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DESIGN, SYNTHESIS, ANTIMICROBIAL ACTIVITY AND MOLECULAR DOCKING STUDIES OF SOME NOVELORGANOBISMUTH (III) COMPLEXES

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ABSTRACT

Some novel structural synthons, organobismuth (III)complexes [RBiL, where R is phenyl group; Ligand (L) is a benzoic acid derivative] were designed and synthesized by the reaction of diorganobismuth(III) halide and respective ligands. After elemental and spectral investigation, the compounds exhibit a sharp melting point and trigonal/pyramidal shape. In this context, we thought it would be motivating to further investigate these compounds through computational modeling to investigate structure-activity relationship analysis as potential antimicrobial agents with Cefotaxime complexed with the streptomyces R61 DD-peptidase protein with PDB ID: 1CEF. The antimicrobial activity of synthesized organobismuth compounds was investigated against *E. coli, S. aureus, P. aeruginosa, A. niger & C. Albicans* using the agar well diffusion method. The findings indicated that the synthesized compounds outperformed the conventional medication in terms of antimicrobial activity.

Keywords: Organobismuth, Antimicrobial Agents, Computational Molecular Modeling.

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INTRODUCTION

Antimicrobial resistance seems to be the most serious public health concern, and it is spreading in the arena of infectious diseases caused mostly by bacteria, fungi, viruses, and parasites.[1] Antibiotic usage and misuse in animals and people, and often poor productivity for antibiotic exploration (a significant decrease of developing antibiotic categories of drug), were among the primary drivers of antimicrobial resistance development and transmission.[2]A cluster of Multiple drug-resistant bacteria termed "ESKAPE," which are comprises of both Gram+ve and Gram-ve species (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* spp.), is commonly detected in healthcare settings and are usually the outcome of hospital-acquired infections.[3] Gram-positive bacteria in particular have evolved resistance to all existing antibiotics, posing a severe concern not just within hospitals as well as in the overall population. Methicillin-resistant Staphylococcus aureus (MRSA) infections seem to be of particular interest.[4]Fungal infections have also become more common, which is now being connected to a spike in the number of immune-compromised hosts, like individuals experiencing organ transplantation, taking anticancer treatment, dealing with AIDS, or getting broad-spectrum antimicrobial therapy.[5]This feature, as well as the restrictions of currently existing antifungal medicines and the rise in antibiotic resistance, have produced a significant requirement for the implementation of efficient broad-spectrum and safe antifungal drugs, primarily having new modes of action.[6]Organobismuth chemicals are extremely good at protecting the gastrointestinal and gastro-duodenal tracts. A bismuth-containing quintuple therapy is an alternate medication for treating *H. pylori* infection[7] since it is non-toxic and has local effects.[8] Resistance to bismuth medications has not yet been described[9] in *H. pylori* or extra pathogenic organisms. There are many bismuth-based preparations available, like CBS- for dyspepsia, duodenal ulcer, and gastric ulcer, BSS- for Traveller's diarrhea, dyspepsia, and bismuth subnitrate- for stomach problems, and RBC- for *H. pylori*, duodenal and gastric ulcer. They are also utilized

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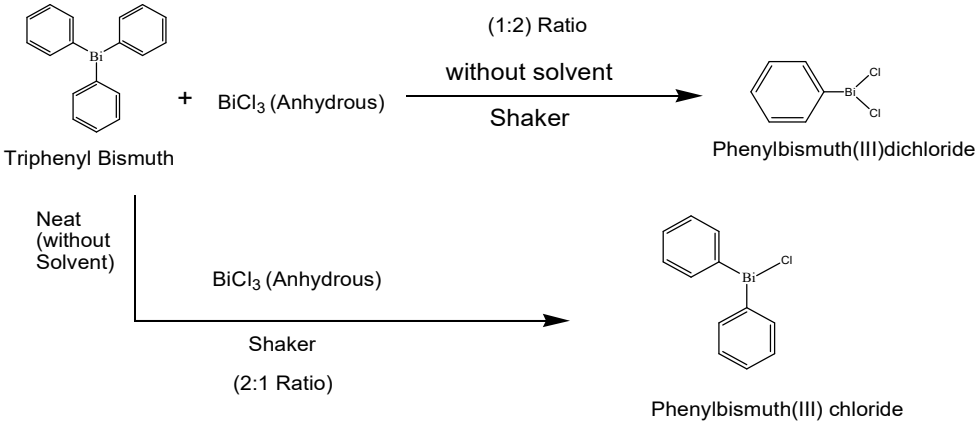
as antimicrobial agents in contagions such as syphilis, colitis, diarrhea, and wound infections, and they are active against a variety of gastrointestinal pathogens.The present manuscript deals with designing and molecular docking of a new series of structural synthons, organobismuth (III) complexes [RBiL, where R is phenyl group; Ligand (L) is benzoic acid derivative]. The best-docked molecules having minimum energy scores were further analyzed for molecular properties and drug-likeness properties and then were synthesized, and characterized and their antimicrobial activities were performed to achieve an effective lead molecule as an antimicrobial agent.

EXPERIMENTAL

General Procedure

The diorganobismuth (III) chloride was synthesized using the previously described processes.[10,11] The ligands were recrystallized previously prior to use while the operations were carried out in an inert/nitrogen environment. In 10 ml THF, one equivalent benzoic acid derivative was dissolved. The above solution was then treated with 0.5 ml of triethylamine. The resulting solution of benzoic acid derivative was cooled to 0 °C before adding one equivalent of diorganobismuth (III) chloride. For overnight, the resulting mixture had been stirred. The obtained precipitate was then filtered and washed by using THF to yield the mono-substitute diphenyl bismuth(III) complex.



$$R_2BiCl + HL \xrightarrow{2Et_3N} R_2BiL + Et_3N.HCl$$

R = [C_6H_5]; HL = [benzoic acid derivative]

Scheme-1: Synthesis of Organobismuth (III) Complexes

TLC was used to determine the purity of the synthesized chemical, with Silica gel G as the stationary phase and chloroform hexane mixture (40%) as the solvent system. The spots were observed under an ultraviolet lamp. The compounds were characterized using spectral analysis, m.p., and elemental analysis, which confirmed the compound's synthesis.

Molecular Docking Studies

The compounds were subjected to a computational molecular docking investigation to determine their feasibility as new drug candidates. The various computational tools and software like Cresset (Flare) software[12,13], Open babel, Pymol, Chem draws ultra 12.0.2, and Protein data bank is used to analyze the protein structure to study the binding energy properties with organobismuth (III) compounds. Protein with PDB ID: 1CEF sequence was obtained from the protein data bank.

Docking Methodology

The Flare 3.0.0 tool of Cresset software was used to perform molecular docking experiments against 1CEF[14] with the organobismuth (III) complexes as ligands. The Flare tool's protein planning and preparation feature were employed to minimize energy. To improve the stability of the ligands, hydrogen atoms were added. By organizing the grid coordinates, the active pocket within the protein assembly is selected and a grid box should be assessed based on the intrinsic ligand placement on the binding site. Docking was performed in normal mode with default parameters & the best free energy of binding-energy ranking, average binding energy/ligand efficiency, and binding energy predictions were chosen.

Molecular Properties and Drug Likeness Properties

The designed compounds were scrutinized for their molecular properties to check for Lipinski`s Rule of 5 via molecular properties and bioactivity predictor of Molinspiration Cheminformatics Software. Various important molecular properties like logP[16], polar surface area[17], and the number of H-bond donors, and acceptors; of the synthesized compounds were predicted using this software. The properties of the produced compounds were investigated for pharmacokinetic and drug-like properties based on Lipinski's rule.[18] The MLogP (octanol-water partition coefficientis utilized to calculate the drug's lipophilic efficiency since it is a critical metric in drug absorption and distribution within the body.

Antibacterial Activity

The antibacterial activity was evaluated using the Agar well diffusion method[19,20] with ampicillin as the positive control. For this purpose, three bacterial strains are used: *Pseudomonas aeruginosa* (MTCC 741)*, Staphylococcus aureus*(MTCC 902),and *Escherichia coli* (MTCC 1687). The culture media for this experiment was nutrient agar. 60ml molten nutritional agar was poured into pre-sterilized petri dish (25 ml each) and cooled down. 20µl of the test bacterium was evenly distributed across these agar plates. The plates were then allowed to harden. After solidification, 6 mm diameter holes/wells (cups) were punched into agar with a flamed cork borer. For each plate, four wells were made. Two of these four wells were filled with 50µl of the sample compound (7-10 µg/mL), the third with 50µl of standard antibiotic solution (ampicillin 2 µg/mL), and the fourth with blank (DMSO). The Petri dishes were incubated for a period of 24 hours at 37 degrees Celsius. The diameter of the inhibition zone created around each hole (well/cup) was observed and recorded after the incubation time. Each bacterium was subjected to testing.

Antifungal Activity

The antifungal activity of the synthesized compounds was evaluated using the Agar well diffusion technique with test chemical doses of 10, 20, 50, and 100 µg/ml against *Aspergillus niger* and *Candida albicans* (Lab isolates). The fungal organism was cultured on potato Dextrose Agar. The plates were inoculated with a 24-hour culture of the corresponding fungus. 8 mm wells were cut out with a flamed cork borer, and 50µl of the sample compound (of varying concentrations) was aseptically poured into each well with a sterile syringe. For 60 minutes, the plates were placed cool to allow the test solution to diffuse. After that, the plates were incubated at room temperature. The diameter of the inhibition zone was measured after 72 hours to determine inhibition. Fluconazole (66 µg/mL) was employed as a positive control.

RESULTS AND DISCUSSION

All of the reactions were carried out at 0°C in an inert/nitrogen environment. The products were recrystallized in benzene or petroleum ether. The complexes are off-white to white solids that were isolated as a sticky mass and crystallized using benzene/pet-ether.The complexes have a sharp melting point & are air and moisture stable. The melting points of the complexes do not follow a consistent pattern and they melt without decomposition. Complexes can also be dissolved in chloroform and acetonitrile. They will not decompose if stored at room temperature for quite a few weeks. The absence of a reactant mixture was ruled out by the consistency of MP after repeated crystallization, along with TLC performed in chloroform: hexane combination (40 percent) with detection of a single spot. The molar conductance of these compounds in 10^{-3} M solution was measured in methanol and found to be in the range of 15-25 Ohm^{-1} $mole^{-1}$ cm^2, demonstrating in lack of ionic species in the solution. In nitrobenzene, the complexes were discovered to be monomeric.

Compound 1a: ((diphenylbismuthino)oxy)(2-(trifluoromethyl)phenyl)methanone: White solid (65%); M.P. 164-166 °C; IR (KBR, cm^{-1}) 3045 (Ar C-H), 1756 (Asymmetric OCO), 1535 (Ar C=C), 1472 (Ar C=C), 1383 (Symmetric OCO), 847 (Ar C-H, bending), 771(Ar C-H, bending), 725 (Ar C-H, bending), 690 (Ar C-H, bending); 1HNMR (400MHz, DMSO): δ = 7.306-7.403 (m,10H, Ar-H), 7.314-7.734 (m,4H, Ar-H), TOF-MS ES+: 553.03 (M+H)+, calcd. 552. Elemental Anal. calcd. for $C_{20}H_{14}BiF_3O_2$:C, 43.49; H, 2.55 Found: C, 43.25; H, 2.49.

Compound 1b: ((diphenylbismuthino)oxy)(perfluorophenyl)methanone: Yield: White solid (70%); M.P. 150-152 °C; 1HNMR (400MHz, DMSO): δ = 7.288-7.404 (m, 6H, Ar-H), 7.593-7.735 (m, 4H, Ar-

H), TOF-MS ES-: 573.05 (M+H)+, calcd. 574. Elemental Anal. calcd. for $C_{19}H_{10}BiF_5O_2$: C, 39.74; H, 1.76Found: C, 39.53; H, 1.49.

Compound 1c: 3-(((diphenylbismuthino)oxy)carbonyl)-1-ethyl-7-methyl-1,8-naphthyridin-4(1H)-one: Yield: White solid (75%); M.P. 152-154 °C; 1HNMR (400MHz, DMSO): δ = 0.847-1.844 (m,8H, CH_3), 3.464-3.482 (d,1H,CH_2), 4.591-4.596 (s,1H,pyridine-H), 7.002 (s,1H,Ar-H), 7.306-7.403 (m,6H,Ar-H), 7.713-7.731 (m,3H, Ar-H), 8.109 (s,1H, Ar-H) TOF-MS ES-: 593.43 M^+, calcd. 594. Elemental Anal. calcd. for $C_{24}H_{21}BiN_2O_3$: C, 48.49; H, 3.56, N, 4.71 Found: C, 48.11; H, 3.25, N, 4.43.

Compound 1d: ((diphenylbismuthino)oxy)(4-fluoro-3-(trifluoromethyl)phenyl)methanone: Yield: White solid (68%); M.P. 151-153 °C; IR (KBR, cm^{-1}) 3045 (Ar C-H), 1727 (Asymmetric OCO), 1600 (Ph ring), 1559 (Ar C=C), 1504 (Ar C=C), 847(Ar C-H, bending), 812 (Ar C-H, bending) , 725 (Ar C-H, bending) , 690 (Ar C-H, bending); 1HNMR (400MHz, DMSO): δ = 7.205-7.736 (m,7H, Ar-H), 8.022-8.071 (m,6H,Ar-H), TOF-MS ES+: 571.25 (M+H)+, calcd. 570. Elemental Anal. calcd. for $C_{20}H_{13}BiF_4O_2$: C, 42.12; H, 2.30 Found: C, 42.12; H, 2.15.

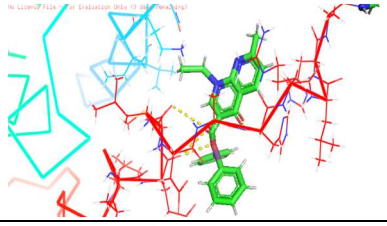
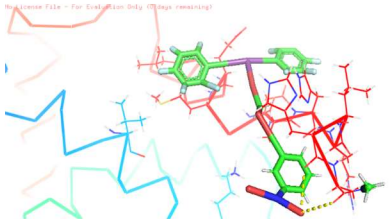
Table-1: Physicochemical Properties of Synthesized Organobismuth (III) Compounds

S.No.	Compound	Empirical Formula	Formula Weight	M.P.(ºC)	Yield (%)
1.	1a	$C_{20}H_{14}BiF_3O_2$	552	164-166	65
2.	1b	$C_{19}H_{10}BiF_5O_2$	574	150-152	70
3.	1c	$C_{24}H_{21}BiN_2O_3$	594	152-154	75
4.	1d	$C_{20}H_{13}BiF_4O_2$	570	151-153	68

Computational/ Molecular Docking Studies

Mathematical modeling (docking) is the simulated study of drug binding to a target protein. It entails complexing the drug candidate in the binding pocket of the target protein's crystallographic structure in order to anticipate the structure-activity connection. The binding analysis indicates that the receptor protein 1CEF was successfully docked with ampicillin as standard and the designed organobismuth complexes. Compound docking scores ranged from -7.14761 kcal/mol to -4.67543 kcal/mol. Compound 1c showed a high ranking score of-6.76741 followed by compound 1b having a ranking score of -4.19147. Addison of more heterocyclic rings and substitution of fluorine had a considerable docking score, according to the results. The oxygen of the C=O group shows interaction withARG285 and ARG287 in 1CEF which helps in the formation of H-bonds and results in good interaction of the ligand and receptor. The results of interaction and energy were tabulated in Table-2 and 3.

Table-2: Protein-Ligand Interaction Studies with 1CEF

S No.	Code	1CEF	Key residues	H-bonds
1.	1c		ASP114, THR116, ASN117, PHE120, ALA121, THR123, and THR301	3
2.	1b		VAL302, GLN303. SER62, CYS65, TYR159, and ASN161	2

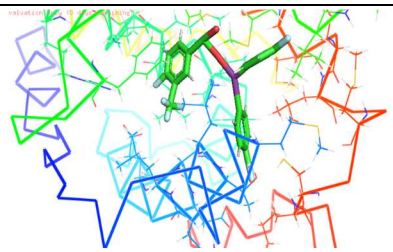
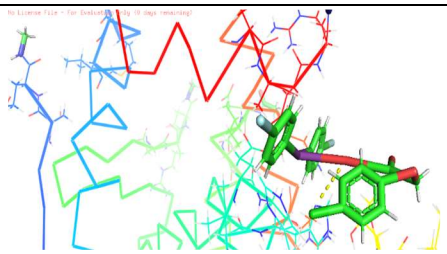
3.	1a		THR116, ASN117, PHE120, VAL302, GLN303,and SER62	2
4.	1d		ASP114, THR116,ASN117, PHE120, ALA121, CYS65, TYR159, and ASN161	2

Table-3: Energy of the Docked Molecule with 1CEF

S.No.	1CEF	dG, kcal/mol	LE, (kcal/mol)/atom	Rank score
1.	Ampicillin	-6.83095	-0.28462	-11.69861
2.	1c	-7.14761	-0.24647	-6.76741
3.	1b	-5.89168	-0.24549	-4.19147
4.	1a	-7.58249	-0.21664	-3.83947
5.	1d	-4.67543	-0.23451	-1.2348

Molecular Properties and Drug Likeness Properties

Molecular Properties were studied for the best docked organobismuth compounds. The structures were drawn and SMILES strings were generated for calculation of logP, the total polar surface area, total number of atoms, H-bond donor and acceptors, number of ratable bonds, and number of violations for checking Lipinski`s Rule of 5 of the organobismuth complexes and are tabulated in table IV. The results of the calculation show that compounds 1c and 1b may have only one violation of the rule so they may have the probability of successful in-vivo absorption. The bioactivity of the synthesized compounds was further validated by performing the antimicrobial activity.

Table-4: Predicted Molecular Properties of the Synthesized Compounds for Lipinski`s Rule of 5

Compound	Mi LogP	TPSA	n atoms	n ON	n rot b	N violations
Rule	<5	-	20-70	<5	≤10	
Std.	6.06	12.47	28	2	8	1
1a	5.52	24.70	26	2	3	1
1b	4.89	26.30	27	2	5	1
1c	3.66	61.20	30	5	6	1
1d	3.74	30.55	27	4	4	1

Antibacterial Activity

The diameter of inhibition zones in each sample was contrasted to that of a standard antibiotic (ampicillin 2 µg/mL). The inhibition zones of the samples were found to be consistent with the inhibition zones of the standard. Using a 7-10 µg/mL concentration of the test chemical, the antibacterial activity of the produced molecules was tested against three bacterial strains. The chemicals are effective against bacterial strains. These chemicals might interact with the peptidoglycan layer of the bacterial cell wall, penetrating it and allowing the phenyl ring to enter the cell, resulting in the bacterial cell's death. In low concentrations, these chemicals may induce bacteriostatic conditions by slowing bacterial growth. The diameter of the inhibition

zone is greatest in the case of *Staphylococcus aureus* (21.7mm) followed by *Pseudomonas aeruginosa*(18.2mm) and lowest in *Escherichia coli* (20.6mm) for compound 1c.

Table-5: Antibacterial Activity of Organobismuth Complexes

S. No.	Compounds	Concentration µg/mL	*Pseudomonas aeruginosa* ZOI (mm)	*Staphylococcus aureus* ZOI (mm)	*Escherichia coli* ZOI (mm)
1	Ampicillin	2	20	23.4	21.8
2	1a	7	7	15	14
		8	9.8	16	15
		9	14.2	18	16.7
		10	15.3	20.3	18.7
3	1b	7	9	16	15
		8	11	17	16
		9	15	18	18
		10	16.2	19.3	19.7
4	1c	7	13	18	16
		8	15	19	17
		9	17	20	19
		10	18.2	21.7	20.6
5	1d	7	10	14.3	14
		8	11	15.9	15
		9	13	17	16
		10	14.7	18.6	17.6

Antifungal Activity

All of these substances were evaluated for antifungal activity against *Aspergillus niger* and *Candida albicans* via concentrations of 10, 20, 50, and 100 µg/mL,and the results cleared that all the test compounds demonstrated antifungal action against both fungi. The antifungal activity is seen as an inhibition zone generated around every well, the diameter of which reflects the extent of inhibition. The activity of these compounds was found to be varied, but at greater concentrations, all of the compounds showed strong activity against fungal strains. The use of several benzoic acid derivatives as ligands was also commendable. These chemicals usually harm fungal strains by puncturing the cell wall in the same way that bacteria do. The inhibition zone diameter produced in every sample against each fungus was found to be less than that of standard antibiotics.

Table-6: Antifungal Activity of Organobismuth Complexes

S. No.	Compounds	Concentration µg/mL	*Aspergillus niger* ZOI (mm)	*Candida albicans* ZOI (mm)
1	Fluconazole	66	3	5
2	1a	10	1	1
		20	1.2	3
		50	2	3.6
		100	2.1	4.1
3	1b	10	1.5	2
		20	2	2

		50	2.2	3.4
		100	2.5	4.3
4	1c	10	1.2	3
		20	2.1	3
		50	2.2	4.5
		100	2.8	4.7
5	1d	10	-	2
		20	2	3
		50	2	4
		100	2.3	4.2

CONCLUSION

Ultimately, we discuss the synthesis and antimicrobial screening of new organobismuth complexes as antimicrobial agents. Concerning to anticipating the binding affinity with the receptor, these compounds were docked with receptor protein having PDB ID: 1CEF. With strong docking scores, complex 1c demonstrated outstanding effectiveness against bacterial and fungal strains followed by compound 1b. The results showed that the ADME properties are also comparable to the standard ampicillin. If the substance is properly manufactured & formulated, it can be utilized to protect people. However, thorough toxicological research is required to determine the compound's harmful consequences. A detailed investigation of the compound's method of action and side effects is also necessary.

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REFERENCES

1 M. Hussain, T. Qadri, Z. Hussain, A. Saeed, P.A. Channar, S. A. Shehzadi, M. Hassan, F.A. Larik, T. Mahmood, and Malik, *Heliyon*, **5(11)**, (2019), https://doi.org/10.1016/j.heliyon.2019.e02812

2 R. J. Fair, and Y. Tor, *Perspectives in Medicinal Chemistry*, **6**, PMC-S14459(2014), https://doi.org/10.4137/PMC.S14459

3 L.B. Rice, *The Journal of Infectious Dis*eases, **197(8)**, 1079(2008), https://doi.org/10.1086/533452

4 E.Y. Garoy, Y.B. Gebreab, O.O. Achila, D.G. Tekeste, R. Kesete, R. Ghirmay, R. Kiflay, and T. Tesfu, *Journal of Infectious Diseases and Medical Microbiol*ogy, **2019**, 8321834 (2019), https://doi.org/10.1155/2019/8321834

5 E. Rusu, M. Radu-Popescu, D. Pelinescu, and T. Vassu, *Brazilian Journal of Microbiology*, **45(4)**, 1379 (2014), https://doi.org/10.1590/s1517-83822014000400031

6 R. Sharanappa, and G. M. Vidyasagar, *International Journal Pharmacy and Pharmaceutial Sciences*, **5(4)**, 9(2013).

7 P. Malfertheiner, F. Megraud, C. O'Morain, F. Bazzoli, E. El-Omar, D. Graham, R. Hunt, T. Rokkas, N. Vakil, and E.J. Kuipers, *Gut*, **56**, 772(2007), https://doi.org/10.1136/gut.2006.101634

8 J.R. Lambert, and P. Midolo.*Alimentary Pharmacology & Therapeutics*, **11(Suppl 1)**, 27(1997), https://doi.org/10.1046/j.1365-2036.11.s1.13.x

9 F. Megraud, *Therapeutic Advances in Gastroenterol*ogy, **5(2)**, 103(2012), https://doi.org/10.1177/1756283X11432492

10 P.C. Andrews, R.L. Ferrero, P.C. Junk, J.G. Maclellan, and R. M. Peiris, *Australian. Journal of Chemistry*, **65**, 883(2012), https://doi.org/10.1071/CH12042

11 P. Andreas, S. Stefan, S. Hermann, F. Roland, and K. Danuta, Compounds for use as contrast agents in magnetic resonance imaging, European Patent No. 16188270.9 (2016).
12 Premila, R. Sangeetha and K. Vijayalakshmi, *International Journal of Current Research and Academic Review,* **Special Issue-4**, 145(2017).
13 C. Jaynthy, G. Shanmugalakshmi, and A.B. Mathan, *International Journal of Pharmaceutical and Clinical Research*, **10(3)**, 62(2018).
14 A. P. Kuzin, H. Liu, J. A. Kelly, and J.R., Knox, *Biochemistry*, **34**, 9532(1995), https://doi.org/10.1021/bi00029a030
15 G. Caron, M. Vallaro, and G. Ermondi, *Drug Discovery Today: Technologies*, **27**, 65(2018), https://doi.org/10.1016/j.ddtec.2018.03.001
16 S.C. Yam, S.M. Zain, V.S. Lee, and K.H. Chew, *The European Physical Journal E*, **41(7)**, 86 (2018), https://doi.org/10.1140/epje/i2018-11696-5
17 J. Suganya, M. Radha, D.L. Naorem, and M. Nishandhini, M. *Asian Pacific Journal of Cancer Prevention*, **19**, 8155(2015), https://doi.org/10.7314/apjcp.2014.15.19.8155
18 S. Zheng, S. Xu, G. Wang, Q. Tang, X. Jiang, Z. Li, Y. Xu, R. Wang, and F. Lin, *Journal of Chemical Information and Modeling*, Jul. (2017), https://doi.org/10.1021/acs.jcim.7b00022
19 A. Brantner, K.P. Pfeiffer, and H. Brantner, *Pharmazie*, **49(7)**, 512(1994)
20 A. Palaniammal, and S. Vedanayaki, *Rasayan Journal of Chemistry*, **15(2)**, 767(2022), https://doi.org/10.31788/RJC.2022.1526699

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