by spectral data like UV−vis, FT-IR, ^{1}H and ^{13}C NMR, and MS.

In the molecular docking study, it was observed that triazole derivatives bind in the lipophilic pocket of the 17β-HSD1 protein by the aromatic ring. The triazole ring has strong interactions with the protein through hydrogen bonds with Lys195, Ser142, and Tyr155.

After analyzing the results, we can conclude that to obtain the best binding affinity with the hydrophilic catalytic zone, an unsubstituted phenyl ring is necessary to decrease steric interactions to fit into the pocket, and the other ring must contain an electron-withdrawing group to enhance HB interactions. Activity prediction showed that **4c**, **4d**, **4f**, **4g**, and **4j** compounds have the best IC_{50} from 0.33 to 0.57 μM values. There is not a direct correlation between IC_{50} values and binding affinity. Finally, triazole derivatives with the best IC_{50} can be used as potential anticancer agents by inhibiting the protein 17β-HSD1 in breast cancer.

METHODS AND MATERIALS

Chemistry. Aromatic azides were obtained from their amino analogues using the methodology described by Leyva et al.[53] Reagents and solvents were purchased with commercial suppliers without further purification. The reaction describes copper-catalyzed Huisgen cycloaddition (Figure 1), where phenyl acetylene was used as a dipolarophile, and like 1−3 dipole, a series of derivatives of para-substituted aromatic azides (COOH, $CONH_2$, $COOCH_3$, CN, NO_2, Cl, F, CH_3, and OCH_3) and a disubstituted aromatic azide (1-azido-4-bromo-2-methylbenzene) were used. The reaction was carried out in a mixture of water/dichloromethane (1:1), where copper sulfate added as the catalyst and sodium ascorbate as the reducing agent. The progress of the reaction was monitored by TLC using ethyl acetate/*n*-hexane (80:20, v/v). The reaction was left under stirring for 24 h, and the products were vacuum-filtered and recrystallized with acetonitrile.

Table 3. Predicted IC_{50} (μM) Values for Compounds 4a to 4j

molecules	IC_{50pred} (μM)
4a	3.26
4b	1.28
4c	0.44
4d	0.48
4e	7.55
4f	0.57
4g	0.35
4h	0.61
4i	2.56
4j	0.33

Computational Details. *Molecule Preparation.* All the molecular structures of the compounds in this study were fully optimized, without symmetry constraints at a semiempirical level of precision, with the parametric method number 6 (PM6). Finally, to ensure that the geometry of all the compounds is minima on the potential energy surface, a harmonic frequency analysis was performed. Furthermore, to acquire a more precise energy value and electronic density characteristics, a single-point energy calculation at a density functional theory level of precision with the B3LYP hybrid functional[54] and the 6-31+G* basis set[55] for H, C, N, O, F, S, and Cl atoms and LACVP pseudopotential and basis set for the Br atom were employed.[56] With these results, the construction of the electrostatic potential molecular graphics was accomplished. All the calculations were done in Spartan 18.[57,58]

Molecular Similarity Analysis. In order to find a possible application of our synthesized compounds, we employed the ChEMBL database[59] using the biphenyl-triazole scaffold (Figure 2) as a template for the search of similar compounds with experimental biological activity. From the molecular similarity analysis (MSA), we found a series of triazole derivatives synthesized by Bey et al.,[4] which were evaluated as nonsteroidal inhibitors of 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) for the treatment of estrogen-dependent diseases.[60] These compounds showed selectivity and a

Table 2. Experimental, Calculated, and Predicted log IC_{50} Values of the Compounds 4l, 4m, and 5a to 5d

molecules	log Y_{exp}	log Y_{calc}	log Y_{pred}	error calc	error pred	std. err calc	std. err pred
4l	3.12	2.90	2.83	−0.23	−0.29	−1.29	−1.64
4m	2.92		3.31		0.39		
5a	3.21	3.30	3.35	0.09	0.15	0.59	0.94
5b	1.70	1.68	1.50	−0.02	−0.02	−0.32	−3.13
5c	2.49	2.72	2.77	0.23	0.28	1.29	1.61
5d	3.27	3.20	3.16	−0.07	−0.10	−0.44	−0.64

https://dx.doi.org/10.1021/acsomega.0c01519
ACS Omega 2020, 5, 14061−14068

considerable inhibitory potency over 17β-HSD1 (Figure 2). Also, oxazole and thiazole derivatives with inhibitory activity over this enzyme were included in this study as a reference.

Molecular Docking Methodology. For the molecular docking calculations, we used the crystal structures of the 17β-HSD1 cocrystallized with estradiol (PDB:1FDT).[61] The crystal structure for 17β-HSD1 was selected to be in accordance with the experiments done by Bey et al.[4] and because of the higher structural information of 17β-HSD1 catalytic site besides its crystal resolution value (2.2 Å); according to the crystal resolution, 6MNE was the better option, but much structural information was lacking. All water molecules were removed from the crystal. For the catalytic cavity calculation (volume of 146.43 Å^3), the expanded van der Waals sphere method was applied (Figure 3).

We employed the optimized geometries of all the compounds and used three different partial charge schemes: Mulliken, electrostatic, and Molegro internal scheme. From this validation process, the electrostatic partial charges, obtained from the PM6 calculation, were our final option because of the reproducibility of the crystallographic conformation of estradiol according to the root-mean-square deviation value (RMSD = 0.25 Å). As a first step, we performed a rigid docking of all the compounds with 17β-HSD1 using as search and scoring function the MolDock Optimizer and MolDock score [GRID], respectively.

The parameters employed were a 0.2 Å GRID partition and a 12 Å radius for the search sphere, a total of 30 runs with a maximum of 2000 iterations and 50 individuals per run. Finally, a flexible docking calculation was carried out, where all the residues within 6 Å were set as flexible (18 residues). For the energy analysis of the ligand, the internal electrostatic interactions, internal hydrogen bonds, and the sp^2-sp^2 torsions were considered. Docking calculations were performed with Molegro Virtual Docker (MVD) 6.0.[56,57]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c01519.

Structure of **4a−j** triazole compounds confirmed by UV−vis, FTIR, ^{1}H and ^{13}C NMR, and MS analysis and computational details of ligand preparation, MEP, and molecular docking analysis (PDF)

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All the authors contributed equally to this work

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We wish to thank CONACYT (SEP-82585) for its financial support and Dr. Erick Cuevas-Yáñez of the Autonomous University of Mexico State for helping with NMR spectroscopic characterization. RSRH thanks to the National Supercomputing Laboratory (NSL, Puebla) for the computer time, and Dr. Zeferino Gómez-Sandoval of the University of Colima for the software facilities.

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