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INSILICO DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL THIAZOLE DERIVATIVES POSSESSING ANTIOSTEOPOROTIC ACTIVITY

Mopuri Deepa¹, Y.Pradeep Kumar^{2*}, J.Sumalatha³, D Anusha Reddy⁴, B.Swapna⁵, Vadde Vishalakshi⁶

^{1,2,,5,6}Annacharya College of Pharmacy, Newboyanapalli, Rajampet, Andhrapradesh

³P.Ramireddy Memorial College of Pharmacy, Utukur, Kadapa, Andhrapradesh

⁴Vasavi Institute of Pharmaceutical Sciences, Kadapa

Corresponding author mail: venkatdeepa19@gmail.com

ABSTRACT:

Thiazoles and fused heterocyclic thiazole derivatives constitute an interesting class of heterocyclic compounds due to their synthetic versatility and effective biological activities. Thiazoles and their derivatives exhibit a wide variety of biological activities like antidiabetic, anti-inflammatory, anti-convulsant etc. Special attention is warranted towards the synthetic design and development of Thiazoles because of their high demand in academic and pharmaceutical sectors. Keeping in view of the biological importance of Thiazoles, in the present work, we have planned to synthesize some novel Thiazoles, to characterize them by using TLC and IR and to evaluate them for *in-silico* antiosteoporosis activity. The structures of these synthesized compounds were confirmed by IR. All the values and results of this spectral and elemental analysis are found to be in the normal range. These compounds can be further exploited to get the lead compound.

Keywords: Thiazole derivatives, characterization, *insilico* anti osteoporotic activity.

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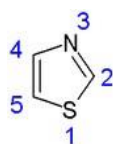
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INTRODUCTION:

Thiazole, or **1, 3-thiazole**^{7,8}, is a heterocyclic compound that contains both sulfur and nitrogen; the term 'thiazole' also refers to a large family of derivatives. Thiazole itself is a pale yellow liquid with a pyridine-like odor and the molecular formula C₃H₃NS. The thiazole is notable as a component of the vitamin thiamine (B₁).



Thiazoles are members of the azoles, heterocycles that include imidazoles and oxazoles. Thiazole can also be considered a functional group. Oxazoles are related compounds, with sulfur replaced by oxygen. Thiazoles are structurally similar to imidazoles, with the thiazole sulfur replaced by nitrogen.

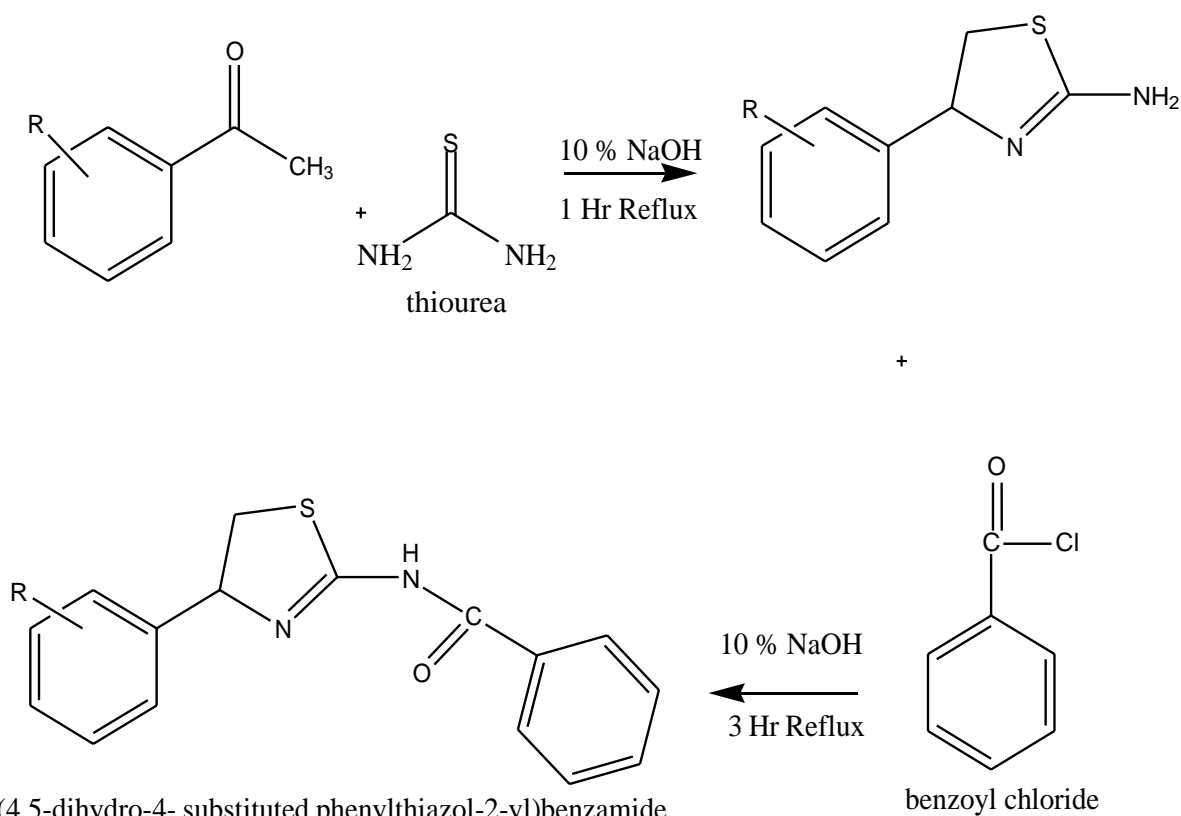
Thiazole rings are planar and aromatic. Thiazoles are characterized by larger pi-electron delocalization than the corresponding oxazoles and have therefore greater aromaticity. This aromaticity is evidenced by the chemical shift of the ring protons in proton NMR spectroscopy (between 7.27 and 8.77 ppm), clearly indicating a strong diamagnetic ring current. The calculated pi-electron density marks C5 as the primary site for electrophilic substitution, and C2 as the site for nucleophilic substitution.

In this study Novel thiazole derivatives were prepared for anti - osteoporotic activity.

Materials and Methods:

Melting points were determined in open capillary tubes using ANALAB melting point apparatus and are uncorrected. Purity of the compounds was verified by a single spot in TLC using E- Merck Silica Gel F254, 0.25mm aluminum plates. Visualization was accomplished with U.V light (254nm) and iodine chamber. The IR spectra were recorded on BRUKER FT IR SPECTROPHOTOMETER by using 1% potassium bromide discs. All the compounds gave satisfactory elemental analysis.

Docking Protocol: AutoDock4.2 is parameterized to use a model of the protein and ligand that includes polar hydrogen atoms, but not hydrogen atoms bonded to carbon atoms. An extended PDB format, termed PDBQT, is used for coordinate files, which includes atomic partial charges and atom types. The current Auto Dock force field uses several atom types for the most common atoms, including separate types for aliphatic and aromatic carbon atoms, and separate types for polar atoms that form hydrogen bonds and those that do not. PDBQT files also include information on the torsional degrees of freedom. In cases where specific side chains in the protein are treated as flexible, a separate PDBQT file is also created for the side chain coordinates. AutoDock Tools, the Graphical User Interface for AutoDock, may be used for creating PDBQT files from traditional PDBfiles. AutoDockTools includes a number of methods for analyzing the results of docking simulations, including tools for clustering results by conformational similarity, visualizing conformations, visualizing interactions between ligands and proteins, and visualizing the affinity potentials created by Auto Grid. All the docking studies are done using AUTODOCK 4.2 version and the images are rendered using Discovery studio visualizer v4.0 interface.

SYNTHETIC SCHEME:**PROCEDURE****STEP-1: Preparation of 2-Amino thiazole:**

0.01mol of acetophenones and 1 mol of thiourea were taken in a RBF and to the above mixture 15-20 ml of 10% sodium hydroxide was added and refluxed for 1hour .Cool the solution to room temperature and add cool water until the product precipitates out. The product was collected through filtration on a Buchner funnel.

STEP 2:

0.01 Moles of 2- Amino thiazole is taken in a RBF and to this 0.01 moles of Benzoyl chloride was added in small amounts and refluxed in the presence of Sodium Hydroxide at a temperature of 80-90⁰C for 3 hours to give final compounds.

Table 1: Codes given for prepared novel compounds with its IUPAC name

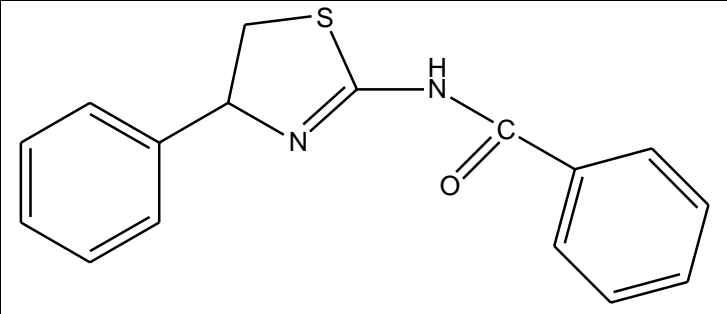
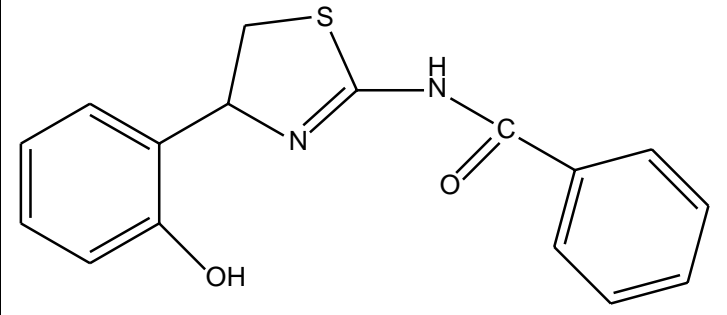
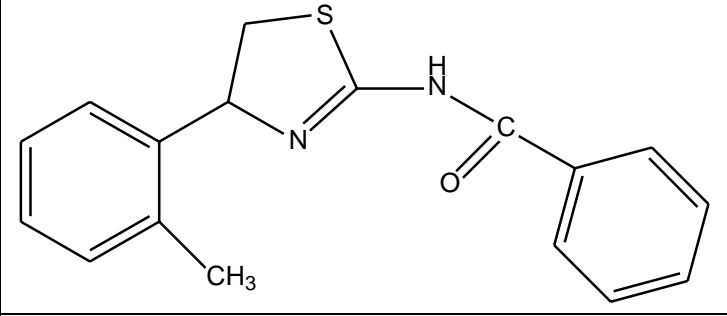
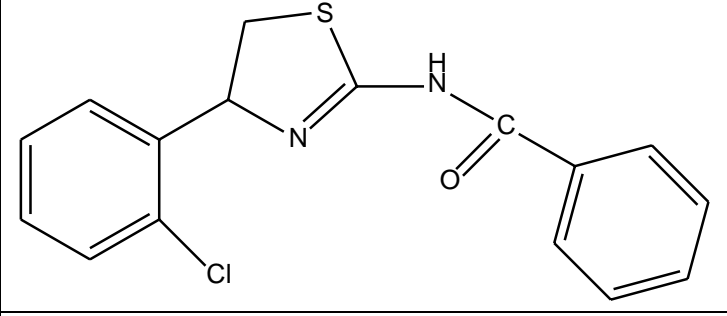
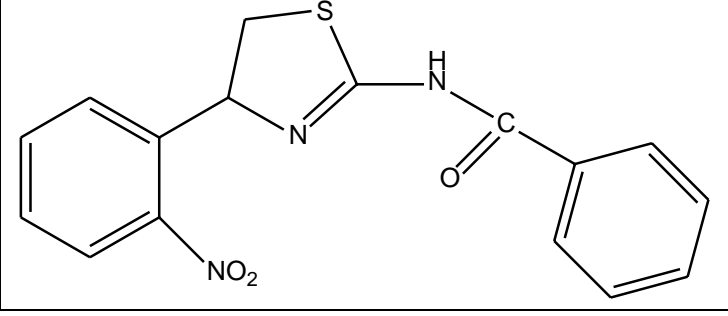
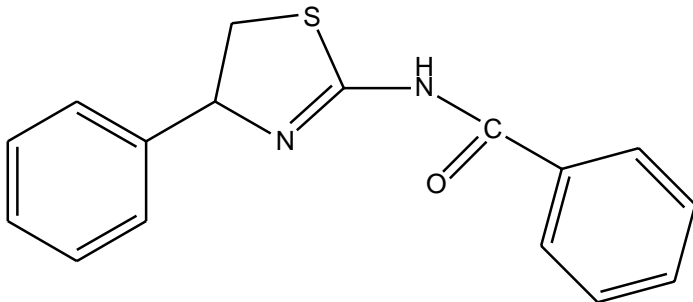
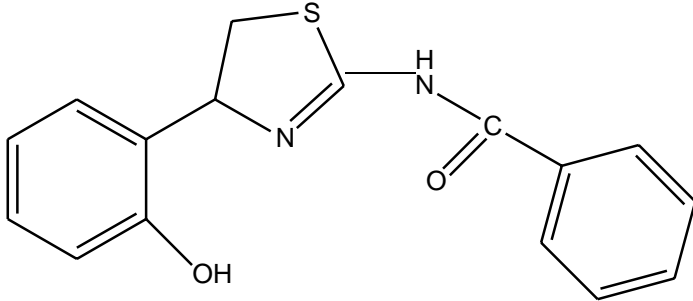
S. No	Code	Structure	IUPAC Name
1	Cpd 1		<i>N</i> -(4-phenyl-1,3-thiazol-2-yl)benzamide
2	Cpd 2		<i>N</i> -[4-(2-hydroxyphenyl)-1,3-thiazol-2-yl]benzamide
3	Cpd 3		<i>N</i> -[4-(2-methylphenyl)-1,3-thiazol-2-yl]benzamide
4	Cpd 4		<i>N</i> -[4-(2-chlorophenyl)-1,3-thiazol-2-yl]benzamide
5	Cpd 5		<i>N</i> -[4-(2-nitrophenyl)-1,3-thiazol-2-yl]benzamide

Table 2: Physical Data of the Novel Compounds

S.No	Compound	R	Molecular formula	Color	Solubility	Molecular Weight	Rf Value
1	Cpd1	H	C ₁₆ H ₁₂ N ₂ O ₂ S	Light Brown crystal	Chloroform	280.34428	0.57
2	Cpd2	2-OH	C ₁₆ H ₁₂ N ₂ O ₂ S	Yellow Amorphous Powder	Methanol	296.34368	0.39
3	Cpd3	2-CH ₃	C ₁₇ H ₁₄ N ₂ O ₂ S	Brownish Crystals	Methanol	294.37086	0.62
4	Cpd4	2-Cl	C ₁₆ H ₁₁ ClN ₂ O ₂ S	Orange to Yellow crystals	Chloroform	314.78934	0.27
5	Cpd5	2-NO ₂	C ₁₆ H ₁₁ N ₃ O ₃ S	Pale orange crstals	Chloroform	325.34184	0.45

Mobile phase :n-hexane: Ethylacetate (8:2,7:3)

Table 3: Spectral Data of Novel Compounds

S. No	Code	Structure	IR Values Absorption Frequency (cm ⁻¹)
1	Cpd 1		Aromatic (N-H) - 3335.55, Aromatic (C-H)- 2821.10, (C=C)-1603.95, Aliphatic C=N, 1448.70
2	Cpd 2		Aromatic (N-H) - 3342.94, Aromatic (C-H)- 3124.87, Aromatic (C=C)-1514.26, Aromatic (C=N)- 1488.18

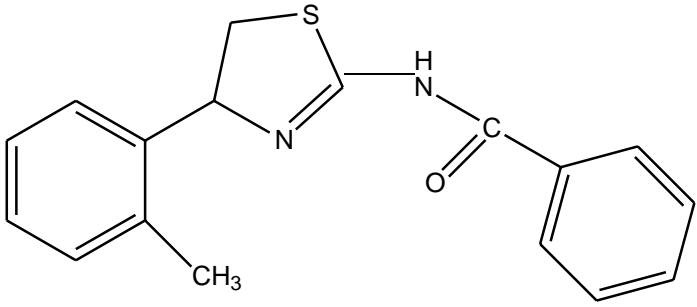
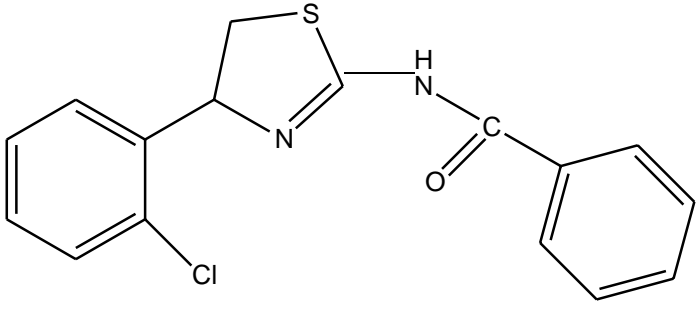
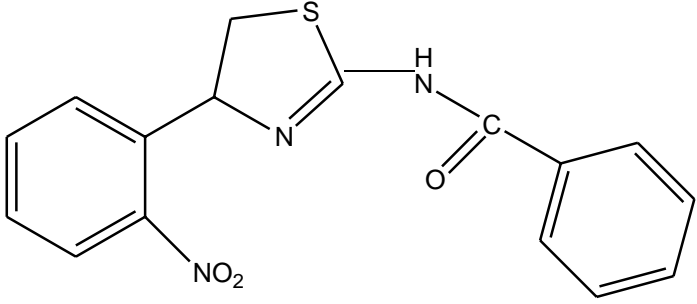
3	Cpd 3		Aromatic (N-H) - 3343.83, Aromatic (C-H)-3014.13, Aromatic (C=C)-1514.63, Aromatic (C=N)-1481.18
4	Cpd 4		Aromatic (N-H) - 3392.23, Aromatic (C-H)-3007.34, Aromatic (C=C)-1554.83, Aromatic (C=N)-1488.81
5	Cpd 5		Aromatic (N-H) - 3353.72, Aromatic (C-H)-3021.24, Aromatic (C=C)-1576.69, Aromatic (C=N)-1465.18

Table 4: Molecular docking studies of compounds with Tyrosine kinase using SWISS DOCK, MCULE

S. No.	Compound Code	R	Binding interactions
1	cpd1	H	Conventional hydrogen bond carbon hydrogen bond Pi-Alkyl
2	cpd2	2-OH	Conventional hydrogen bond Pi-carbon,hydrogen bond Pi-alkyl
3	cpd3	2-CH ₃	conventional hydrogen bond, Pi-Carbon hydrogen bond Pi-Alkyl
4	cpd4	2-Cl	conventional hydrogen bond pi-Carbon hydrogen bond pi-alkyl

5	Cpd5	2-NO ₂	conventional hydrogen bond pi- Carbon hydrogen bond pi-alkyl
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Table 5: Docking results for five new derivative compounds targeting interleukin-1 for anti- osteoporotic activity

S. No	Code	Bonding Interactions with Target	Binding Energy in K cal/mol
1.	cpd1	<p>Interactions: ■ Conventional Hydrogen Bond ■ Pi-Donor Hydrogen Bond ■ Pi-Alkyl</p>	-6.6
2.	cpd2	<p>Interactions: ■ Conventional Hydrogen Bond ■ Pi-Donor Hydrogen Bond ■ Pi-Alkyl</p>	-6.8
3.	cpd3	<p>Interactions: ■ Conventional Hydrogen Bond ■ Pi-Alkyl ■ Pi-Pi Stacked</p>	-6.8
4.	cpd4	<p>Interactions: ■ Conventional Hydrogen Bond ■ Pi-Pi Stacked ■ Pi-Alkyl</p>	-6.4

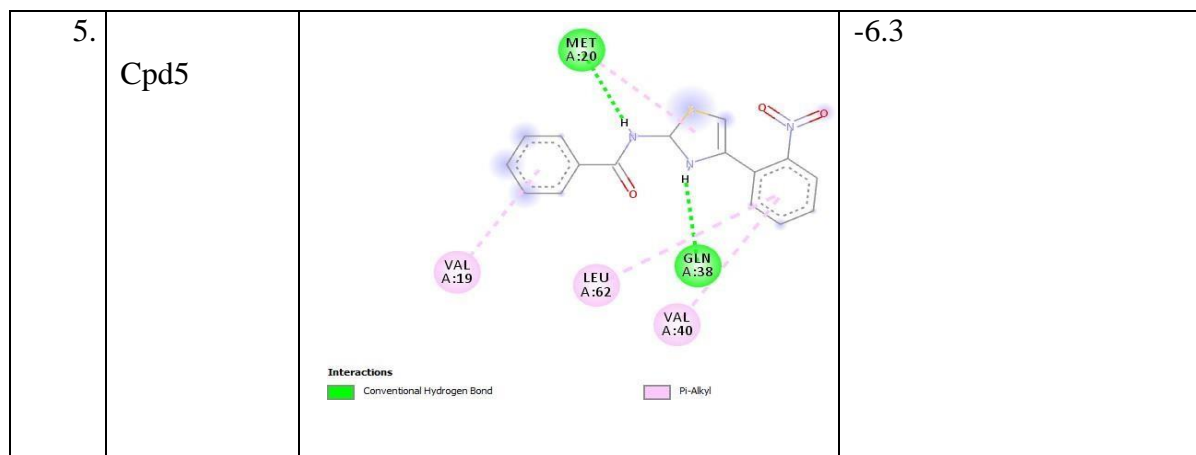


Table 6: QSAR molecular descriptor values of the compounds 1-5 for ADME prediction according to Lipinski's rule of 5

Name of descriptor	Recommended values
Hydrogen bonding donors	0.0 to 6.0
Hydrogen bonding acceptors	2.0 to 20.0
Predicted octanol/water partition coefficient	-2.0 to 6.5
Predicted IC50 value for blocking of HERG K ⁺ channels	Concern below -5
Predicted brain/blood partition coefficient	-3.0 to 1.2 CNS negative- more polar
Percent human oral absorption	>80- high, <25- poor

CONCLUSION AND FUTURE SCOPE OF WORK:

In this present research work, based on the wide literature survey, novel derivatives of benzamides of Thiazoles were synthesized in two step facile procedure using simple techniques with the use of minimal solvent and in good yields. The chemical structures of synthesized compound were confirmed on the basis of physical and spectral data. All the reactions were monitored by TLC and purification was done by recrystallization process. All the derivatives were characterized using special studies like FT-IR spectroscopy. All the five derivatives were screened for their insilico anti-osteoporotic activity study using docking methodology against Interleukin-1 as a target. by AUTODOCK 4.2 version for theoretical prediction of anti-osteoporotic activity using "Interleukin-1" as the target site. Results revealed that the synthesized derivatives possess good binding affinity towards the target. Based on the results the derivatives with -OH and -CH₃ in the ring or in substituted groups showed high binding affinity to the target.

CpdII>CpdIIIC>CpdI>CpdIV>CpdV

QSAR parameters:

All the derivatives were subjected to QSAR study to obtain the QSAR of parameters data like molecular weight, Log P, number hydrogen bond donors, no. of hydrogen bond acceptors, no. of rotatable bonds, total polar surface area and ADME test. Based on the results obtained, all the derivatives were found to follow Lipinski's rule of 5 and passes ADME test.

Further suitable modifications of the compounds may show profound biological activities

REFERENCES:

1. Wilson & Gisvolds Textbook Of Organic Medicinal and Pharmaceutical Chemistry JH Block , JM Beale Jr, Lippincott Williams &Wilkins 11th Edition,3-5.2004.
2. Burger, J.Abraham, Burgers Medicinal Chemistry and drug Discovery, 6th edition,vol.1:Drug discovery 1-42
3. Graham Patrick. L, An Introduction to Medicinal Chemistry, 5th edition, pp: 187
4. Igor G.Safonov, Dirt A. Heerding, Richard M.Keenan, Alan T.Price, Connie L.Levin, Kennet A.Lord and Peter M. Tapley, Bioorganic and Medicinal Chemistry Letters ,2006,16, 1212-1216
5. James R. Fromm, An Introduction to Heterocyclic Compounds, 1997.
6. Joule, J.A. and Mills, K. Heterocyclic Chemistry, 4th edn, Blackwell, Oxford, (2000).
7. Singh, Inder P.; Gupta, Shiv; Kumar, Sanjay, Thiazole Compounds as Antiviral Agents: An Update, , Medicinal Chemistry, Volume 16, Number 1, 2020, pp. 4-23(20)
8. YassineKaddouri,FaridAbrigachel,BekayeYousfi,Mohamed,ElKodad,RachidTouzani,New thiazole, pyridine and pyrazole derivatives as antioxidant candidates: synthesis, DFT calculations and molecular docking
9. Kexin Chen, Xu Yao, Ting Tang, Li-Mei Chen, Can Xiao, Jing-Yi Wang, Hong-Fei Chen, Zhong-Xing Jiang, Yi Liu & Xing Zheng, Thiazole-based and thiazolidine-based protein tyrosine phosphatase 1B inhibitors as potential anti-diabetes agents, .Medicinal Chemistry Research volume 30, pages 519–534 (2021).
10. . Sharma, Diksha; Bansal, Kushal K.; Sharma, Archana; Pathak, Meenakshi; Sharma, PrabodhC A Brief Literature and Review of Patents on Thiazole Related Derivatives, .Current Bioactive Compounds, Volume 15, Number 3, 2019, pp. 304-315(12)
11. Abida Qureshi, Short Review on Thiazole Derivative ,Vol 9 No 4-A (2019): Volume 9, Issue 4-A, July-Aug 2019 (Supplement Issue-2).
12. Nayak, Swarnagowri, Gaonkar, Santhosh L.A Review on Recent Synthetic Strategies and Pharmacological Importance of 1,3-Thiazole Derivatives, ,Bentham Science Publishers
13. Agarwal, Shikha; Kalal, Priyanka; Gandhi, Divyani; Prajapat, Prakash,, Thiazole Containing Heterocycles with CNS Activity, Agarwal, Shikha Current Drug Discovery Technologies, Volume 15, Number 3, 2018, pp. 178-195(18),Bentham Science Publishers
14. Kumawat, Mukesh K. Thiazole Containing Heterocycles with Antimalarial Activity, Current Drug Discovery Technologies, Volume 15, Number 3, 2018, pp. 196-200(5)
15. Jain, Shweta; Pattnaik, Satyanarayan; Pathak, Kamla; Kumar, Sushant; Pathak, Devender; Jain, Surendra; Vaidya, Ankur, Anticancer Potential of Thiazole Derivatives: A Retrospective Review, , Mini Reviews in Medicinal Chemistry, Volume 18, Number 8, 2018, pp. 640-655(16)

16. Singh, Inder P.; Gupta, Shiv; Kumar, Sanjay, Thiazole Compounds as Antiviral Agents: An Update, , Medicinal Chemistry, Volume 16, Number 1, 2020, pp. 4-23(20).
17. Mokhles M. Abd-Elzaher, Ammar A. Labib, Hanan A. Mousa ,Samia A. Moustafa , Mamdouh M. Ali , Ahmed A. El-Rashedy Mokhles M. Abd-Elzaher , Synthesis, anticancer activity and molecular docking study of Schiff base complexes containing thiazole moiety Available online at www.sciencedirect.com/journal.
18. Preeti Arora, Rakesh Narang, Sonam Bhatia, Surendra Kumar Nayak, Sachin Kumar Singh, Balasubramanian Narasimhan, Synthesis, molecular docking and QSAR studies of 2, 4-disubstituted thiazoles as antimicrobial agents Journal of Applied Pharmaceutical Science Vol. 5 (02), pp. 028-042, February, 2015 Unported License (<http://creativecommons.org/licenses/by-nc-sa/3.0/>). Available online at _ DOI: 10.7324/JAPS.2015.50206, ISSN 2231-3354
19. Muhammad Taha ,Maryam Irshad,Syahrul Imran, Fazal Rahim, Manikandan Selvaraj, Noor Barak Almandil, Ashik Mosaddik, Sridevi Chigurupati ,Faisal Nawaz, Nor Hadiani Ismail, and Mohamed Ibrahim, Thiazole Based Carbohydrazide Derivatives as α -Amylase Inhibitor and Their Molecular Docking Study Hindawi, Volume 2019, Article ID 7502347, 8 pages, <https://doi.org/10.1155/2019/7502347>
20. Aamer Saeed ,Parvez Ali Mahesar , Pervaiz Ali Channar , Qamar Abbas , Fayaz Ali Larik, Mubashir Hassan , Hussain Raza , Sung-Yum Seo Synthesis, molecular docking studies of coumarinyl-pyrazolanyl substituted thiazoles as non-competitive inhibitors of mushroom tyrosinase ,Direct Bioorganic Chemistry
21. Sobhi M Gomha, Hyam A Abdelhady, Doaa ZH Hassain, Aboubakr, H Abdelmonsef Mohamed El-Naggar, Mahmoud M Elaasser, Huda K Mahmoud Thiazole-Based Thiosemicarbazones: Synthesis, Cytotoxicity Evaluation and Molecular Docking Studying Development and Therapy downloaded from <https://www.dovepress.com/> by 223.187.79.134 on 14-Jul-2021
22. Iswatun Hasanah Abdullah Ripain, Norashikin Roslan, Nurul Shazana Norshahimi, Siti Salwa Mohamed Salleh, Noraslinda Muhamad Bunnori, Nurziana Ngah, Synthesis And Molecular Docking Of 2,4,5-Trisubstituted-1,3-Thiazole Derivatives As Antibacterial Agents, Malaysian Journal Of Analytical Sciences, 1394 – 2506
23. Ismail Althagafi , Nashwa El-Metwaly, and Thoraya A. Farghaly, New Series of Thiazole Derivatives: Synthesis, Structural Elucidation, Antimicrobial Activity, Molecular Modeling and MOE Docking of Substituted Thiazoles and Methods of Use. Biocontrol Sci. 2013, 18, 59–73
24. Huda R. M. Rashdan , Mohamed El-Naggar and Aboubakr H. Abdelmonsef, Synthesis, Molecular Docking Studies and In Silico ADMET Screening of New Heterocycles Linked Thiazole Conjugates as Potent Anti-Hepatic Cancer Agents, Molecules 2021, 26, 1705.
25. Rizk E. Khidre & Ibrahim Ali M. Radini, Design, synthesis and docking studies of novel thiazole derivatives incorporating pyridine moiety and assessment as antimicrobial agents, <https://doi.org/10.1038/s41598-021-86424-7>.
26. Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S. and Olson, A. J. (2009) Autodock4 and AutoDockTools4: automated docking with selective receptor flexibility. *J. Computational Chemistry* 2009, **16**: 2785-91.