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A novel acyl hydrazone schiff's bases of benzimidazole-2-thiol

Abstract

A series of novel acyl hydrazone derivatives of benzimidazole-2-thiol were synthesized. The acylhydrazide was condensed with a series of aromatic substituted aldehydes to yield the tetra decylhydrazone Schiff"s bases of benzimidazole-2-thiol. The acylhydrazide was taken in methanol in round bottom flask added 2-3 drops acetic acid and refluxed on hotplate the reaction mixture was monitored with TLC. After completion of reaction the product was precipitated in ice cool water, washed and dried. The synthesized compounds were screened for different biological activities such as antimicrobial, antihistamine, neutropic, analgesic, antiprotozoal, antimalarial, antiallergic, antioxidant, anticonvulsant, anti-tubercular and have shown a good results.

Keywords: acyl hydrazone, schiff"s bases, benzimidazole-2-thiol, aromatic aldehydes

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Amir Hassan, Nawaz Khan
Department of Chemistry Government Post Graduate College Mardan, Abdul Wali Khan University, Pakistan

Correspondence: Amir Hassan, Department of Chemistry Government Post Graduate College Mardan, Abdul Wali Khan University, Mardan 23200, Khyber Pakhtunkhwa, Pakistan, Email amirhassan741@gmail.com

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Introduction

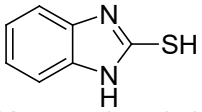
Organic compounds are carbon based compounds. Organic compounds are subdivided into aliphatic, aromatic and heterocyclic compounds. These may be natural or prepared in laboratory. An organic heterocyclic is one which possesses at least one atom other than carbon such as nitrogen, sulfur and oxygen. Such atoms are said to be the heteroatoms. They play a key role in medicines, biochemistry, agriculture and industries Organic heterocycles are classified as 3, 4, 5, 6, and 7 member rings and fused rings.[1,2]

A crystalline base $C_7H_6N_2$ that is composed of benzene ring fused with an imidazole ring and is structurally similar to purine ; also: any of various derivatives (such as thiabendazole omeprazole, or benomyl) of this base typically possessing therapeutic properties including broad-spectrum of biological activities such as anthelmintic, fungicidal, or antimicrobial action.

Literature survey reveals that when one heterocyclic compound is coupled with another, a new compound results and its biological activity is enhanced. Therefore heterocyclic compounds have got much attention in the modern era.[3] Benzimidazole, which is a heterocyclic aromatic organic compound, is a privileged structure in medicinal chemistry.[4] It contains a phenyl ring fused to imidazole ring. It was synthesized by Hoebrecker in 1872 who obtained 2,5(or 2,6)-dimethylbenzimidazole by the reduction of 2-nitro-4-methylacetanilide.[5]

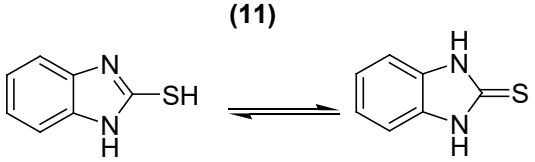
This nucleus plays a role in synthesis of different bioactive derivatives which are used as medicinal compounds. These compounds act as anti-ulcer, anti-viral, anti-tumor, anti-microbial anti-hypertensive and anti-oxidants etc.[6]

2-Mercaptobenzimidazole is derived from benzimidazole with thiol group at 2- position. It is also called o-phenylene thiourea, benzimidazol-2- thione with formula of $C_7H_6N_2S$. It possesses a hydrogen atom attached to the nitrogen at position 1 which is readily tautomerised.[7] It is known to exist in two tautomeric forms i.e. the thiol and thione form. As 2-mercaptobenzimidazole (2MBI) is a heterocyclic derivative of the benzimidazole. Their derivatives exhibited extensive and interesting biological applications such as antimicrobial, antihistamine, neutropic, analgesic, antiprotozoal, antimalarial, antiallergic, antioxidant, anticonvulsant, anti-tubercular.[8-10] Derivatives of 2-MBI benzoxazole, benzothiazole, quinazolinon and 5 subsituted 1, 3, 4-oxadizols find commercial applications in severals therapeutic areas.[11] 2MBI also used in non-biological applications as it control of both microbially- influenced and abiotic corrosion for alloys and metals.[9] It also used for the determination of heavy metals like mercury, copper,iron and cadmium in industrial and sewage water.[13] For manufacutring of industrial rubber and plastic, 2MBI is used as an antioxidant.[14] It is used as plant growth regulator andinsecticide.[15]



2-Mercaptobenzimidazole

(11)



Benzimidazole-2-Thiole

(12)

benzimidazole-2-Thione

(13)

Materials and methods

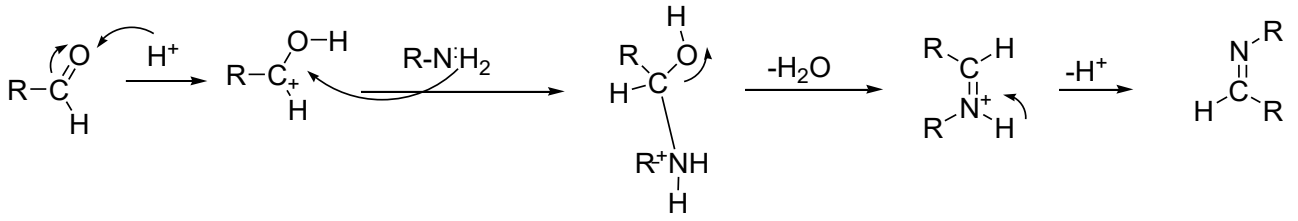
General

The proposed synthesis was conducted using synthetic grade reagents and solvents obtained from BDH, Alfa Aesar, Merk and Aldrich. All the reactions were carried out in clean and dry glass wares. The reaction progress was monitored by performing TLC using different solvent systems of n-Hexane, ethyl acetate and acetone while UV lamp was used as visualizing agent. Standard procedures were followed for synthesizing the acyl hydrazone derivatives of 2-mercaptobenzimidazole.

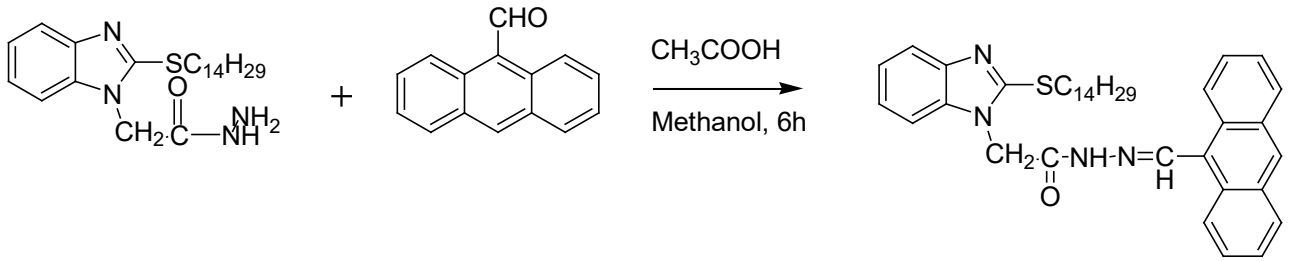
General synthetic route for schiff base formation (68-71)

The acylhydrazide was taken in methanol in round bottom flask added 2-3 drops acetic acid and refluxed on hotplate with continues stirring. After sometime appropriate amount of the aldehyde was added and the reaction was stirred for about 6h. The reaction mixture was monitored with TLC. After completion of reaction the product was precipitated in ice cool water, washed and dried.

General mechanism for schiff base formation

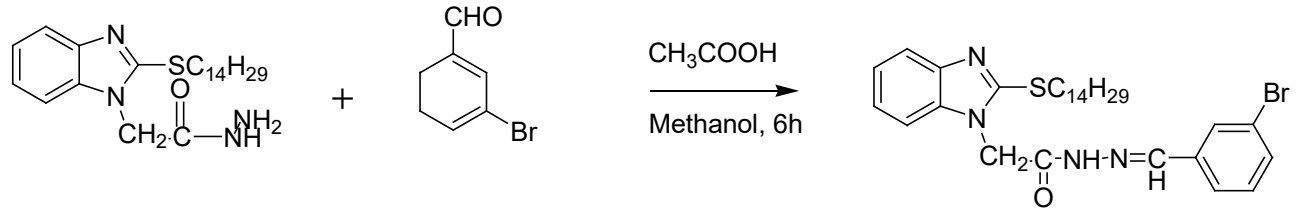


Synthesis of N'-(anthracen-9-ylmethylene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazol-1-yl) acetohydrazide (68)



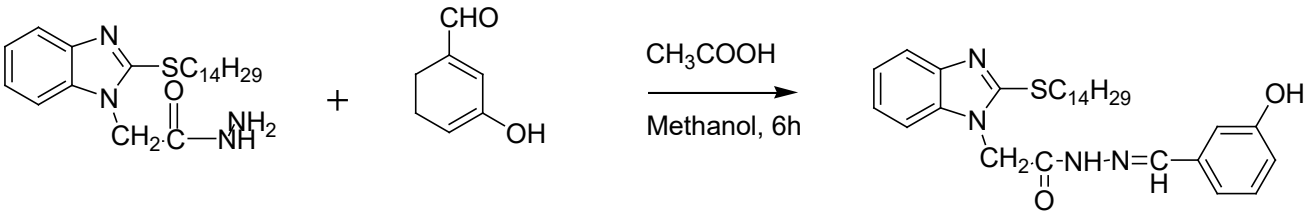
Scheme-1: Synthesis of N'-(anthracen-9-ylmethylene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazol-1-yl) acetohydrazide (68)

Synthesis of N'-(3-bromobenzylidene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazol-1-yl) acetohydrazide (69)



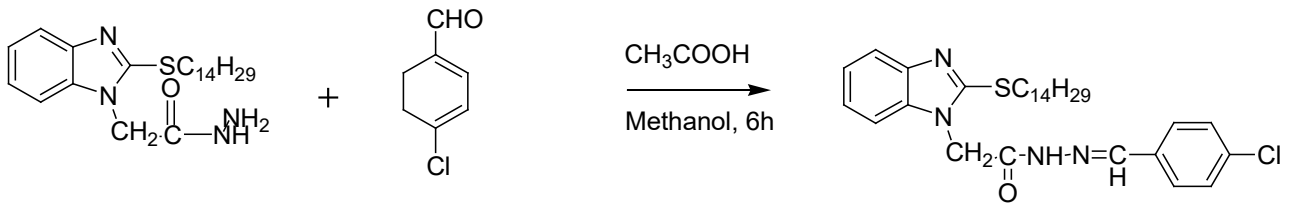
Scheme-2: Synthesis of N'-(3-bromobenzylidene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazol-1-yl) acetohydrazide (69)

Synthesis of N'-(3-hydroxybenzylidene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazol-1-yl) acetohydrazide (70)



Scheme-3: Synthesis of N'-(3-hydroxybenzylidene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazol-1-yl) acetohydrazide (70)

Synthesis of N'-(4-chlorobenzylidene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazol-1-yl) acetohydrazide (71)



Scheme-4: Synthesis of N'-(4-chlorobenzylidene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazol-1-yl) acetohydrazide (71)

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Results and discussion

General

The acylhydrazide was taken in methanol in round bottom flask added 2-3 drops acetic acid and refluxed on hotplate with continues stirring. After sometime appropriate amount of the aldehyde was added and the reaction was stirred for about 6h. The reaction mixture was monitored with TLC. After completion of reaction the product was precipitated in ice cool water, washed and dried.

General procedure for synthesis of schiff bases

As outlined in the Scheme, 2–mercaptobenzimidazole was alkylated using hexylbromide to get 2-(hexyllthio) benzimidazole which was esterified with ethylchloroacetate to result in ethyl 2-(hexylthio)benzimidazolyl)acetate.The ester upon reaction with hydrazine condensed yielded 2-(2-hexylthio)benzimidazolyl) acetohydrazide which was then condensed with various aromatic substituted aldehydes to furnish the desired Schiff base derivatives 2–mercaptobenzimidazole.

Synthesis of N'-(anthracen-9-ylmethylene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazol-1-yl) acetohydrazide

0.119 mmol (24 mg) of 9-anthraldehyde was taken in 15ml of methanol in 100 ml R.B flask. 2 drops of acetic acid was added and refluxed. Then 0.119 mmol (50 mg) of acetohydrazide was added refluxed for about 6 hrs. The solution was precipitated in freezing water. The precipitate was collected and washed with water. **Physical data** Greenish-Yellowish colored compound**,** Molecular weight: 606.86**,** Molecular Formula: $C_{38}H_{46}N_4OS$**,** Yield: 78%.

Synthesis of N'-(3-bromobenzylidene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazol-1-yl) acetohydrazide

0.119 mmol (22 mg) of 3-bromobenzaldehyde was taken in 15ml of methanol in 100 ml R.B flask. 2 drops of acetic acid was added and refluxed. Then 0.119 mmol (50 mg) of acetohydrazide was added refluxed for about 6 hrs. The solution was precipitated in freezing water. The precipitate was collected and washed with water. **Physical data** Cloudy colored compound Molecular weight: 585.64 Molecular Formula: $C_{30}H_{41}BrN_4OS$**,** Yield: 75%.

Synthesis of N'-(3-hydroxybenzylidene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazol-1-yl) acetohydrazide

0.119 mmol (15 mg) of 3-hydroxybenzaldehyde was taken in 15ml of methanol in 100 ml R.B flask. 2 drops of acetic acid was added and refluxed. Then 0.119 mmol (50 mg) of acetohydrazide was added refluxed for about 6 hrs. The solution was precipitated in freezing water. The precipitate was collected and washed with water. **Physical data** White colored compound Molecular weight: 522.75 Molecular Formula: $C_{30}H_{42}N_4O_2S$ Yield: 85%.

Synthesis of N'-(4-chlorobenzylidene)-2-(2-(tetradecylthio)-1H-benzo[d]imidazol-1-yl) acetohydrazide

0.119 mmol (17 mg) of 4-chlorobenzaldehyde was taken in 15ml of methanol in 100 ml R.B flask. 2 drops of acetic acid was added and refluxed. Then 0.119 mmol (50 mg) of acetohydrazide was added refluxed for about 6 hrs. The solution was precipitated in freezing water. The precipitate was collected and washed with water. Physical data Light yellow colored compound Molecular weight: 541.19 Molecular Formula: $C_{30}H_{41}ClN_4OS$ Yield: 82%.

The B. Bhriguia *et al.* prepared a series of new 2-[(1-substituted phenylethylidine) hydrazine]-N-phenyl-1H-benzo[d]imidazole-1-carbothioamides by the combination of 2-mercaptobenzimidazole with hydrazine hydrate and substituted acetophenone.These compounds were evaluated for anti- convulsant activity.[16] G. O. Prakash synthesized 3-substituted-2-phenyl-benzimidazo [2, 1b] pyrazolo [3,4 d] [1, 3] thiazole which is obtained by the reaction of 2-mercapto benzimidazole with chloroacetic acid. It affords benzimidazol-2-thio acetic acid which on cyclization with a mixture of acetic anhydride and pyridine furnishes thiazo lo benzimidazole-3 (2H)-one, upon condensation with different aryl aldehydes furnishes arylidine thiazolidinone followed by treatment with phenyl hydrazine in the presence of sodium acetate affords 20.The synthesized compounds showed antimicrobial activity.[17] V Mohan Goud et al. synthesized mercapto benzimidazole derivatives by treating 2-MBI with chloroacetic acid to yield benzimidazol-2-thioacetic acid which was then refluxed with pyridine to get thiazolodinone Synthesized Compound was then refluxed with various substituted or Unsubstitued aniline to obtain the target compound 2- (1H-benzimidazol-2ylsulfanyl)-N-(2-hydroxy-5-methylphenyl) acetamide.[18]

P. P. Maske *et.al*. found two groups of substituted benzimidazoles, namely the 5,6-dinitro and 2-trifluoromethyl derivatives to be promising candidates for antimicrobial drugs.[19] G Yaseen et al.[20] reported the in vitro screening to obtain best fit molecules as DHFR inhibitors. These compounds were then subjected for in vitro antimicrobial activity against gram +ve and gram -ve bacteria.[20] S Vijayaraghavan et al.[21] synthesized 2MBI derivatives by the reaction of 5–{2–(ethylthio)–1H– benzimidazol–1–yl}–methyl–1,3,4–oxadiazole–2–thione 4 with formaldehyde and appropriate amines by conventional and microwave techniques. The antibacterial screening against *S. aureus, E. coli and P. aeruginosa* at three different concentrations revealed that these compounds are significantly active.[21] M. S. AL-Jawady., *et al*. (2017) condensed 2-Mercaptobenzimidazole with chloroacetic acid to produce (1H-benzimidazole-2-ylthio) acetic acid later compound was condensed with thiosemicarbazide to produce 5-[(1H-benzimidazole-2ylthio) methyl]-1,3,4-thiadiazole-2-amino which condensed with different aromatic aldehydes and isatin to afford Sciff bases The structure of the synthesized compounds were confirmed on the basis of their physical and spectral data.[22] M. R. Ahamed., *et al.* (2013) presented his work which involved three steps: First step include synthesis of 2-mercaptobenzimidazole from reaction of o-phenylenediamine with carbon disulfide.

In the second step alkylation of the 2-mercaptobenzimidazole with different alkyl or aryl halides to obtain thioether. Third step include oxidation of 2-mercaptobenzimidazole to disulfide the 2-mercaptobenzimidazole was prepared in autoclave.[23] Shingalapur *et al.* (2010) reported that benzimidazole is an important pharmacophore which was included in several biologically active compounds resulted in the development of several classes of drugs. This review discusses the synthesis of benzimidazole derivatives as a target agents for antidiabetic by different mechanism such as peroxisome proliferator – activated receptor α transcriptional activity, glycosidases receptor, dipeptidyl peptidase IV, glucokinase, human glucagon receptor (HGCGR) antagonist , aldose reductase enzyme and stearoyl- CoA desaturase.[24] V. M. Dianov *et al.* (1991) prepared 2MBI different derivatives by treating 2MBI with 1, 3 dichloroacetone in acetone

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treating with conc.sulphuric acid reaction with amines gives tricyclic amino compounds.[25] M. S.Reddy et al (2011) reported the Synthesis and biological assessment of six novel 2-substituted mercaptobenzimidazole derivatives.

The title compounds were characterized by their analytical and spectral data. All the synthesized compounds were screened for their anti-ulcer and anti-microbial activity. 2-(1H-benzimidazole-2-sulfinyl) –N-(4-benzyloxy-phenyl)-acetamide, N-(4-benzyloxy-phenyl)-4-(1H-benzimidazole-2 sulfinyl)-butyramide, N-(4-benzyloxy phenyl)-4-(5-methoxy 1H-benzimidazole-2-sulfinyl)-butyramide showed significant antiulcer activity. All the compounds exhibited moderate antibacterial and antifungal activity.[26] S. Rao *et al.* (2012) synthesized N-alkyl-2-mercaptobenzimidazoles 5 ($R=CH_3,C_2H_5,CH_2PH$) under different conditions from N-alkyl-2-chlorobenzimidazole (I. e. CH_3,C_2H_5,CH_2Ph) by reaction with thiourea by physical grinding or by using green solvents like ethanol,PEG-600, or by using microwave irradiation technique.[27] S. Gurrala. *et al*. **(2010)** synthesized bis-mercapto benzimidazoles compounds from starting material i.e substituted 2-mercapto benzimidazole was prepared from substituted o-phenylene diamine and carbon disulfide in presence of KOH. Initially the substituted 2-mercapto benzimidazole were subjected to S-acylation by treating with acetyl chloride formation of acylated compounds was further treated with 1,2 –dibromo ethane and 1,3-dibromo propane in ethanol using potassium carbonate as deacidifying agent to get their respective substituted bis type 2-mercapto benzimidazole derivatives.[28] G. R. Patel *et al.* **(2015)** synthesized azomethines in which carbonyl group is replaced by imine of acid hydrazides. The intermediates prepared by using 2-mercapto benzimidazole with N-(4-Acetylphenyl)-2-chloro-acetamide Resulted product was further treated with different substituted acid hydrazides in ethanol to yield compounds and were examined for their antibacterial activity against Grampositive and Gram-negative strains and antifungal activity. They were found to be highly potent with lowest MIC Values.[29]

Conclusion

A total of four novel acyl hydrazone derivatives of 2-MBI were synthesized. The results were found in good agreement with the literature. The current research will open a new era in the chemistry of benzimidazole. The work may be utilized in future for deriving synthetic analogues of benzimidazole. The biological evaluation of the synthesized compounds will be helpful in driving the structure activity correlation (S.A.R).

Data availability

All the supporting data are available within the article.

Conflicts of interest

There is no conflict of interest regarding the publication of this paper.

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