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

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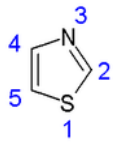
ABSTRACT:

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.

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 C_3H_3NS. The thiazole is notable as a component of the vitamin thiamine (B_1).



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.

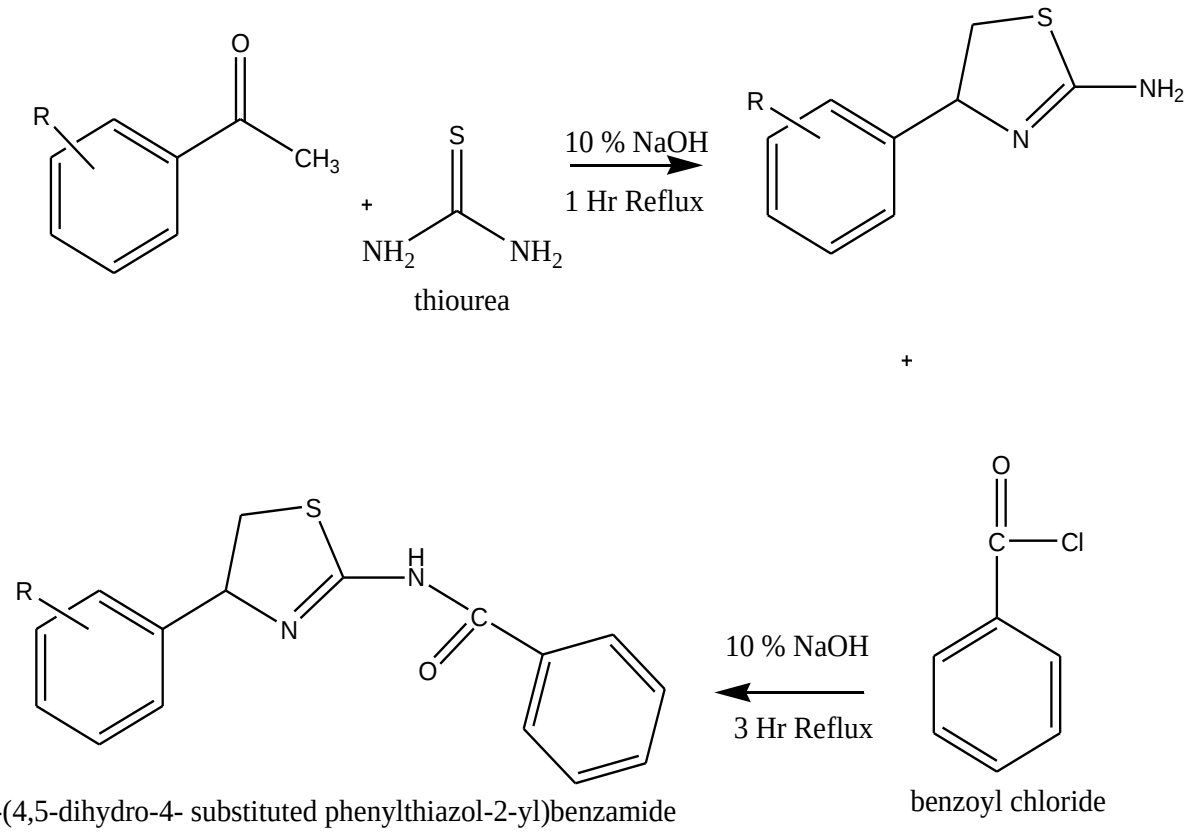
In this study Novel thiazole derivatives were prepared for anti - osteoporotic activity.

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:



N-(4,5-dihydro-4- substituted phenylthiazol-2-yl)benzamide

benzoyl chloride

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 80-90^{0}C for 3 hours to give final compounds.

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

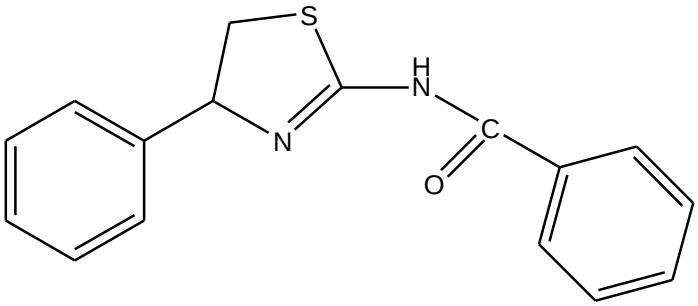
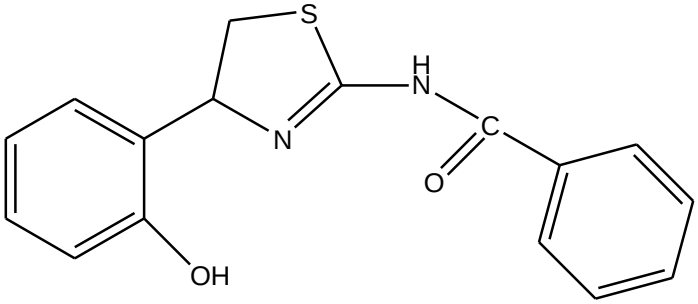
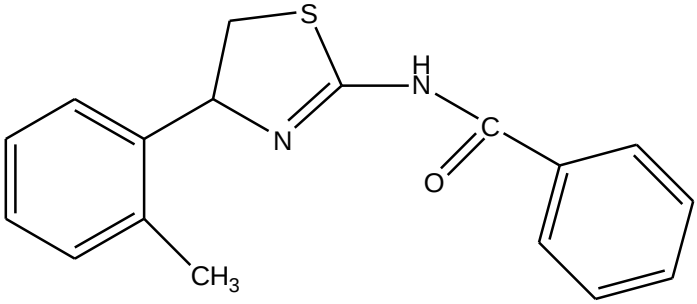
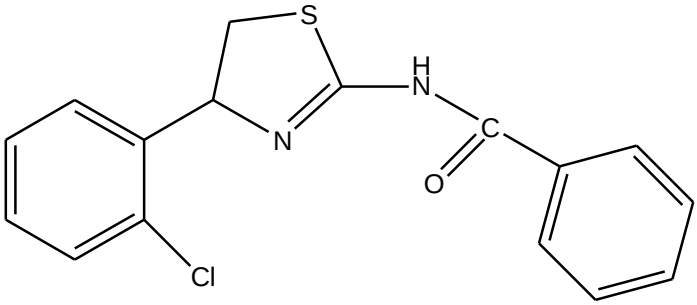
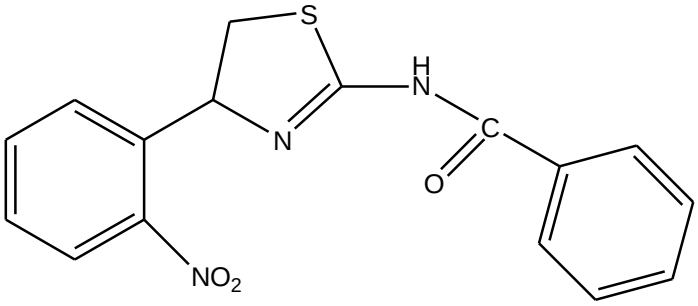
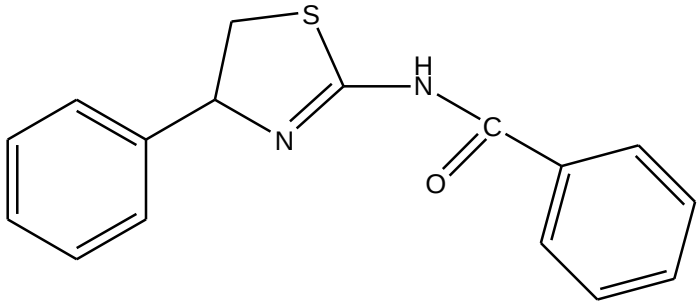
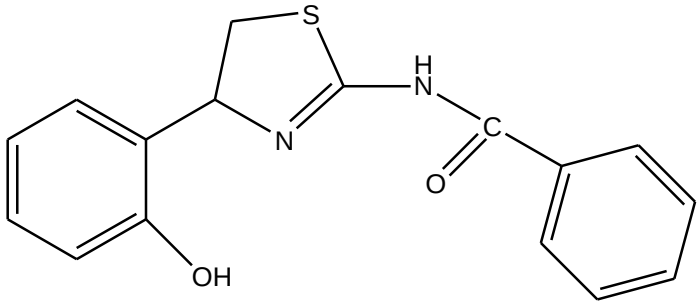
S. No	Code	Structure	IUPAC Name
1	Cpd 1		*N*-(4-phenyl-1,3-thiazol-2-yl)benzamide
2	Cpd 2		*N*-[4-(2-hydroxyphenyl)-1,3-thiazol-2-yl]benzamide
3	Cpd 3		*N*-[4-(2-methylphenyl)-1,3-thiazol-2-yl]benzamide
4	Cpd 4		*N*-[4-(2-chlorophenyl)-1,3-thiazol-2-yl]benzamide
5	Cpd 5		*N*-[4-(2-nitrophenyl)-1,3-thiazol-2-yl]benzamide

Table 2: Physical Data of the Novel Compounds

S.No	Compound	R	Molecular formula	Color	Solubility	Molecular Weight	Rf Value
1	Cpd1	H	C16H12N2OS	Light Brown crystal	Chloroform	280.34428	0.57
2	Cpd2	2-OH	C16H12N2O2S	Yellow Amorphous Powder	Methanol	296.34368	0.39
3	Cpd3	2-CH_3	C17H14N2OS	Brownish Crystals	Methanol	294.37086	0.62
4	Cpd4	2-Cl	C16H11ClN2OS	Orange to Yellow crystals	Chloroform	314.78934	0.27
5	Cpd5	2-NO_2	C16H11N3O3S	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

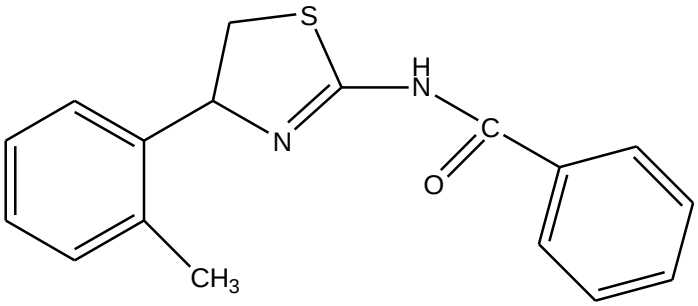
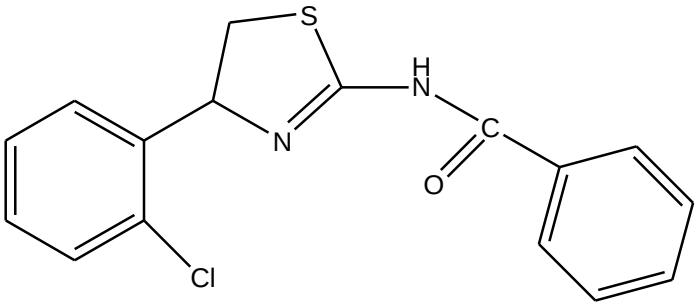
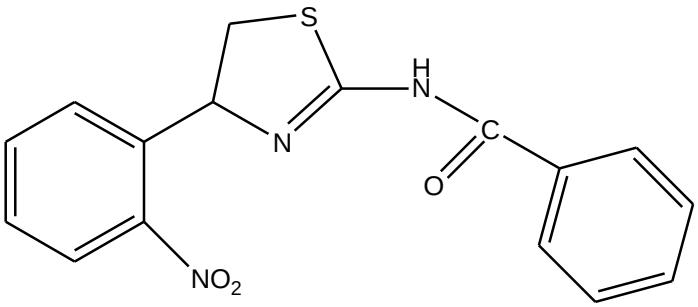
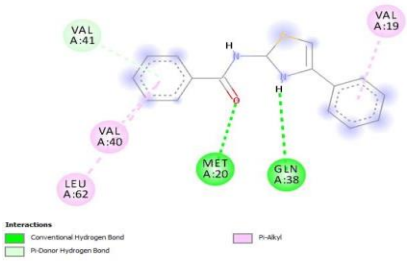
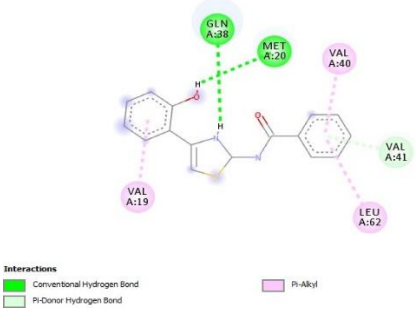
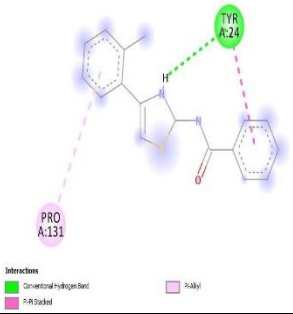
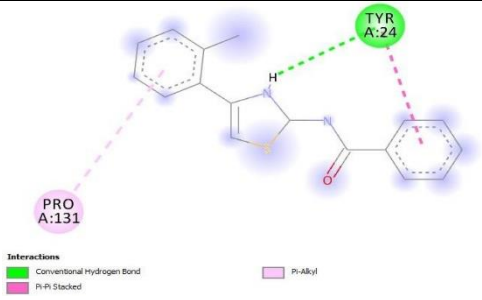
3	Cpd 3		Aromatic (N-H) - 3343.83,Aromatic (C-H)-3014.13, Aromatic (C=C)-1514.63, Aromatic (C=N)-1481.18
4	Cpd 4		Aromatic (N-H) - 3392.23, Aromatic (C-H)-3007.34, Aromatic (C=C)-1554.83, Aromatic (C=N)-1488.81
5	Cpd 5		Aromatic (N-H) - 3353.72,Aromatic (C-H)-3021.24, Aromatic (C=C)-1576.69, Aromatic (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-NO2	conventional hydrogen bond pi- Carbon hydrogen bond pi-alkyl

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		-6.6
2.	cpd2		-6.8
3.	cpd3		-6.8
4.	cpd4		-6.4

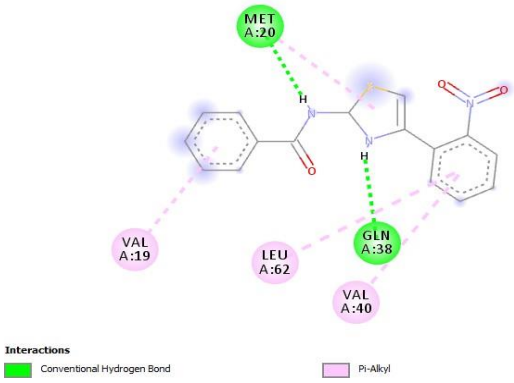
5.	Cpd5		-6.3

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 reaction**s** 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 -CH_3 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

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