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Synthesis and Anticonvulsant Screening of 2 Mercaptobenzimidazole Derivatives

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ABSTRACT

The novel 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. This was main aim of present study. Same derivatives were synthesized by using Microwave technique & reaction time, practice yield were compared. 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. These Compounds were screened for their Anticonvulsant activity. Anticonvulsant activity was evaluated by PTZ induced model.

Keyword- 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 METHOD

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.

Melting points were determined by open capillary tube method and are uncorrected.

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.

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 glinting 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.

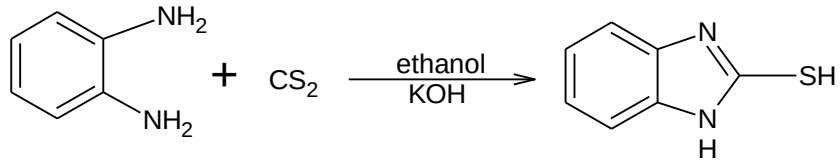
Step -2

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

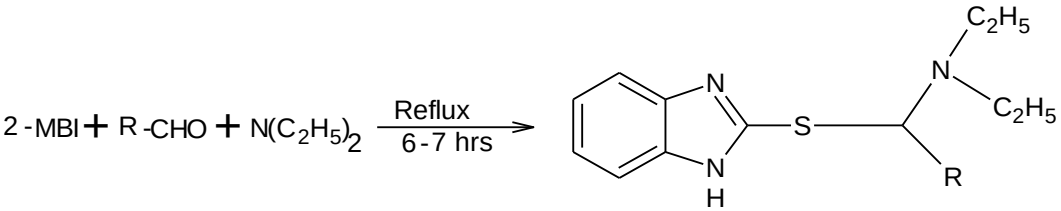
Experimental Design

Step -1



O-phylenediamine 2-Mercaptcaptobenzimidazole

Step -2



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

Table 1 List of Derivative

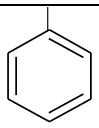
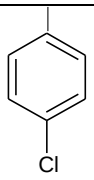
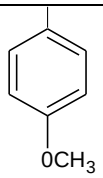
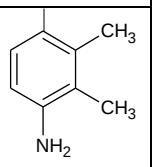
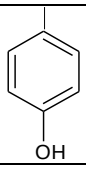
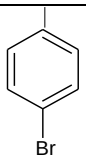
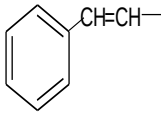
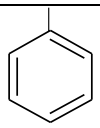
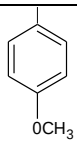
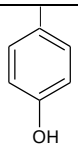
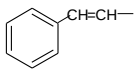
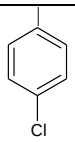
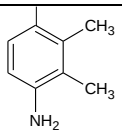
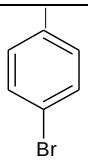
Comp. code	R	Comp. Code	R
1A		1E	
1B		1F	
1C		1G	
1D			

Table 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

Microwave Assisted Technique-

Same derivatives were synthesized by using Microwave technique. Comparative study was done between conventional and Microwave technique with respect of reaction time and practical yield. The reaction time required for microwave technique is less and practical yield was high as compared to conventional technique. This data was shown in Table no 3.

Table 3 Comparative study between Conventional and Microwave Technique

Compound Code	Time & Watt		% yield	
	Conventional	Microwave	Conventional	Microwave
1A	Reflux, 7hrs	210watt,15min	40.16	60
1B	Reflux, 7hrs	210watt,15min	46.13	65.35
1C	Reflux, 7hrs	210watt,15min	51.03	63.77
1D	Reflux, 7hrs	210watt,15min	56.66	65.18
1E	Reflux, 7hrs	210watt,15min	58.84	67.24
1F	Reflux, 7hrs	210watt,15min	54.17	62.09
1G	Reflux, 7hrs	210watt,15min	52.19	61.23

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)

Anticonvulsant activity

Adult albino mice (20-30 g) were used for this study. All the animals were housed in standard Cages, at room temperature (25 ± 3°C), with 12 h dark/12 h light cycles and were fed with Standard pellets and water was provided ad libitum. All animal experiments were conducted under the standard conditions of the Animal Scientific Procedures. The experimental protocol for animal study was approved by the institutional animal ethical committee.

Method

The anticonvulsant activity was carried out by PTZ induced convulsion Method. The synthesized Compound were administered i.p. at a dose of 20mg/kg 30 min before i.p. injection of PTZ (80

mg/kg) and mice were observed for onset of mylonic convulsions, nature and severity of Convulsions. One group received & other group received Diazepam (5mg/kg) as a reference standard .animals was observed for 1 hr.

Statistical analysis

All the results are expressed as mean ± SEM. The values obtained for the above parameters in Synthesized compounds were compared with control group using One-Way ANOVA followed By students "t" test. The values of $P < 0.01$ and $P < 0.001$ were considered to indicate a significant difference between the groups.

RESULTS AND DISCUSSION

The result of anticonvulsant activity of synthesized compounds was given in table. Compound 1B, 1C &1E exhibited significant anticonvulsant effect by increasing the latency and onset of tonic & colonic convulsions. After 1 hr 75% & 67% animals survived at a dose of 20mg/kg of 1E and 1C respectively.

Table 4 Anticonvulsant activity of 2-Mercaptobenzimidazole Derivatives.

Group	Treatment (20mg/kg)	Convulsions		
		Onset of clonic convulsions(sec)	Onset of tonic convulsions (sec)	% protection
Group I	Control (Tween80)	37.18±0.60	344±0.15	0
Group II	Diazepam (5mg/kg)	No convulsions	--	100
Group III	1A	49.32±0.68	265.44±0.76	34
Group IV	1B	54.84±1.18	232.24±0.44	50
Group V	1C	29.44±0.92	318.23±1.76	67
Group VI	1D	47.00±0.94	287.36±1.22	34
Group VII	1E	43.50±0.98	323.47±1.21	75
Group VIII	1F	48.34±0.64	274.22±0.84	+ + +

Values are mean ± SEM, $p \leq 0.05$ as compared to vehicle treated group.

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 anticonvulsant activity. The compound 1E, 1C & 1B showed the higher Anticonvulsant activity.

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