Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(4):1-5
(http://derpharmachemica.com/archive.html)

Synthesis and antimicrobial screening of 2-mercaptobenzimidazole derivatives

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ABSTRACT

The new series of 2-mercaptobenzimodazole derivative were synthesized by using secondary amine i.e. diethyl amine and aromatic aldehyde. In Mannish reaction instead of formaldehyde other aromatic aldehyde was used. That was main aim of present study. The purity of synthesized compounds was checked by Melting point and TLC and their structure was established by various analytical techniques such as IR,^{1}HNMR, Mass spectral studies.Thsese Compounds were screened for their Antimicrobial, Anticonvulsant activity. Antibacterial activity was screened by using Paper disc method. Anticonvulsant activity was evaluated by PTZ induced model.

Key words: Mannich reaction, 2-Mercapto Benzimidazole, Aromatic aldehyde

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INTRODUCTION

Discovery of new drugs that is therapeutically useful and goes in to clinics is a lifetime dream for medicinal chemist. Carbocyclic or heterocyclic ring systems comprise the core of chemical structures of the vast majority of therapeutic agents. The exploitation of a simple molecule with different functionalities for the synthesis of heterocyclic compounds is a worthwhile contribution in the chemistry of hetero cycles. There is still interest in the synthesis of benzimidazole derivatives for obtaining new biologically active compounds because of their diverse biological activity such as anti-HIV, anthelmintic, antibacterial, and antifungal, CNS depressant, analgesic and anti-inflammatory activities. 2mercaptobenzimidazole derivatives, one of the most important derivatives of benzimidazole exhibited a wide variety of interesting biological activities such as antimicrobial, antihistamine, neutropic and analgesic activities. In recent years, the field of anticonvulsant drug development has become quite dynamic, affording many promising research opportunities[1-9].

Chemistry

O-phylenediamine & carbon disulphide reacts in presence of aqueous ethanolic KOH to form 2-mercaptobenzimidazole.one of amino group of O-phylenediamine is alkylated with CS_2 to from the mercapto derivative which on further removal of H_2S gas gets cyclizes to form Benzimidazole nucleus substituted at second position as 2-Mercaptobenzimidazol. Compound 1a- g were prepared by nucleophilic addition of amine to the carbon of aromatic aldehyde followed by condensation of the Mannich base on reaction with 2mercaptobenzimidazole gives the final product.[1-9]

MATERIALS AND METHODS

1) All chemicals and solvents were procured from commercial sources, purified and dried using standard procedures from literature whenever required .the reagents were purchased from Samarth lab ,loba research lab ,raj lab and issued from Ashokrao Mane college of pharmacy, Peth vadagaon.
2) Melting points were determined by open capillary tube method and are uncorrected.
3)Thin layer chromatography was used to assess the course of reaction and the purity of the intermediates and the final compound were confirmed by applying a single spot on TLC plate (silica gel G) using various solvents such as Chloroform, n-Hexene, ethanol
4) TLC plates were visualized using iodine chamber.
5) IR spectra were recorded using KBR disc on jasco FTIR-410.H^1NMR spectra were performed in DMSO solution and their chemical shift are reported in δ unit with respect to TMS as internal standard at Shivaji University, Kolhapur. Mass spectra were obtained from Shivaji University.

Step -1

Preparation of 2- mercaptobenzimidazole

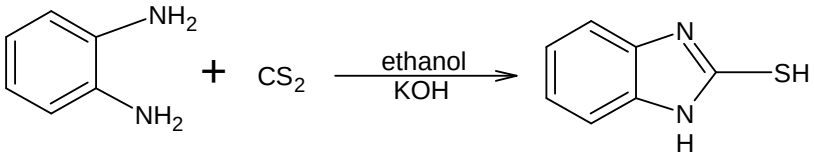
A mixture of 10.8 gm (0.1 mole) of o-phenylenediamine, 5.65 gm (0.1 mole) of potassium hydroxide and 7.67 gm (0.1 mole, 6.19 ml) carbon disulphide, 100 ml of 95% ethanol and 15 ml of water in 500 ml of round bottom flask were heated under reflux for 3 hr. Then added 1.15 gm of charcoal cautiously and then mixture was further heated at the reflux for 10 minutes, the charcoal was removed by filtration. The filtrate was heated to 60-70 ^{0}C; 100 ml of warm water was added and acidified with dilute acetic acid with good stirring. The product separated as glisting white crystals, and the mixture was placed in a refrigerator for 3hr to complete crystallization. The product was collected on a Buckner funnel and dried overnight at 40^{0}c. The dried product was recrystalized by ethanol and melting point is 300-302^{0}C.

Step -2

Preparation of 2- mercaptobenzimidazole derivatives

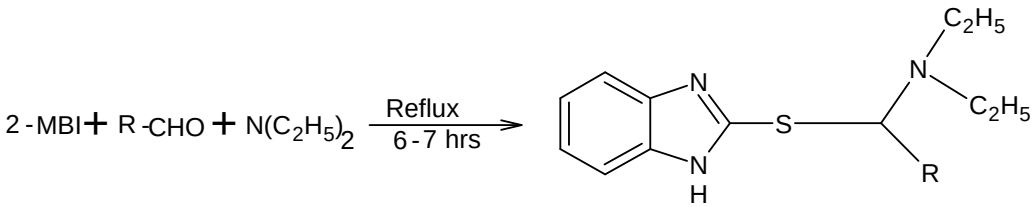
Equimolar quantities (0.02 mol) of 2-Mercaptobenzimidazole and the sec. amine i.e. Diethyl amine (o.o2mol, 1.5ml) were dissolved in (60ml) ethanol, a beaker under perfect ice-cold condition and stirred constantly. Stirred reaction mixture on magnetic stirrer for 1 hr. Aromatic aldehyde (0.02mol) was added slowly to reaction mixture. Refluxed reaction mixture for about 6-7 hrs. .after completion of reaction, kept content in freezer for about overnight. Crystals were formed, Recrystallized with ethanol

Step -1



O-phylenediamine **2-Mercaptcaptobenzimidazole**

Step -2



N-[1H- Benzimidazole-2yl (sulfanyl) substituted (Phenyl) Methyl]-N-ethylethanamine

Table No-1 List of Derivatives

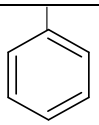
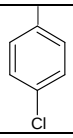
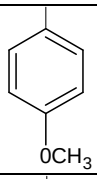
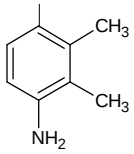
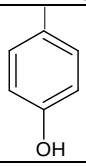
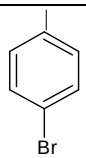
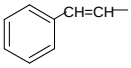
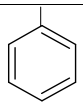
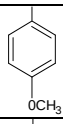
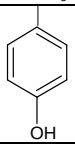
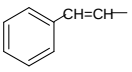
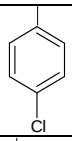
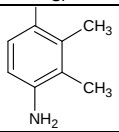
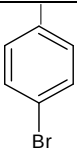
Comp. code	R	Comp. Code	R
1A		1E	
1B		1F	
1C		1G	
1D			

Table No-2 Physiochemical data of derivatives (1A-1G)

Comp. Code	R	Theoretical yield	Practical yield	% Practical yield	Melting point	R.F. value	Molecular formula	Molecular wt.
1A]		6.24 gm.	1.820 gm	29.16	216-218^{0}c	0.53	$C_{18}H_{21}N_3S$	312 gm
1B]		6.86 gm.	1.8 gm	26.63	212-214^{0}c	0.5	$C_{19}H_{23}N_3OS$	341.5 gm
1C]		6.58 gm	2.7 gm	41.03	238-240^{0}c	0.48	$C_{18}H_{21}N_3OS$	327.47 gm
1D]		7.8 gm	3.5 gm	46.66	248-250^{0}c	0.47	$C_{20}H_{23}N_3S$	337.51 gm
1E]		10.02 gm	4.2 gm	41.84	254-256^{0}c	0.41	$C_{18}H_{20}N_3ClS$	345.92 gm
1F]		8.59 gm	2.2 gm	25.77	220-222^{0}c	0.36	$C_{20}H_{26}N_4S$	354.54 gm
1G]		8.30	2.8 gm	28.30	258-260^{0}c	0.5	$C_{18}H_{20}N_3BrS$	390.3 gm

1A] N-[(1*H*-benzimidazol-2-ylsulfanyl) (phenyl) methyl]-*N*-ethylethanamine
Mp 216-218^{0}c, IR (kBr): (cm^{-1}) 3157 (Aldehydic- CH), 744(C-s stretching), 919N-H bending (2^0 amine), ($CDCl_3$-DMSO-d_6): δ (ppm) 6.9-7.4 (m, Ar-8H benzimidazole 4, phenyl 4), 5.6(s 1H of NH), 2.4(s 5H of C_2H_5), 4.21(s 1H of CH).

1B] N-[(1*H*-benzimidazol-2-ylsulfanyl) (4-methoxyphenyl) methyl]-*E*thylethanamine
Mp212-214^{0}c, 3013(Aldehydic CH), 1017(C-O stretching), 740(C-S stre), 916 [N-H bending (2^0 amine)],($CDCl_3$-DMSO-d_6): δ (ppm) 6.9-7.4 (m, Ar-8H benzimidazole 4, phenyl 4), 5.6(s 1H of NH), 2.4(s 5H of C_2H_5), 8.4 (3H of OCH_3).

1c] 4-[(1*H*-benzimidazol-2-ylsulfanyl) (diethyl amino) methyl] phenol
Mp-238-240^{0}c, 3100 (Aldehydic CH), 1180 (C-O stretching), 741(C-S stre), 1351 [N-H bending (2^0 amine)], 1553 (C=N),($CDCl_3$-DMSO-d_6): δ (ppm) 7.1-7.4 (m, Ar-8H benzimidazole 4, phenyl 4), 5.4(s 1H of NH), 2.4(s 5H of C_2H_5), 4.21(s 1H of OH).

1D] *N*-[(1*H*-benzimidazol-2-ylsulfanyl) (4-ethenephenyl) methyl]-*E*thylethanamine
Mp-248-250^{0}c,) 3154(Aldehydic CH, 1463 (C=C stretching, aromatic), 602 (C-S stre) 1263 [N-H bending (2^0 amine)], 1158(C=N), 1596(C-N stretching),($CDCl_3$-DMSO-d_6): δ (ppm) 6.9-7.4 (m, Ar-8H benzimidazole 4, phenyl 4), 5.6(s 1H of NH), 2.4(s 5H of C_2H_5), 4.21(s 1H of CH).

1E] *N*-[(1*H*-benzimidazol-2-ylsulfanyl) (4-chlorophenyl) methyl]-*E*thylethanamine
Mp-254-256^{0}c, 3152(Aldehydic CH), 1465 (C=C stretching, aromatic), 741 (C-S stre) 1351 [N-H bending (2^0 amine)], 660(C-Cl),), ($CDCl_3$-DMSO-d_6): δ (ppm) 6.9-7.4 (m, Ar-8H Benzimidazole 4, phenyl 4), 5.6(s 1H of NH), 2.43(s 5H of C_2H_5), 4.9(s 1H of CH).

1F]-*N*-[(1*H*-benzimidazol-2-ylsulfanyl)(4-aminodimethylphenyl)methyl]-*E*thylethanamine,Mp-220-
222^{0}c,3154(Aldehydic CH), 1654 (C=C stretching, aromatic),600 (C-S stre)1157[N-H bending (2^0 amine)], 1562(C=N) ,),($CDCl_3$-DMSO-d_6): δ (ppm) 7.1-7.4 (m, Ar-8H benzimidazole 4, phenyl 4), 5.4(s 1H of NH), 2.4(s 5H of C_2H_5), 4.9(s 1H of CH).

1G] *N*-[(1*H*-benzimidazol-2-ylsulfanyl)(4-bromophenyl)methyl]-*N*-ethylethanamine
Mp-258-260^{0}c, 3152(Aldehydic CH), 1510 (C=C stretching, aromatic), 739 (C-S stre) 1465[N-H bending (2^0 amine)], 599(C-Br),),($CDCl_3$-DMSO-d_6): δ (ppm) 7.6-8.4 (m, Ar-8H benzimidazole 4, phenyl 4), 6.4(1H of NH), 2.2-2.3(s 5H of C_2H_5), 4.9(s 1H of CH).

Antimicrobial activity
Disc- diffusion method
Inoculation of suspension of bacteria on culture media.

Sterile, non-toxic swab were dipped into the standardized inoculum and then the entire agar surface of the plate was streaked with the swab three times, turning the plate at 60 angle between streaking. Then the streaked inoculum was allowed to dry for 5-15min with lid.

Sterile whatman paper disc were dipped separately into the solutions containing synthesized drug (200µg/ml) and standard drug amoxicillin (10mg/ml) in aseptic condition with the help of sterile forceps and placed on the surface of inoculated culture media after which the plates were kept in refrigerator for 30 min. for the diffusion of the compound from the paper disc into the culture media. After 30 min. the plates were incubated at 37C for 24 hrs. All the synthesized compounds (A-G) were observed for antimicrobial activity against gram positive and gram negative species. Observation were recorded in tables by measuring the zone of inhibition in millimeters.[8-9]

RESULTS AND DISCUSSION

The antimicrobial activities of synthesized compounds (A-G) was carried out by using disc diffusion method and screened against E.coli, Bacillussubtilis, salmonella typhae, styphylococcus aureus microorganism using standard amoxicillin (10mg/ml) and test compounds 200µg /ml in (DMSO).

Compound 1A was shown higher antimicrobial activity against E.Coli, while Compound 1A, 1D, 1G were shown higher antimicrobial activity against S.typhi. Compound 1A&1G were shown Moderate antimicrobial activity against E.Coli, while Compound 1C, 1E were shown Moderate antimicrobial activity against S.aureus and Compound 1C, 1F were shown Moderate antimicrobial activity against S.Typhae.[8-9]

Table No-3 Antimicrobial screening results of synthesized compounds measuring the zone of inhibition in millimeter

Sr. NO.	Comp. No	Name of organisms (zone of inhibition)			
		E.coli	*B.subtilis*	*S. aureus*	*S. typhae*
1.	1A	+ + +	+ +	-	+ + +
2.	1B	+ +	+ +	+	-
3.	1C	+	+	+ +	+ +
4.	1D	-	-	+	+ + +
5.	1E	-	+	+ +	-
6.	1F	-	-	+	+ +
7.	1G	+ +	-	+	+ + +
8.	amoxicillin	+ +	+ + +	+ + +	+ + +

Zone of Inhibition: Below 6 mm- (-) Inactive, 6-9mm (+) slightly active; 9-12mm (+ +) Moderate active, 12-16mm (+ + +) Higher active

CONCLUSION

The series of 2- Mercapto benzimidazole derivatives (1A-1G) were synthesized by using different aromatic Aldehydes other than formaldehyde. Diethyl amine was used as a secondary amine. The reaction mechanism was based upon mannich base reaction.

All synthesized compound shows satisfactory IR, ^{1}H NMR & MASS Spectroscopy.

The presence of aldehydic C-H band 3157 $cm^{(-1)}$ (3200-2700) in IR spectrum confirmed formation of derivatives.

All synthesized compounds were screened for their antimicrobial activity. The compound 1A, 1D & 1G showed the higher Antimicrobial activity.

Acknowledgements
The authors are thankful to Dr. S. K. Mohite from Rajarambapu college of Pharmacy, Kasegaon, Maharashtra, India, for providing research facilities to do work and their constant support during work.

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