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Molecular Docking and *In silico* Study of Some 3,5-disubstituted-2,4-thiazolidinediones as Antimicrobial Agents

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ABSTRACT

The rise of multi-drug-resistant pathogens makes infections increasingly difficult to treat, highlighting an urgent need for novel therapeutic agents. Thiazolidinedione a key five-membered heterocyclic compound, has shown a broad range of biological activities in medicinal chemistry. In response to this need, we designed a series of 3,5-disubstituted-2,4-thiazolidinedione drug conjugates. We subjected them to *in silico* molecular docking analysis as MurB enzyme inhibitors, an essential enzyme involved in the synthesis of bacterial cellwall. Out of the Fifteen compounds designed, based on structure-activity relationship (SAR) insights, molecular docking studies, compounds IIIc, IIId, IIIm exhibited better Glide d score than the standard ciprofloxacin and compound IIIm exhibited the highest d score-5.866kcal/mol and a binding energy-50.6788kcal/mol. *In silico* pharmacokinetic studies exhibited that all the molecules followed Lipinski Rule of five. Thus, the conjugate IIIm is proposed to serve as a prominent candidate for further experimental evaluation as an antibacterial agent.

Keywords: Thiazolidinediones, Molecular docking, *In silico*, Antimicrobial agents, Mur B enzyme inhibitors.

INTRODUCTION

Infections caused by microbes such as viruses, fungi, parasites, and bacteria are increasingly posing chronic threats to both human and animal health. Many of these infections are highly contagious, resulting in serious or fatal complications, and thus represent a substantial portion of global infectious diseases, impacting public health worldwide. Bacteria, which are unique among prokaryotes and present in nearly all environments, can cause diseases across various age groups and demographics.[1] Factors such as a microbe's infectivity, pathogenicity, and virulence play crucial roles in its ability to cause illness. These factors work through mechanisms like tissue invasion, toxin production, and exploiting host vulnerability, collectively elevating the risk of infection.[2] The rise in bacterial resistance has become a critical issue, with current antimicrobial drugs losing their effectiveness

against the bacteria. Misuse of antibiotics in both humans and animals is a primary contributor to this acceleration in antibiotic resistance, leading to severe conditions, especially in individuals whose capacity to fight infections has been compromised.[3] These infections significantly contribute to morbidity and mortality, negatively impacting patients' health and slowing their recovery process. With the increasing prevalence of bacterial strains resistant to currently available first-line antibiotics, there is a rush for the evolution of brand new therapeutic agents.[4] Consequently, sustained research efforts are essential to develop more effective antimicrobial treatments to manage chronic microbial infections and overcome the limitations of existing therapies.

Among various heterocyclic compounds, thiazolidinediones hold a prominent position in the fields of medicinal chemistry and pharmacology.[5] Thiazolidinedione, a five-membered heterocycle chemically represented as 1,3-thiazolidine-2,4-dione, contains two carbonyl groups at the 2nd and 4th position and sulphur and nitrogen atoms positioned at the 1st and 3rd locations on the ring.[6] Thiazolidinedione derivatives serve as valuable scaffolds with diversified activities like antidiabetic[7,8], antioxidant[9,10], antimicrobial[11], anti-inflammatory[12], antiviral[13], antibacterial[14] and many more. A lot of research revealed the potency of thiazolidinediones as antimicrobial agents. Few thiazolidinedione derivatives are reported to have broad spectrum activity.[15] Thiazolidinediones antimicrobial efficacy is attributed to their ability to inhibit few antibacterial enzymes like DNAgyrase, and Topoisomerase IV and interferes with peptidoglycan layer formation of bacterial cell wall.[16]

By contemplating the versatile activities of thiazolidinediones we were prompted to design 3,5-disubstituted thiazolidinediones, evaluate their *In silico* antimicrobial potency, and understand, elucidate the molecules binding interactions at the receptor active site.

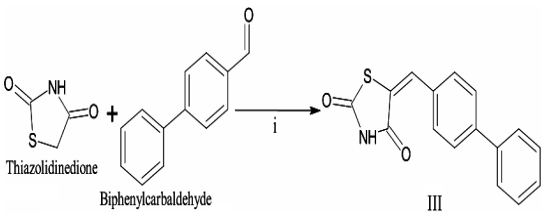
MATERIALS AND METHODS

Design of some 3,5-disubstituted thiazolidinedione derivatives

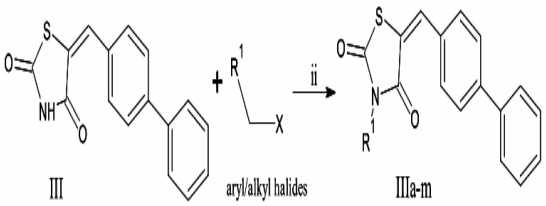
During the propagation of the bacterial cell wall, the MurB enzyme is utilised in the formation of a pentapeptide portion utilised in its cell wall precursor. It was reported that thiazolidinediones bring about their antimicrobial activity by the inhibition of MurB enzyme.[17] It was also established that it is not the substitution on the aromatic ring but the substitution on the heterocyclic ring that is responsible for the antibacterial activity.[18] In this study we designed few 3-substituted-5-[(1,1-bipheny)-4yl]methylene-2,4-thiazolidinedione by Knoevenagel condensation reaction[19] followed by the reaction with various alkyl aryl and heterocyclic halides to produce the desired compounds 3,5-disubstituted thiazolidinediones[20].(Figure 1)

Figure 1. Schematic representation for the synthesis of 3,5-disubstituted thiazolidine-2,4-dione

Step I



Step II



Where: III-5-[(1,1-bipheny)-4yl]methylene-2,4-thiazolidinedione; IIIa-m: 3-substituted-5-[(1,1-bipheny)-4yl]methylene-2,4-thiazolidinedione; i- pipeidine, ethanol; ii- sodium hydroxide,ethanol

Molecular docking studies

The antibacterial potency of the designed compounds was evaluated by their capability in the inhibition of the Mur B enzyme which is an essential enzyme involved in the propagation of peptidoglycan layer of the cell wall of bacteria.[21] The structural analysis of the *E. coli* MurB enzyme complexed with naphthyl tetronic acid (PDB ID: 2Q85) was initiated by retrieving the digital structure from the receptor Data Bank and devised by utilising the Schrödinger Suite 2021-4 Protein Preparation Wizard module, minimized with the optimized for simulations-3 (OPLS-3) molecular force field, and the RMSD of the crystallographic atom set to 0.3 Å[22]. A grid box was designed so as to exemplify the reactive site.[23]

The 2D structures were transformed to 3D, energy minimized, refined the geometry, desalted, and chirality amended. Ligands were diminished using the OPLS-3 force field until an RMSD of 2.0 Å was achieved. Docking was performed using the Glide (XP) module of the Schrödinger Suite 2021-version 4, the default parameters for the compounds in binding modes with the best Glide scores.

ADME Studies

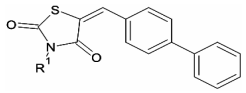
In-silico ADME studies for the described compounds (III, IIIa-IIIn) were conducted using the QikProp module within the Schrödinger suite 2021. The prepared ligands were analyzed for ADME properties, including molecular weight, total surface area accessible by solvent, the hydrogen bond donors and acceptors, oral absorption potential, log P values, and adherence to rule of five. According to the rule, a molecule with two or more violations of these parameters is less likely to be considered drug-like.[24]

RESULTS AND DISCUSSION

Fifteen compounds were designed to target the MurB enzyme (PDB ID: 2Q85) receptor. These compounds were designed by substituting thiazolidinedione with an aromatic biphenyl methylene group at the 5th position followed by substituting various aryl/alkyl groups at the 3rd position. The chemical structure of the designed molecules were given the Table 1.

Table 1: Structures of the 3-substituted-5-[(1,1-bipheny)-4yl]methylene-2,4-thiazolidinediones

General structure



Sr. No	Compound	R^1
1	III	H
2	IIIa	CH_3
3	IIIb	$HC\equiv C\text{-}CH_2\text{-}$
4	IIIc	$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}$
5	IIId	$OH\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}$
6	IIIe	$CH_3\text{-}CH_2\text{-}O\text{-}C(=O)\text{-}CH_2\text{-}$
7	IIIf	$C_6H_5\text{-}CH_2\text{-}$
8	IIIg	$C_6H_4N\text{-}CH_2\text{-}$
9	IIIh	$3\text{-}CF_3C_6H_4\text{-}CH_2\text{-}$
10	IIIi	$2\text{-}CF_3C_6H_4\text{-}CH_2\text{-}$
11	IIIj	$Et\text{-}O\text{-}C(=O)\text{-}CH_2\text{-}C_6H_4\text{-}CH_2\text{-}$
12	IIIk	(3,5-OCH3) $C_6H_3\text{-}CH_2\text{-}$
13	IIII	3-Cl $C_6H_4\text{-}CH_2\text{-}$
14	IIIm	$2\text{-}CNC_6H_4\text{-}C_6H_4\text{-}CH_2\text{-}$
15	IIIn	2-Cl $C_6H_4\text{-}CH_2\text{-}$

From the docking studies at the reactive site of the target *E.coli* MurB enzyme (PDB ID: 2Q85) it was observed that all the designed compounds showed affinity towards the active site. The glide dock scores along with the standard ciprofloxacin, binding energies and aminoacids interacted were depicted in the Table 2.

Table 2: Docking results of the compounds III, IIIa-IIIn

Sr. No	Compound	Glide D Score (Kcal/mol)	Binding Energy (Kcal/mol)	Aminoacids interacted
1	III	-4.36302	-40.5898	Asn 233
2	IIIa	-4.79188	-37.5616	Asn233
3	IIIb	-4.34228	-35.2776	Asn226
4	IIIc	-5.47508	-41.9288	Asn226, Gln 288
5	IIId	-5.8565	-35.1242	Asn253
6	IIIe	-4.97122	-44.5651	Asn233
7	IIIf	-4.32312	-38.7796	Ser 229
8	IIIg	-4.66501	-39.2575	Ser 229
9	IIIh	-5.43972	-35.6772	Asn253
10	IIIi	-4.99895	-41.2482	Asn253
11	IIIj	-3.97275	-45.1835	Tyr 190
12	IIIk	-4.9917	-45.2187	Asn253
13	IIII	-5.1071	-44.0797	Asn233
14	IIIm	-5.86601	-50.6788	Asn233, Gln266
15	IIIn	-4.121	-43.185	Asn233
16	STD	-5.22685	-34.2252	Lys275, Gln287

The designed compounds interlinkages with the prime site of the *E.coli* MurB enzyme were predominantly hydrophobic. All the designed compounds form hydrophobic bonds with the aminoacids Ala124, Tyr125,Tyr158, Tyr190, Leu218, Pro219, Pro221, Pro252, Tyr254, Leu263, Ala264, Ala289, Leu290, Val291. The Glide docking score of all the compounds ranged between -3.97 Kcal to -5.86 Kcal and were found to be good inhibitors of *E.coli* MurB enzyme. Among the designed compounds, IIIc, IIId, and IIIm derivatives exhibited better binding interactions at the active site with pentyl, hydroxyhexyl and 2-cyanobiphenyl substitutions. Compound IIIm showed the highest potency with a glide score of -5.866 Kcal, followed by compound IIId -5.8565 Kcal and compound IIIc -5.474 Kcal with the binding energies of -50.678, -35.1242, -41.9288 Kcal/mol respectively. These compounds showed better glide dock score than the standard ciprofloxacin which had a docking score of -5.226Kcal/mol. The compounds exhibited polar hydrogen bonding interactions majorly with

aminoacids Asn226, Ser 229, Asn233, Gln288, Gln287. All these interactions displayed that hydrophobic substitutions on the thiazolidinedione increased antimicrobial activity of thiazolidinediones as was reported earlier. Further it was revealed that introduction of electron withdrawing groups on the hydrophibic groups increased the antimicrobial activity further[25].

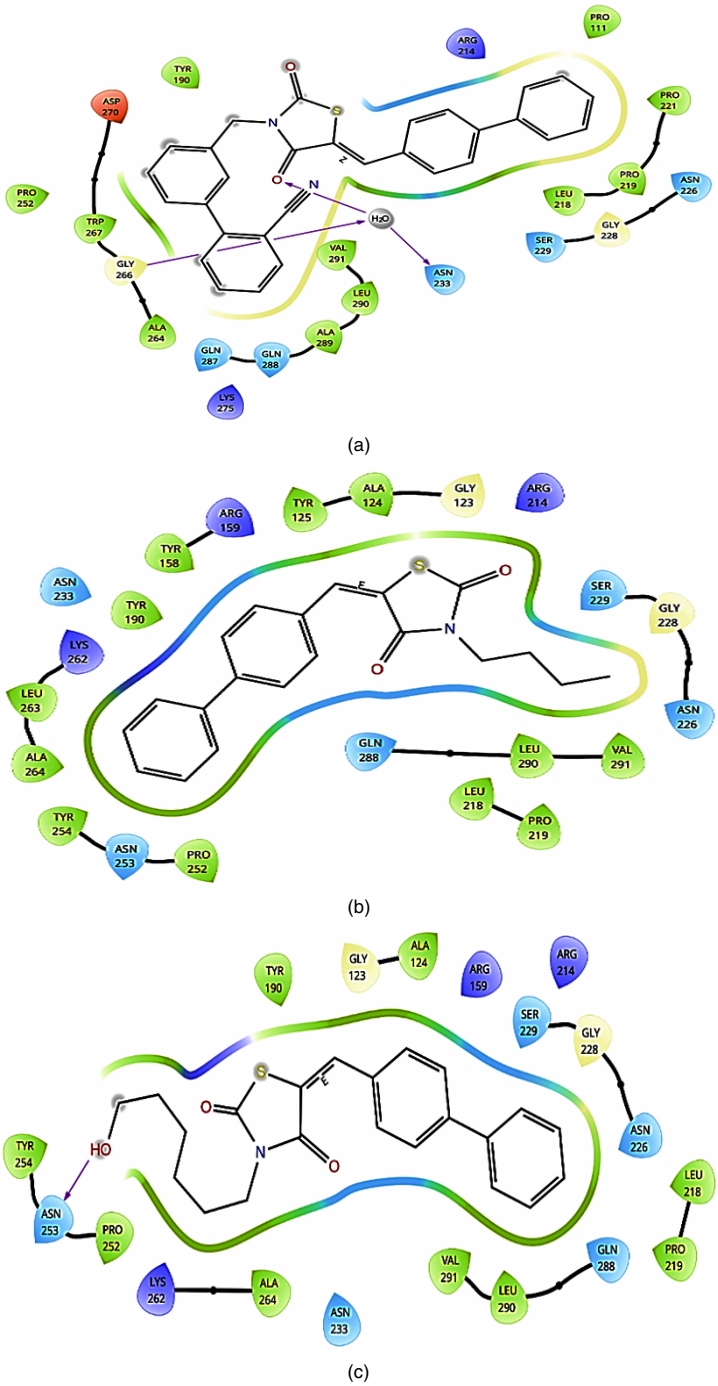


Fig. 1. 2D interactions of the compounds IIIm(A), IIIc(B) and IIId(C) with *E. coli* Mur B enzyme

ADME properties

The *In silico* ADME properties of all molecules have been determined using QikProp Schrodinger Suite and have been reported in

Table 3. The molecular weight of the molecules ranged from 281.328 to 472.56, the total solvent-accessible area 506.697 to 830.021, the donor hydrogen bonds were less than 2, the acceptor hydrogen bonds were ranging from 3 to 5, the QPlog Po/w values ranged from 3.18 to 6.784, the QPlogS values ranged from -4.156 to -8.172 and the percent human oral absorption was found to be100 %. All the molecules designed followed Lipinski's Rule of Five and thus were more likely to be drug-like.

Table 3: ADME properties of the compounds III, IIIa-IIIn

Sr. No	Compound	MW	SASA	HB Donor	HB Accept	QP logPo/w	Q Plog S	%Human Oral Absorption	Rule of Five
1	III	281.328	506.697	1	3	3.183	-4.156	100	0
2	IIIa	295.355	558.751	0	3	3.97	-4.951	100	0
3	IIIb	319.377	604.498	0.5	3	4.616	-5.642	100	0
4	IIIc	351.462	686.663	0	3	5.465	-6.665	100	1
5	IIId	381.489	728.997	1	4.7	4.949	-6.39	100	0
6	IIIe	367.419	675.736	0	5	4.112	-5.568	100	0
7	IIIf	371.453	664.472	0	3	5.788	-6.629	100	1
8	IIIg	372.441	661.926	0	4.5	4.623	-5.737	100	0
9	IIIh	439.451	716.851	0	3	6.784	-8.114	100	1
10	IIIi	439.451	707.635	0	3	6.566	-7.809	100	1
11	IIIj	457.543	830.021	0	5	6.174	-8.172	100	1
12	IIIk	431.505	740.074	0	4.5	5.818	-6.892	100	1
13	IIII	405.898	692.239	0	3	6.175	-4.156	100	0
14	IIIm	472.56	764.433	0	4.5	6.529	-4.951	100	0
15	IIIn	405.898	686.697	1	3	3.183	-5.642	100	0
16	STD	331.35	576.031	1	6	0.272	-3.904	48.588	0

CONCLUSION

The present study focussed on the design of fifteen 3,5-disubstituted-2,4-thiazolidinediones and evaluated their antimicrobial activity by their ability to inhibit the *E. coli* Mur B, an enzyme involved in the biogenesis of the bacterial cell wall. It was revealed that all the compounds interacted well with the receptor active site and among thee derivatives, compounds IIIc, IId, IIIm exhibited the highest glide docking scores indicating the prominence of the presence of hydrophobic groups on the thiazolidineone ring. Further from the ADME molecular properties it was observed that all the designed molecules followed Lipinskis rule of five. From all the results it can be observed that compound IIIm could be a promising antibacterial agent among the designed compounds and can be further investigated for conducting experimental studies.

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Conflict of intrest

The authors assure that, no competing financial interests exist.

REFERENCES

1. Prestinaci, F.; Pezzotti, P.; Pantosti, A., *Pathog Glob Health.*, **2015**, *109*(7), 309-18. doi: 10.1179/2047773215Y.0000000030. Epub 2015 Sep 7. PMID: 26343252;
2. Livermore, D.M., *Clinical Microbiol Infect.*, **2004**, *10*(Suppl. 4), 1–9.
3. Tanvir Mahtab Uddin.; Arka Jyoti, Chakraborty.; Ameer Khusro.; Redwan Matin Zidan, B.M.; Saikat Mitra, B.M.; Talha Bin Emran.; Kuldeep Dhama.; Md. Kamal Hossain, Ripon.; Márió, Gajdács.; Muhammad Umar Khayam, Sahibzada.; Md. Jamal Hossain.; Niranjan, Koirala., *Journal of Infection and Public Health.*,**2021,** *14*(12), 1750-1766.
4. Hermann, Fongang.; Armelle, T.; Mbaveng.; Victor, Kuete.; Advances in Botanical Research., **2023**, *106*, 1-20.
5. Sucheta.; Sumit, Tahlan.; Prabhakar Kumar, Verma., *Chemistry Central J.,* **2017**, *11*, 130.
6. Laxmi Madhuri, P.; Rajitha, G., *Int. J. Life Sci. Pharma Res.*, **2023**, *13*(5), 25-50. Doi: 10.22376 /ijlpr. 2023.13.5 P25-P50.

7. Prasanna, A. Datar.; Sainath, B. Aher., *Journal of Saudi Chemical Society.*, **2016,** *20*(1), S196-S201.
8. Laxmi Madhuri, P.; Rajitha, G., *Afr. J. Bio. Sc.*, **2024**, *6*(13), 1267-1276.
9. Gabriel Marc.; Anca Stana.; Smaranda Dafina Oniga.; Adrian Pîrnu., *Molecules.,* **2019**, *24*, 2060; doi:10.3390/molecules24112060
10. Laxmi Madhuri, P.; Rajitha, G., *Journal of Xidian University.*, **2024,** *18*(4), 868.
11. Meltem.; Rahmiye., *Turk J Chem.*, **2006**, *30*, 355–360.
12. Pattan, S. R.; Khade, A. B.; Pawar, P. D.; Tarnalli, A. D.; Kittur, B. S.; Borkar, S. D., *Indian J Heterocyclic Chem.*, **2007**, *16*, 299-300.
13. Tanaka, T.; Okuyama-Dobashi, K.; Motohashi, R.; Yokoe, H.; Takahashi, K.; Wiriyasermkul, P.; Kasai, H.; Yamashita, A.; Maekawa, S.; Enomoto, N.; Ryo, A.; Nagamori, S.; Tsubuki, M.; Moriishi, K., *Antiviral Res.*, **2021,** *194*, 105165.
14. Kallanagouda, R.; Shankar, A.; Alegaon, G., *Arabian Journal of Chemistry.*, **2011**, *4*(4), 465-472.
15. Abd Alhameed, R.; Almarhoon, Z.; Bukhari, S.I.; El-Faham, A.; de la Torre, B.G.; Albericio, F., *Molecules.*, **2020**, *25*, 105. https://doi.org/10.3390/molecules25010105
16. Sneha, Gupta.; Sumeet, Jha.; Supriya, Rani.; Pinky, Arora.; Shubham, Kumar., *Chemistry Open.*, **2024**, e202400147 (1 of 30).
17. Haroun, M.; Tratrat, C.; Kolokotroni, A.; Petrou, A.; Geronikaki, A.; Ivanov, M.; Kostic, M.; Sokovic, M.; Carazo, A.; Mladenka, P., *Antibiotics.*, **2021**, *10*, 309. https:// doi.org/10.3390/antibiotics10030309
18. Navjot, Singh sethi.; Prasad, D.N.; Deepak, Bhagwat.; Anuradha, Kumari.; Madhu, sharma.; Sangeeta, Kaundal., *Asian J Pharm Clin Res.*, **2018,** *11*(11), 363-367.
19. Swapna,D.; Sivagami,B.; Manasa ,K.; Rajitha, Galla.; Alagarsamy, Veerchamy., *International Research Journal of Pharmacy.*, **2016**, *7*, 15-19. 10.7897/2230-8407.07544.
20. Shubhanjali, Shukla.; Pankaj, Kumar.; Nirupam, Das.; Hari Narayana Moorthy, N.S.; Sushant Kumar, Shrivastava.; Piyush, Trivedi.; Radhey Shyam, Srivastava., *Med. Chem.*, **2012**, *8*, 834-845.
21. Charles, J Andres.; Joanne, J Bronson.; Stanley, V D'Andrea.; Milind, S Deshpande.; Paul, J Falk.; Katharine, A Grant-Young.; William, E Harte.; Hsu-Tso, Ho.; Peter, F Misco.; James, G Robertson.; David, Stock.; Yaxiong, Sun.; Ann, W Walsh., *Bioorganic & Medicinal Chemistry Letters.*, **2000**, *10*(8), 715-717.
22. Sasikala, M.; Rajitha, G., *Journal of Receptors and Signal Transduction.*, **2019**, *39*(5-6), 1–10.
23. Lucia Fernanda, C.; da Costa, Leite.; Rosa Helena, Veras Mourao.; Maria do Carmo Alves de Lima.; Suely Lins Galdino.; Marcelo Zaldini Hernandes., *Eur. J. Med. Chem.*, **2007**, *42*, 1263e1271 doi:10.1016/j.ejmech.2007.02.015.
24. Cheng, F.; Li W.; Liu G.; Tang Y., *Curr Top Med Chem.*, **2013**, *13*(11), 1273-89. doi: 10.2174/15680266113139990033. PMID: 23675935.
25. Moorthya, Perumal.; Sanmuga Priya Ekambaram, b.; Senthamil Selvan, Perumal., *Arabian Journal of Chemistry.*, **2019**, *12*, 413–419.