Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2021.36.005895

Molecular Docking Study of Chlamydia Trachomatis Using Salicylidene Acylhydrazides as Inhibitors

Emmanuel Israel Edache[1,2]*, Adamu Uzairu[2], Paul Andrew Mamza[2] and Gideon Adamu Shallangwa[2]

[1]*Department of Pure and Applied Chemistry, University of Maiduguri, Borno State, Nigeria*

[2]*Department of Chemistry, Ahmadu Bello University, Zaria, Nigeria*

***Corresponding author:** Emmanuel Israel Edache, Department of Pure and Applied Chemistry, University of Maiduguri, Borno State, Department of Chemistry, Ahmadu Bello University, Zaria, Nigeria

ARTICLE INFO

Received: May 25, 2021

Published: June 23, 2021

Citation: Emmanuel Israel Edache, Adamu Uzairu, Paul Andrew Mamza, Gideon Adamu Shallangwa. Molecular Docking Study of Chlamydia Trachomatis Using Salicylidene Acylhydrazides as Inhibitors. Biomed J Sci & Tech Res 36(4)-2021. BJSTR. MS.ID.005895.

Keywords: Bacteria; Chlamydia Trachomatis; Docking Simulations; Salicylidene Acylhydrazides Derivatives; Igemdock

ABSTRACT

The main task in current drug discovery has been the design and growth of new antibacterial drugs with better efficacy and no side effects. We conducted docking simulation to salicylidene acylhydrazides derivatives as ligands into the crystal structure of IncA as the receptor. The 3D crystal structure of IncA as the receptor was downloaded from PDB (Code ID: 6e7e). The structure of ligands and protein were prepared using Spartan and Discovery studio, respectively. The docking process, the interaction, and binding of ligands – protein was done and visualized using iGemdock software and Discovery studio visualizer. The results showed Van der Waals, Pi-donor hydrogen bond, Pi-pi stacked, and amide-pi stacked interaction between compound 44 (N'-[(Z)-(2-hydroxy-3,5-dinitrophenyl)methylidene]-2-[(3R,5S,7s)-adamantan-1-yl] acetohydrazid) with Plk1, but this compound have more Van der Waals interaction with His253, His250, Lys246, Arg245, Thr238 and Ser154 of the crystal structure of IncA as the receptor. iGemdock (drug screening) scores of compounds 44, is -87.3827 kcal/mol. It is predicted that compound 44 has potency as a lead compound to find a new anti-Chlamydia trachomatis candidate for possible therapeutic agents.

Introduction

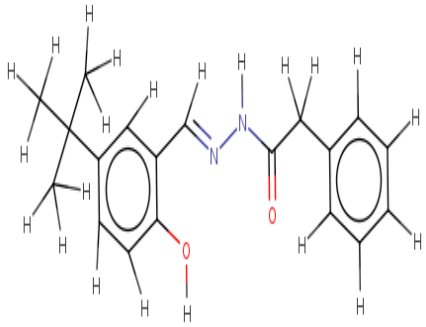
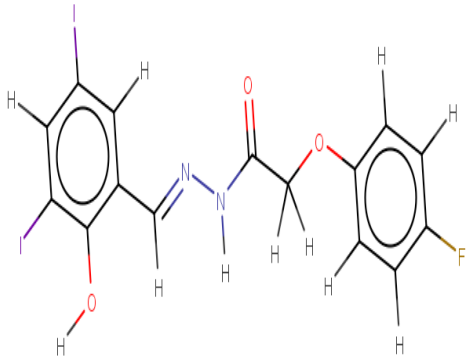
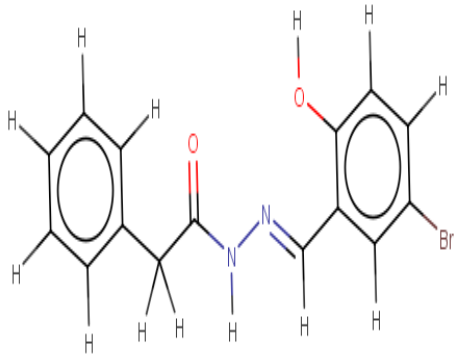
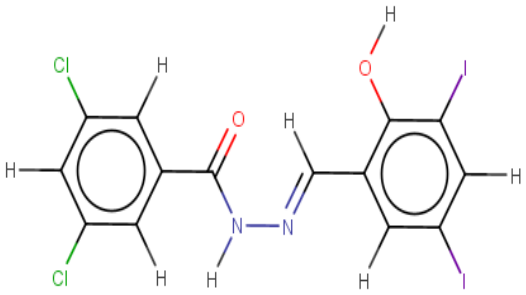
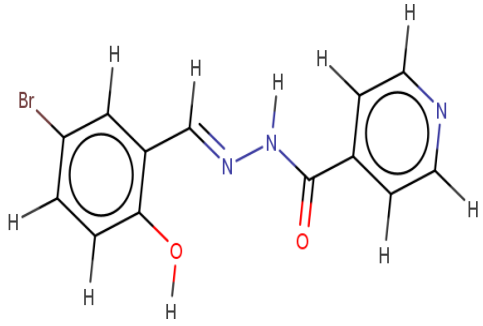
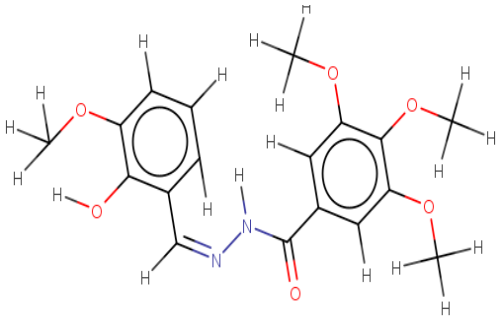
Chlamydia trachomatis is a typical human microorganism that causes explicitly sent infections, fruitlessness, trachoma, and visual deficiency in individuals everywhere on the world [1]. As indicated by the World Health Organization (WHO), 85 million individuals got anti-microbials for trachoma, a blinding eye contamination that influences 42 nations [2], also, in excess of 100 million instances of explicitly communicated Chlamydia trachomatis are analyzed every year overall [3]. Contaminations with these commit intracellular microorganisms have few therapeutic choices, and the most effective treatment is a single dose of azithromycin [4]. Over time, these drugs lead to side effects such as abdominal pain, diarrhea, and other gastrointestinal disorders in chronic treatment. Tetracycline (e.g., Oxytetracycline and Chlortetracycline) were discovered in the 1940s and exhibited activity against a wide scope of microorganism including gram-positive and gram-negative microscopic organisms, chlamydia, mycoplasma, rickettsia, and protozoan parasites [5]. Like another tetracycline, Chlortetracycline can inhibit bone and tooth mineralization in growing and unborn animals, and color their teeth yellow or brown. It can also unpair liver and kidney function, Allergic reactions are rare [6]. Oxytetracycline can cause gastrointestinal and photosensitive unfavorably susceptible responses. It can likewise harm calcium-rich organs, for example, teeth and bones [7].

Accordingly, exploitation of new potent, safer, and cheaper Chlamydia trachomatis or bacterial inhibitors becomes the biggest challenge the human race is facing nowadays. For this reason, the

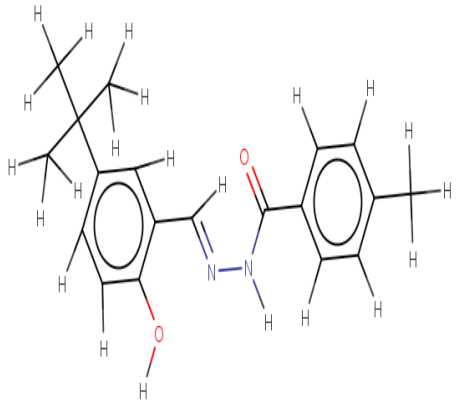
development of new drugs able to fight Chlamydia trachomatis is still in great interest. Lately, the utilization of molecular modeling has delivered exceptionally amazing outcomes in the medication disclosure measure [8]. To seek after our past work on Chlamydia trachomatis [1] and the molecular modeling study on salicylidene acylhydrazides derivatives [9]. In this place, we report the molecular modeling of salicylidene acylhydrazides derivatives. To pursue, our ongoing research on molecular modeling of Chlamydia trachomatis inhibitors. We aim in this study to find a specific interaction that may provide the best affinity with the protein than the current therapy.

Materials and Methods

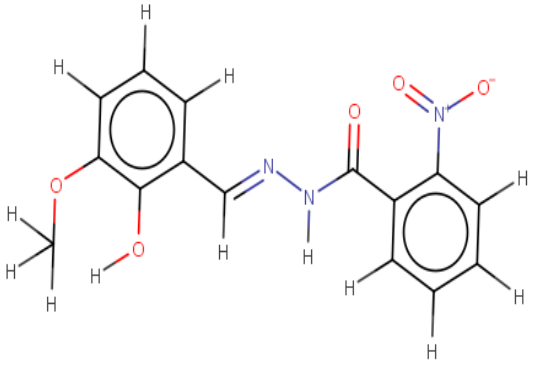
Table 1: PubChem_CID number, corresponding activity pIC_{50} of salicylidene acylhydrazides derivatives.

 1: PUBCHEM_CID 135804387; pIC_{50}=8.000	 13: PUBCHEM_CID 136167956; pIC_{50}=7.678
 2: PUBCHEM_CID 135504477; pIC_{50}=7.824	 14: PUBCHEM_CID 136167957; pIC_{50}=7.638
 3: PUBCHEM_CID 135480441; pIC_{50}=7.367	 15: PUBCHEM_CID 135615180; pIC_{50}=7.699

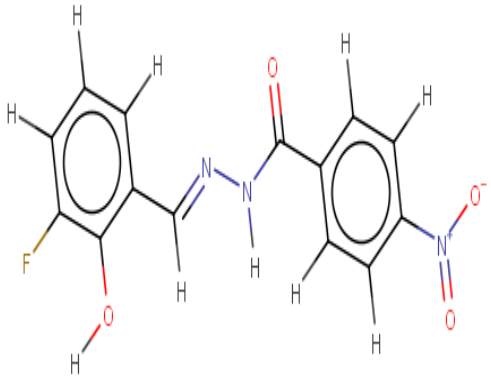
DOI: 10.26717/BJSTR.2021.36.005895



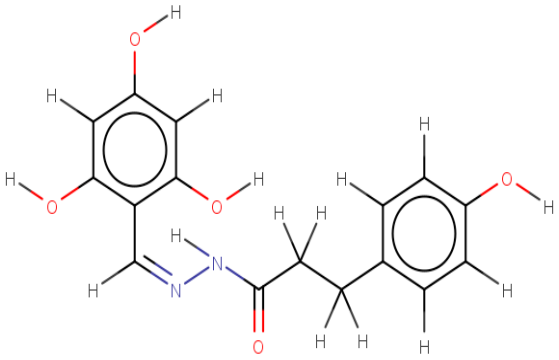
4: PUBCHEM_CID 136167947; pIC_{50}=7.699



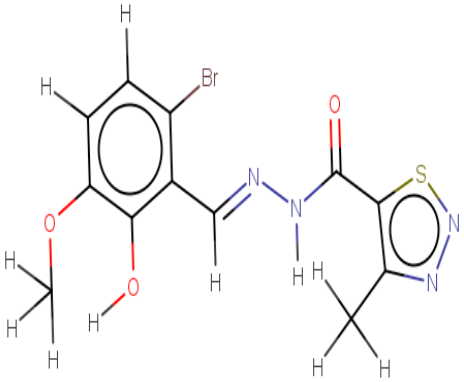
16: PUBCHEM_CID 135472433; pIC_{50}=7.721



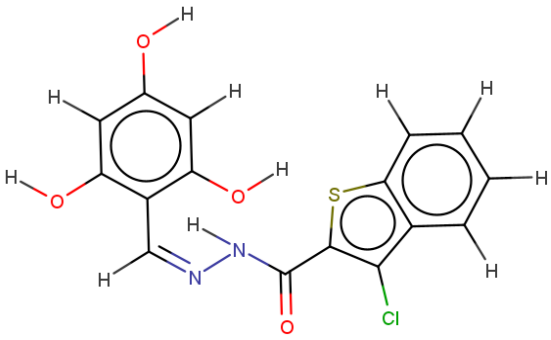
5: PUBCHEM_CID 136167948; pIC_{50}=7.721



17: PUBCHEM_CID 136167958; pIC_{50}=7.602

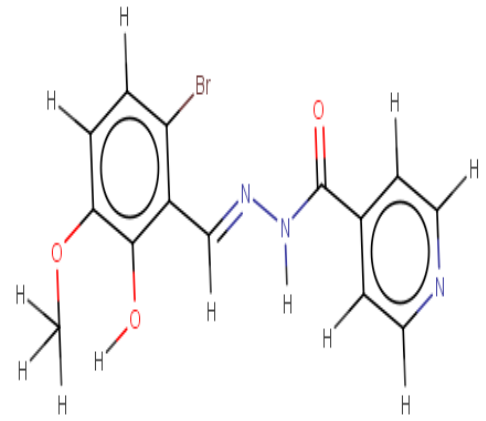


6: PUBCHEM_CID 136167949; pIC_{50}=7.469

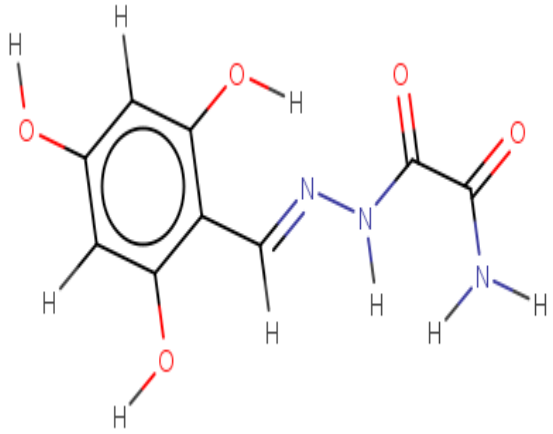


18: PUBCHEM_CID 136167959; pIC_{50}=7.357

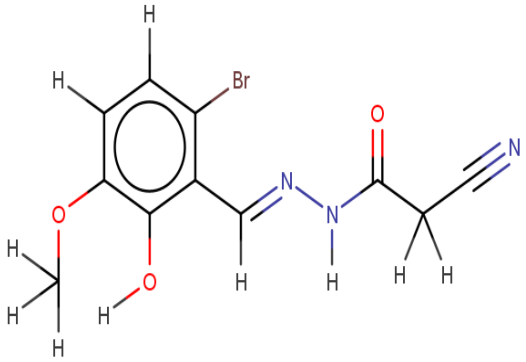
DOI: 10.26717/BJSTR.2021.36.005895



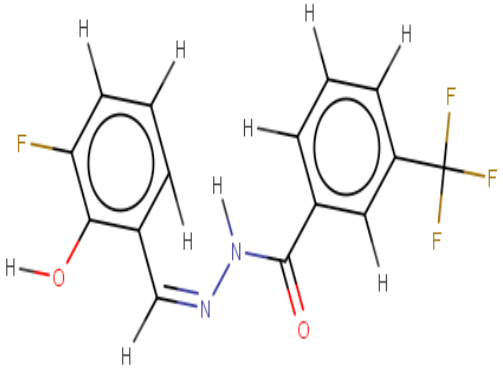
7: PUBCHEM_CID 136167950; pIC_{50}=7.569



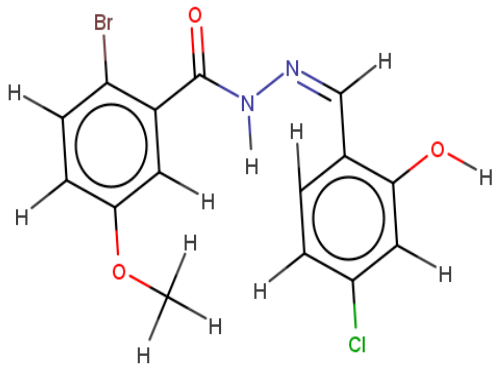
19: PUBCHEM_CID 136167960; pIC_{50}=7.585



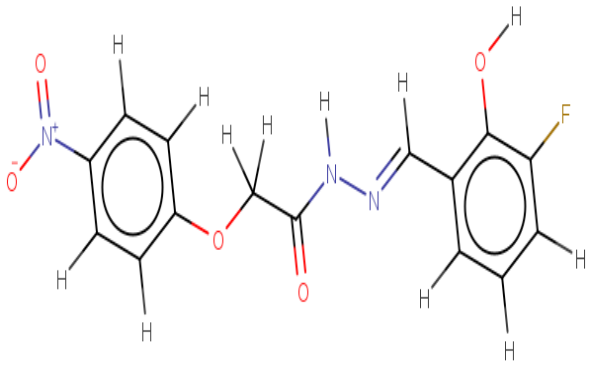
8: PUBCHEM_CID 136167951; pIC_{50}=7.699



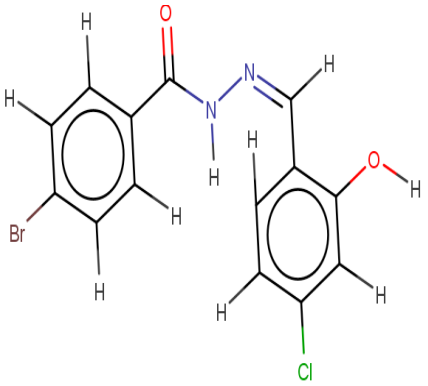
20: PUBCHEM_CID 136167961; pIC_{50}=7.523



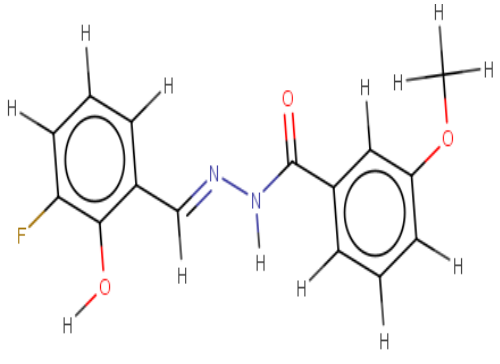
9: PUBCHEM_CID 136167952; pIC_{50}=7.509



21: PUBCHEM_CID 136167962; pIC_{50}=7.602

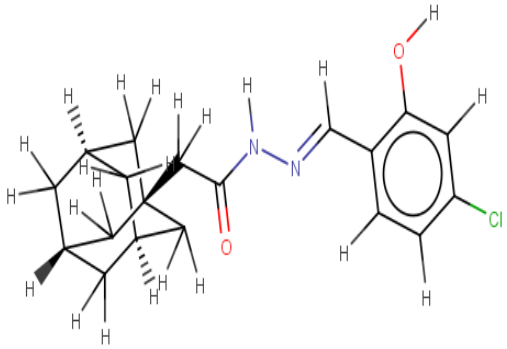


10: PUBCHEM_CID 136167953; pIC_{50}=7.538

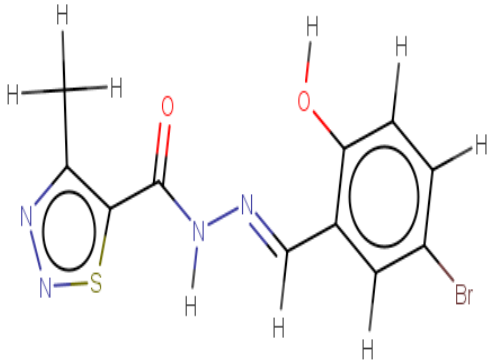


22: PUBCHEM_CID 136167963; pIC_{50}=7.770

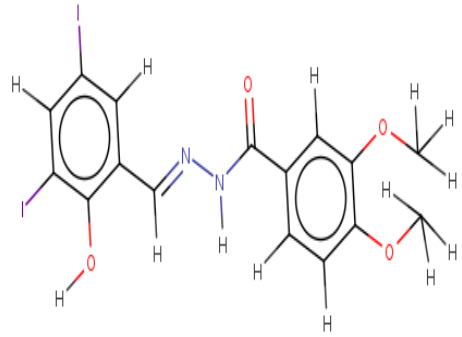
DOI: 10.26717/BJSTR.2021.36.005895



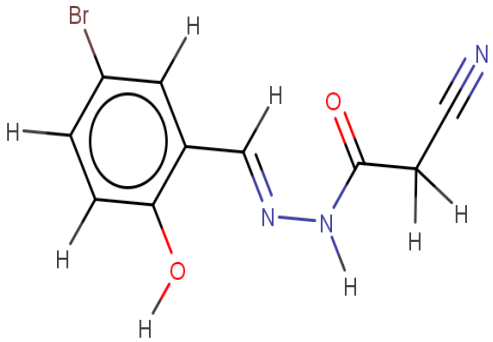
11: PUBCHEM_CID 136167954; pIC_{50}=7.602



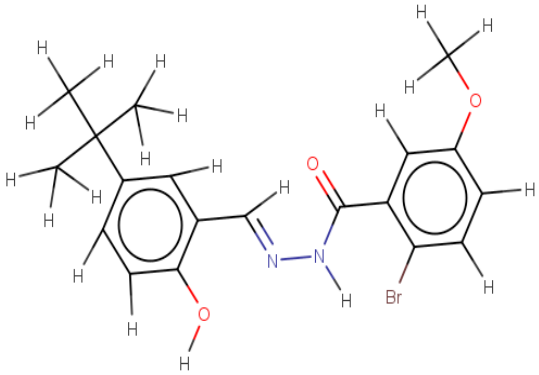
23: PUBCHEM_CID 135501372; pIC_{50}=7.699



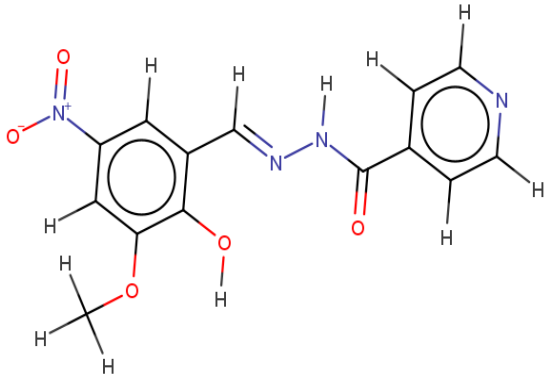
12: PUBCHEM_CID 136167955; pIC50=7.529



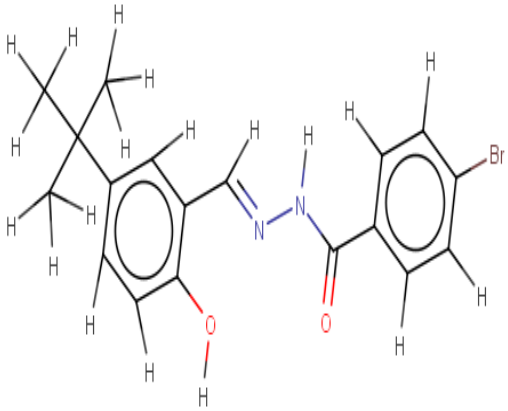
24: PUBCHEM_CID 135567720; pIC_{50}=7.260



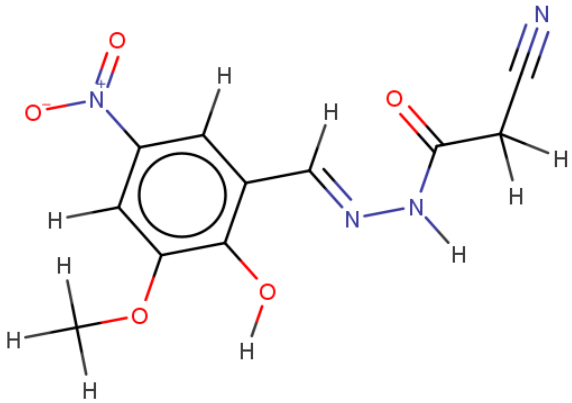
25: PUBCHEM_CID 136167964; pIC_{50}=7.745



40: PUBCHEM_CID 135589440; pIC_{50}=7.553

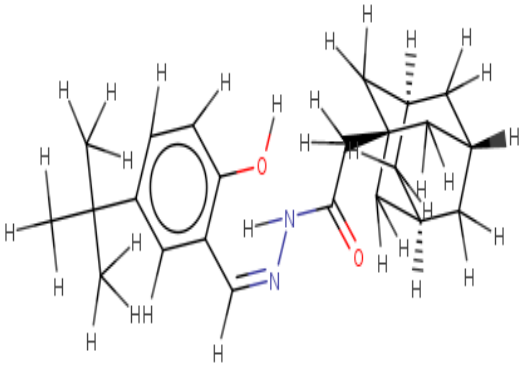


26: PUBCHEM_CID 136167965; pIC_{50}=7.469

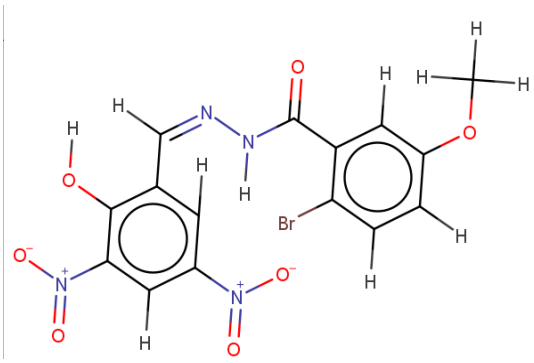


41: PUBCHEM_CID 135439717; pIC_{50}=7.569

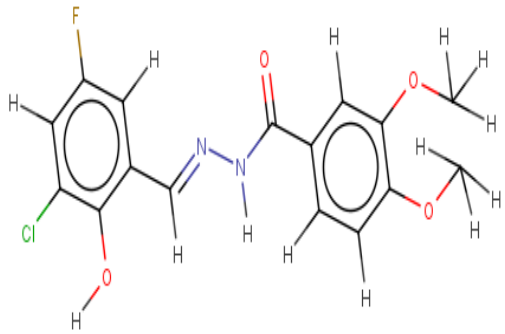
DOI: 10.26717/BJSTR.2021.36.005895



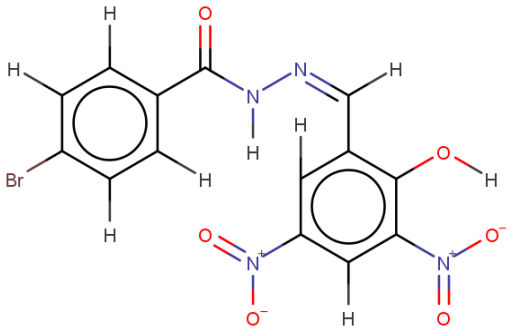
27: PUBCHEM_CID 136167966; pIC_{50}=7.770



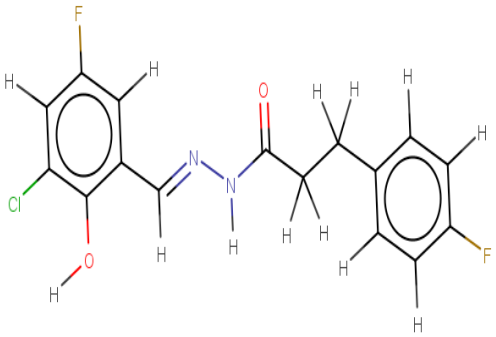
42: PUBCHEM_CID 136167977; pIC_{50}=7.638



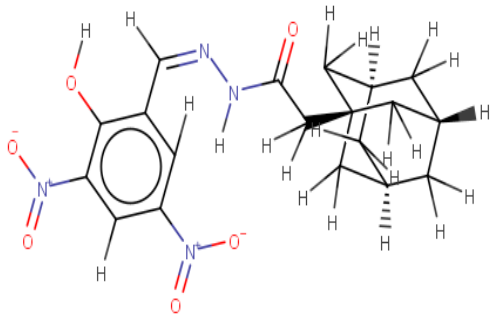
28: PUBCHEM_CID 136167967; pIC_{50}=8.000



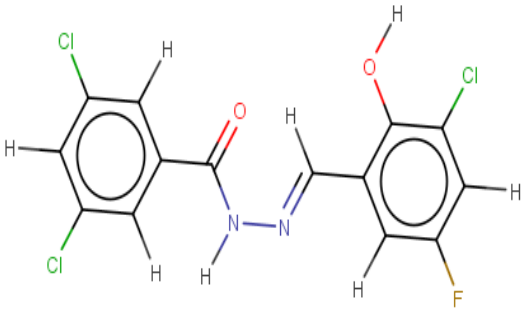
43: PUBCHEM_CID 135628628; pIC_{50}=7.721



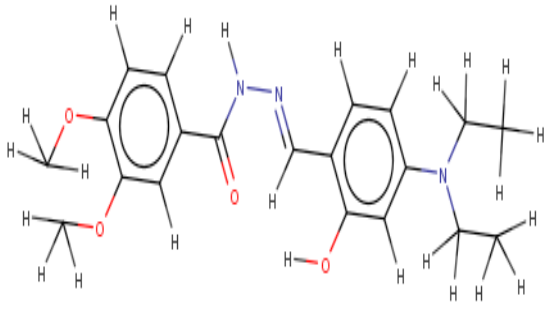
29: PUBCHEM_CID 136167968; pIC_{50}=7.824



44: PUBCHEM_CID 136167978; pIC_{50}=8.222

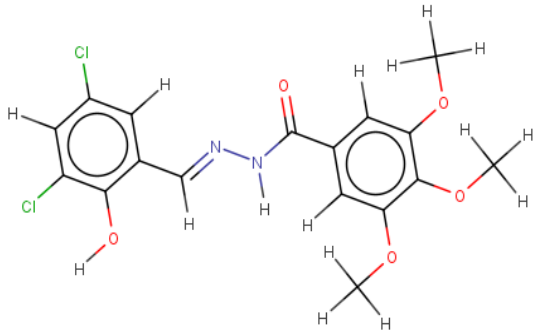


30: PUBCHEM_CID 136167969; pIC_{50}=7.959

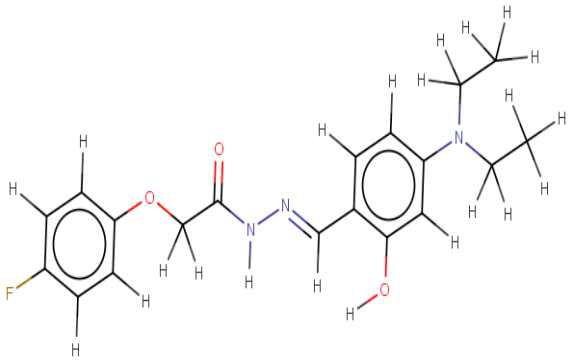


45: PUBCHEM_CID 135518293; pIC_{50}=7.357

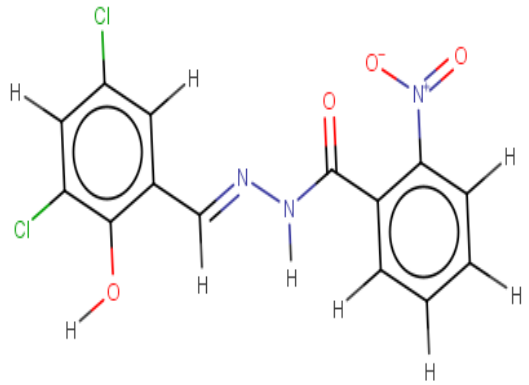
DOI: 10.26717/BJSTR.2021.36.005895



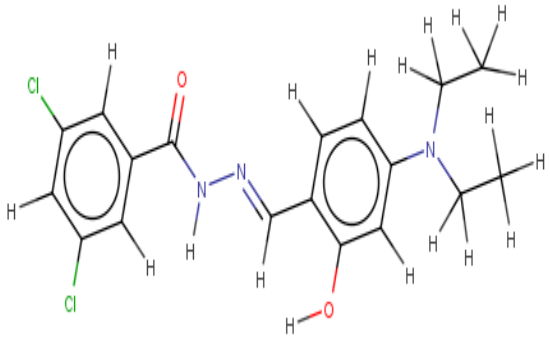
31: PUBCHEM_CID 135643056; pIC_{50}=7.745



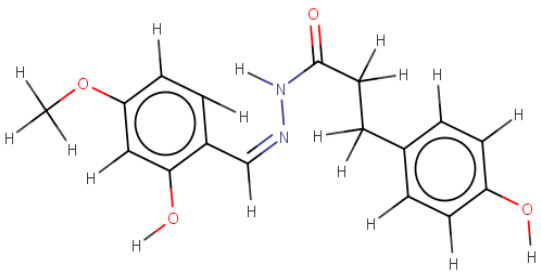
46: PUBCHEM_CID 136142892; pIC_{50}=7.456



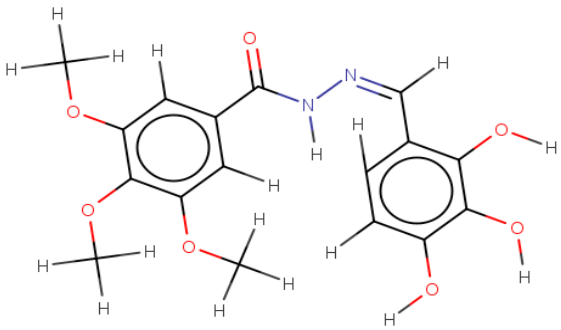
32: PUBCHEM_CID 135495624; pIC_{50}=7.745



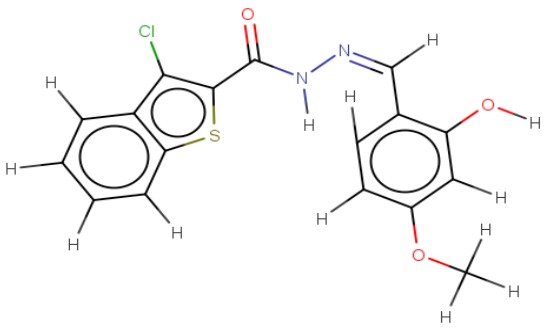
47: PUBCHEM_CID 136167979; pIC_{50}=7.469



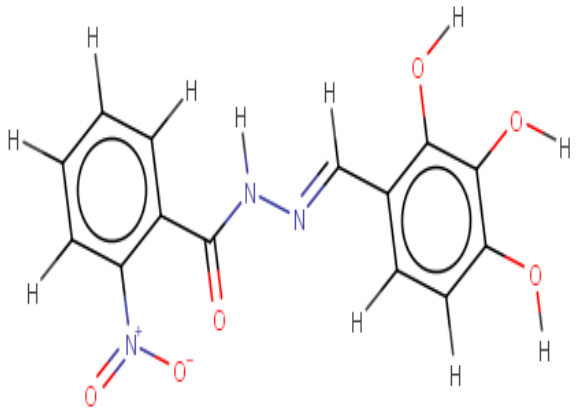
33: PUBCHEM_CID 136167970; pIC_{50}=7.921



48: PUBCHEM_CID 136167980; pIC_{50}=7.509

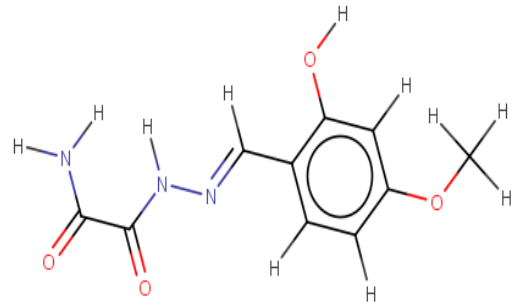


34: PUBCHEM_CID 136167971; pIC_{50}=7.824

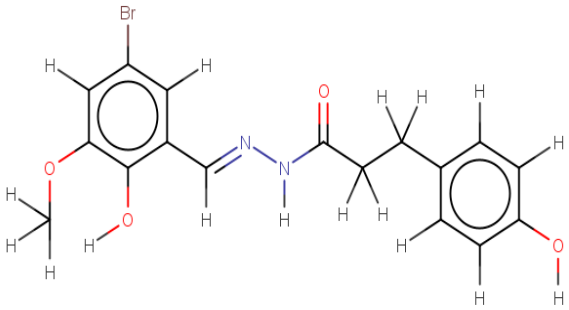


49: PUBCHEM_CID 136167981; pIC_{50}=7.658

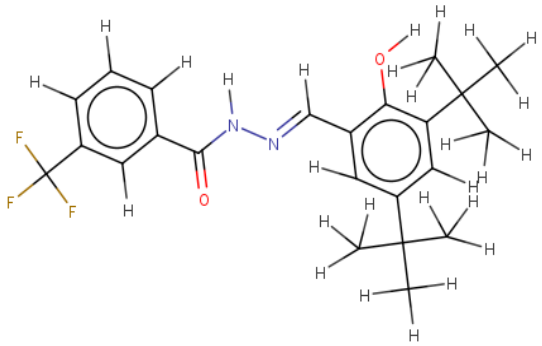
DOI: 10.26717/BJSTR.2021.36.005895



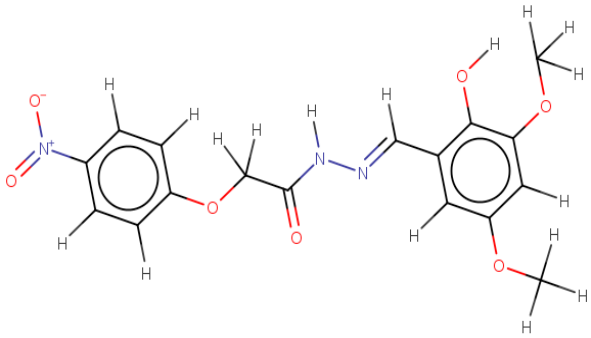
35: PUBCHEM_CID 136167972; pIC_{50}=7.886



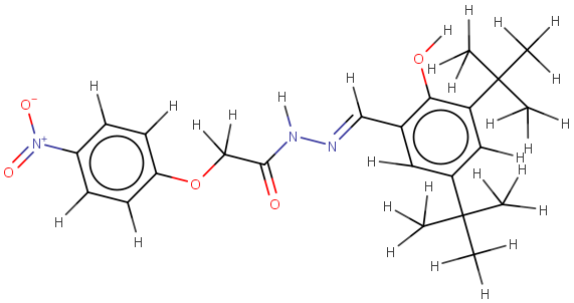
50: PUBCHEM_CID 136167982; pIC_{50}=7.745



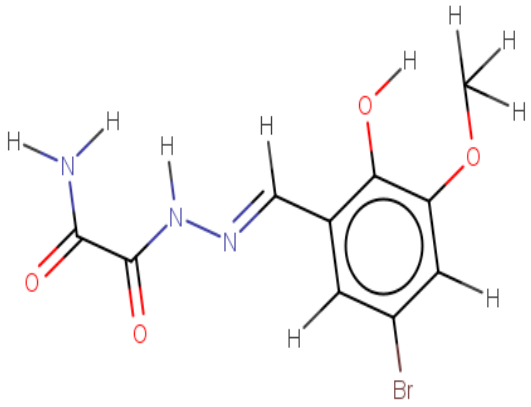
36: PUBCHEM_CID 136167973; pIC_{50}=8.222



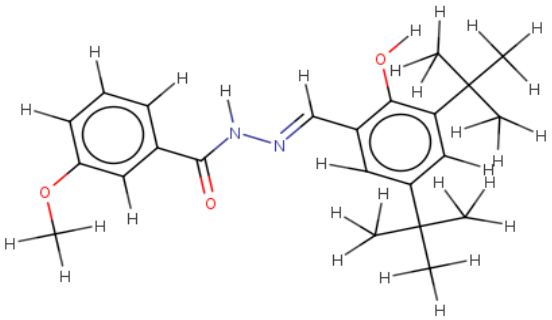
51: PUBCHEM_CID 136167983; pIC_{50}=7.745



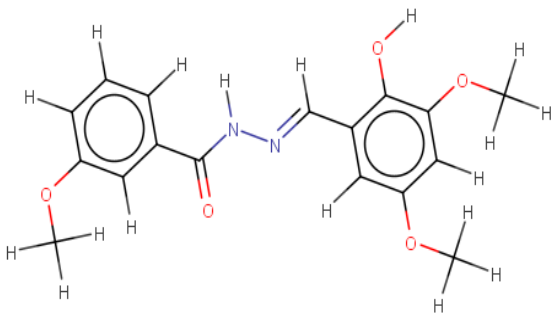
37: PUBCHEM_CID 136167974; pIC_{50}=7.921



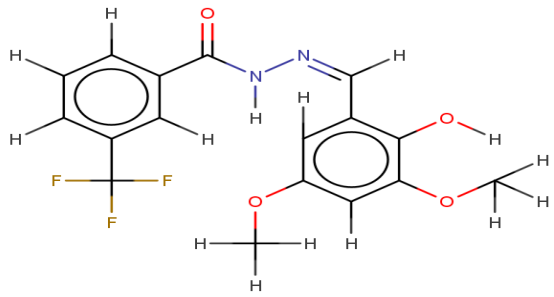
52: PUBCHEM_CID 135815951; pIC_{50}=8.000



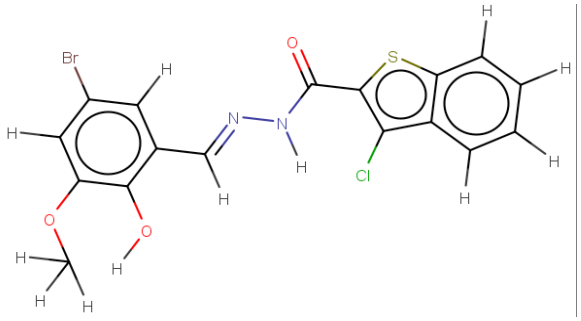
38: PUBCHEM_CID 136167975; pIC_{50}=7.854



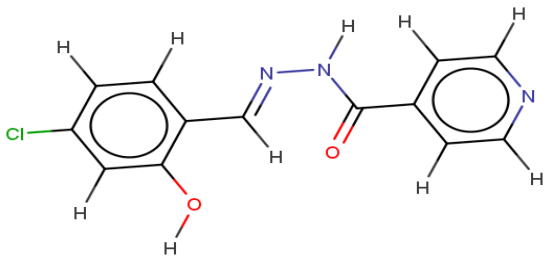
53: PUBCHEM_CID 136167984; pIC_{50}=7.699



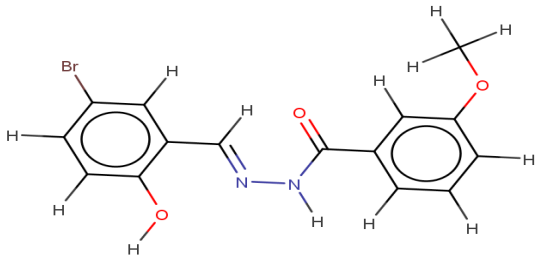
39: PUBCHEM_CID 136167976; pIC_{50}=7.409



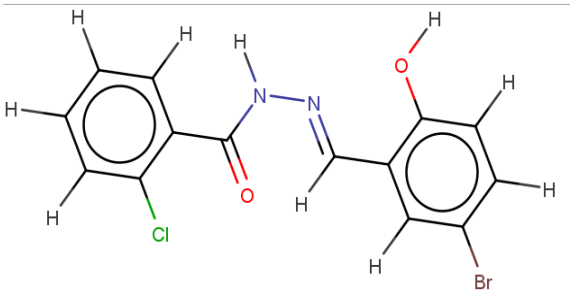
54: PUBCHEM_CID 136167985; pIC_{50}=7.638



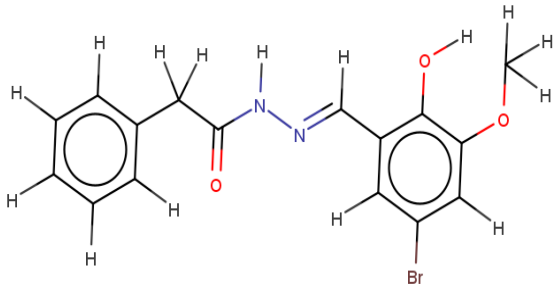
55: PUBCHEM_CID 136167986; pIC_{50}=7.569



57: PUBCHEM_CID 135615174; pIC_{50}=7.658



56: PUBCHEM_CID 135521406; pIC_{50}=7.959



58: PUBCHEM_CID 135536260; pIC_{50}=8.046

In the present study, we have selected 58 salicylidene acylhydrazides derivatives from the literature [9] that have been already validated to have antimicrobial activity. All compounds were tried utilizing a similar test strategy and a wide scope of Chlamydia trachomatis hindrance biological activities were covered. Structures picked out were modify to achieve maximum efficiency in storage capacity, time or cost with the semiempirical PM3 method using the Spartan'14 software (www.wavefun.com) (Table 1). The modify to achieve maximum efficiency in storage capacity (optimized) structures were saved in .pdb format for further studies as docking software takes .pdb format as an input file.

Protein Preparation

The strength of association or binding affinity between two molecules can be predicted by molecular docking techniques. In the current study, we have selected 58 phytochemical compounds that have been suggested to possess potential antimicrobial activity. The three-dimensional structure of receptors such as the crystal structure of IncA was retrieved from RCSB (www.rcsb.org/pdb) protein data bank (PDB Code: 6e7e) [10]. The whole structure of the receptors was targeted for our molecular docking study except heteroatoms that were detected from the receptors. Docking analysis was performed using iGemdock, [11] which uses empirical scoring function and Generic Evolutionary Method for molecular docking. It has a graphical user interface that recognizes the pharmacological interactions and performs virtual screening. It has been decided to select the following parameters for docking as Population size: 200, Number of generations: 70, and Number of solutions: 3. The docking simulation interaction was visualized through Discovery studio software.

Results and Discussion

Four anti-chlamydia trachomatis drugs- Ampicillin, Oxytetracycline, Chlortetracycline, and Ceftriaxone (Azithromycin) were used as a control for the following study. The four were docked

into the enzyme; iGemdock by calculating their binding energy, Vander Waals energy, electrostatic energy, hydrogen bonding. The post analysis tools of iGemdock works by using K-means and hierarchal clustering methods. (Table 2) shows the summary of docking results. Binding energies of the receptor-ligand interactions are very important to report how fit the drug binds to the target macromolecule. It can be calculated that according to iGemdock docking results Ampicillin is the best binding receptor because of its total energy of -92.5875kcal/mol. The lesser the energy greater will be acceptability of the chemical as a drug. (Figure 1), shows the binding interactions of the controls (drugs) with the studied protein, where Ampicillin (Figure 1a), Oxytetracycline (Figure 1b), and Chlortetracycline (Figure 1c) was found to have unfavorable interactions with the protein. Ceftriaxone (Azithromycin) has a Van der Waals interaction of -55.1418 kcal/mol, electrostatic interaction of -1.65517 kcal/mol, the total binding energy is equal to -82.7819 kcal/mol with no unfavorable bump or donor-donor interaction (Figure 1d).

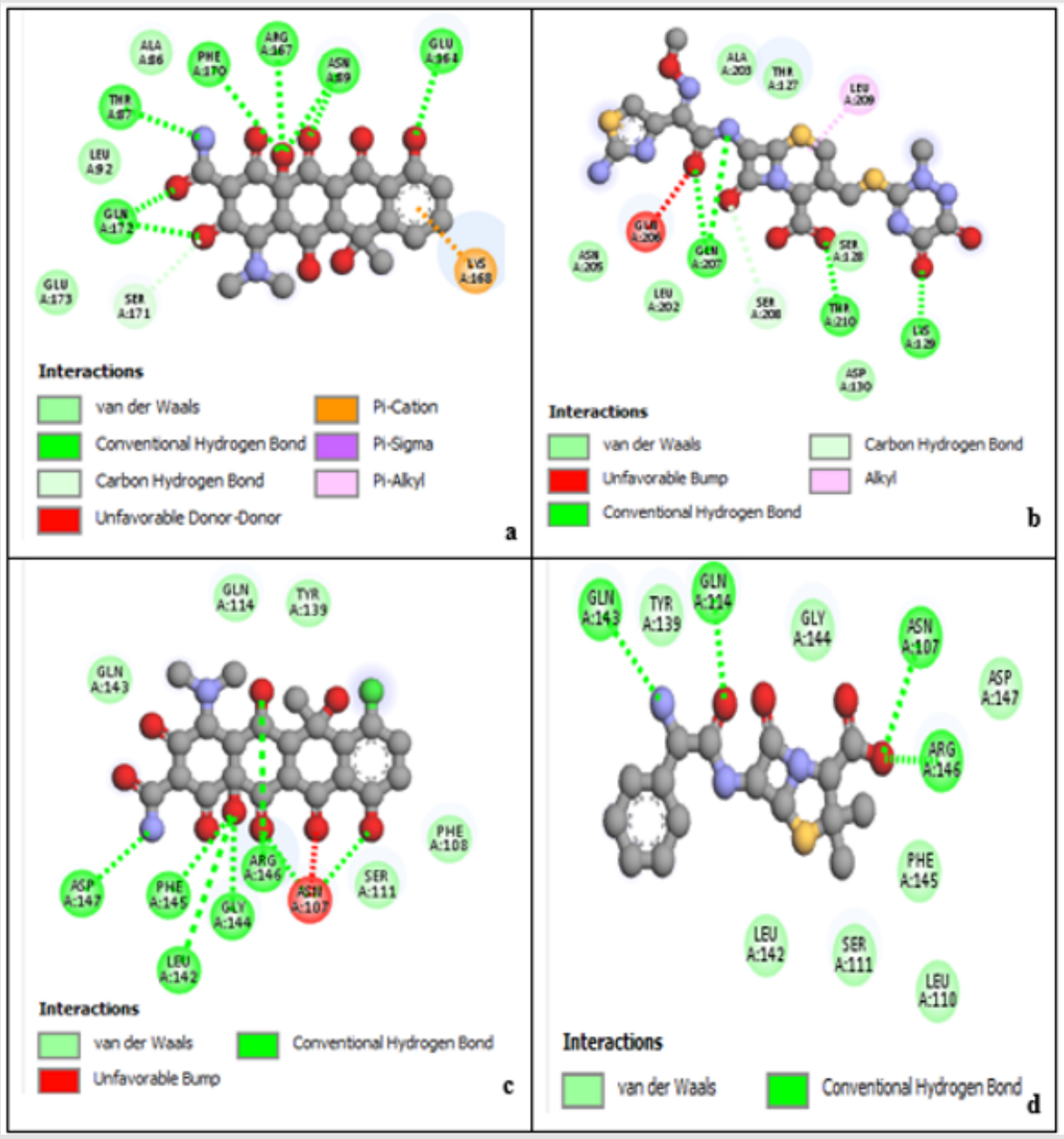
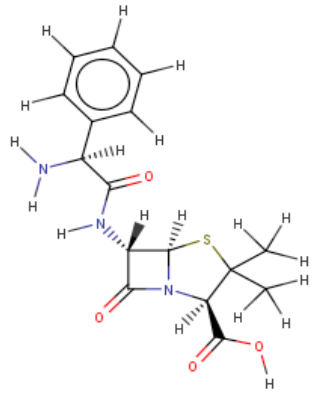
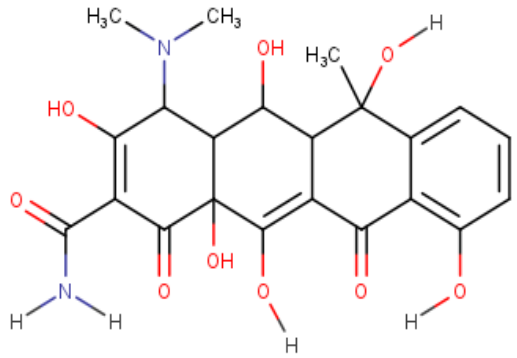


Figure 1: Binding interaction of the control/standard drugs with the macromolecule.

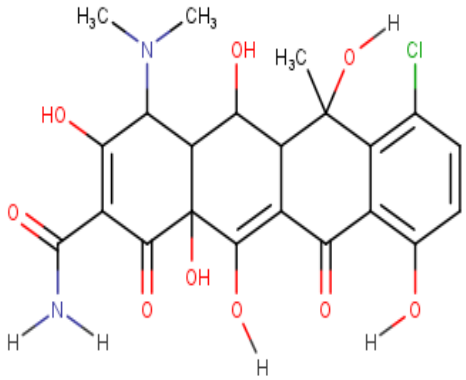
Table 2: Structures and docking results (kcal/mol) of standard in the active site of the protein.



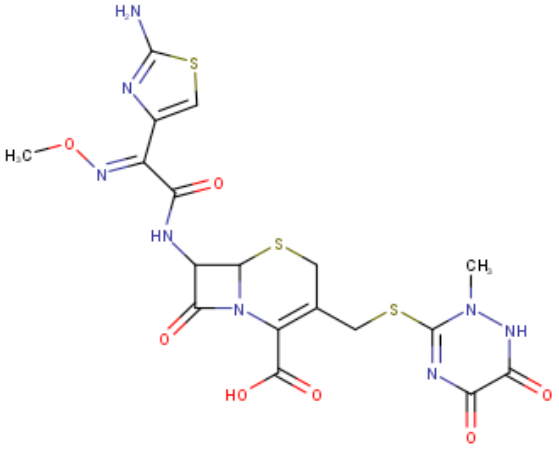
Ampicillin



Oxytetracycline



Chlortetracycline



Ceftriaxone

#Ligand	Total Energy	VDW	H-Bond	Elec
Ampicillin	-92.5875	-64.7854	-27.8021	0
Oxytetracycline	-90.744	-62.8534	-27.8906	0
Chlortetracycline	-90.6709	-54.49	-36.1809	0
Ceftriaxona	-82.7819	-55.1418	-25.9849	-1.65517

According to research, Ceftriaxone (Azithromycin) has common side effects include pain at the side of injection and allergic reaction. Other possible side effects include gall bladder disease, seizures, hemolytic, anemia, etc. (Table 3) show the molecular docking results of the salicylidene acylhydrazides derivatives were Compound 44 (N'-[(Z)-(2-hydroxy-3,5-dinitrophenyl) methylidene]-2-[(3R,5S,7s)-adamantan-1-yl]acetohydrazid) has the best binding energy of -87.3827 kcal/mol and (Figure 2) shows the binding interaction with the protein. Compound 44 however, was found to have the lowest Van der Waals interaction (−87.3827) than the standards (control) and engaged in pi-donor hydrogen bond between HIS249, pi-pi-Stacked and Amide-pi-Stacked interaction. Compound 44 was showing better interaction than the standard or control drugs available in the market. It also showed better binding energy than the Ceftriaxone. The possible binding modes of compound 44 at the target protein active sites have been shown in (Figure 2). The protein residues Ser154, Ile241, Arg245, Thr238, Ala242, His249, Lys246, His250, and His253 were found interacting with the ligand without unfavorable bumps shows that compound 44 is better than the standard drugs with side effects and unfavorable bumps interactions.

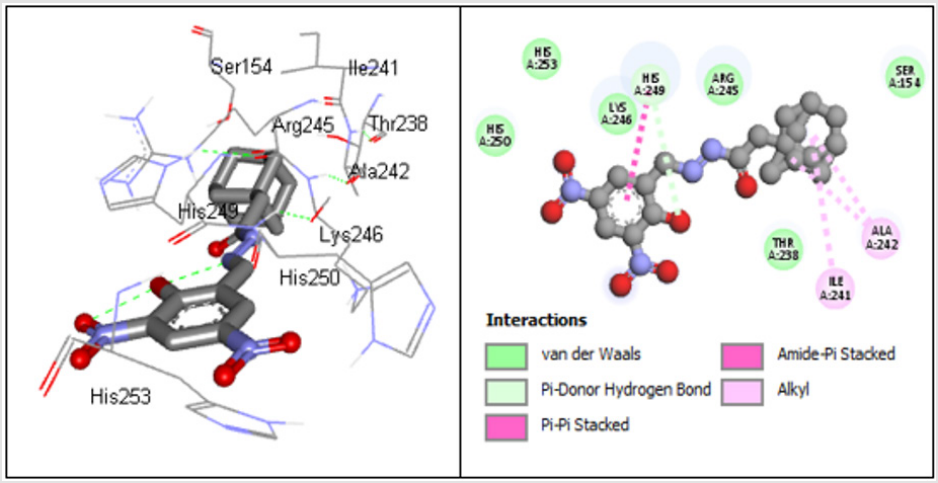


Figure 2: Interaction of compound 44 with the protein structure.

Table 3: Docking results (kcal/mol) of salicylidene acylhydrazides derivatives in the active site of the protein.

No.	#Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
1	6e7e-44-0.pdb	-87.3827	-87.3827	0	0	18.4138
2	6e7e-43-0.pdb	-78.9421	-78.9421	0	0	19.04
3	6e7e-4-2.pdb	-78.3402	-78.3402	0	0	20.3478
4	6e7e-48-1.pdb	-77.9572	-77.9572	0	0	19.2308
5	6e7e-38-1.pdb	-76.561	-76.561	0	0	17.25
6	6e7e-54-0.pdb	-75.6408	-75.6408	0	0	18.92
7	6e7e-40-1.pdb	-74.12	-74.12	0	0	19.2609
8	6e7e-29-0.pdb	-73.4891	-73.4891	0	0	20
9	6e7e-45-1.pdb	-73.338	-73.338	0	0	18.8889
10	6e7e-45-1.pdb	-73.338	-73.338	0	0	18.8889
11	6e7e-5-2.pdb	-72.2371	-72.2371	0	0	19.0455
12	6e7e-14-1.pdb	-71.4777	-71.4777	0	0	20.3636
13	6e7e-6-1.pdb	-71.3965	-71.3965	0	0	19.7143
14	6e7e-39-0.pdb	-71.2635	-71.2635	0	0	17.0769
15	6e7e-46-1.pdb	-71.1864	-71.1864	0	0	16.4231
16	6e7e-57-1.pdb	-70.8057	-70.8057	0	0	20.1905
17	6e7e-13-0.pdb	-70.6842	-70.6842	0	0	19.4348
18	6e7e-1-2.pdb	-70.1351	-70.1351	0	0	18.2174
19	6e7e-34-0.pdb	-70.0374	-70.0374	0	0	18
20	6e7e-30-2.pdb	-69.8395	-69.8395	0	0	20.4091
21	6e7e-12-0.pdb	-69.6612	-69.6612	0	0	18.7083
22	6e7e-47-0.pdb	-69.4781	-69.4781	0	0	16.88
23	6e7e-28-1.pdb	-69.0599	-69.0599	0	0	17.4167
24	6e7e-41-1.pdb	-68.9204	-68.9204	0	0	20.05
25	6e7e-22-1.pdb	-68.7563	-68.7563	0	0	19.5238
26	6e7e-16-0.pdb	-67.8887	-67.8887	0	0	18.5652
27	6e7e-17-1.pdb	-67.8206	-67.8206	0	0	16.3478
28	6e7e-33-0.pdb	-67.7813	-67.7813	0	0	17.1739
29	6e7e-23-1.pdb	-66.7408	-66.7408	0	0	20.4737
30	6e7e-57-0.pdb	-66.5272	-66.5272	0	0	17.8095

31	6e7e-10-0.pdb	-64.5692	-64.5692	0	0	20.15
32	6e7e-26-2.pdb	-63.4082	-63.4082	0	0	18.2609
33	6e7e-35-0.pdb	-61.2651	-61.2651	0	0	21.6471
34	6e7e-52-2.pdb	-61.1252	-61.1252	0	0	19.3333
35	6e7e-19-0.pdb	-57.6773	-57.6773	0	0	21.4706
36	6e7e-8-0.pdb	-57.1784	-57.1784	0	0	21.3333
37	6e7e-8-0.pdb	-57.1784	-57.1784	0	0	21.3333
38	6e7e-24-1.pdb	-56.8114	-56.8114	0	0	23.5625
39	6e7e-37-0.pdb	-38.9493	-38.9493	0	0	13.2258
40	6e7e-58-0.pdb	-31.2029	-31.2029	0	0	13.3182
41	6e7e-21-0.pdb	-9.41303	-9.41303	0	0	12.375
42	6e7e-15-0.pdb	-1.74972	-1.74972	0	0	10
43	6e7e-50-0.pdb	0.890899	0.890899	0	0	14.0417
44	6e7e-18-0.pdb	11.5326	11.5326	0	0	17.625
45	6e7e-27-0.pdb	18.0226	18.0226	0	0	18.2222
46	6e7e-31-0.pdb	29.5633	29.5633	0	0	12.8846
47	6e7e-2-0.pdb	30.294	30.294	0	0	17.2
48	6e7e-9-0.pdb	56.4153	56.4153	0	0	16.5455
49	6e7e-9-0.pdb	56.4153	56.4153	0	0	16.5455
50	6e7e-51-0.pdb	70.1743	70.1743	0	0	16.1481
51	6e7e-42-0.pdb	91.6956	91.6956	0	0	13.8889
52	6e7e-25-0.pdb	98.3126	98.3126	0	0	15.44
53	6e7e-11-0.pdb	143.872	143.872	0	0	22.2917
54	6e7e-53-0.pdb	144.199	144.199	0	0	21.4583
55	6e7e-36-0.pdb	181.578	181.578	0	0	16.2
56	6e7e-20-0.pdb	195.275	195.275	0	0	36.8696

Conclusion

There is an urgent need to explore new therapeutic compounds which will offer safer, efficacious, and cost-effective treatment, that will improve the life quality of patients. In this study, using the molecular docking method, compound 44 (N'-[(Z)-(2-hydroxy-3,5-dinitrophenyl)methylidene]-2-[(3R,5S,7s)-adamantan-1-yl] acetohydrazid) has been identified to inhibit Chlamydia trachomatis. Therefore, this compound can be an effective drug candidate for controlling bacteria than the four standard drugs with side effects.

Acknowledgment

The authors gratefully acknowledge the Department of Chemistry, Ahmadu Bello University, Zaria (Samaru, Zaria-Nigeria); for computational studies, and as part of the Ph.D. thesis.

References

1. Edache EI, Uzairu A, Mamza PA, Shallangwa GA (2020) Computational Modeling and Molecular dynamics Simulations of Thiazolino 2-pyridone amide analog compounds as Chlamydia trachomatis inhibitor. J Chem Lett 1: 123-138.
2. Thabit AA, Al-Khatib T, Hail WHM, Al-Soofi A, Thabit ANA, et al. (2018) Prevalence of trachoma in Yemen: Results of population-based prevalence surveys of 42 evaluation units in nine governorates. Ophthalmic epidemiology 25(1): 62-69.
3. Mojica SA, Eriksson AU, Davis RA, Bahnan W, Elofsson M, et al. (2018) Red Fluorescent Chlamydia trachomatis Applied to Live Cell Imaging and Screening for Antibacterial Agents. Frontiers in microbiology 9: 3151.
4. Stamm WE (1991) Azithromycin in the treatment of uncomplicated genital chlamydial infections. The American journal of medicine 91(3): S19-S22.
5. Chopra I, Roberts M (2001) Tetracycline antibiotics: Mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiology and molecular biology reviews 65(2): 232-260.
6. Whitaker ED (2017) The Trouble with Human Nature: Health, Conflict, and Difference in Biocultural Perspective. Taylor & Francis.
7. Ngangom BL, Tamunjoh SSA, Boyom FF (2019) Antibiotic residues in food animals: Public health concern. Acta Ecologica Sinica 39(5): 411-415.
8. Hadni H, Elhallaoui M (2020) 2D and 3D-QSAR, molecular docking and ADMET properties in silico studies of azaaurones as antimalarial agents. New J Chem.
9. Edache EI, Uzairu A, Mamza PA, Shallangwa GA (2021) Docking Simulations and Virtual Screening to find Novel Ligands for T3S in Yersinia pseudotuberculosis YPIII, A drug target for type III secretion (T3S) in the Gram-negative pathogen Yersinia pseudotuberculosis. Chemical Reviews and Letters 4: 130-144.
10. Cingolani G, McCauley M, Lobley A, Bryer AJ, Wesolowski J, et al. (2019) Structural basis for the homotypic fusion of chlamydial inclusions by the SNARE-like protein IncA. Nature Communications 10: 2747.
11. Yang JM, Chen CC (2004) Gemdock: A generic evolutionary method for molecular docking. Proteins 55: 288-304.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2021.36.005895

Emmanuel Israel Edache. Biomed J Sci & Tech Res

Submission Link: https://biomedres.us/submit-manuscript.php