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Design and synthesis of oxadiazole derivatives based on 2-Mercaptobenzimidazole

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Abstract: In the present work, novel oxadiazole derivatives of 2-mercaptobenzimidazole were synthesized following standard multistep synthetic pathways. Synthetic organic chemistry is concerned with the shaping of a new organic compound from the preexisting precursor. The present work aimed to obtain several Schiff bases from the benzimidazole heterocycle. 2-MBI was modified using analytical grade reagents and solvents and the results obtained were satisfactory and parallel with the standard procedures of the laboritories.2-MBI was converted to thioether which was then converted to respective ester, hydrazide and finally to imine derivatives called Schiff Bases. The Schiff bases obtained may be used in several ways for example as a complexing agent and precursor of many compounds in the future. These derivatives have large applications in various fields, such as organometallics, agriculture, medicinal, industrial, explosives, polymers, and petrochemicals The products were obtained in good yields and purity. further oxadiazoles may be synthesized using different carbonyl compounds. This work may be utilized in the future for the derivation of potential medicinal agents. The bioactivity of the synthesized compounds may be conducted for establishing the medicinal property of these compounds.
Keywords: Organic Chemistry, Oxadiazole, and 2-Mercaptobenzimidazole.

1. Introduction

1.1 Organic Chemistry

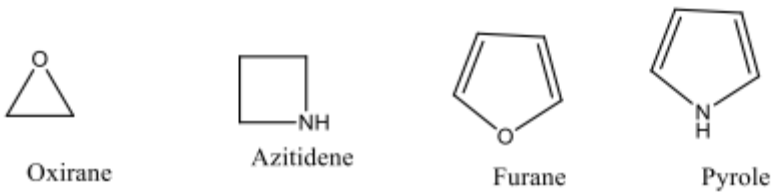
Synthetic organic chemistry is concerned with the shaping of a new organic compound from the preexisting precursor. These derivatives have large applications in various fields, such as organometallics, agriculture, medicinal, industrial, explosives, polymers, and petrochemicals [1]. In 1816, Michel cheureui, isolating different acids from fats rejected the concept of vitalism, and in 1828 Friedrich Wholer synthesized urea [2]. Organic synthesis is based upon synthetic analysis in a well-planned manner. Reaction planning includes the activation, deactivation, protection, and stereo control of the reacting compound [3]. The major aims of organic synthesis are to prepare more complex and specialized organic compounds of socioeconomic and environmental interests as well as to obtain new synthetic routes [1].

1.2 Organic Compounds

Organic compounds are classified as Aliphatic, Aromatic, and Heterocyclic compounds. These occur naturally as well as obtained synthetically [4].

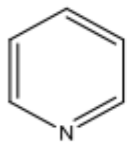
1.3 Heterocyclic Compounds

An organic heterocyclic is a cyclic compound having at least one hetero atom in the ring. It is a vast class of organic compounds. They find applications in biochemical, medical, and industrial fields [5]. Heterocyclic compounds are further divided into three, four, five, six, and seven-membered and fused ring heterocycles [6].



Oxirane Azitidene Furane Pyrole

1 **2** **3** **4**



Pyridine

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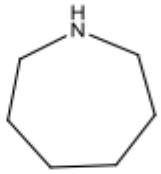

Azepane

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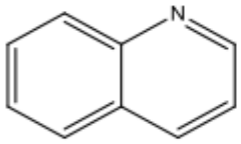
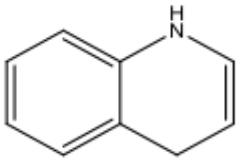


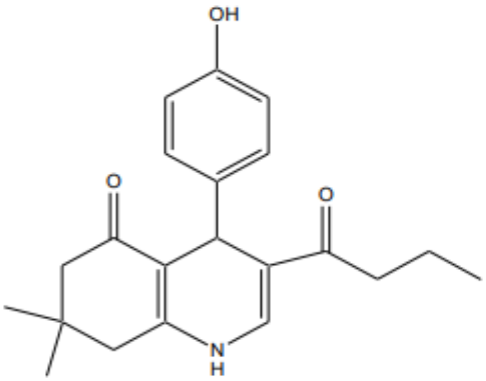
Qunioline

7



Hydro Qunioline

8



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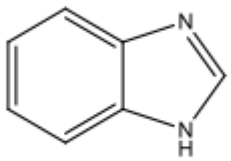
1.0.3. Benzimidazole

Benzimidazole is a heterocyclic compound consisting of a benzene ring fused with an imidazole ring. Benzene and its compounds display tautomerism [7].



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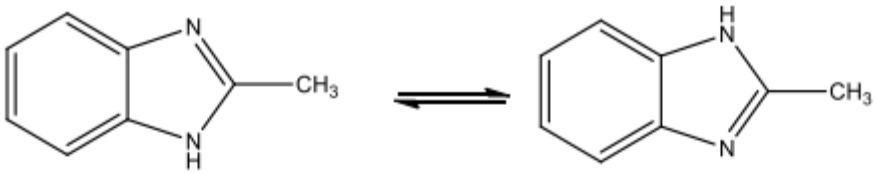

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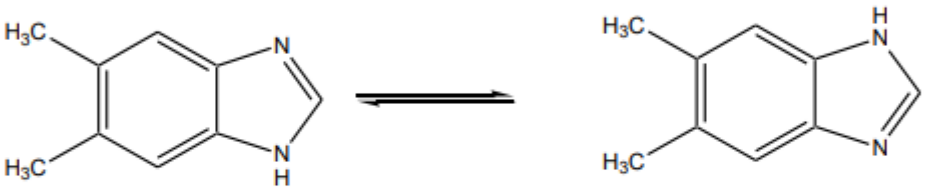

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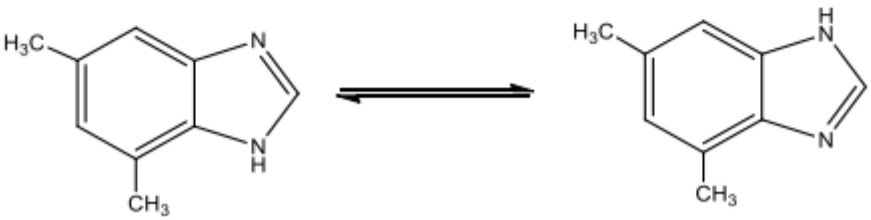
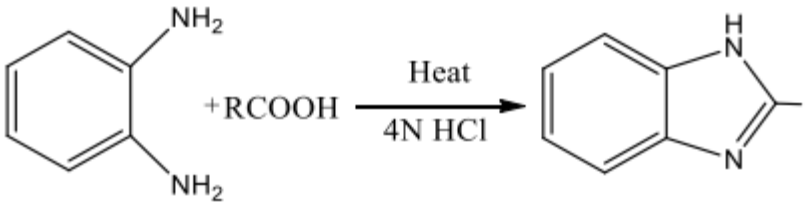


15 **16**

Benzimidazole is prepared from o-phenylenediamine and a carboxylic acid or acid anhydride in dilute hydrochloric acid [7].



17 **18**

1.4 Physical Properties

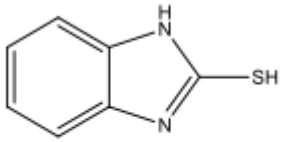
Benz-imidazole is a white solid (M.p 1700 °C). It is Soluble in polar solvents and sparingly soluble in nonpolar solvents. Lowering of the boiling and melting points occurs by the substitution of amino hydrogen [7].

1.5 Chemical Properties

The PKa value for Benzimidazole is 5.5, lower than imidazole PKa (7.0) it possesses two active sites for substitution. benzimidazole reacts with several reagents such as chloroacetic acid, chloroethyl acetate, alkyl, and aryl amines. Mercaptoacetic acids and dihalides etc. at different conditions. Due to the aromatic benzene nucleus, the compound is resistant to addition reactions. However electrophilic substitution may occur at the benzene ring such as Friedel crafts reaction, sulphonation, nitration, etc.

1.6 2-MERCAPTOBENZIMIDAZOLE

2-mercaptobenzimidazole is a derivation of benzimidazole. An since it possesses a thiol group at carbon-2 therefore, it is called 2-mercaptobenzimidazole or Benzimidazole-2-thiol



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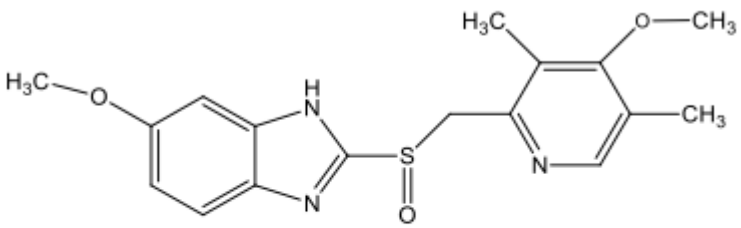
1.7 Biological Activities

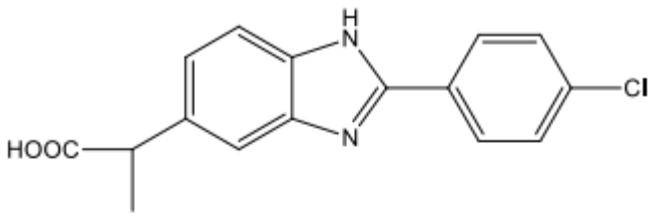
Benzimidazoles and 2-mercaptobenzimidazole display some biological activities like antimicrobial, antiviral, anticancer, anti-inflammatory, anthelmintic, analgesic**,** antihistamine, psychopharmacological, amoebicidal, fungicidal, antibacterial, antiviral, anticonvulsive, ant parasitic, antioxidants, antihypertensive, proton pump inhibitor, anticoagulant, immunomodulator [8].

Some of the medicinally active Benzimidazoles are mentioned



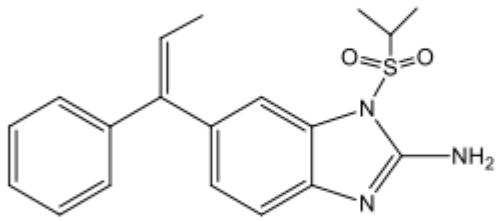
Omeprazole (antiulcer)

20



Benoxaprofen analog (anti-inflammatory)

21



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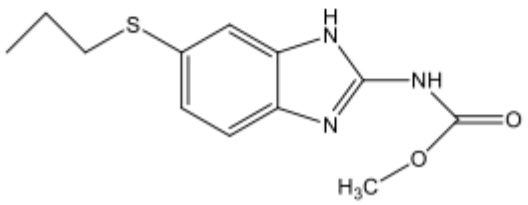
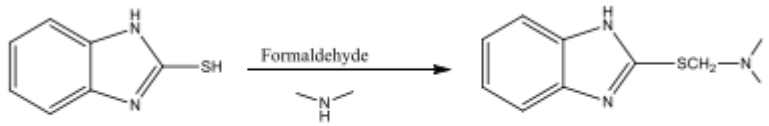
Bendamustine (antitumor)



23

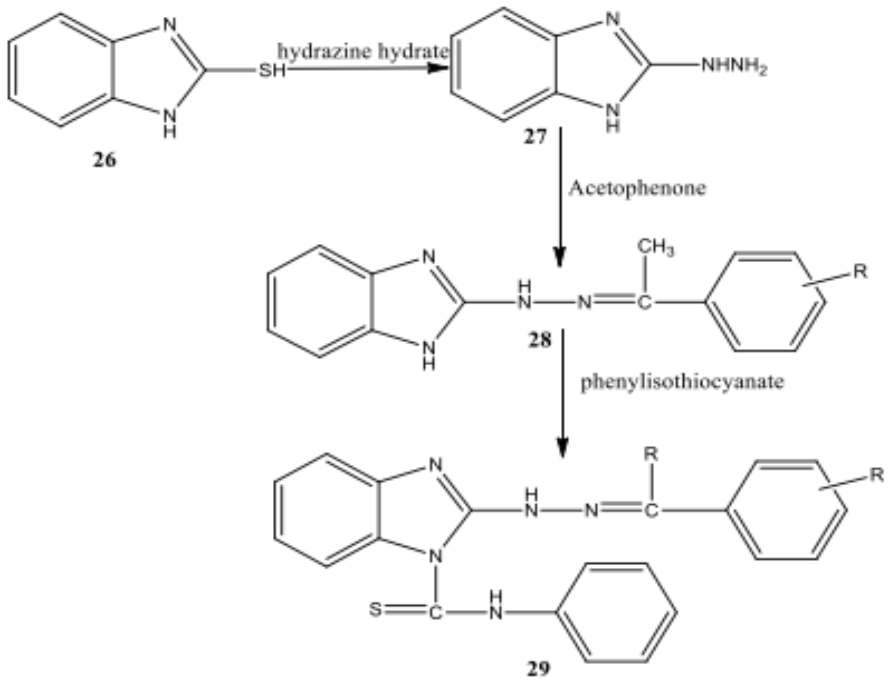
1.8 Literature review

Benzimidazole and its derivatives play a significant role in medicinal chemistry. They are found to have various biological activities such as antimicrobial, antiviral, antidiabetic, and anticancer activities [9]. K. Anandarajopal et.al. (2010), synthesized the manic base derivatives of 2mercaptoenzimidazole. Benzimidazole compounds were reported to have anticonvulsant activities [10].

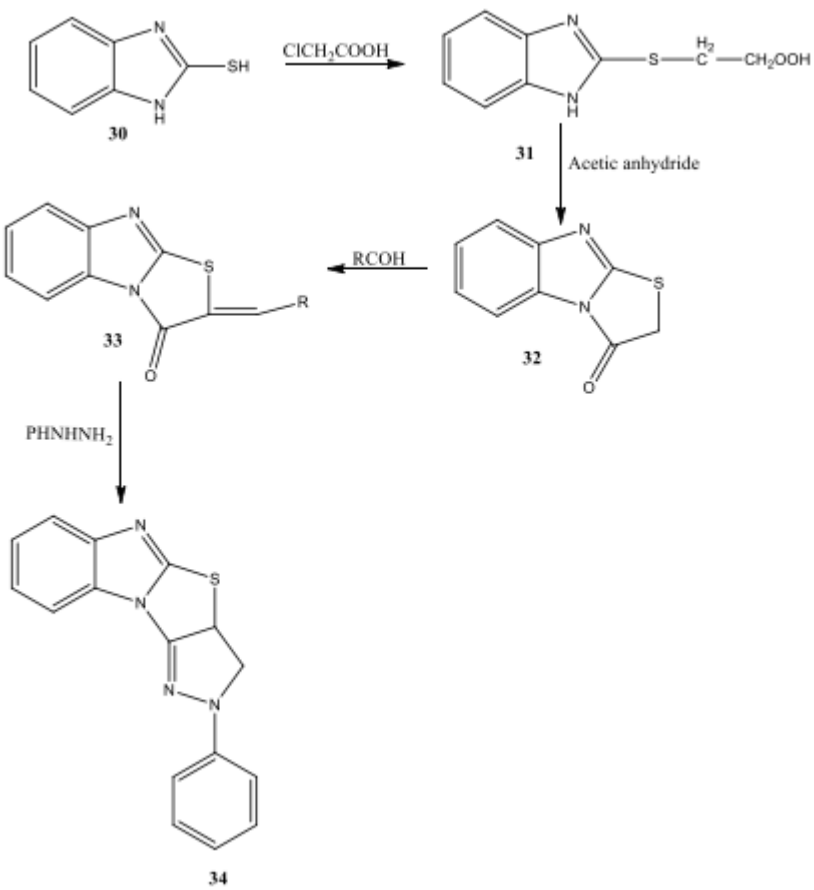


24 **25**

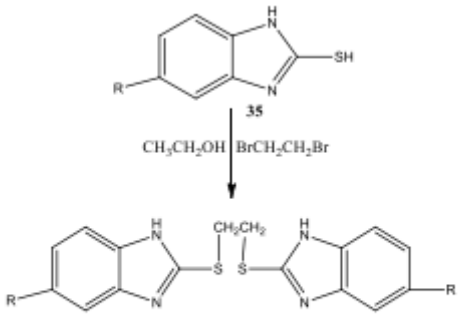
Bahanupriya Bhrigu et.al. (2012) synthesized a series of new benzimidazole carbothio amides. The compounds showed anticonvulsant activities. The process involves the reaction of 2mercaptobenimidazole with hydrazine hydrate, substituted acetophenones, and phenyl iso thiocyanate to obtain the product [11].



G. O. Prakash et. al. (2010) synthesized pyrazole thiazole derivatives of 2-mercapto Benzimidazole. 2-mercaptobenzimidazole upon reaction with chloroacetic acid resulted in Benzimidazole-2-thio acetic acid (19) which in acetic anhydride and pyridine produced thiazole benzimidazole. Further condensation with arylaldehydes yielded arylidinethiazolidinone (21) followed by treatment with phenylhydrazone furnished, 3-substituted-2-phenyl-benzimidazole [2, 1b] pyrazolo [3,4 d] [1, 3] thiazole (22). These compounds displayed antimicrobial activities [12].



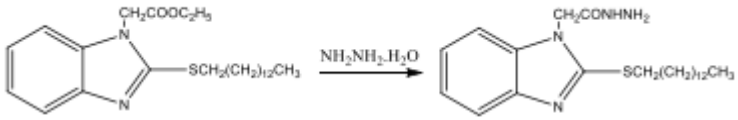
Srikanth Gurrala. et.al. (2011) reported the symmetrical coupling of 5_substituted 2_ mercaptobenzimidazoles through 1,2-di bromo ethane and 1,3_di bromopropane. They were found to have anti-bacterial and antifungal activities against *S. aureus*, *E. coli*, and *Candida albicans* [13].



36

R=H, OCH_3, $OCHF_2$

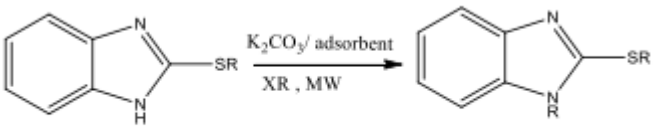
S Srinavas Rao (2013) synthesized N-alkyl 2-mercaptobenzimidazole the under various conditions using solvents such as ethanol and PEG-600 or physical grinding [14]



37 **38**

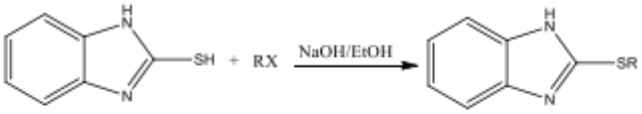
R=CH_3, C_2H_5, C_2H_5Ph

H.P. Narkhede et.al (2008) derived 2-mercaptobenimidazole using solid support such as silica gel/ neutral alumina/fly ash under microwave-assisted solvent-less conditions [15].



39 **40**

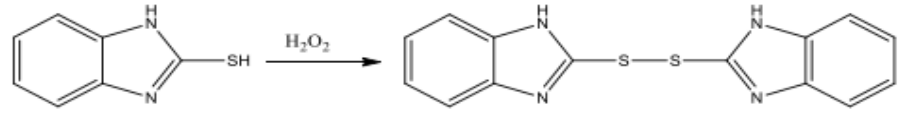
Mohammad R. Ahamad (2013) reported the alkylation and oxidation of 2mercaptobenzimidazole to yield disulfides and sulfones [16].



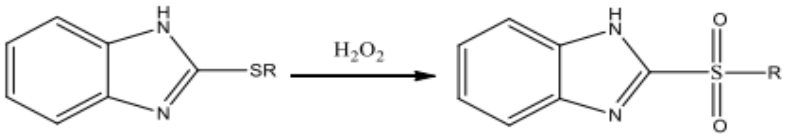
41 **42**

Thioether

R= aryl or alkyl halides

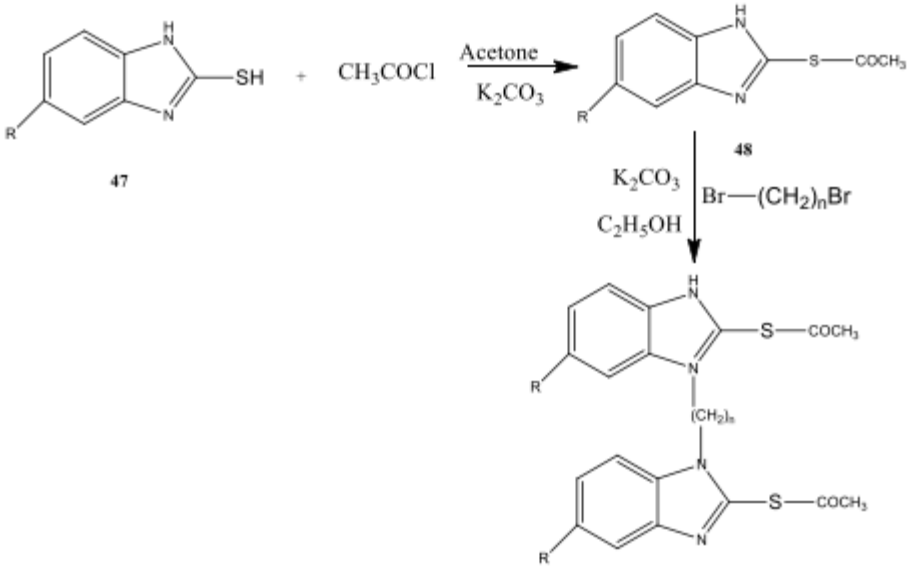


43 **44** Disulpune



45 **46** sulfone

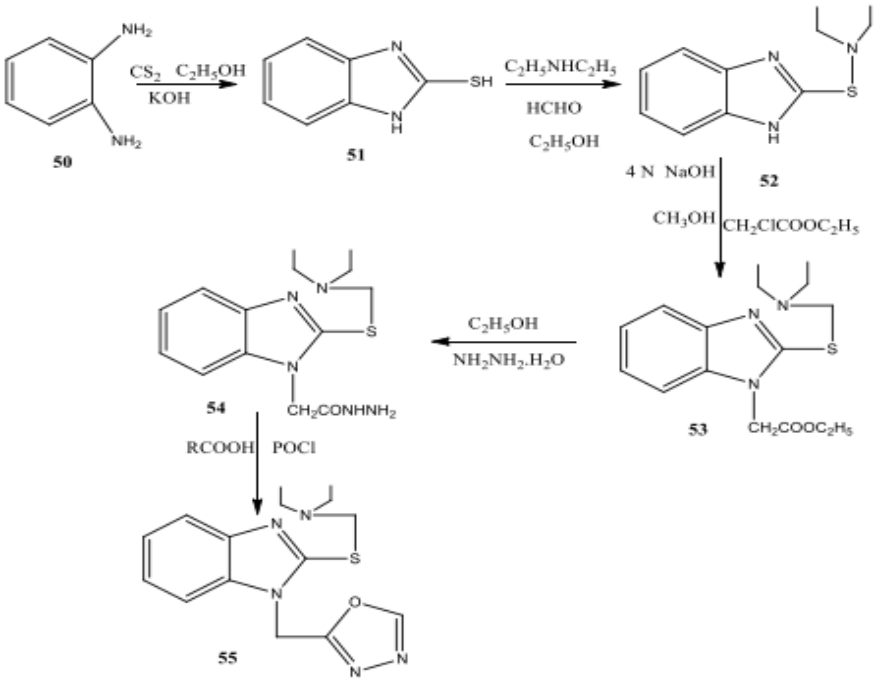
R.V. Heralagi et.al conducted the acylation of 2-mercaptobenzimidazole by treating it with acetyl chloride in acetone. It was treated with 1, 3-dibromopropane and 1,2-dibromoethane to obtain bis -2-mercaptobenzimidazole [17].



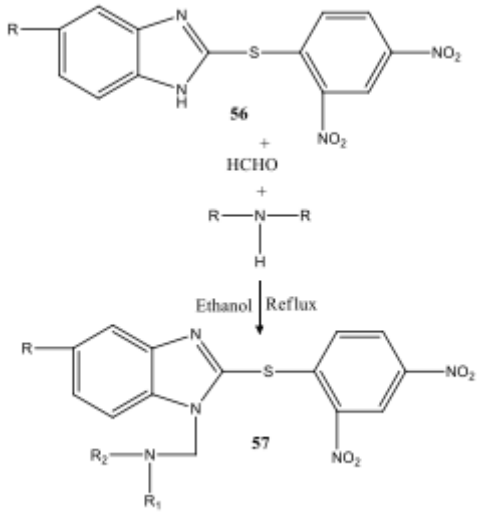
Derivative

49

Pratik.P. Maske reported the preparation of two groups of substituted benzimidazoles namely 5,6-dinitro and 2 trifluoromethyl derivatives. they were found to have antimicrobial properties [18].

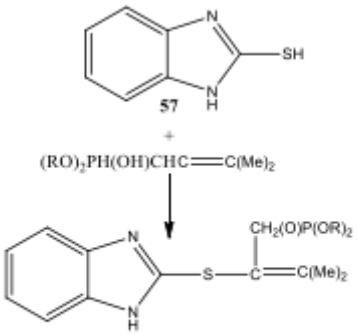


Gangula Mohan Raho et.al. synthesized a series of new compounds by Manich reaction between 2-(2,4-dinitrophenyl) sulphanyl]-6-substituted -1H-benzimidazole and an appropriate secondary amine. The synthesized compounds have been evaluated for analgesic and anti-inflammatory activities [19].



R1, R2 = CH3, C2H5, C2H4OH

Narkis khusainova et.al conducted the reaction of 2-mercaptobenzimidazole with 3-methylbuta1,2-dienylphosphnates [20].

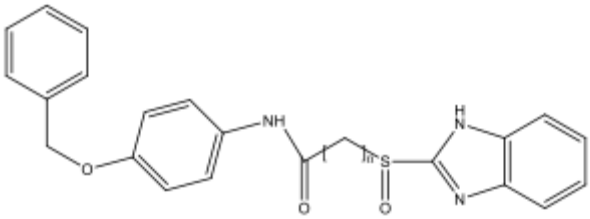


58

Latifa Ousaif et.al prepared some novel benzimidazoles by the condensation of 2-MBI with the different alkylating agents under a phase transfer catalyst. The synthesized compounds were evaluated for antibacterial and anti-oxidant activities [21].

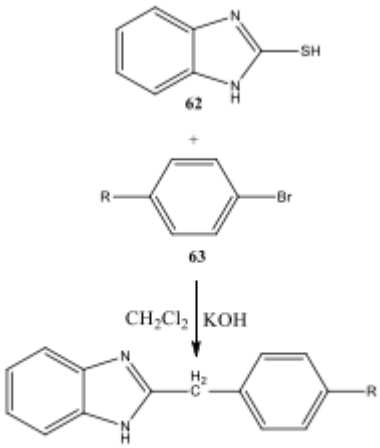
59 **60**

Mallidi sarinivas Reddy et.al reported the synthesis and evaluation of novel 2-substituted mercaptobenzimidazole derivatives. The synthesized compounds were evaluated for antiulcer and antimicrobial activities [22].



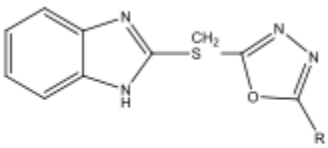
61

L.wang and C. Liu (2008) carried out the S-alkylation of 2-mercaptobenzimidazole with alpha- bromo-m-xylene catalyzed by tetra butyl ammonium bromide. During this process, no N alkylation was found [23].



64

Shingalapur et.al (2010) derived various oxadiazoles from 2- mercaptobenzimidazole. These compounds were evaluated for antidiabetic activities through an oral glucose tolerance test. Some of them showed good antidiabetic activity [24].



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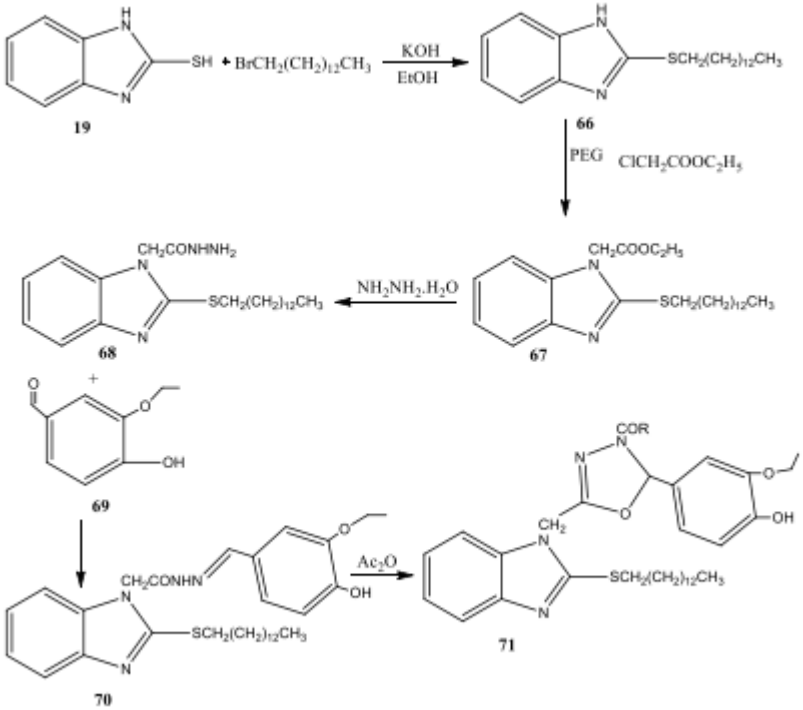
2. Experimental Work

2.1 General

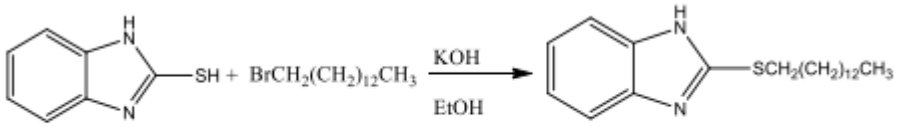
The present work was conducted using analytical grade reagents and distilled solvents were used. The product purities were inspected via TLC plates and visualized under a UV lamp. Standard procedures were followed for synthesizing the derivatives of 2-Mercaptobenzimidazole.

2.2 General scheme of synthesis

As outlined in the Scheme, 2–mercaptobenzimidazole was alkylated using myristyl bromide to get 2-(tetradecylthio) Benzimidazole. It was reacted with ethylchloroacetate to get 2(2(tetradecylthio) Benz imidazolyl) acetate. The ester upon reaction with hydrazine produced the respective hydrazide which was then condensed with a carbonyl compound to derive different desired Schiff bases of 2–mercaptobenzimidazole. The synthetic pathway is summarized.



2.3 2-(tetradecylthio)-1H-benzo(d)imidazole

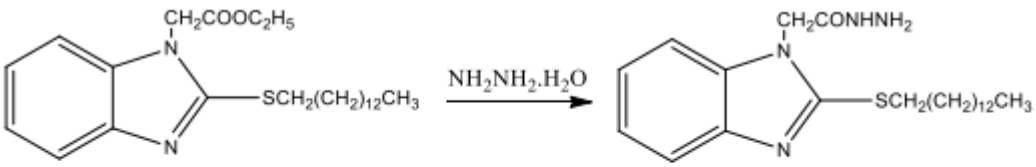


19 **66**

2.3 Ethyl2-(2-(tetradecylthio)-1H-benzo[d]imdazol-1-yl) acetate

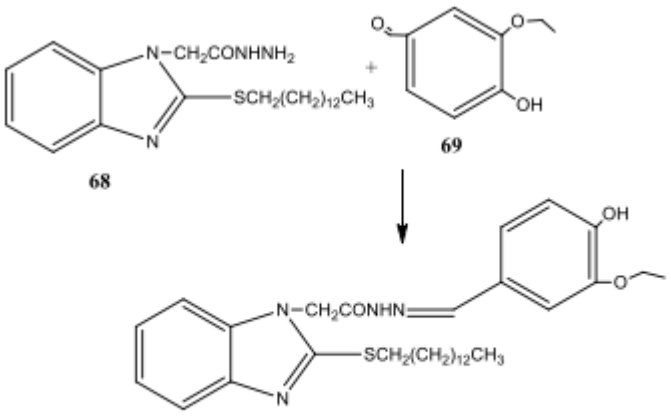
66 **67**

2.4 2-(2-(tetredecylthio)-1H-benzo[d]imidazole-1-yl) acetohydrazide



67 **68**

2.5 N-(3-ethoxy-4-hydroxybenzlidene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazoleyl) acetohydrazide



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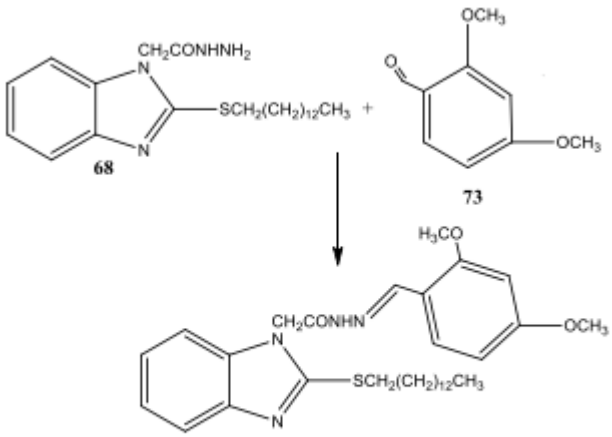
2.6 Synthesis of N-(2,4-dimethoxybenzylidene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazole-1- yl) acetohydrazide



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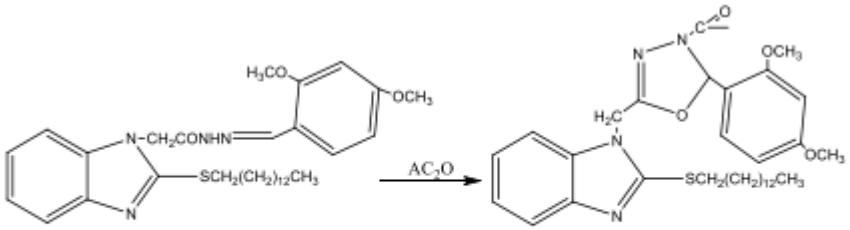
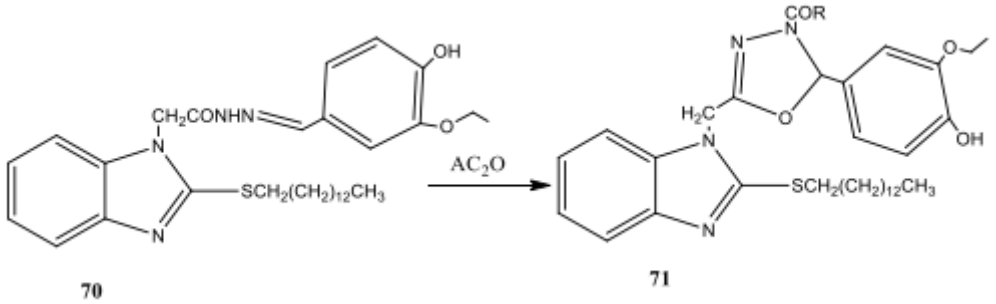
2.7 1-(2-(2,4-dimethoxyphenyl)-5-((2-(tetradecylthio)-1H-benzo[d]imidazole-1-yl) methyl)-1,3,4-oxadiazole-3(2H)-yl) ethenone



74 **75**

2.8 Synthesis of 1-(2-(3-ethoxy-4-hydroxyphenyl)-5-((2-(tetradecylthio)-1Hbenzo[d]imidazole-1-yl) methyl)-1,3,4-oxadiazol-3(2H)-yl) ethenone



3. Result and Discussion

3.1 General

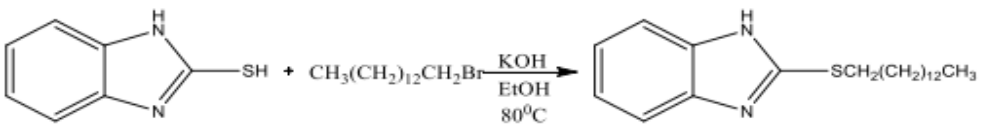
As per the plan of work described before, attempts were made to synthesize various oxadiazole derivatives of 2-Mercaptobenzimidazole (2-MBI). synthesis was conducted based on the standard procedures available in the literature. The product confirmation was checked by doing their thin layer chromatography (TLC). As a result of the present work, the aim has been successfully achieved.
The detail of the percentage yield, purity, and other physical property of the synthesized compounds are discussed.

3.2 Preparation of Derivatives of benzimidazole-2-thiol.

Various oxadiazoles of 2- mercaptobenzimidazole were synthesized following a multistep reaction

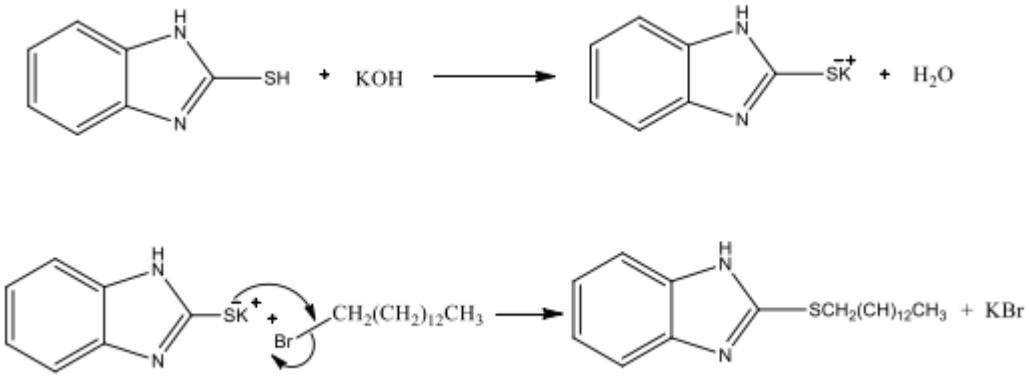
3.3 Synthesis of 2-(tetradecylthio)-1Hbenzo[d]imidazole

This is the first step leading to the synthesis of compound **66**. To Synthesize 2(tetradecylthio)-1H-benzimidazole **(66)**, 30 mmol (5g) of 2-MBI was added to a 10 ml alkaline ethanolic solution and mixed in the round bottom flask with regular stirring using a magnetic stirrer by heating over a hot plate. The solution was made alkaline by adding 30 mmol (4.14 g) of KOH. Then 30 mmol (8.3 g, 8.9 ml) of Myristyl bromide (1-bromotetradecane), was added dropwise and refluxed for about 9 hours. It was then filtered and dried to get white shiny, needle-like crystals of 2-Myristylthiobenzimidazole.



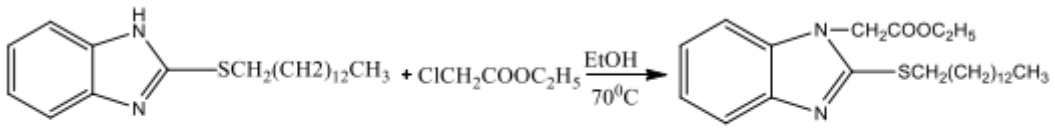
19 66

Mechanism:



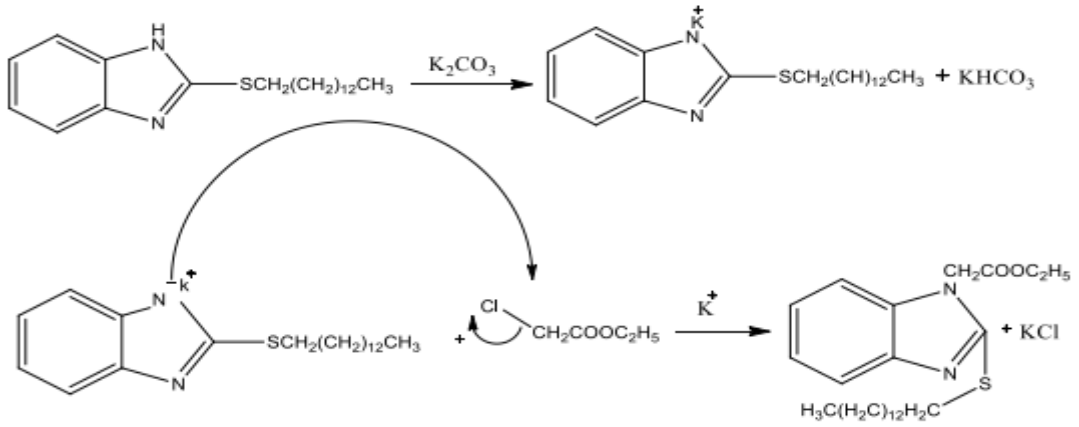
3.4 Synthesis of Ethyl-2-(2-(tetradecylthio)-1H-benzoimidazolyl) acetate (67)

In a round bottom flask, 5 mmol of 2-Myristylthiobenzimidazole (1.81 g) and, 5 mmol of anhydrous K_2CO_3 (0.69 g) were added. Then 20 ml ethyl acetate and 5 mmol of polyethylene glycol (8.86 ml) were added to the flask and stirred well. After complete stirring, 5 mmol of chloroethylacetate (0.53 ml) was added dropwise and the reaction was agitated at ambient temperature for 24 hrs. It was then filtered and the filtrate was condensed and washed to obtain the brown semisolid.



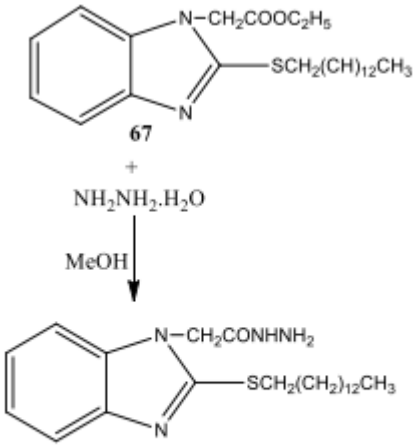
66 **67**

Mechanism



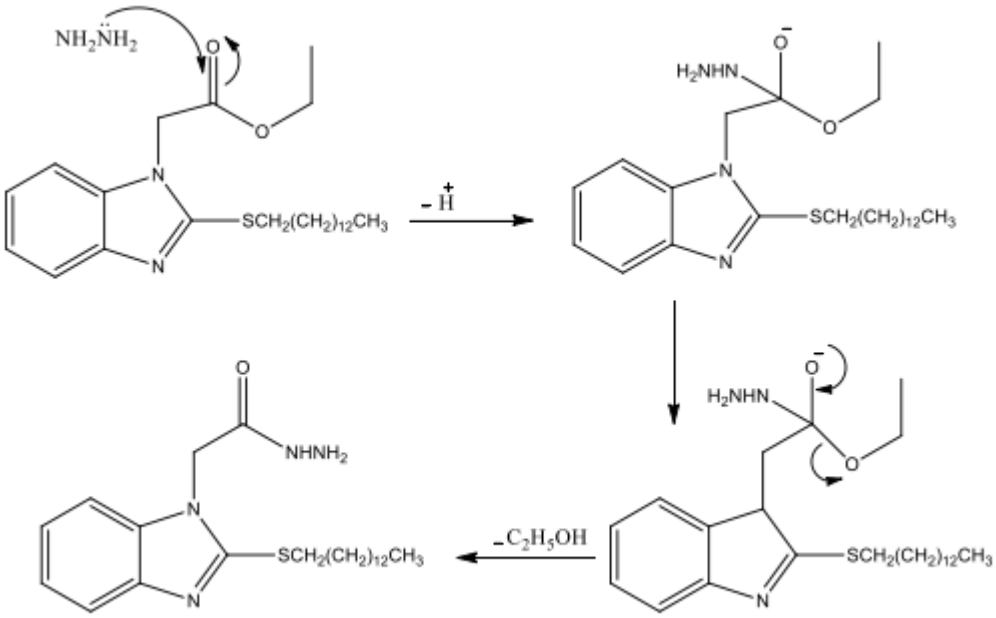
3.5 Synthesis of 2-(2-(tetradecylthio) benzimidazolyl) acetohydrazide (68)

5 mmol (2.01 g) ethyl- -(2(tetradecylthio)benzimidazolyl) acetate (**67**) was dissolved in methanol in a 100 ml round bottom flask over a magnetic stirrer. Then 17 mmol (0.851 g, 0.833 ml) of $N_2H_4.H_2O$ was introduced into the reaction mixture and refluxed for 10 hrs. The progress of the reaction was supervised by TLC (ethyl acetate: n-hexane = 4: 1). The Reaction mixture was decanted into distilled ice-cold water to get the precipitated product. The product was collected by filtration, washed with water, and then dried in the open air to yield the off-white crystalline compound.



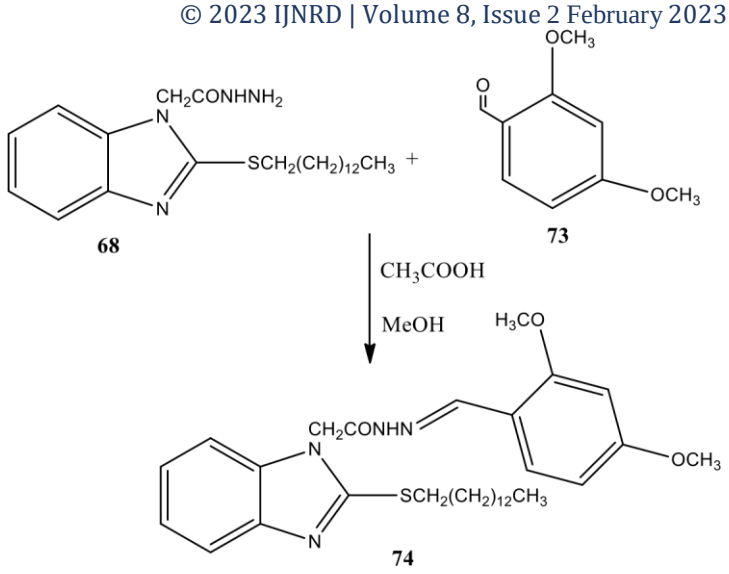
68

Mechanism



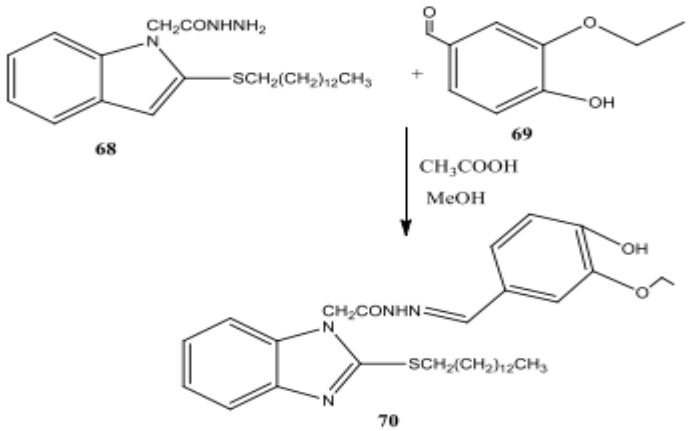
3.6 Synthesis of N-(2,4dihydrodenzildene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazole-1yl) acetohydrazide (74)

To synthesize compound **70,** 0.122 moles (0.0202 g) of aldehyde (**69**) were taken in methanol in a round bottom flask over a hot plate stirrer. Three drops of glacial acetic acid were added and stirred for 5-10 minutes. Then 0.122mmole (0.051g) of ethyl-2-(2tetradecylthio) benzimidazolyl) acetohydrazide **69** was added and refluxed for 2-3 hours. Reaction progress was supervised by establishing TLC in ethyl acetate and n-hexane (2:3). After completion. The hot reaction mixture was decanted into distilled cold water. The product precipitate was collected by filtration, washed with water, and dried in the open air. It was further crystalized in ethanol.

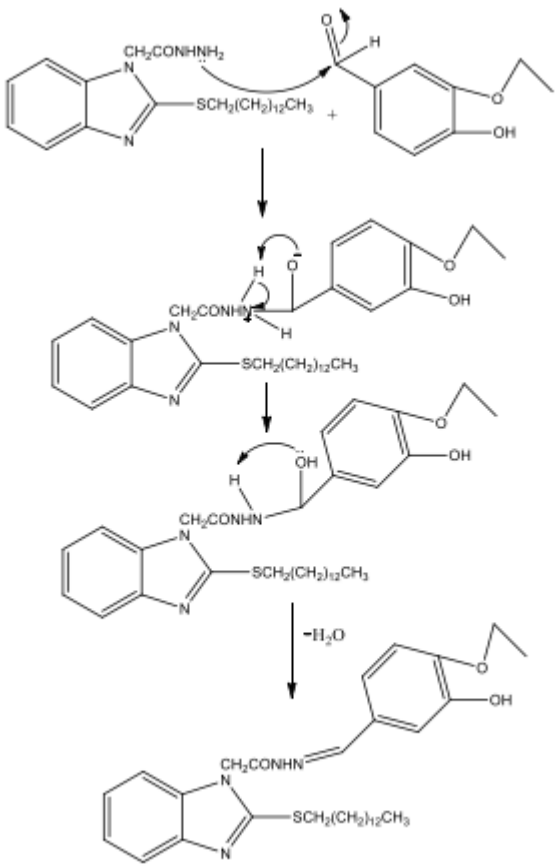


3.7 Synthesis of N-(3-ethoxy-4-hydroxybenzylidene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazole-1-yl)2-acetohydrazide (70)

In an RB flask 0.122m mole (0.0202g) aldehyde **71** was taken along with two drops of acetic acid. Then 0.122mmole (0.051g) of ethyl-2-(2-tetradecylthio) benzimidazolyl) acetohydrazide (**69)** was added and refluxed for 2-3 hours. Reaction progress was supervised by establishing TLC in ethyl acetate and n-hexane (2:3). The hot reaction mixture was decanted into distilled cold water. The precipitate was collected by filtration, washed with water, and dried in the open air.

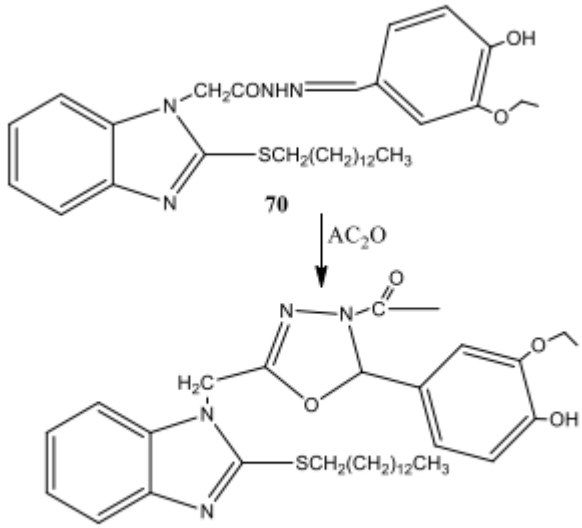


Mechanism



3.8 Synthesis of 1-(2-(3-ethoxy-4-hydroxyphenyl)-5-((2-tetradecylthio))-1Hbenzo[d]imidazole-1-yl) methyl)-1,3,4-oxadiazol-3-(2H)-yl) ethenone (71)

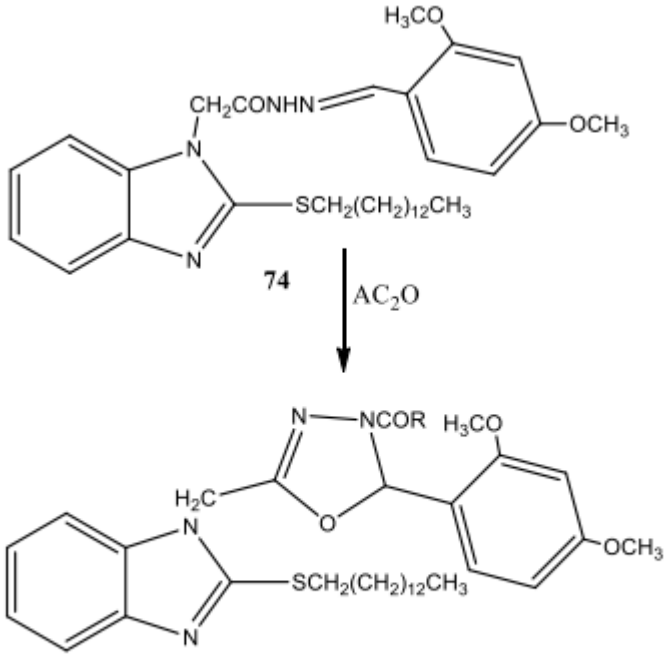
0.05mmole (0.03 g) of the synthesized Schiff base (**70) was** taken in Acetic anhydride and refluxed at 90 ^{0}C for 12 hrs. After reaction completion, the reaction mixture was decanted into ice-cold water. The precipitated product was collected washed and dried to get the title of oxadiazole.



71

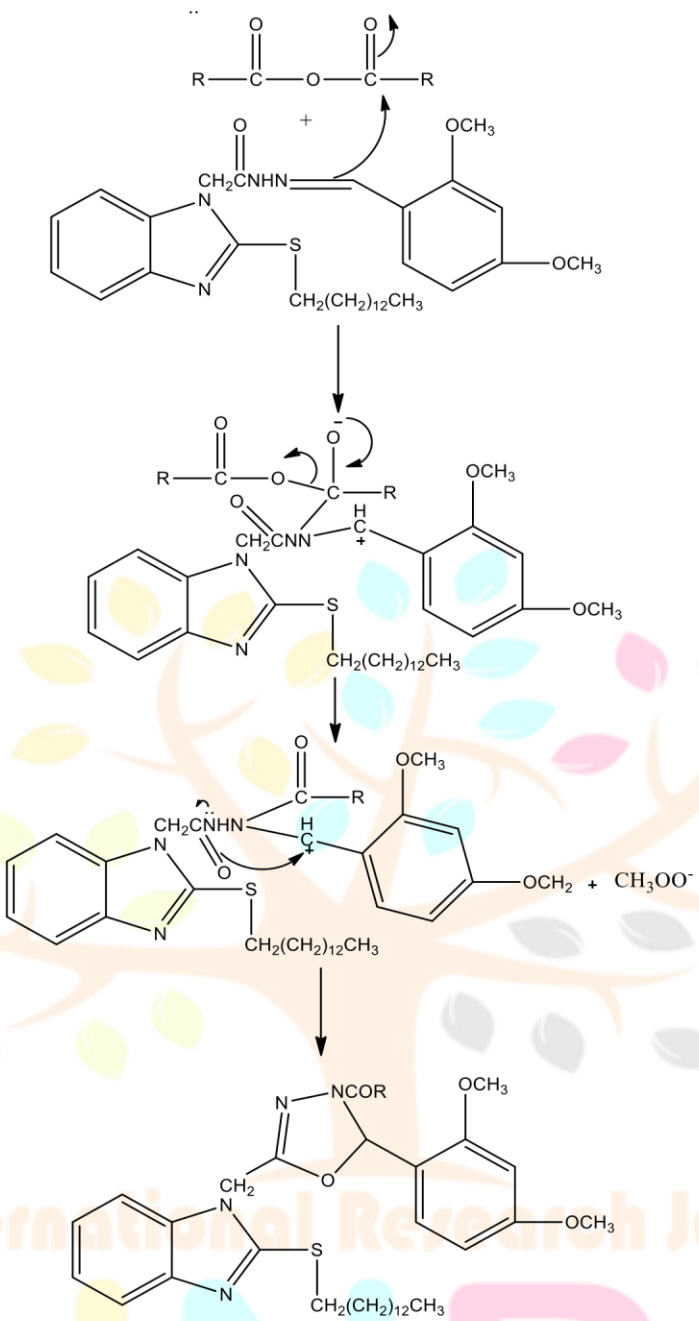
3.9 Synthesis of 2-(2,4-dimethoxy)-3-(prop-1-en-2-yl)-5-((2-(tetradecylthio)-1Hbenzo[d]imidazole-1-yl) methyl-2,3-dihydro-1,3,4-oxadiazole (75)

From the synthesized Schiff base (**74**) 0.05mmol (0.03 g) (**74**) **was** taken in Acetic anhydride and refluxed at 90 °C for 12 hrs. After reaction completion, the reaction mixture was decanted into ice-cold water. The precipitated product was collected washed and dried to get the title oxadiazole.



75

Mechanism



4. Conclusion

In the present work, novel oxadiazole derivatives of 2-mercaptobenzimidazole were synthesized following standard multistep synthetic pathways. The products were obtained with good yields and purity. Furthered oxadiazoles may be synthesized using different carbonyl compounds. This work may be utilized in the future for the derivation of potential medicinal agents. The bioactivity of the synthesized compounds may be conducted for establishing the medicinal property of these compounds.

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