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ANTI-BACTERIAL ACTIVITY AND IN SILICO STUDIES OF PERILLYL-4H- PYRANTRIAZOLE DERIVATIVES

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ABSTRACT

The development of chemical compounds that exhibit broad-spectrum antibacterial activity requires an attentive selection of chemical entities because of the fast growth of antimicrobial resistance. In this study, we analyzed 12 Perillyl-4H-pyrantriazole derivatives **(6a-6l)** for antibacterial activity (*in vitro*) on Gram +ve and Gram -ve bacteria (*Staphylococcus aureus, Enterococcus, Bacillus subtilis, Salmonella, Escherichia coli,* and *Klebsiella*). The obtained results have shown that some derivatives are potential antibacterial agents compared to a standard streptomycin drug. Additionally, molecular properties, docking studies, ADMET, and TOP KAT studies were performed for all the compounds through *in silico* method. Among all, the compound **(6i)** has shown a potential antibacterial activity along with a high Lib dock value of 184.315 Kcal/mol.

Keywords: ADMET, Antimicrobial Resistance, Molecular Docking, Streptomycin, TOP KAT.

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INTRODUCTION

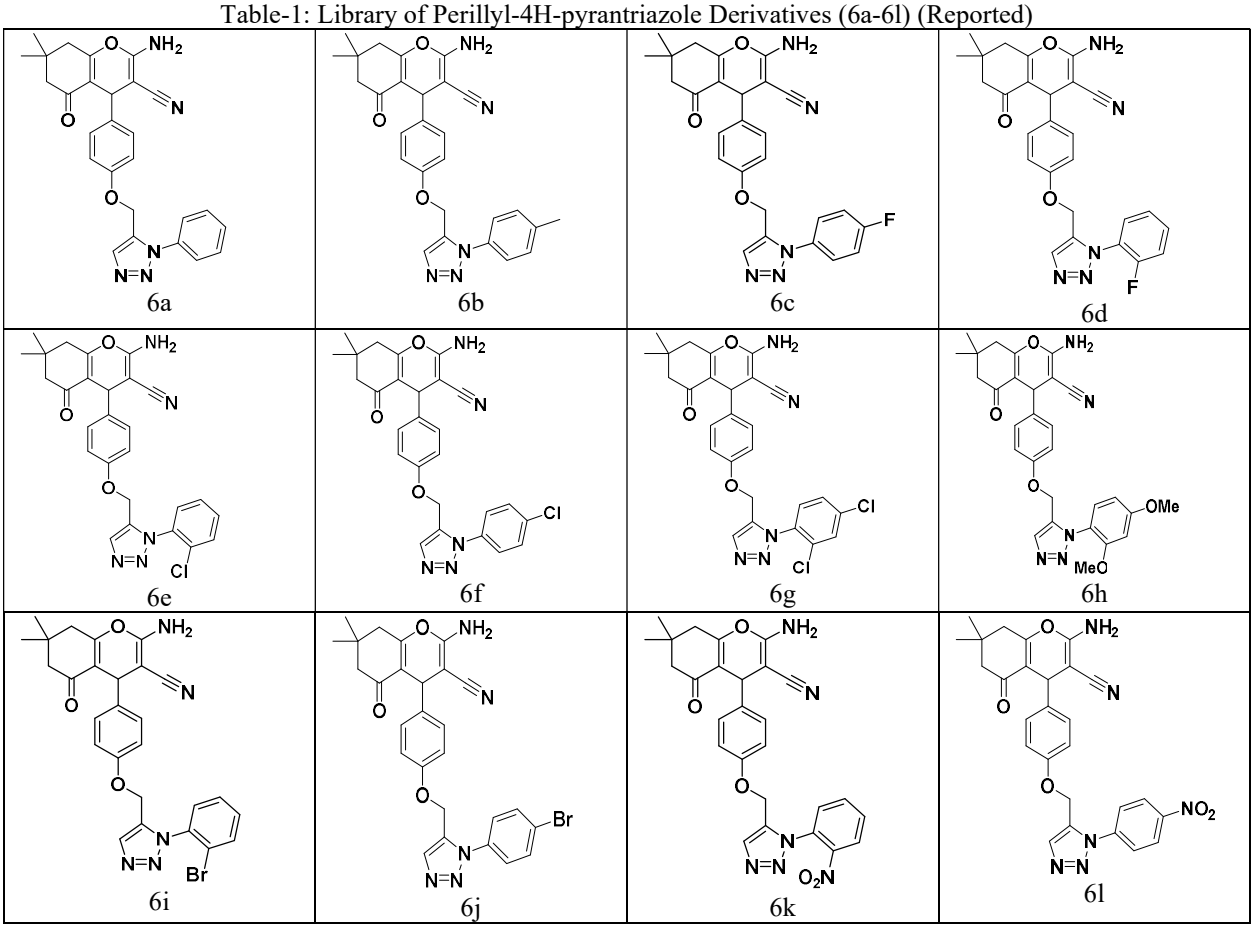
Antimicrobial resistance (AMR) is the process by which a few pathogenic microorganisms and bacteria acquire resistance to antibiotics over time, which is considered a serious global threat.[1,2] The growing AMR for many of the pathogenic microorganisms is of global concern pushing researchers worldwide for the development of novel antimicrobial agents that can combat AMR and save millions of lives.[3] Moreover, curing microbial infections with drug resistance is difficult or even impossible and affects the developing and poor countries' economies.[4,5] Significant progress has been made in recent years in terms of developing novel heterocyclic molecules with broad-spectrum antibacterial properties to combat the growing drug resistance from industry and academia as well. The significant progress in the past decades is greatly due to the understanding of mechanisms of microbes developing resistance, prevention mechanisms, and access to the new tools for designing potentially active molecules.[6-10] Most of the heterocyclic compounds are biologically active and have many applications like antibacterial, antiviral, antiallergic, antitumor, and antitubercular agents. In heterocyclic compounds, pyran and triazole scaffolds exhibit considerable antibacterial properties.[11-16] In this study, a series of twelve substituted perillyl-4H-pyrantriazole derivatives Table-1 (6a-6l), Scheme-1 were analyzed for antibacterial activity upon Gram +ve (*S.aureus, Bacillus subtilis, Enterococcus*) bacteria and Gram -ve (*E.coli, Klebsiella, Salmonella*) bacteria.[17] In order to know the modes of interaction of synthesized molecules with protein active site, molecular docking studies, molecular properties, ADMET, and TOP KAT studies are performed. The outcome of in-silico and in-vitro studies showed that substituted perillyl-4H-pyrantriazole derivatives may combat the growing antimicrobial resistance.

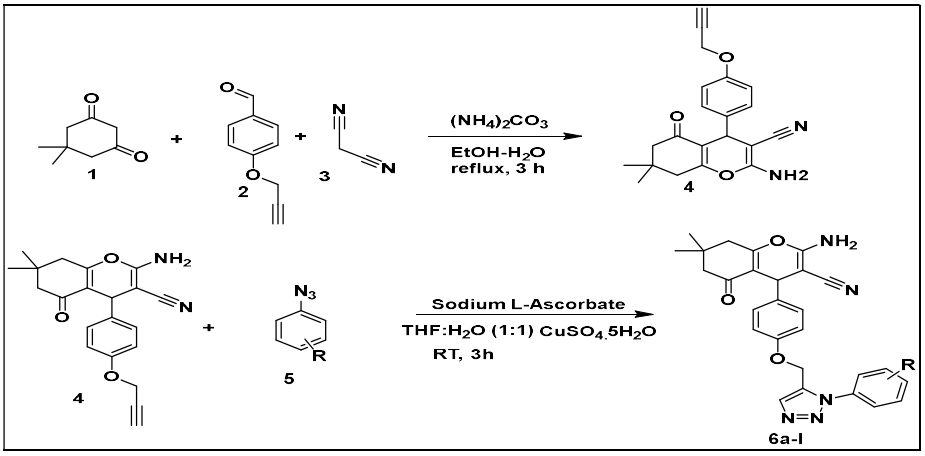
EXPERIMENTAL

Antibacterial Studies

The antibacterial strains i.e., Gram +ve (*Enterococcus, S.aureus, Bacillus subtilis*) and Gram-ve (*Salmonella, E.coli, Klebsiella*) obtained from the Lavin Laboratories, Nallakunta, Hyderabad, Telangana, India.

Table-1: Library of Perillyl-4H-pyrantriazole Derivatives (6a-6l) (Reported)





Scheme-1: Reported synthesis of perillyl-4H-pyrantriazole derivatives (6a-6l)

The well-established and broadly accepted zone of inhibition method using nutrient agar medium was employed to evaluate the antibacterial potency of the prepared library of molecules **(6a-6l)** and also compared with the standard (streptomycin). The stock cultures of bacteria were preserved in the nutrient agar media and its subcultures for antibacterial potency screening were prepared as required. Antibacterial potency of the compounds was prepared on the bacteria and evaluated by measuring the radius of a zone of inhibition i.e., the higher the radius greater the activity. The library of compounds under study was placed into agar plates containing specific bacteria, and it is incubated at the temperature of 37 °C. The zone of inhibition radii was calculated and compared across the library of compounds containing diverse chemical substitutes after the completion of 24 hrs incubation and then experimental errors were ruled out.

Molecular Docking Studies

For the accurate docking of compounds **(6a-6l)**, molecular docking is carried out using the LibDock module of Discovery Studio 2.1 (Averinbiotech Laboratories, Hyderabad). The 3D structure of a protein is taken from the PDB database (PDB ID: 5CDP) and it has a 2.45A° resolution. The crystallographic protein structure with the known inhibitor was chosen for the docking process and validated by redocking. Based on high LibDock scores and binding energies, the best ligand was confirmed.

Pharmacokinetic Properties

To evaluate the drug likeness, an ADMET study and TOP KAT toxicity are carried out for synthesized compounds in Accelrys Discovery Studio 2.1. This study includes absorption, plasma protein binding, hepatotoxicity, blood–brain barrier, aqueous solubility, cytochrome P450 CYP2D6_Probability, and the polar surface area. Moreover, the bioavailability of compounds was assessed using the topological polar surface area analysis. TOPKAT determines the value of Toxicity for all the prepared compounds. Molecular properties that include Hydrogen bond donors, molecular weight, log P, and Hydrogen bond acceptors were determined for all derivatives and obeyed Lipinski's rule.

RESULTS AND DISCUSSION

The library of perillyl-4H-pyrantriazole derivatives **(6a-6l)** was screened for potential antibacterial properties *in vitro* on selected Gram +ve and Gram –ve bacteria (*Enterococcus, B. subtilis, S. aureus, Klebsiella, Salmonella, and E. coli*). The molecules **(6a-6l)** were evaluated using a zone of inhibition method to study the anticipated broad-spectrum antibacterial properties. A zone of inhibition technique was considered to evaluate anticipated antibacterial properties owing to the advantages of being fast and inexpensive in nature, suitability for a wide range of molecules and bacteria, scalability to several samples along with its established suitability for a wide variety of antibacterial products types such as liquids, solids, and their coatings. The antibacterial potential of each of the twelve perillyl-4H-pyrantriazole derivatives **(6a-6l)** was measured in terms of the average zone of inhibition exhibited by them on Gram +ve and Gram –ve bacteria with standard concentration at 10 µg/mL and attained results are shown in Table-2. The phenyl triazole derivative **6a** showed antibacterial activity on Gram +ve bacteria (*s.aureus* (17 mm), *Bacillus subtilis* (25 mm)) and on Gram -ve bacteria (*E. coli* (12 mm), *Klebsiella* (12mm)), exhibited by a zone of the inhibition method (Table-2). 4-methyl phenyl triazole derivative **6b**, chloro phenyl triazole derivatives **6e** and **6f**, dichloro phenyl triazole derivative **6g**, and p-nitro phenyl triazole derivative **6l** exhibited considerable antibacterial activity on the studied bacteria (Table-2). 4-Fluoro phenyl triazole derivate **6c** showed reasonably good antibacterial activity on Gram-negative bacteria (Table-2). 2-fluro phenyl triazole derivative **6d** turned out to be a strong antibacterial agent on the Gram-negative bacteria (*Klebsiella* (22 mm) and *E. coli* (22 mm)). The dimethoxy phenyl derivative **6h** demonstrated strong antibacterial activity on Gram +ve and moderate activity on Gram -ve bacteria (Table-2). The bromophenyl derivative with Bromo on the para-position **6j** exhibited strong antibacterial potential selectively on Gram-negative bacteria, *Escherichia coli*. Interestingly, nitrophenyl triazole derivative with nitro on the ortho-position **6k** exhibited strong antibacterial activity on Gram +ve bacteria, but almost no observable activity on Gram -ve (Table-2). The differential antibacterial potentials of **6j** and **6k** on Gram +ve and Gram -ve bacteria emphasize the significance of the judicious choice of chemical entities and their substitution position in successful antimicrobial development. The 2-Bromo phenyl triazole derivative **6i** showed strong activity on Gram +ve bacteria (*S. aureus* (27 mm), *Bacillus subtilis* (24 mm)), and also on Gram-ve bacteria (*Klebsiella* (21 mm), *E. coli* (11 mm)) (Table-2). Overall antibacterial studies using perillyl-4H-pyrantriazole derivatives **(6a-6l)** represent the rational design strategy for developing novel antibacterial agents. For all compounds, antibacterial studies along with reference drug i.e., streptomycin are graphically represented in Fig.-1 and 2.

Molecular Docking Studies

In order to know the interaction of ligand and its inhibitory potential to DNA gyrase (PDB ID: 5CDP), molecular docking was performed in Discovery Studio 2.1(LibDock). A docking study was performed on perillyl-4H-pyrantriazole derivatives and also known as standard streptomycin drugs. The best compound was confirmed on the basis of calculated binding energy and good LibDock value.

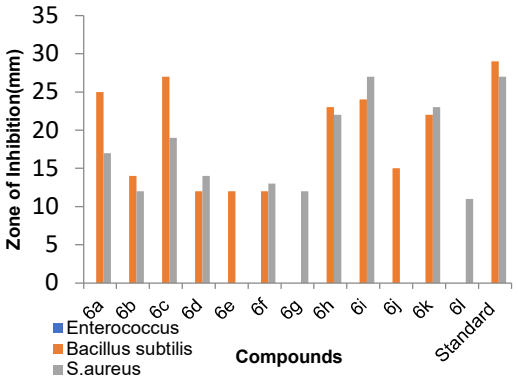


Fig.-1: Zone of inhibition of prepared perillyl-4H-pyrantriazole derivatives (6a-6l) and standard drug on Gram +ve bacteria

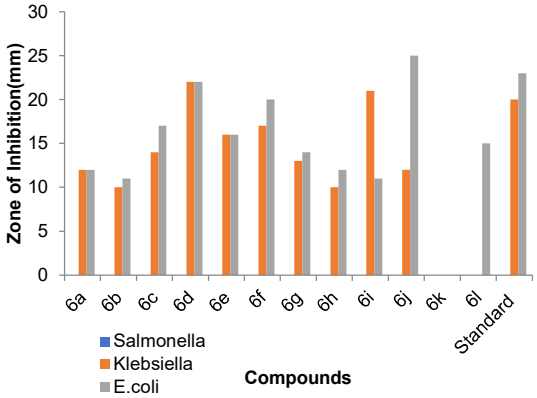


Fig.-2: Zone of inhibition of prepared perillyl-4H-pyrantriazole derivatives (6a-6l) and standard drug on Gram -ve bacteria.

The docking data of compounds are shown in Table-3, with a comparison of streptomycin 187.377kcal/mol, the *in vitro*, an active compound **(6i)** showed a good docking score of 184.315 kcal/mol. The Fig.-3 shows that the compound **(6i)** has the best conformation for H-bond interaction. Therefore, for verification of docking and to know the effectiveness of the binding, the co-crystallized ligand (etoposide) was redocked.

Table-2: Antibacterial Activity of perillyl-4H-pyrantriazole Derivatives (6a-6l) (µg/ml concentration)

Compound	Zone_ Inhibition (mm)					
	Gram +ve			Gram -ve		
	Entero-coccus	*Bacillus subtilis*	*S. aureus*	*Salmonella*	*Klebsiella*	*E. coli*
6a	-	25	17	-	12	12
6b	-	14	12	-	10	11
6c	-	27	19	-	14	17
6d	-	12	14	-	22	22
6e	-	12	-	-	16	16
6f	-	12	13	-	17	20
6g	-	-	12	-	13	14
6h	-	23	22	-	10	12
6i	-	24	27	-	21	11
6j	-	15	-	-	12	25
6k	-	22	23	-	-	-
6l	-	-	11	-	-	15
Standard (Streptomycin)	-	29	27	-	20	23

- denotes no activity

Table-3: Molecular Docking of Synthesized Derivatives (6a-6l)

Name	LibDock Score	Binding Energy (Kcal/Mol)	H-bond Count	Interacting atoms	H-Bond Distance
6a	185.203	-11.92597	2	B: ARG458:HH21 - 6a.mol: N13 6a.mol: H44 – H: DC2012:O2	2.260000 2.464000
6b	183.577	42.7999	2	B:ASP437:HN - 6b.mol: N13 6b.mol: H45 - G: DT2010: O4'	2.138000 2.122000
6c	180.629	-38.65697	3	B: ARG458: HH21 - 6c.mol: N3 G: DG2009: H21 - 6c.mol: N2 G: DG2009: H21 - 6c.mol: N3	2.166000 2.304000 1.721000
6d	173.376	-46.55734	2	B: ASP437: HN - 6d.mol: N13 6d.mol: H45 - G: DT2010: O4'	1.964000 2.104000
6e	184.29	-52.62597	3	6e.mol: H45 - G: DT2010: O4' 6e.mol: H44 - B: ASP437: OD2 B: ASP437: HN - 6e. mol: N13 G:DG2009: H21 - 6e.mol: C27	2.283000 2.497000 2.462000 2.115000
6f	189.635	-54.12597	2	B: ASP437: HN - 6f.mol: N13 6f.mol:H45 – G: DT2010: O4' G: DG2009:H21 - 6f.mol:C27	2.489000 2.190000 2.088000
6g	173.545	-19.67597	2	B: ASP437: HN - 6g.mol: N2 B: ASP437: HN - 6g.mol: N3	2.256000 2.137000
6h	196.388	-54.96467	2	B: ASP437: HN - 6h.mol: N13 6h.mol: H47 - B:ASP437: OD2 6h.mol: H48 – G: DT2010: O4' G: DG2009: H21 - 6h.mol: C27	2.354000 2.402000 2.311000 2.092000
6i	184.315	-39.23371	2	6i.mol: H45 - H: DC2012: O2 B: ARG458: HH21 - 6i.mol: N13 H:DC2012: C1' - 6i.mol:H45 G: DG2009:C6 - 6i.mol: H51	2.438000 2.157000 2.204000 2.167000

				G: DG2009: O6 - 6i.mol: H51	1.997000
6j	185.88	-39.00238	2	B: ASP437: HN - 6j.mol: N13 6j.mol: H45 – G: DT2010:O4' G: DG2009: H21 - 6j.mol: C27	2.299000 2.124000 2.084000
6k	173.36	-17.62853	3	B:ASP437: HN - 6k.mol: O37 B:ASP437: HN - 6k.mol: N3 B: ASP437: HN - 6k.mol: N2	2.418000 2.384000 2.264000
6l	196.278	-59.73394	2	B: ASP437: HN - 6l.mol: N13 6l.mol:H47 - G: DT2010: O4' G: DG2009: H21 - 6l.mol:C27 G: DT2010:C4'- 6l.mol:H47	2.324000 2.088000 2.166000 2.150000
Streptom-ycin	187.377	-102.86163	4	Streptomycin: H42 - E: DG8: O3' Streptomycin: H47- E: DG8:N7 Streptomycin: H50- E: DG8:OP1 Streptomycin: H52- E: DG8:OP2 Streptomycin: H5 - B: GLU435:O	1.959000 2.388000 1.931000 2.444000 2.064000
etoposide	209.899	-68.48204	3	H: DC2013: H42 - etoposide: O3 B:ASP437: HN - etoposide: O13 etoposide: H45 - G: DG2009: O3'	2.440000 2.138000 2.388000

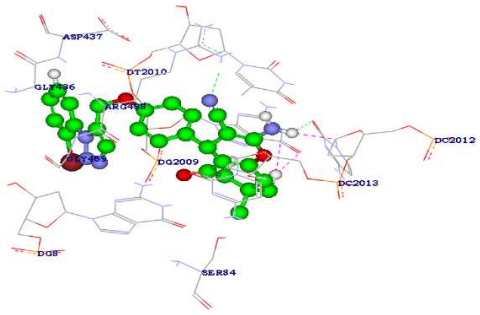


Fig.-3: Hydrogen bond interactions of 6i derivative, Pink colour indicates bumps and Green dotted lines indicate Hydrogen bonds.

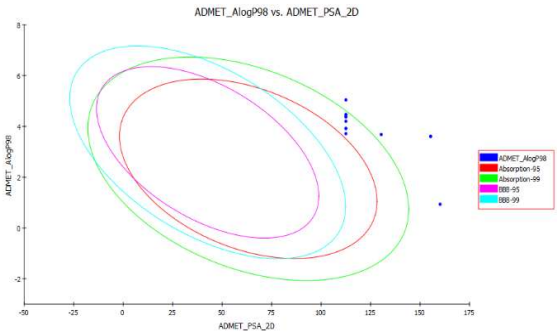


Fig.-4: PSA Vs. logP for all the synthesized derivatives.

Molecular Properties

The movement of drugs in humans describes absorption, metabolism, distribution, and also excretion is identified by Lipinski rule five (mol. wt. ≤500, Hydrogen bond acceptor ≤10, Hydrogen bond donor ≤5,

logp ≤5). The drug likeness of all the compounds is listed in Table-4. It was observed that all synthetic derivatives followed Lipinski rules.

Table-4: Molecular Properties of Synthesized Derivatives (6a-6l)

Compound	LogP	M.Wt	No. of H-bond Acceptors	No. of H-bond Donors	Rotatable Bonds
6a	3.714	467.519	7	1	5
6b	4.201	481.546	7	1	5
6c	3.92	485.51	7	1	5
6d	3.92	485.51	7	1	5
6e	4.379	501.964	7	1	5
6f	4.379	501.964	7	1	5
6g	5.043	536.409	7	1	5
6h	3.682	527.571	9	1	7
6i	4.463	546.415	7	1	5
6j	4.463	546.415	7	1	5
6k	3.609	512.517	9	1	6
6l	3.609	512.517	9	1	6

ADMET Studies

ADMET studies were analyzed using Discovery Studio 2.1 and properties such as solubility, absorption, hepatotoxicity, blood-brain barrier, hepatotoxicity probability, probability enzyme inhibition study, polar surface area, cytochrome P450, CYP2D6, and PPB level are discussed, and tabulated in Table-5. According to ADMET analysis, all the synthesized compounds were expected to possess low to moderate Human Intestinal Absorption (HIA), low BBB penetration level, and low solubility. It was observed that the hepatotoxicity probability values of the compounds lie in the 0.62-0.74 range. Hence, compounds may possess hepatotoxicity and be classified as non-inhibitors of CYP2D6. An ADME model comprises 95% and 99% confidence ellipses by descriptors 2D PSA and AlogP98 was developed to predict the absorption and BBB penetration[18]. Some of the derivatives fall inside the ADME model which shows good BBB penetration ability and good intestinal absorption. For all the compounds, the polar surface area and ALogP are plotted and represented in Fig.-4.

Table-5: ADMET of Synthesized Compounds (6a-6l)

Name	BBB	Absorption	Solubility	Solubility Level	Hepatotoxicity	Hepatotoxicity Probability	CYP2D6	CYP2D6 Probability	PPB Level	AlogP 98	PSA 2D
6a	4	1	-5.475	2	1	0.629	0	0.297	2	3.714	112.506
6b	4	1	-5.851	2	1	0.741	0	0.287	2	4.201	112.506
6c	4	1	-5.775	2	1	0.741	0	0.287	2	3.92	112.506
6d	4	1	-5.803	2	1	0.649	0	0.297	0	3.92	112.506
6e	4	1	-6.204	1	1	0.649	0	0.297	1	4.379	112.506
6f	4	1	-6.176	1	1	0.721	0	0.287	2	4.379	112.506
6g	4	2	-6.902	1	1	0.688	0	0.287	2	5.043	112.506
6h	4	2	-5.321	2	1	0.642	0	0.277	0	3.682	130.366
6i	4	1	-6.277	1	1	0.649	0	0.297	1	4.463	112.506
6j	4	1	-6.249	1	1	0.741	0	0.287	2	4.463	112.506
6k	4	3	-5.579	2	1	0.622	0	0.277	0	3.609	155.329

6l	4	3	-5.493	2	1	0.649	0	0.247	2	3.609	155.329
Etoposide	4	3	-3.861	3	1	0.993	0	0.386	2	0.935	160.118

***In-silico* Toxicity Assessment**

Through Accelrys Discovery studio 2.1, the drug potency of toxicity was identified by TOPKAT studies. The effect of consumption of drugs for synthesized derivatives has been evaluated and toxicological endpoints were determined. For all the derivatives, toxicity screening results (TOPKAT) are shown which has no risk of mutagenicity, no skin irritation, and the risk of carcinogenicity. But, at excessive doses and long-term use in human beings, it acquires excessive developmental or reproductive toxicity ability.[19] All compounds showed strong skin sensitization capacity. However, the 6d derivative showed mild skin irritancy. The toxicity test resulting in values of carcinogenicity, aerobic biodegradability, developmental toxicity potential, skin irritancy, Ames mutagenicity, and ocular irritancy are summarized in Table-7.

Pharmacophore Modeling

Pharmacophore modeling is carried out for a good understanding of the significant biological function of synthesized derivatives. In the pharmacophore model, all the synthesized compounds are mapped, and their fit values are predicted and summarized in Table-6. Fit values range from 1.3 to 2.2 and Fig.-5 shows the pharmacophore model structure. The compound **(6k)** with a good fit value of 2.267 fitted very well on the pharmacophore and Fig.-6 and 7 show the active compounds **(6k and 6i)** mapping on the pharmacophore model.

Table-6: Fit Values of Synthesized Compounds (6a-6l)

Compound	Acceptor 28	Acceptor 5	Donor 141	Donor 259	Fit Value	Hydrophobe 27	Hydrophobe 54	Pharmprint
6a	1	0	1	0	1.369	0	1	'011001'
6b	1	0	0	1	1.684	0	1	'010101'
6c	1	0	1	0	1.649	0	1	'011001'
6d	1	0	1	0	1.479	0	1	'011001'
6e	1	0	1	0	1.812	1	0	'011010'
6f	1	0	0	1	1.682	0	1	'010101'
6g	1	0	0	1	1.497	0	1	'010101'
6h	1	0	1	0	2.219	0	1	'011001'
6i	1	0	1	0	1.436	0	1	'011001'
6j	1	0	0	1	1.527	0	1	'010101'
6k	1	0	1	0	2.267	0	1	'011001'
6l	1	0	1	0	2.146	0	1	'011001'
Streptomycin	0	1	1	1	3.692	0	1	'011101'
Etoposide	0	0	1	1	2.725	0	1	'001101'

Table-7: Compliance with Synthesized Compounds

Name of Assay	6a	6b	6c	6d	6e	6f	6g	6h	6i	6j	6k	6l	Etoposide
Rat Male	CA	CA	CA	CA	CA	CA	CA	CA	CA	CA	CA	CA	NCA
Rat Female	CA	CA	CA	CA	CA	CA	CA	CA	CA	CA	CA	NCA	NCA
Mouse Male	CA	CA	CA	CA	CA	CA	CA	NCA	CA	CA	CA	NC	NCA
Mouse Female	CA	CA	CA	CA	CA	CA	CA	NCA	CA	CA	CA	CA	NCA
Ames Mutagenicity	NMG	NMG	NMG	NMG	NMG	NMG	NMG	NMG	NMG	NMG	MG	MG	NMG

Developmental Toxicity potential	TX	TX	TX	NTX	TX	TX	TX	TX	TX	TX	TX	TX	NTX
Aerobic biodegradability	N-B	N-B	N-B	N-B	N-B	N-B	N-B	B	N-B	N-B	N-B	N-B	B
Ocular Irritancy	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	NS
Skin Irritancy	N-I	N-I	N-I	I	N-I	N-I	N-I	N-I	N-I	N-I	N-I	N-I	N-I

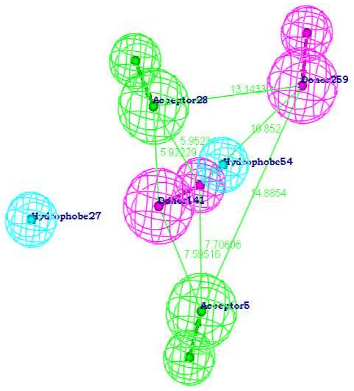


Fig.-5: pharmacophore model based on a structure with inter featured distances

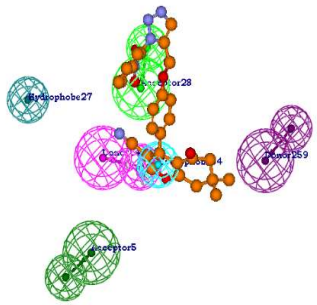


Fig.-6: The structure based pharmacophore modeling of (6k) derivative

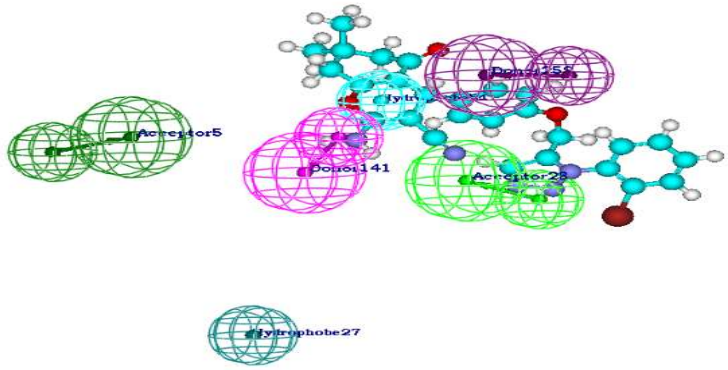


Fig.-7: Structure-Based Pharmacophore Modelling of 6i Derivative

CONCLUSION

The antibacterial studies of the designed molecules were evaluated on Gram +ve and Gram -ve bacteria, *in vitro*. The in-detail *in vitro* antibacterial activity analysis emphasized that the compound **6i** acts as a strong antibacterial agent, **6a, 6c, 6h, and 6k** show effective antibacterial properties on Gram-positive, and **6d** shows, a good antibacterial property on Gram-negative bacteria. By comparing *in vitro* studies with *in silico* studies, it was approved that compound **6i** has shown a strong biological activity. Hence, we are certain that the study presented here i.e., systematic evaluation of broad-spectrum antibacterial properties of perillyl-4H-pyrantriazole derivatives would aid in the development of new molecules having potential antibacterial properties and addressing the threat of global antimicrobial resistance.

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Hyderabad, Telangana, India for *in vitro* studies and also Averinbiotech Laboratories, Hyderabad for *in silico* studies.

REFERENCES

1. M. Frieri, K. Kumar, and A. Boutin, *Journal of Infection and Public Health*, **10(4)**, 369(2017), http://doi.org/10.1016/j.jiph.2016.08.007
2. B.Aslam, W. Wang, M. I. Arshad, M. Khurshid, S. Muzammil, M.H. Rasool, M.A. Nisar, R.F. Alvi, M.A. Aslam, M.U. Qamar, M.K.F. Salamat and Z. Baloch, *Infection and Drug Resistance*, **11**, 1645(2018), https://doi.org/10.2147/IDR.S173867
3. E. Medina, and D.H. Pieper, *Current Topics in Microbiology and Immunology*, **398**, 3(2016), http://doi.org/ 10.1007/82_2016_492
4. C. Ardal, M. Balasegaram, R. Laxminarayan, D. McAdams, K. Outterson, J.H. Rex, and N. Sumparadit, *Nature Reviews Microbiology*, **18(5)**, 267(2020), http://doi.org/ 10.1038/s41579-019-02933
5. M. Lomazzi, M.Moore, A. Johnson, M. Balasegaram, and B. Borisch, *BMC Public Health*, **19(1)**, 858(2019), http://doi.org/ 10.1186/s12889-019-7173-7
6. M. Laws, A. Shaaban and K. M. Rahman, *FEMS Microbiology Reviews*, **43(5)**, 490(2019), http://doi.org/ 10.1093/femsre/fuz014
7. L.A. Richardson, *PloS Biol*ogy, **15(8)**, e2003775(2017), http://doi.org/10.1371/journal.pbio.2003775
8. N.K. Maddali, I.V.K. Viswanath, Y.L.N. Murthy, R. Bera, M. Takhi, N.S. Rao and V. Gudla, *Medicinal Chemistry Research*, **28(4)**, 559(2019), https://doi.org/10.1007/s00044-019-02313-9
9. M.R. Mannam, S.S, P. Kumar, N.R. Chamarthi and P.K.R.S, *Phosphorus Sulfur, and Silicon and the Related Elements,* **195(1)**, 65(2019), http://doi.org/ 10.1080/10426507.2019.1635596
10. Y. Hu, Y. Zhu, and N. Lu, *Frontiers in Cellular and Infection Microbiology,* **7**, 168(2017), https://doi.org/10.3389/fcimb.2017.00168
11. J. Jampilek, *Molecules*, 24(21), 3839(2019), https://doi.org/10.3390/molecules24213839
12. N. Depa and H. Erothu, *ChemistrySelect*, **4(33)**, 9722(2019), https://doi.org/10.1002/slct.201902832
13. N. Depa, and H. Erothu, *Medicinal Chemistry Research*, **30**, 1087(2021), https://doi.org/10.1007/s00044-021-02710-z
14. T. N. Reddy, M. Ravinder, R. Bikshapathi, P. Sujitha, C.G. Kumar and V. J. Rao, *Medicinal Chemistry Research*, **26(11)**, 2832(2017), https://doi.org/10.1007/s00044-017-1982-y
15. I.H. El Azab, H.S. El-Sheshtawy, R.B. Bakr and N.A.A. Elkanzi, *Molecules,* **26(3)**, 708(2021), https://doi.org/10.3390/molecules26030708
16. L. Qi, S.J. Wu, M.C. Li, J.C. Bai, H.X. Ma and Y.H. Ren, *ChemistrySelect*, **5(6)**, 14753(2020), https://doi.org/10.1002/slct.201904418
17. N. Depa and H. Erothu, *Rasayan Journal of Chemistry*, **15(1)**, 302(2022), http://dx.doi.org/10.31788/RJC.2022.1516629
18. G. Zhang, S. Guo, H. Cui, J. Qi, *Molecules,* **23(3)**, 524(2018), http://doi.org/10.3390/molecules23030524
19. A. Shukla, P. Sharma, O. Prakash, M. Singh, K. Kalani, F. Khan, D.U. Bawankule, S. Luqman, and S.K. Srivastava, *PloS One*, **9(7)**, e100797(2014), https://doi.org/10.1371/journal.pone.0100797

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