EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 4
Issue: 11
76-81
Year: 2017

SYNTHESIS, CHARACTERIZATION, AND ANTIBACTERIAL EVALUATION OF NEW BENZIMIDAZOLE BEARING THIOESTER MOIETY

Muayed Ahmed Redayan*[1], Maha Salih Hussein[2] and Ashraf Tark Lafta[3]

[1]Department of Chemistry, College of Education for Pure Sciences, Diyala University, Diyala, Iraq.
[2,3]Department of Chemistry, College of Education, Samarra University, Salahaldin, Iraq.

***Corresponding Author: Muayed Ahmed Redayan**
Department of Chemistry, College of Education for Pure Sciences, Diyala University, Diyala, Iraq.

Article Received on 04/09/2017 **Article Revised on 25/09/2017** **Article Accepted on 16/10/2017**

ABSTRACT
The present work comprises synthesis of new derivatives for benzimidazole. The Compounds 1(a-d) were prepared by reaction of (4) un-substituted-o-phenylenediamine with carbon disulfite. Then compounds 1(a-d) used to prepare The thioester compounds 2(a-d) by reaction of compounds 1(a-d) with chloro acetyl chloride. The chemical structure of all synthesized compounds were confirmed by FT-IR and some by ^{1}H, ^{13}C-NMR. Some selected compounds were evaluated in vitro for their antibacterial activity against two types of Gram-positive bacteria namely (Staphylococco usaureus, Bacillus subtilis) and Gram-negative bacteria namely (Pseudomonas aeruginosa, Esherichia coli). Most of the results of the antibacterial activity of these compounds were good when comparison with the standard antibiotic ampicillin and ciprofloxacin

KEYWORDS: 2-Mercaptobenzimidazole, thioester, o-phenylenediamine.

INTRODUCTION
Benzimidazole derivatives are of wide significance because of their various biological Activities and clinical application.[1] This parent nucleus is found in different antiparasitic, fungicidal, antihelmintic and anti-inflammatory drugs.[2-5] Optimization of the substituent around the benzimidazole nucleus has resulted in many drugs as antihelminthics like albendazole, mebendazole, thiabendazole; proton pump inhibitors, like omeprazole, lansoprazole, pantoprazole, and many other compounds in the field of medicinal and therapeutic area.[6] The structural modification, of the benzimidazole moiety, can be carried out to all seven positions of the ring, with different chemical functional groups, but most of the biologically active benzimidazole-based compounds bear different entities at 1,2 and /or 5 (or 6) positions.[7] 2 Mercaptobenzimidazole derived from benzimidazole with thiol group in the 2-position. It possesses other chemical names such as, o-phenylen thiourea, benzimidazol-2-thion,[8,9] Some characteristic of 2-mercaptobenzimidazole are containing of thioamide group (-N-C=S), therefore it is considered one of thioamide compounds for its ability to react under special conditions to give derivatives having substituent at either nitrogen or sulfur atoms[10,11] 2-mercaptobenzimidazole possess the form dimer, because it has (C=S) group, this preferable product is the dimer,[12] it is known to exist in two tautomerism forms the thiol and thione from.[13-14] Various derivatives of 2-mercaptobenzimidazole have been synthesized by several investigators and have been reported to exhibit a wide range of biological activities such as anti-microbial[15] antihistamine[16] neutropic[17] and analgesic[18] activities. Although a great deal of the scientific literature concerning 2-mercapto-benzimidazole is in the area of medicinal chemistry, 2-mercaptobenzimidazole is also used in non-biological application, it serve as plant growth regulators[19] and used as corrosion inhibitor for mild steel in sulfuric acid solution,[20] stainless steel in aqueous solutionsof NaCl,[14] mild steel and zinc in phosphoric acid,[21,22] Also, it is widely used as an accelerator in rubber processing,[23] and anti-oxidant for rubber and plastics.[24] Mercaptobenzimidazole and its deriva- tives display insecticidal properties,[25] it is also a well-known analytical reagent for mercury, and have been used for the determination Fe(II), Cu(II), and Cd(II) metal ions in sewage water and industrial waste waters samples.[26-27]

Experimental Part
General
Melting points were taken in an electrically heated using stuart SMP3 instrument and are uncorrected. FT-IR spectra were recorded on Shimadzu (FTIR- 8400 S) Infrared spectrophotometer by KBr disc. The ^{1}H and ^{13}C-NMR spectra were recorded on Bruker (400MHZ) instrument using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as solvent. The purity of the compounds was checked by TLC on silicagel plates using ultraviolet lamp.

General procedure for synthesis of compounds 1(a-d).[28]

A mixture (10.8gm,0.1mole) of 4-un-substituted-O-phenylenediamine, (5.65g, 0.1mol) of potassium hydroxide and (7.67g, 0.1mol) of carbon disultie CS_2 were dissolved in (100 ml of Ethanol and 15ml of water) The resulting mixture was heated under reflux for 3 hours, after the reflux, add (1-1.5mg) of activated charcoal with caution and then climp the mixture for 10 min. Activated charcoal was removed by filtration and the solution was heated to (60-70 ^{o}C) after that add 100ml of water. Acid using diluted acetic acid with stirring. The product is separated as white crystals and the mixture is placed in a snow bath for three hours to complete the crystallization and the deposit is collected on buechner funnel and drying in 24 hours at 40 °C.

1H-benzo[d]imidazole-2-thiol (1a): Off White, m.p: 299 – 301 °C, IR ν_{max} (KBr/cm^{-1}): N-H benzimidazole (3157), aromatic C-H (3057), S-H (2571), C=N (1625), aromatic C=C (1467, 1514). ^{1}H –NMR (400 MHZ, DMSO – d_6) δ: 3.13 (1H, s, N-H), 1.80 (1H, s, S-H), 7.51-7.75 (4H, m, Ar – H) as shown in figure 1. ^{13}C – NMR (400 MHZ, DMSO) δ: 168.04 (C=N of benzimidazole), 109.39-132.22 (aromatic carbon), yield 60%.

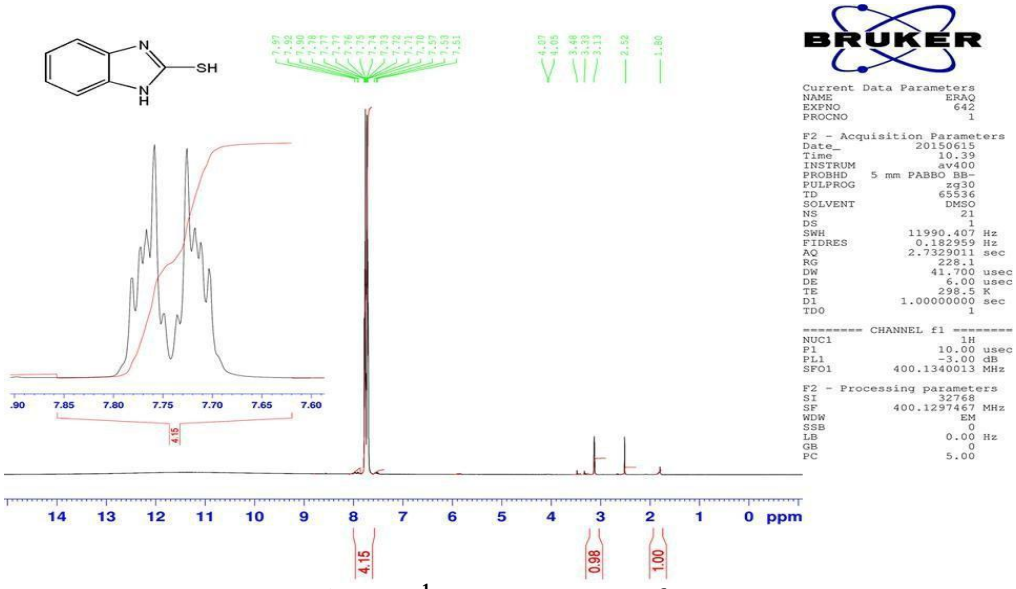


Figure 1: ^{1}H-NMR spectrum of 1a.

5-methyl-1H-benzo[d]imidazole-2-thiol (1b): Brown, m. p: 286 – 288 °C, IR ν_{max} (KBr/cm^{-1}): N-H benzimidazole (3124), S-H (2567), aromatic C-H (3041, 3093), aliphatic C-H (2962, 2868), C=N (1620), aromatic C=C (1467-1521). ^{1}H –NMR (400 MHZ, DMSO – d_6) δ : 3.03 (3H, d, CH_3), 1.93 (1H, S-H), 3.19 (1H, s, N-H benzimidazole), 7.61-7.87 (3H, m, Ar – H) as shown in figure 2.^{13}C–NMR (400 MHZ, DMSO) δ: 20.86 (CH_3), 167.76 (C=N of benzimidazole), 109.06-132.66 (aromatic carbon), yield 62%.

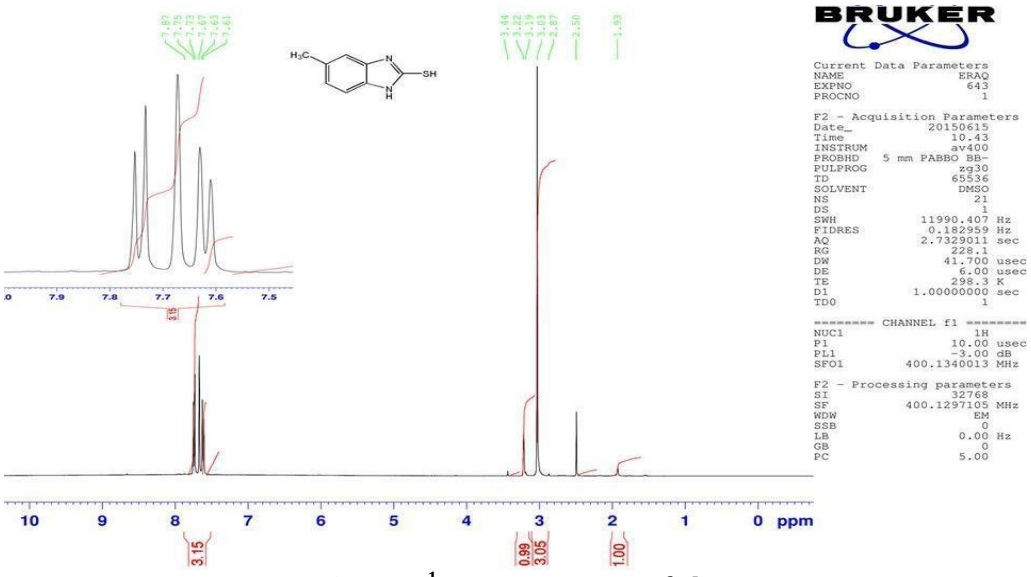


Figure 2: ^{1}H-NMR spectrum of 1b.

2-mercapto-1H-benzo[d]imidazole-5-carboxylic acid (1c): Pink, m.p: >350 °C, IR ν_{max} (KBr/cm^{-1}): N-H benzimidazole (3450), O-H (2500-3500), S-H (2598), aromatic C-H (3057, 3091), C=O (1680), C=N (1627), aromatic C=C (1460-1570). ^{1}H –NMR (400 MHZ, DMSO – d_6) δ : 12.31 (O-H), 1.24 (1H, S-H), 3.58 (1H, s, N-H benzimidazole), 6.58-7.78 (3H, m, Ar – H).^{13} C–NMR (400 MHZ, DMSO) δ: 168.27 (C=O), 169.09 (C=N of benzimidazole), 107.76-134.73 (aromatic carbon) as shown in figure 3, yield85%.

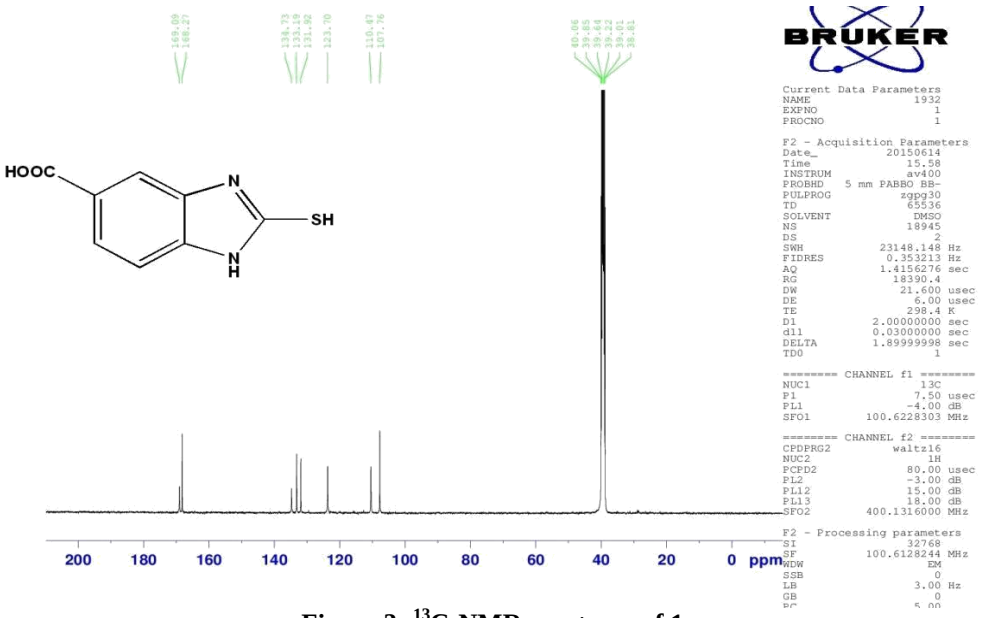


Figure 3: ^{13}C-NMR spectrum of 1c.

2-mercapto-1H-benzo[d]imidazol-5-yl)(Phenyl) methanone (1d): Yellow, m.p: 257–259 °C, IR ν_{max} (KBr/cm^{-1}): N-H benzimidazole (3398), S-H (2573), aromatic C-H (3041, 3055), C=O (1643), C=N (1620), aromatic C=C (1475-1516). ^{1}H –NMR (400 MHZ, DMSO – d_6) 1.88 (1H, S-H), 5.48 (1H, s, N-H benzimidazole), 7.26-7.71 (8H, m, Ar – H).^{13}C–NMR (400 MHZ, DMSO) δ: 170, 74 (C=O), 195.07 (C=N of benzimidazole), 109.27-137.98(aromatic carbon) as shown in figure 4, yield 94%.

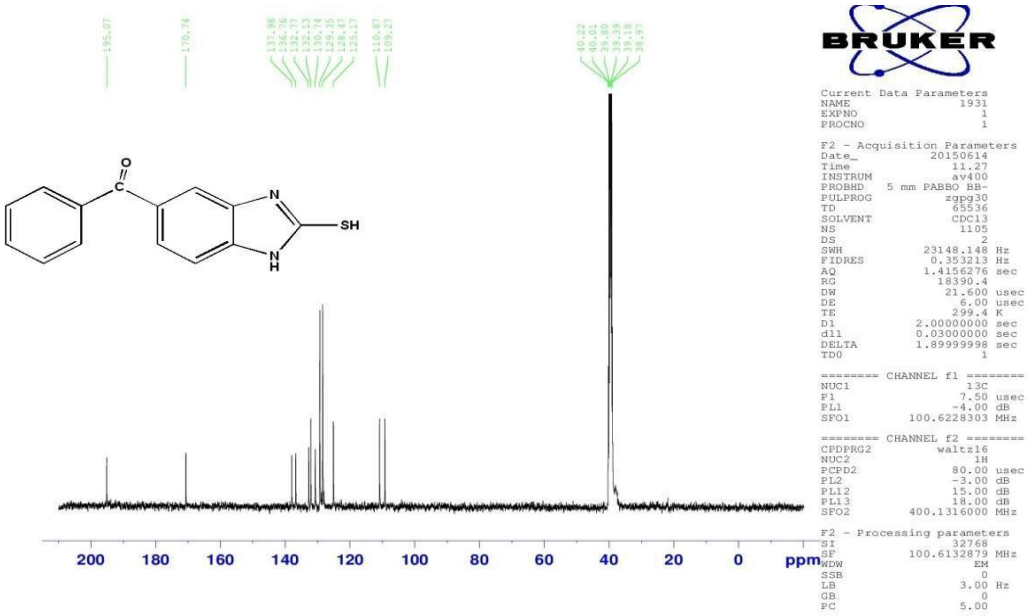


Figure 4: ^{13}C-NMR spectrum of 1d.

General procedure for synthesis of compounds 2(a-d).[29]

Prepare an equal solution moles of (1.5 g, 0.01 mol 1(a-d)) with (1.22ml 0.01mol) of chloroacetyl chloride in 20ml of acetone with (1gm) of anhydrous potassium carbonate. The mixture was refluxed on water bath for 6 hours and the solvent was removed by vacuum distillation and the product was recrystallized by using chloroform was as a solvent.

S-(1H-benzo[d]imidazol-2-yl) 2-chloroethanethioate (2a): Brown, m.p: 329-331°C, IR ν_{max} (KBr/cm^{-1}): N-H benzimidazole (3385), aromatic C-H (3047,3105), aliphatic C-H (2854, 2974) C=O(1728), C=N (1622), aromatic C=C (1458-1521), C-Cl (775). Yield 52%.

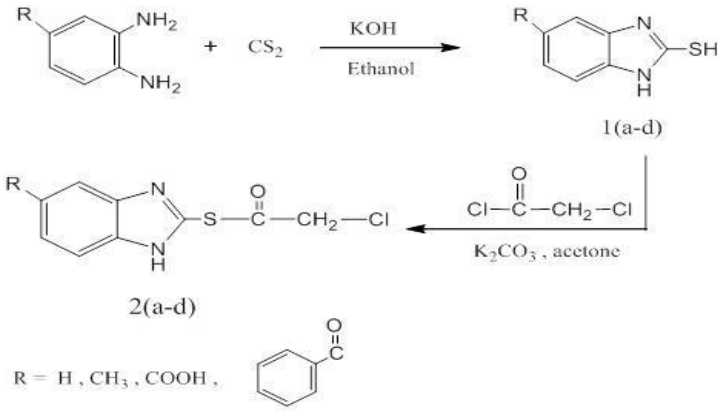
S-(5-methyl-1H-benzo[d]imidazol-2-yl)2-chloroethanethioate (2b): Yellow, m. p: 321–323°C, IR ν_{max} (KBr/cm^{-1}): N-H benzimidazole (3157), aromatic C-H (3041,3093), aliphatic C-H (2879, 2966) C=O(1724), C=N (1620), aromatic C=C (1467-1521), C-Cl (721). yield 61%.

2-((2-chloroacetyl)thio)-1H-benzo[d]imidazole-5-carboxylic acid (2c): Black, m.p >350°C, IR ν_{max} (KBr/cm^{-1}): N-H benzimidazole (3125),O-H (2500-3500), aromatic C-H (3064), aliphatic C-H (2860, 2987), thioesteric C=O (1708), carboxylic C=O(1653), C=N (1616), aromatic C=C (1473-1570), C-Cl (767). Yield 71%.

(2-((chloromethyl) thio)-1H-benzo[d]imidazol-5-yl) (phenyl) methanone (2d): Off White, m.p : 336–338°C, IR ν_{max} (KBr/cm^{-1}): N-H benzimidazole (3159), aromatic C-H (3057), aliphatic C-H (2875, 2956), thioesteric C=O (1716), ketonic C=O(1645), C=N (1618), aromatic C=C (1473-1597), C-Cl (717). yield 78%.

RESULT AND DISCUSSION

In the present work, 2-mercptobenzimidazole derivatives 1(a-d) were synthesized by reaction of (4) un-substituted-o-phenylenediamine with carbon disulfite using the escalation method and the presence of activated charcoal and used a mixture of water and ethanol as a solvent. The compounds 2(a-d) were synthesized by reaction of compounds 1(a-d) with chloro acetyl chloride in the presence of anhydrous potassium carbonate and using acetone as a solvent. The reaction proceeds according to the scheme.



Scheme: The preparation route of compounds 1(a-d) and 2(a-d)

The structure of the prepared compounds was established on the basis of ^{1}H-NMR and IR spectroscopy. In all cases TLC of the product showed the presence of one single spot referring to only one product. The IR spectra of compounds 1(a-d) exhibited broad absorption bands, one of which appearing at (3450-3124) was attributed to the NH imidazole group. And other, observed at (2598-2567) to S-H stretching frequency and absorved at (1627-1620) to C=N stretching frequency. In ^{1}H-NMR spectra of compounds 1(a-d) exhibited two different signals at (δ 3.13-5.58 ppm) for (1H, s, N-H benzimidazole) which assigned to NH imidazole protons and singals at (1.24-2.03) for (S-H) group. The ^{13}C-NMR spectra of compounds 1(a-d) exhibited signals at(δ 167.76– 195.07 ppm) which attributed to the group (C=N). the structure of compounds 2(a-d) was confirmed by FT-IR, The IR spectra of these compounds exhibited broad absorption band at (3385-3125)cm^{-1} was attributed to the NH imidazole group `and absorption band at (1708-1728) cm^{-1} which assigned to thioesteric carbonyl group(C=O). The IR spectra of compound 2d exhibited absorption band at (1645)cm^{-1} was attributed to the Ketonic C=O group.

Table 1: Physical properties of the compounds.

Comp no.	M.p (°C)	Color	M. wt (g/mole)	M. Formula	Yield %
1a	299-301	Off white	150.20	$C_7H_6N_2S$	60%
1b	286-288	Brown	164.23	$C_8H_8N_2S$	62%
1c	>350	Pink	194.21	$C_8H_6N_2O_2S$	85%
1d	257-259	Yellow	254.3	$C_{14}H_{10}N_2OS$	94%
2a	329-331	Brown	226.10	$C_9H_7ClN_2OS$	52%
2b	321-323	Yellow	240.71	$C_{10}H_9ClN_2OS$	61%
2c	>350	Black	270.69	$C_{10}H_7ClN_2O_3S$	71%
2d	336-338	Off white	330.79	$C_{16}H_{11}ClN_2O_2S$	78%

Antibacterial activity

The disk diffusion method was used to screened antibacterial activities of the some compounds synthesized herein against different strains of Gram-positive bacteria namely (Staphylococco usaureus, Bacillus subtilis) and Gram-negative bacteria (Pseudomonas aeruginosa, Esherichia coli) The compounds were tested at concentration of (10 mg /ml and 100 mg /ml). The zone of inhibition was measured in millimeters and was compared with reference standard antibiotic namely ampicillin and ciprofloxacin. The test compound was dissolved in DMSO to obtain solution of different concentration. The results show in (Table2) which demonstrates that compounds 1a, 1b, 2a and 2b showed signficant activities. Wheras the other compounds displayed middle activities when comparison with the standard antibiotic ampicillin and ciprofloxacin.

Table 2: Antibacterial activity of synthesized compounds.

Comp no.	Concentration	Zone of inhibition (in mm)			
	(mg / ml)	Gram-positive		Gram-negative	
		S. aureus	B. subtilis	P. aeruginosa	E. coli
1a	10	19	15	12	19
	100	11	12	13	12
1d	10	14	15	17	17
	100	17	14	16	-
1c	10	-	-	8	10
	100	-	15	-	12
1d	10	-	-	-	-
	100	-	-	-	-
2a	10	12	18	19	20
	100	15	19	17	13
2b	10	15	23	20	27
	100	12	11	13	12
2d	10	12	11	9	17
	100	13	14	10	-
Ampicillin		22	23	-	10
Ciprofloxacin		19	23	29	-
DMSO solvent		0	0	0	0

CONCLUSION

New compounds derived from 2-mercpto benzimidazole have been synthesized successfully by reaction (4) un-substituted-o-phenylenediamine with carbon disulfite. the resulting compounds were reaction with chloro acetyl chloride to prepare new derivatives. Some of these compounds shown good antibacterial activity.

ACKNOWLEDGMENT

The authors express their thanks and appreciation to Department of Chemistry, Collage of Education, Samara University, as well as Department OF Chemistry, Collage of Education for pure sciences, Diyala University for their support and assistance.

REFERENCES

1. Shatha. I. A." Synthetic a roaches to benzimidazolesfrom O-phenylenediamine: Aliterature review"; Journal of Saudi Chemical Society., 2016; 21(2): 229-237.
2. Habib. N. S, Soliman. R, Ashour. F. A, el-Taiebi. M" Synthesis and antimicrobial testing of novel oxadiazole benzimidazole derivatives"; Die Pharmazie, 1997; 52(10): 746– 749.
3. Tuncbilek, M., Goker, H., Ertan, R., Eryigit, R., Kendi, E. & Altanlar E. Synthesis and antimicrobial activity of some new aniline benzimidazoles, Arch. Pharm, 1997; 330(12): 372–376.
4. Eswara Rao. G, & Srinivasa .B, Sai K, Sharmila .R, Vijayabharathi .M, Maruthikumar. S, Prathyusha. R, Pavankumar. P."Areview on chemistry of benzimidazole nucleus and its biological significance"; IJPCBS, 2016; 6(2): 227-232.
5. Haider .J. A, Ammar A. R. M." Synthesis, Characterization and Antimicrobial Evaluation of New 5-Methoxy-2-Mercapto Benzimidazole Derivatives" J. Pharm. Sci. & Res., 2017; 9(2): 260-266.
6. Yogita B, Om S" The therapeutic journey of benzimidazoles: A review"; Bioorganic and med. chem., 2012; 20(21): 6208-6236.
7. Haider. J, Ammar A. R, Nada N, Ammar A. "Synthesis, characterization and anticonvulsant evaluation of new derivatives derived from 5-methoxy-2-mercapto benzimidazole"; Der Pharmacia Lettre., 2016; 8(18): 96-101.
8. Bennamane. N, Zaioua. K, Akacem. Y," Synthesis of Benzimidazole-2- thiones from Dimedone: An unexpected Cyclisation into a Five-Membered Ring"; Org. Common, 2009; 2(2): 49-59.
9. Husain. A, Varshney. M, Rashid. M, Akhter. A." Benzimidazole: A valuable Insight into the Recent

Advances and Biological Activities"; J. Pharm. Rese., 2011; 4(2): 413-419.
10. Chaudhari. V. K., Pathak. D, Singh S." Benzimidazole: as potential biologically active agent" International Research Journal of Pharmacy, 2014; 5(12).
11. Narkhede. H, More. V, Dalal. D, Mahulikar. P." Solid Supported Synthesis of 2-Mercaptobenzthiazole Derivatives Using Microwaves"; J. Scie. Indus. Rese., 2008; 67(5), 374-376.
12. Selvam P" Synthesis of novel 2-substituted benzimidazole derivatives as potential anti-microbial agents"; Research in Biotechnology, 2011; 2: 50-27.
13. Hosseini. M, Shahrabi. T, Nichols. R," Characterization of Mercapto benzthiazole Adsorption on an Au (111) Electrode" Iran J. Sci. Tech., 2005; 29(1): 49-63.
14. Rangareddy. S, Kalyani. P, Rajes R.B, Manikyamba. P. "Computation Studies and Reactivity of Nucleophiles in Benzylation Reactions"; J. Ind. Chem., 2008; 47(2): 236-239.
15. Mauro. V, Silvia. H, Joao. V, Marcus. V." Synthesis of 2-Mercapto benzthiazole and 2-Mercaptobenzimidazole Derivatives Condensed with Carbohydrates as A potential Antimicrobial Agents"; J. Sulfur, Chem., 2007; 28(1): 17-22.
16. Mauro V. De Almeida, Sílvia. H, Cardoso, João. V, De Assis, Marcus .V. De Souza N." Synthesis of 2-mercaptobenzothiazole and 2-mercaptobenzimidazole derivatives condensed with carbohydrates as a potential antimicrobial agents";Journal of Sulfur Chemistry., 2007; 28(1): 17–22.
17. Pratik .P.M, Sachin. G .L, Dhanashri. N, John. I. D." Synthesis and antiprotozoal activity of nitro and halogeno substituted some novel mercapto benzimidazole derivatives"; Der Pharma Chemica., 2012; 4(3): 1283-1287.
18. Anandarajagopal. K, Timari. R, Venkatesshan. N, Vinothapooshan. G. "Synthesis and Characterization of 2-Mercaptobenzimidazole Derivatives as Potential Analgesic Agens" J. Chem. Pharm. Res., 2010; 2(3): 230.
19. Gurusamy .M, Rajib. H, Furk A, Rashmi K. U, Patangia S." Synthesis and biological evaluation of 2-substituted benzimidazole derivatives"; Arabian journal chemistry, 2015; 8(5): 715-719.
20. Heralagi. R, Jayaveera. K, Shivkumar. B." Synthesis of Some Novel Bis Type 2-Mercapto Benzimidazole Derivatives"; RJPBCS, 2012; 3(2): 407-414.
21. Eugene U, Odonnell P. S, Ifeoma. V. J, Feyisayo V. A. "The effect of corrosion inhibitors on stainless steels and aluminium alloys: A review" Afr. J. Pure Appl. Chem., 2016; 10(2): 23-32.
22. Wang, L., "Evaluation of 2-Mercaptobenzimidazole as Corrosion Inhibitor for Mild Steel in Phosphoric Acid"; Corros. Sci., 2001; 43(12): 2281-2289.
23. Wang, L.; Pu, J.; Luo, H., "Corrosion Inhibition of Zing in Phosphoric Acid Solution by 2-Mercaptobenzimidazole"; Corros. Sci., 2003; 45(4): 677-683.
24. Norford. D, Meaten. D, Cullen. J, Collins. J. "Pituitary and Thyroid Gland Lesions Induced by 2-Mercaptobenzimidazole Inhalation in Male Fischer-344 Rats"; Soci, Toxical-Patho., 1993; 21(5): 456.
25. Salman. M, Abu-Krisha, M, El-Sheshtawy. H." Charge Transfer Complexes of MBI with α-and Π-Electron Acceptor"; Cand. J. Analy. Sci. Spect., 2004; 49(5): 282-289.
26. Karami.B, Montazerzohori. M, Habibi. M. "Urea-hydrogen peroxide (UHP) Oxidation of Thiols to The Corresponding Disulfides Promoted by Maleic anhydride as Mediator"; Molecules, 2005; 10(10): 1358-1363.
27. Chalapathi.K, Rameshbabu. L, Madhu. P, Maddaiah.G."2-Mercapto benzimidazole Immobilized with Amberlite Xad-2 Using as Solid Phase Extractor for the Determination of Fe(II), Cu(II), & Cd(II)"; Adv. Appl. Sci, Res., 2010; 1(2): 27-35.
28. Srikanth. G, Rajesh .B.Y, & Vijayabhaskara .R.G, Madhavilatha B."Symmerical Coupling of 2-Mercapto benzimidazole derivatives and their anti-microbial activity"; International Journal of Pharmacy and Pharmaceutical Sciences., 2011; 3(2): 217-220.
29. Srikanth .G, Venkateshwar. R, Manish. K, Kumara. S." Synthesis of some novel bis type 2-mercapto benzimidazole derivatives"; International Journal of Pharmacy Therapeutics., 2010; 1(2): 92-9.
30.