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Design Sythesis And Molecular Propertiesof Noval Hetero Cyclic Derivatives By Insilco Methods

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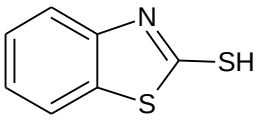
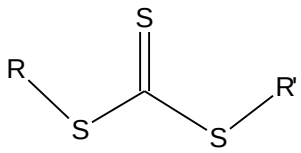
ABSTRACT

2-Mercaptobenzothiazole core is a well-known privileged structure inMedicinalChemistryand ofwide interest because of its diverse biological activities.ringmade from thiazole ring fused with benzenering.Thiazole ring is fivemembered ring consists of one nitrogen and one sulfur atom in thering.A literature survey indicates that benzothiazoles derivatives possess differentpharmacological and biological activities, of which the most potent anti-cancer anti-microbial, antifungal, and anti tumor activities. In view of the above literature survey, wethought to synthesis some new substituted benzothiazoles derivatives containingtrithicarbonatemoiety.2-mercaptobenzothiazole derivatives have pharmacological activitiessuch asanti microbial, antibacterial and fungicidal activity benzothiazolecontainingnucleus are also reported anti allergergic ,anti diabetic ,antitumor and antihelmenthic activities.



(1A)

Trithiocarbonates have industrial, synthetic and medicinal properties. They have been used extensivelyas pharmaceuticals, organic chemicals and intermediates in organic synthesisfor the protection of thiol functional group .Hence, its interesting to see such variation of the Pharmacological activity of 2-mercaptobenzothiazole coupled with thetrithiocarbonate.



(1B)

In the present investigation various class of 1, 3-benzothiazol-2-yl hydrogen carbonotrithioatederivatives have been synthesized by scheme-1. In scheme-1,2-mercaptobenzothiazole(1,3-benzothiazol-2-yl hydrogen carbonotrithioate) the key intermediate, treated with carbondisulfideand various aryl alkyl halides give rise to various 1, 3-benzothiazol-2-yl hydrogen carbonotrithioatederivatives

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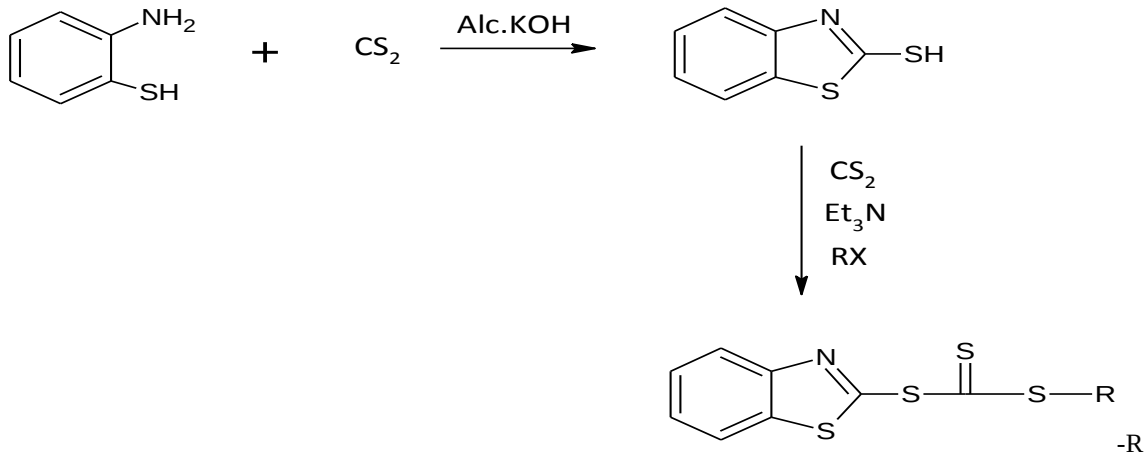
SCHEME

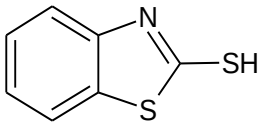


1A: Methyl
1B : Propyl
1C : Butyl
1D : Isobutyl

I. INTRODUTION

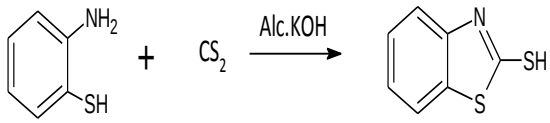
Heterocyclic compounds are widely distributed in nature , play a diverse and important role in the field of Pharmaceutical chemistry.The earliest compounds known to mankind were of heterocyclic origin. Life, like ours, totally dependent on the heterocyclic compounds, it takes birth with purine /pyrimidine bases, nourishes on carbohydrates and in case of disease, is cured from medicines, many of which are heterocyclicnature.Today, the heterocyclic chemistry delivers reagents and synthetic methods of its own traditional activity in synthesis of drugs, pesticides and detergents as well as into the related fields such as biochemistry, polymers and material sciences. They have been also used as optical brightening agents, antioxidants, copolymers, solvents, photographic sensitizers, corrosion inhibitors and additives, dye stuffs and pigments. Heterocyclic compounds are also finding an increasing use as an intermediates in organic synthesis. Heterocyclic compounds like benzothiazole, trithiocarbonates are with several of its derivatives exhibited diversified biological activity.

1,3-benzothiazole-2-thiol:



(1.1)

Over the past years benzothiazole derivatives are one of the most extensively studied classes of heterocyclic compounds. Molecules with benzothiazole nucleus been reported to possesanticancer, antibacterial, antifungal, and anti-HIV properties Substituted benzothiazoles have proven as drug leads which have exhibited pharmacological interest. Benzothiazole is commercially available. The usual synthesismethod involves condensation of2-aminobenzenethiolwith the Alcoholic KOH ,triethylamine and carbondisulphide.



Benzothiazole is hetrocyclic aromatic organic compound consists fusion of benzene and thiazole containing one sulphurone nitrogen atoms with non-adjacent positions which is rather fused to benzene ring.

Trithiocarbonates:

Trithiocarbonates have industrial, synthetic and medicinal properties. They have been used extensively as a pharmaceuticals, organic chemicals and as intermediates in organic synthesis of various compounds and for protection of thiol functional group

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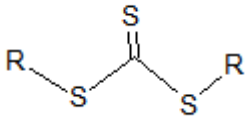
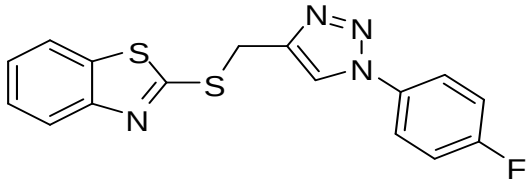


II. LITERATURE REVIEW

2.1 LITERATURE REVIEW ON BENZOTHIAZOLE

Anti-inflammatory activity:

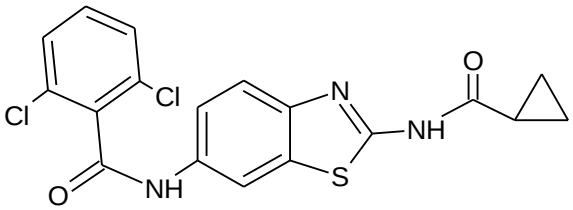
In 2012, Syed Shafi et al., reported synthesis of novel 2-mercapto benzothiazole bis-heterocycles: Their anti-inflammatory and anti-nociceptive activities.The synthesized compounds have been tested their anti-inflammatory activity using biochemical cyclooxygenase (COX) activity assays and carrageenan-induced hind paw edema. Among the tested compounds, compound 4d demonstrated a potent selective COX-2 inhibition with COX-2/COX-1 ratio of 0.44The anti-inflammatory activity profile of compound 4d (77.83% inhibition at 3 h post-carrageenan and 81.13% inhibition at5 h post-carrageenan) was better than that of standard NSAID, Ibuprofen (69.50% inhibition at 3 h as well as 71.69% inhibition at 5 h) and showed a time-dependent increase in the inhibition of inflammation.



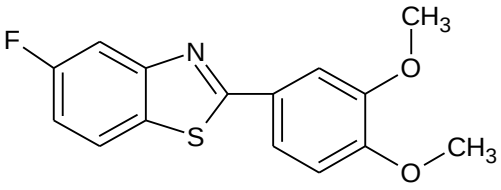
2-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methylthio)benzo[d]thiazole

Antitumor Activity:

Masao Yoshidaet.al reported Synthesis and biological evaluation of benzothiazole derivatives aspotentantitumoragents2,6-dichloro-N-{2-[(cyclopropylcarbonyl)amino]-1,3-benzothiazol-6-yl}benzamide

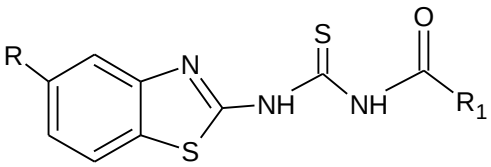


Catriona G.mortimer et.al., synthesised andreported2-(3,4-Dimethoxyphenyl)-5-fluorobenzothiazole (GW 610, NSC 721648), a Simple Fluorinated 2-Arylbenzothiazole, Shows Potent and Selectiveinhibitory Activity against Lung, Colon, and Breast Cancer Cell Lines



Anti-microbial and antitumor Activity:

Sohailsaeedet.al.,reportedSynthesis, characterization and biological evaluation of some thiourea derivatives bearing benzothiazole moiety as potential antimicrobial and anticancer agents



R_1- R-
1a-1d-R_1 -4-nitrophenol
1a-5a R-H
2a-2d R_1 -2-thiophene
1b-5b R-NO_2
3a-3d R_1 - phenyl
1c-5c R-NH_2
4a-4d R_1 -n-butyl
1d-5d R-Br
5a-5d R_1 -4-morpholine

Anti-tubercular activity:

In 2014, Parth Shah et al., reported a synthesis and biological evaluation of Arylalkyl benzo[d]thiazole-2-carboxamides as anti-mycobacterial agents.The present work reveals N-arylmethyl benzo[d]thiazole-2-carboxamide as a new anti-TB scaffold. Twelve compounds displayed good in vitroanti-mycobacterial activity, with MIC in low micromolar range against replicating TB, and they are, in general, non-toxic to HEK 293T cell lines (<50% inhibition at 50 mgmL1). The most potent compound 5bf exhibits MIC of 0.78 mg/mL1(therapeutic index > 60), more than that of the standard drugs E,Z and Cfx. The significant increase in the anti-TB activity with the 5-Cl substituted benzothiazole derivatives

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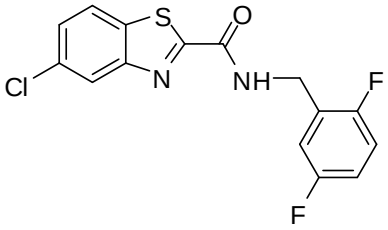
shows furtherscope for improvement in anti-TB activity.



5-chloro-N-(2,5-difluorobenzyl)benzo[d]thiazole-2-carboxamide

2.2 LITERATURE REVIEW ON TRITHIOCARBONATES:

There is very scarce literature review available on trithiocarbonates

2.3PRESENT WORK:

Although many new benzothiazole derivatives have been synthesized as potential chemotherapeutic agents, there is scarce literature data on benzothiazoles possessing trithiocarbonate as substituents. Literature data indicating that benzothiazole and trithiocarbonate as separate entity possessing anticancer, anti-infective, antibacterial an antifungal properties. In view of this we thought worthwhile to synthesize a series of molecule having general structure shown in fig 1. containing both benzothiazole nucleus and trithiocarbonate as side chain.

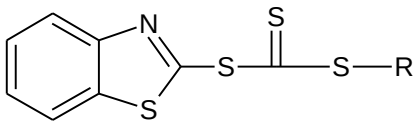
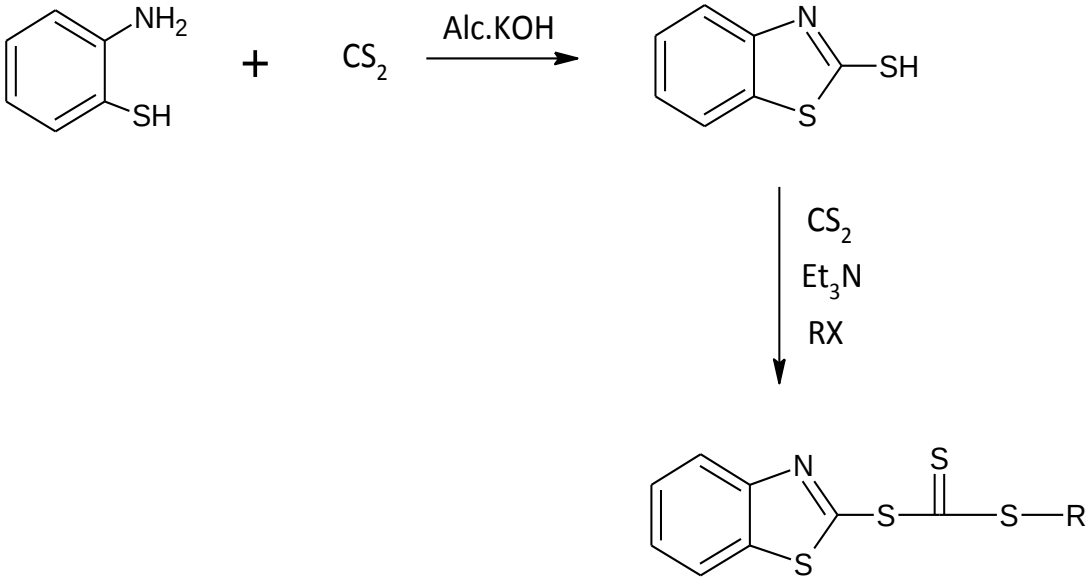


Figure 1

SCHEME-1



-R
1A: Methyl
1B : Propyl
1C : Butyl
1D : Isobutyl

Pharmacologicalactivityof1,3-benzothiazol-2-yl hydrogen carbonotrithioatederivatives:

2-Mercaptobenzothiazole and trithiocarbonate have wide spectrum of activities such as antibacterial, antifungal, antitumor, antioxidant, antihelmenthic and Insecticidal activities. So in present investigation all the synthesized 1,3-benzothiazol-2-yl hydrogen carbonotrithioatederivatives are evaluated and expected to have anti-cancer, anti-bacterial and anti-fungal activities.

2.4 The present work has been carried out with following objectives:

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1. The compounds with general structure shown in fig 1. are synthesized by adopting methodology shown in scheme-1.
2. To perform molecular property prediction of synthesized compounds using molsoft and molinspirationsoftwares.
3. To evaluate the antimicrobial activities of synthesized compounds.
4. To evaluate the title compounds as possible chemotherapeutic agents.

III. METHODOLOGY

Table 1: LIST OF CHEMICALS:

NAME	GRADE	SOURCE
2-Aminothiophenol	AR	Merck
KOH	AR	SD Fine
Alcohol	AR	Merck
Carbondisulphide	AR	Merck
2-Mercaptobenzothiazole	AR	SD Fine
Triethylamine	AR	SD Fine
Methyl Iodide	AR	Sigma Aldrich
Ethyl Iodide	AR	Sigma Aldrich
Propyl Iodide	AR	Sigma Aldrich
Isopropyl Iodide	AR	Sigma Aldrich
Butyl bromide	AR	Sigma Aldrich
Isobutyl bromide	AR	Sigma Aldrich
Benzyl Chloride	AR	Sigma Aldrich

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3.2 .INSTRUMENTS:

1.Melting points were recorded on **METLER FP-51** instrument and are uncorrected..

2.Analytical thin layer chromatography (TLC) is performed on 5-10 cm aluminium plates coated with **silica gel 60F-254 (Merck)** in an appropriate solvent. Visualisation of the spots on the plates is achieved either by exposure to iodine vapor or UV light.

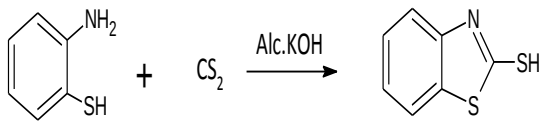
3. All the solvents extracts were washed with water, brine, dried over anhydrous sodium sulphate and concertrated at reduced pressure on **BUCHI-R-300** rotary evaporator below 50℃.

4. All the solvents used for silica gel column chromatography were distilled prior to use. **Silica gel 60-120 mesh** (Merck) was used as an adsorbent for column chromatography.

3.3 EXPERIMENTAL PROCEDURES

Procedure for the synthesis of 1, 3-benzothiazole-2-thiol:

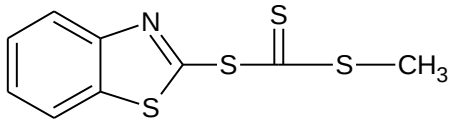
The synthesis has been carried out using a mixture of 2-Aminothiophenol (0.01 mol), carbondisulphide (0.015 mol) and Alc.KOH (100 ml) refluxed for 3 hrs and then cooled and poured into ice cold water and neutralized with 10N HCl. The resulting solid filtered, dried and purified by the recrystallization from methanol to yield 2-Mercaptobenzothiazole(1, 3-benzothiazole-2-thiol).



Molecular formula: $C_7H_5NS_2$
Molecular Weight: 167.25
Melting Point: 167^{0}C
Yield: 75%

Synthesis of 1,3-benzothiazol-2-yl methyl carbonotrithioate:

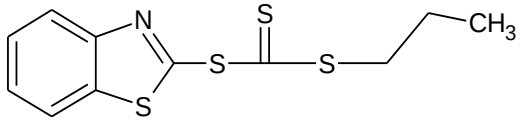
1, 3-benzothiazole-2-thiol andtriethylamine were stirred at room temperature for 30 minutes and then carbon disulphide and distilled water was added dropwise. The reaction mixture stirred for 50 minutes then Methyl iodide was added to solution and allowed to stirr and monitored by TLC. The mixture was extracted usingethylacetateand dried over sodium sulfate and later was subjected to purification by passing through silica gel using mixture of n-hexane and ethylacetateas eluent



Molecular formula: $C_9H_7NS_4$
Molecular Weight : 257.418
Yield : 85%

Synthesis of propyl (1H-benzimidazol-2-ylmethyl)carbamodithioate:

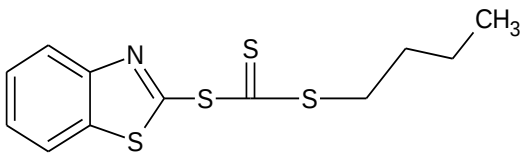
1,3-benzothiazole-2-thiol andtriethylamine were stirred at room temperature for 30 minutes and then carbon disulphide and distilled water was added drop wise. The reaction mixture stirred for 50 minutes at room temperature and then propyl iodide was added to solution and allowed to stirr and reaction is monitored using TLC. The mixture was extracted with ethylacetateand dried over sodium sulfate and later subjected to purification by passing through silica gel using mixture of n-hexane andethylacetateas eluent



Molecular formula : C_{11} H_{11} N S_4
Molecular weight : 285.47
Yield : 76%

Synthesis of 1,3-benzothiazole-2-yl butyl carbonotrithioate:

1,3-benzothiazole-2-thiol andtriethylamine were stirred at room temperature for 30 minutes and then carbon disulphide and distilled water was added drop wise. The reaction mixture stirred for 50 minutes at room temperature and then butyl iodide was added to this solution and allowed to stirr and reaction monitored by TLC. The mixture was extracted with ethylacetateand dried over sodium sulfate and later was subjected to purification by passing through silica gel using mixture of n-hexane andethylacetateas eluent



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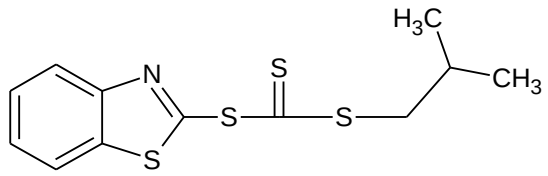
Molecular formula : C_{12} H_{13} N S_4
Molecular weight : 299.49
Yield : 76%

Synthesis of 1,3--benzothiazole-2-yl - 2-methylpropyl carbonotrithioate:

1,3-benzothiazole-2-thiol andtriethylamine were stirred at room temperature for 30 minutes and then carbon disulphide and distilled water was added drop wise. The reaction mixture stirred for 50 minutes at room temperature then Isobutyl bromide was added to this solution and allowed to stirr and reaction monitored by TLC. The mixture was extracted with ethylacetateand dried over sodium sulfate and later was subjected to purification by passing through the silica gel using mixture of n-hexane and ethylacetateas eluent



Molecular formula :C_{12} H_{13} N S_4
Molecular weight : 299.49
Yield : 76%

MOLECULAR PROPERTY PREDICTION
Molinspiration

- Molinspiration Cheminformatics provides calculation of molecular physicochemical properties relevant to drug design and QSAR including log P, polar surface area (PSA), nrotb, HBA/HBD counts and the rule of five descriptors.
- It also offers tools to calculate other properties, such as volume and total number of atoms in the molecule.
- Lipinski's "Rule of Five":-"Rule of 5" properties are a set of simple molecular descriptors.
- The rule states, that most "drug-like" molecules have logP<= 5, molecular weight <= 500, number of hydrogen bond acceptors <= 10, and number of hydrogen bond donors <= 5.
- Molecules violating more than one of these rules may have problems with bioavailability.

compound	Log P	TPSA	n Atoms	M.Wt	nON	nOHNH	n-violations	n-rotb	Volume
$C_9H_7NS_4$	4.02	12.892	14.0	237.43	1	0	0	3	284.83
$C_{11}H_{11}NS_4$	4.90	12. 892	16	285.48	1	0	0	5	246.5
$C_{12}H_{13}NS_4$	5.46	12.89	17	299.5	1	0	0	6	295.74

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$C_{12}H_{13}NS_4$	5.14	12.89	17	299.511	1	0	1	5	251.69

MOLSOFT

- MOLSOFT online tool calculates the properties like Molecular formula, Molecular weight, Number of hydrogen bond acceptors (HBA), Number of hydrogen bond donors (HBD), mol LogP (octanol /water partition coefficient), mol logS (water solubility), Polar surface area (mol PSA), Volume, Number of Stereo centers, Drug likeness model score.
- All the molecular property predictors are calculated using fragment- based contributions.
- Drug likeness is defined as complex balance of various molecular properties and structure features, which determines whether particular molecule is a drug or non-drug

Cmpd	Clogp	TPSA	N Atoms	MW	nON	nOHNH	Nviolation	nrotb	volume
$C_9H_7NS_4$	4.01	12.890	14.0	237.43	1	0	0	3	284.80
$C_{11}H_{11}NS_4$	4.88	12. 890	16	285.48	1	0	0	5	246.50
$C_{12}H_{13}NS_4$	5.42	12.890	17	299.5	1	0	0	6	295.70
$C_{12}H_{13}NS_4$	5.10	12.890	17	299.511	1	0	1	5	251.60

3.4 PHARMACOLOGICAL ACTIVITY:
ANTI MICROBIAL ACTIVITY:
Antibacterial Activity:
The antibacterial activity is tested by agar-cup plate method. The antibacterial activity of 2-mercaptobenzothiazoletrithiocarbonate derivatives were tested and compared with the standard Ampicillin at concentration of 100µg/ml and 200µg/ml. The following organisms were used.
Test organisms:
Gram positive bacteria:
Bacillus aureus.

Gram negative bacteria:
Escherichia coli

Antifungal activity:
The antifungal activity is tested in the same procedure as described in the antibacterial activity except the medium. The antifungal activity of 2-mercaptobenzothiazoletrithiocarbonate derivatives were tested and compared with the standard Greseofulvin concentration of 100µg/ml and 200µg/ml. The following organism was used:
Test organism:
Candida albicans

Experimental procedure for antibacterial activity:
Nutrient agar was dissolved and distributed in 25ml quantities in 100ml conical flasks and were sterilized in an autoclave at 121 ℃ (15lbs/sq.in) for 20 minutes.
The medium was inoculated using 18hrs old cultures of the test organism mentioned above aseptically into sterile petridishes and allowed to settle at room temperatures for about 30 minutes.
In a size of four inches petridishes, five cups of 8mm diameter at equal distance are made in each plate. In each plate, two cups are used for standard i.e Ampicillinwith 100µg/ml and 200µg/ml, one

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cup for control, two cups for test compounds i.e 100µg/ml and 200µg/ml solutions.
The plates thus prepared are left for 90 minutes in refrigerator for diffusion . After incubation for 24hrs at 37 ℃, the plates are examined for inhibition zones (in mm). The Zone of inhibition is measured using Antibiotic zone reader.

Experimental procedure for antifungal activity:

Potato dextrose agar was dissolved and distributed in 25ml quantities in 100ml conical flasks and are sterilized in an autoclave at 121 ℃ (15lbs/sq.in) for 20 minutes.

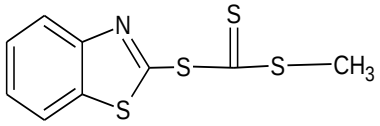
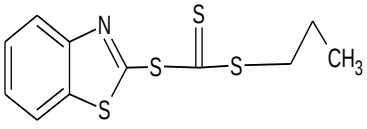
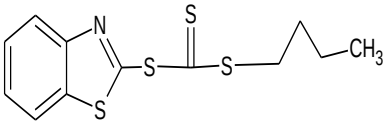
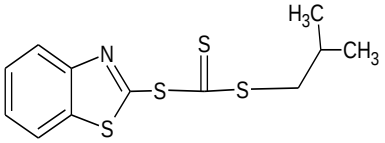
The medium is inoculated using 48hrs old cultures of the test organism mentioned above aseptically into sterile petridishes and allowed to settle at room temperature for about 30 minutes.

In a size of four inches petridishes, five cups of 8 mm diameter at equal distance are made in each plate. In each plate, one cup is used for control, two cups for standard Greseofluvin with 100µg/ml and 200µg/ml, other two cups with concentrations of test compounds i.e 100µg/ml and 200µg/ml solutions.

The plates thus prepared are left for 90 minutes in refrigerator for diffusion . After incubation for 48hrs at 25 ℃, the plates are examined for inhibition zones (in mm). The zone of inhibition is measured using Antibiotic zone reader.

Results and discussions of anti-microbial studies:

Table of antimicrobial activity.

S.No	Compound	Zone of inhibition (in mm)			
		Gram positive organism		Gram negative organism	
		Bacillus subtilis		E.coli	
		100µg	200µg	100µg	200µg
1	 1A	--	--	**09**	**11**
2	 1B	--	--	**10**	**11**
3	 1C	--	--	**08**	**11**
4	 1D	--	--	**10**	**12**
5	Ampicillin	**03**	**04**	**10**	**11**

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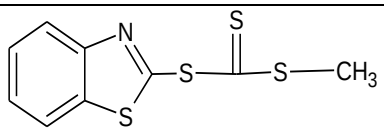
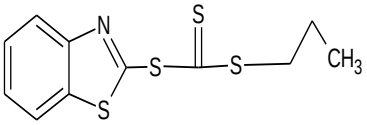
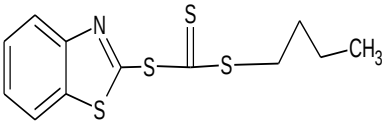
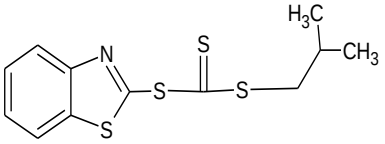
Antifungal activity :-

S.No	Compound	Zone of inhibition	
		Candida albicans	
		100µg	200µg
1	 1A	**06**	**08**
2	 1B	**07**	**08**
3	 1C	**09**	**10**
4	 1D	**09**	**10**
5	Greseofulvin	**10**	**11**

All the synthesized compounds (1A-1D) were evaluated for anti-bacterial activity against one gram positive and one gram negative organisms

The Zone of inhibition (in mm) value was taken as a parameter for activity. The zone of inhibition of test compounds were compared to that of the standard drugs i.e., ampicillin for anti-bacterial.

In a series the synthesized compounds were active against gram negative organisms**.**

IV. DOCKING

Computer aided drug design

Introduction:

The development of new drugs is undoubtedly one of the most challenging tasks of today's science. Human genome project that gave 30,000 or so genes encoded within the human genome, it was expected that a large number of new drug targets would be found expeditiously. But it did not turn out to offer a direct source for drug development, because it is the proteins encoded by the genes are the usual drug targets. This much larger proteome is far more complex than the collection of genes, as proteins may undergo post-translational modifications, associations with other molecules and prosthetic groups, and formation of multimeric complexes. Today, the field of drug development may seem more fertile than ever before, with vast amounts of information from genomic and proteomic studies facilitating the finding of new targets, the usage of rational combinatorial chemistry for the production

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of libraries of compounds, the generation of genetically modified animal models for the development and testing of new drugs, and the possibility of using ultra-high throughput test techniques for the screening of large libraries.

Drug research and development is comprehensive, expensive, time consuming and full of risk. It is estimated that a drug from concept to market would take approximately 12 years and cost more than US$800 million on an average. Several new technologies have hence been developed and applied in drug research and development to shorten the research cycle and to reduce the expenses. In the post genomic era, computer-aided drug design (CADD) has considerably extended its range of applications, spanning almost all stages in the drug discovery pipeline,from target identification to lead discovery, from lead optimization to preclinical or clinical trials.

In early 1960s, quantitative structure-activity relationship (QSAR) analysis emerged as the first computer aided drug design technique. In recent decade the concept of CADD has evolved very quickly, with an unprecedented development of structural biology and computer capabilities. However, despite all these advances, the revolutionary era of drug design has not arrived yet. There is no unique solution to a drug design problem. The appropriate experimental techniques or computational methods to use will depend on the characteristics of the system itself and the information available. A variety of computational approaches can be applied at different stages of the drug-design process: in an early stage, these focuses on the emphasis is on decreasing experimental costs and reducing times.

CADD now plays a critical role in the search for new molecular entities. Current focus includes improved design and management of data sources, creation of computer programs to generate huge libraries of pharmacologically, interesting compounds, development of new algorithms to assess the potency and selectivity of lead candidates, and design of predictive tools to identify potential ADME/Tox liabilities.

There are two major types of drug design. The first is referred to a s **ligand-based drug design** and the second, **structure-based drug design.** These are two distinct approaches used in the computer-aided drug design. When the only lead is a set of known active compounds or knowledge of a biochemical transformation which is to be interrupted, then the path is less direct, this approach is referred as ligand (analogue) based drug design (LBDD).Currentlyfavored tactics include the use of molecular similarity methods and the employment of neural networks. Recent advances include the prediction of the relative potency of different chiral forms of drugs. If the molecular structure of the target macromolecule is known the methods are direct and have a high level of sophistication, this approach is referred as structure based drug design (SBDD).

Ligand-based drug design (LBDD) relies on knowledge of analogue molecules that bind to the biological target of a particular interest. These analogues are used to derive a pharmacophore model which defines the minimum necessary structural characteristics required for a molecule to bind to the target. Another approach in which a correlation between calculated properties of molecules and their experimentally determined biological activity is derived, it is referred as quantitative structure-activity relationship (QSAR). These QSAR relationships in turn may be used to predict the activity of new analogs.

Structure-based drug design (SBDD) relies on knowledge of thethree dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy. SBDD is based on the observation that drugs bind to a specific defined molecular targets. A strong and selective binding can be obtained from high structural and chemical complementarities between the macromolecular target and the ligand. If an experimental structure of a target is not available, it may be possible to create a homology model of the target based on the experimental structure of a related protein. Based on the 3D structure of the target receptor, molecular modeling techniques are first applied to understand the mechanism of interaction between the target and its ligand. The vital structural features of the target are identified, such as electrostatic interaction regions, hydrophobic interaction regions, hydrogen bond donors and acceptors. Based on these features, rational drug design methods are then applied to obtain possible starting structures for leads optimization.

Three types of drug design process can be preformed based on the type of target molecule selected.

- Design of inhibitors based on the architecture of an enzyme active site.

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- Design of agonist or antagonists based on the bioactivity of the protein engineered by site directed mutagenesis.
- Design of small molecular agonists or antagonists based on the interface of hormone and receptor binding epitopes.

Energy minimization:

A method which minimized the potential energy is known as energy minimization technique. This technique is used as an optimization of a system's structure to find the local minimum starting from an initial conformation. Energy minimizations result in an optimized arrangement of electrostatic interactions, hydrogen bonding and vanderwaals contacts (based on the initial structure). Energy minimization method can be divided into different classes depending on the order of the derivative use for locating a minimum on the energy surface. Zero order methods are those that use the energy function to identify regions of low energy through a grid search approach. The most well known method of this kind is the SIMPLEX method. There are several methods in first-derivative techniques like the steepest descent method or the conjugate gradient method, these makes use of the gradient of the functions. Newton-Raphson algorithm is a second derivative method that makes use of the hessian to locate minima. In the present study first derivative conjugate gradient method is used. The conjugate gradient algorithm accumulates the information about the function from one iteration to the next; with this proceeding the reverse of the progress made in an earlier iteration can be avoided. For each minimization step the gradient is calculated and used as additional information for computing the new directions of the minimization procedure. Thus each successive step refines the direction towards the minimum. Conjugate gradient method is the choice for larger systems. The computational expense and the longer time per iteration is compensated by the more efficient convergence to the minimum achieved by conjugate gradient method.

Molecular docking:

Molecular docking may be defined as an optimization problem, which would describe the best fit orientation of a ligand that binds to a particular protein of interest and is used to predict the structure of the intermolecular complex formed between two or more molecules. In mo9drn structure based drug design the accurate prediction of the binding modes between the ligand and protein is of fundamental importance. The binding of small molecule ligands to large protein targets is central to numerous biological processes. This process is not simple; several entropic and enthalpic factors influence the interactions between them. The mobility of both ligand and receptor, the effect of the protein environment on the charge distribution over the ligand, and the interactions with the surrounding water molecules, further complicate the quantitative description of the process. The idea behind this technique is to generate a comprehensive set of conformations of the receptor complex, and then to rank them according to their stability. Themost popular docking programs include DOCL, AUTO DOCK, FLEX x, GOLD and GLIDE, among others. FLExXandGLIDE programs were utilized in the present work, hence only these will be discussed, before.Molecular docking can be divided into two separate steps, first step is application of search algorithm to create an optimum number of configurations that include the experimentally determined binding modes. In the second step these configurations are evaluated using scoring functions to distinguish the experimental binding modes from all other modes explored through the searching algorithm.

Some common searching algorithm include

- Molecular dynamics.
- Monte Carlo methods.
- Genetic algorithms.
- Fragment-based methods.
- Point complementary methods.
- Distance geometry methods.
- Tabu searches.
- Systematic searches.

Some common scoring functions are

- Force field methods
- Empirical free energy scoring functions.
- Knowledge based potential of mean.

Glide:

Glide (grid-based ligand docking with energetic) has been designed to perform as close to an exhaustive search of the positional, orientational and conformational space available to the ligand as is feasible while retaining sufficient computational speed to screen large libraries. Glide uses a series of hierarchial filters to search for possible locations of the ligand in the active-site region of the receptor. The shape and properties of the receptor are represented on a grid by different sets of fields

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that provide progressively more accurate scoring of the ligand pose. A set of initial ligand conformations are produced, these are selected from an exhaustive enumeration of the minima in the ligand torsion-angle space and are represented in a compact combinatorial form. Initial screens are performed over the entire active site space available to the ligand to locate promising ligand poses. This drastically reduces the region of active site space over which computationally expensive energy and gradient evaluations will later be performed while at the same time avoiding the use of sophisticated methods. Poses selected from the initial screening, is minimized in the field of the receptor using a standard molecular mechanics energy function (OPLS force field) in conjunction with a distance-dependent dielectric model. Finally the three to six lowest-energy poses obtained in this fashion are subjected to a Monte Carlo procedure that examines nearby torsional minima. There are two different mode of GLIDE docking standard precision (SP) docking and extra precision (XP) docking. SP is a softer, more forgiving function that is adept at identifying ligands that have a reasonable propensity to bind, even in cases in which the Glide pose has significant imperfections. This version seeks to minimize false negatives and is appropriate for many database screening applications. In contrast, XP is a harder function that exacts severe penalties for poses that violate established physical chemistry principles such as that charged and strongly polar groups be adequately exposed to solvent. It is more adept at minimizing false positives and can be especially useful in lead optimization or other studies in which only a limited number of compounds will be considered experimentally and each computationally identified compound needs to be as high in quality as possible.

Scoring functions:

The scoring function is a key element of a protein-ligand docking algorithm, because it directly determines the accuracy of the algorithm. Speed and accuracy are the two important aspects of a scoring function. An ideal scoring function would be both computationally efficient and reliable. Numerous scoring functions have been developed in the past decades and can be grouped into three basic categories according to their methods of derivation: force field, empirical, and knowledge-based scoring functions. Force field (FF) scoring functions are based on decomposition of the ligand binding energy into individual interactions terms such as vanderwaals energies, electrostatic energies, bond stretching, bond bending and bond torsional energies etc., using a set of derived force-field parameters.

In empirical scoring functions, the binding energy score of a complex is calculated by summing up a set of weighed empirical energy terms such as vanderwaals energy, electrostatic energy, hydrogen bonding energy,desolvation term, entropy term, hydrophobicity term etc., the potential parameters of knowledge-based scoring functions are directly derived from the structural information in experimentally determined protein-ligand complexes. The principle behind knowledge-based scoring functions is the potential of mean force, which is defined by the inverse Boltzmann relation. Afourth kind of scoring function but a technique in protein-ligand docking. It improves the probability of finding a correct solution by combining the scoring information from multiple scoring functions in hopes of balancing out the errors of the individual scoring functions.

Glide score:

The starting point for Glide scoring is the empirically based ChemScore function of Eldridge et al., which can be written as

$$\Delta G_{bind} = C_o + C_{lipo}\ f(r_{lr}) + C_{hbond} g(\Delta r)\ h(\Delta\alpha) + C_{metal}\ f(r_{lm}) + C_{rotb} H_{rotb}$$

Glidescore modifies and extends the Chemscore function as follows:

$$\Delta G_{bind} = C_{lipo\text{-}lipo}\ f(r_{lr}) + C_{hbond\text{-}neut\text{-}neut}\ g(\Delta r)\ h(\Delta\alpha) + C_{hbond\text{-}neut\text{-}charged}\ g(\Delta r)\ h(\Delta\alpha) + C_{hbond\text{-}charged\text{-}charged}\ g(\Delta r)\ h(\Delta\alpha) + C_{max\text{-}metal\text{-}ion}\ f(r_{lm}) + C_{rotbHrotb} + C_{polar\text{-}phob}\ V_{polar\text{-}phob} + C_{roul} E_{roul} + C_{vdw} E_{vdw} + \text{Solvation terms}$$

WORK PLAN

METHODOLOGY

- **Ligand preparation:**

Protein preparation: .

- **Receptor grid generation:**

Receptor grid generation facility helps in defining the protein active site to prepare grid for the ligands to be docked in. The shape and properties of the receptor are represented on a grid by several different sets of fields that provide progressively more accurate scoring of the ligand poses. The receptor vanderwaals scaling for the non polar atoms to set (the default being 1 for glide) to 0.9 this makes the protein site "roomier" by moving back the surface of non- polar region of the protein and ligand. This kind of adjustment

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emulates to same extent the effect of breathing motion to the protein site (it is a kind of giving breathing to the receptor). The receptor active site is defined either by selecting the co-crystallized ligand or by mentioning the residues of the active site (amino acid to be included). An enclosing box (the box with in which all the ligand atoms should be incorporated) and a bounding box (acceptable positions of the ligand center must lie within. This box gives a truer measure of the effective size of the search space) are used in glide to organize the calculations.

- **Ligand docking:**

The screened low energy conformations of the ligands which are obtained from ligand preparation are docked into the rare receptor grid using standard precision mode. Docking studies give glide score (G-score) which predicts the binding affinity and the ranking order of ligands,is an expanded version of chemscore and Cvdw. Cvdw is the sum of coulomb energy and vanderwaal energy of the non-bonding interactions between the ligand and receptor. E-Model is a combination of Glide score, the ligand-receptor molecular mechanics interactions energy and the ligand strain energy to select the correctly docked pose. The ligands with good docking score will be considered as the lead molecules and will be synthesized.

V. RESULTS AND DISCUSSION

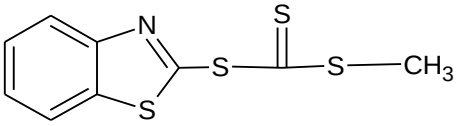
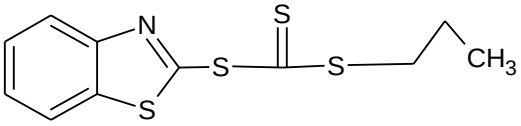
5.1 Results and discussion of synthetic work of benzothiazoletrithiocarbonate derivative:

The title compounds (1A-1D) were synthesized as per scheme-I and the results are discussedMolecular property prediction was done for synthesised compounds using molinspiration and molsoftsoftware all the compounds are found to follow Lipinski rule of five and compounds were tested for antibacterial activity found active against gram negavtive bacteria E.Coli and also tested for antifungal activity and found active against candida albicans.

RESULTS AND DISCUSSIONS OF CYTOTOXIC ACTIVITY.

The compounds (1A-1D) were evaluated for cytotoxic activity. The results obtained are to be compared with the docking studies. Cytotoxic activity is still under process .We have seen a good inhibition of radical growth at concentrations 300 & 400 µmol. So our synthesized compounds possess potent anti-mitotic activity for 300& 400 µmol concentrations. We are planning to evaluate the cytotoxic activity even at lower concentrations.

RESULTS AND DISCUSSIONS OFDOCKINGSTUDIES.

S.No.	Compound	Dock score(k.cal/mole)	Glide E Model
1	 1A	-4.263	-35.972
2	 1B	-4.164	-40.763

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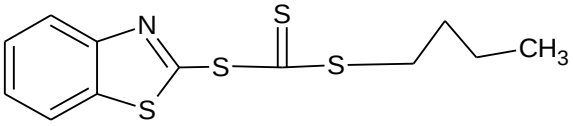
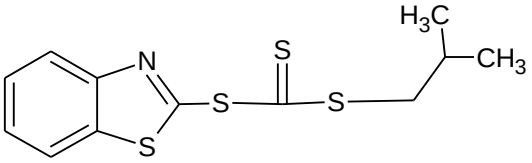
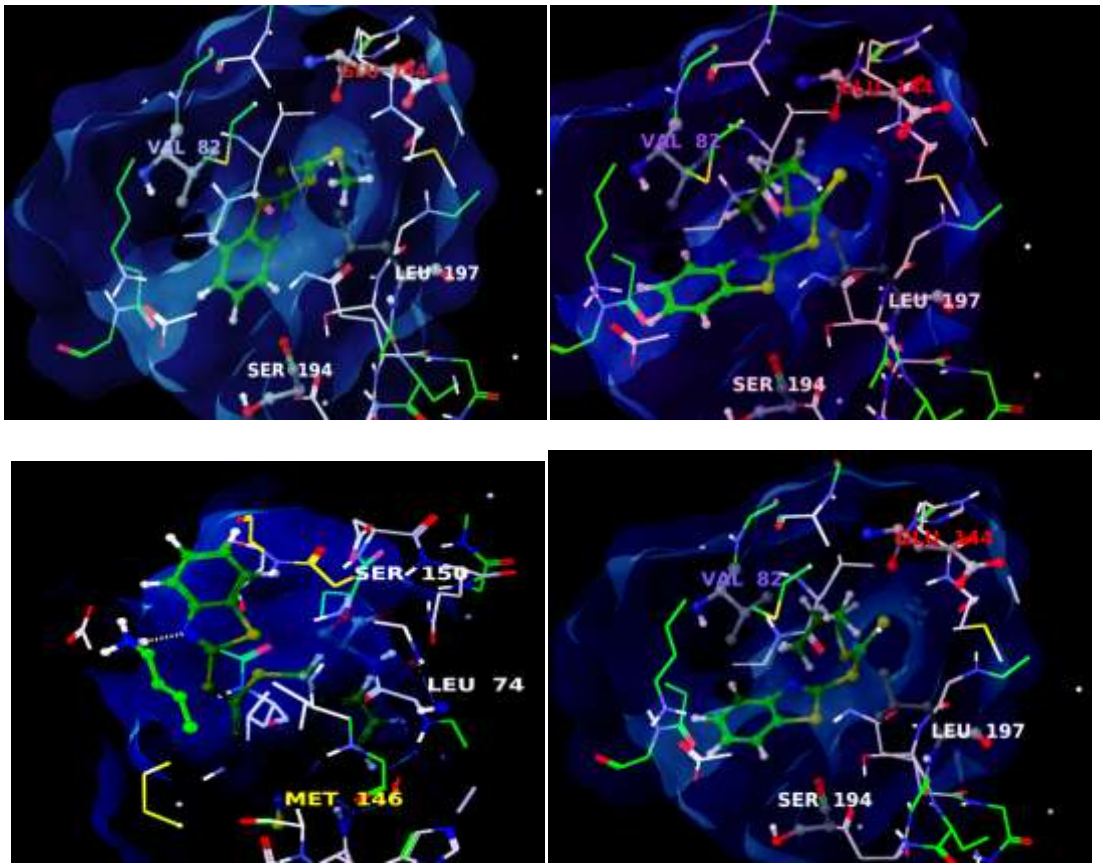
3	 1C	**-4.242**	**-39.262**
4	 1D	**-4.327**	**-39.467**

The crystal structures of MEK1 inhibitor (PDB code: 3ZLY) was downloaded from the protein data bank. GLIDE 5.6 was used for molecular docking.

The phenyl rings and trithiocarbonate moiety occupied hydrophobic grove making significant vanderwaals contacts with the hydrophobic surface having side chain residues of LEU 197 ,SER 194, GLU144, VAL 82

The molecules were deeply embedded into the hydrophobic pocket and no hydrogen bonding interactions suggesting that by increasing the hydrophobic substituents at the trithiocarbonate region may increase the protein ligand binding.



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VI. CONCLUSION

The compounds 1A – 1D are synthesised its molecular properties were interpreted using molsoft and molinspirationsoftwares .Synthesised compounds were found active against E.Coli and candida albicans . The obtained compounds are compared with the docking studies and have shown good docking score . Cytotoxic activity is still under process .We are planning to evaluate the cytotoxic activity even at lower concentrations.

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