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# 2-Mercaptobenzimidazole Derivatives: Synthesis and Anticonvulsant Activity

**K. Anandarajagopal*[1], Ravi N Tiwari[2], K.G.Bothara[2], J.Anbu Jeba Sunilson[1], C. Dineshkumar[1] and P. Promwichit[1]**

*[1]School of Pharmacy, Masterskill University College of Health Sciences, Jalan Kemacahaya, Taman Kemacahaya, Cheras 43200, Selangor, Malaysia*
*[2]SVKM's NMIMS University, School of Pharmacy & Technology Management, Shirpur 425405, Dhule, Maharashtra*

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## ABSTRACT

*Totally a series of 2-mercaptobenzimidazole derivatives (1A-1J) were synthesized by mannich reaction from 2-mercaptobenzimidazole by reaction with compounds having secondary amine and formaldehyde. The purity of the synthesized compounds was checked by melting point and TLC and their structure was established by various analytical techniques such as IR and $^1$HNMR spectral studies. Anticonvulsant activity was evaluated for newly synthesized 2-mercaptobenzimidazole derivatives by maximum electrical shock induced convulsion method. Most of the synthesized compounds exhibited highly significant anticonvulsant activity.*

**Keywords***:* 2-mercaptobenzimidazole, Mannich reaction, Anticonvulsant

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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 heterocycles [1]. 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 [2], anthelmintic [3], antibacterial [4], antifungal [5], CNS depressant [6], analgesic [7] and anti-inflammatory [8] activities.

2-mercaptobenzimidazole derivatives, one of the most important derivatives of benzimidazole exhibited a wide variety of interesting biological activities such as antimicrobial [9], antihistamine [10], neutropic [11] and analgesic [12] activities. In recent years, the field of anticonvulsant drug development has become quite dynamic, affording many promising research opportunities. Our earlier reports with 2-mercaptobenzimidazole derivatives have driven to the present investigation. In continuation to our work on 2-mercaptobenzimidazoles, the present work focuses on 2-mercaptobenzimidazole derivatives and their anticonvulsant evaluation.

## MATERIALS AND METHODS

### General

Starting materials and reagents used were procured from commercial suppliers. Melting points were determined by open-ended capillary tube on Veego electrical melting point apparatus and were uncorrected. The purity of the compounds were checked by TLC using Silica Gel as stationary phase and chloroform-methanol (9:1) as eluent and the spots were visually detected in an Iodine chamber. The structure of the synthesized compounds was elucidated by IR spectra in $\upsilon_{max}$ ($cm^{-1}$) on FT-IR (Shizmadu-8400 series) using KBr disc technique and $^1H$ NMR spectra in δ units (ppm) relative to an internal standard of tetramethylsilane on $^1H$ NMR (Brucker 400 MHz) in DMSO-$d_6$. Elemental analyses for final compounds were performed on Carlo Erba 108 and the observed values were within the acceptable limits (±0.4%). The synthetic method is depicted in Scheme 1.

### Procedure for the synthesis of novel 2-mercaptobenzimidazole derivatives (1A-1J)

2-mercaptobenzimidazole was synthesized by the method described by Maw-Ling Wang *et al* [13]. Equimolar quantities (0.01 mol) of 2-mercaptobenzimidazole and the respective compounds having secondary amine were dissolved in methanol (30 mL) in a beaker under perfect ice-cold condition and stirred constantly. To this solution, formaldehyde (0.01 mol) was added slowly and heated to reflux for 3 h. The content was kept overnight in the freezer. The corresponding crystals of mannich base of 2-mercaptobenimidazole obtained was recrystallized from alcohol [14].

### Physical data of newly synthesized 2-mercaptobenzimidazole derivatives

**2-(isoindol-1,3-dione-N-methyl)mercapto-1*H*-benzimidazole (1A)**

Yield 69%; m.p. 143-145$^0$C; $R_f$ 0.4836. IR (KBr, $cm^{-1}$): 3366 (NH), 3061 (ArCH), 1751 (C=O), 1601 (C=N), 1463 ($CH_2$), 1351 (C-N). $^1H$ NMR (DMSO-d6, ppm)δ: 5.29 (s, 1H, NH), 5.78 (s, 2H, $CH_2$), 7.26 - 8.06 (m, 8H, ArH). Anal. Calc. for $C_{16}H_{11}N_3O_2S$: C 62.12, H 3.58, N 13.58. Found: C 62.10, H 3.56, N 13.56%.

**2-(diphenylamine-N-methyl)mercapto-1*H*-benzimidazole (1B)**

Yield 72%; m.p. 135-138$^0$C; $R_f$ 0.6211. IR (KBr, $cm^{-1}$): 3354 (NH), 3113 (ArCH), 1605 (C=N), 1461 ($CH_2$), 1354 (C-N). $^1H$ NMR (DMSO-d6, ppm)δ: 4.72 (s, 2H, $CH_2$), 5.12 (s, 1H, NH), 6.76 – 7.98 (m, 14H, ArH). Anal. Calc. for $C_{20}H_{17}N_3S$: C 72.48, H 5.17, N 12.68. Found: C 72.42, H 5.14, N 12.64%.

**2-(N-phenylacetamide-N-methyl)mercapto-1*H*-benzimidazole (1C)**
Yield 74%; m.p. 164-166$^0$C; $R_f$ 0.3288. IR (KBr, cm$^{-1}$): 3356 (NH), 3021 (ArCH), 1663 (C=O), 1598 (C=N), 1463 ($CH_2$), 1423 ($CH_3$), 1352 (C-N). $^1$H NMR (DMSO-d6, ppm)δ: 2.38 (s, 3H, $CH_3$), 5.14 (s, 2H, $CH_2$), 5.32 (s, 1H, NH), 7.16 – 7.76 (m, 9H, ArH). Anal. Calc. for $C_{16}H_{15}N_3OS$: C 64.62, H 5.08, N 14.13. Found: C 64.58, H 5.06, N 14.10%.

**2-(indol-N-methyl)mercapto-1*H*-benzimidazole (1D)**
Yield 72%; m.p. 113-115$^0$C; $R_f$ 0.5434. IR (KBr, cm$^{-1}$): 3339 (NH), 3063 (ArCH), 1616 (C=N), 1461 ($CH_2$), 1347 (C-N). $^1$H NMR (DMSO-d6, ppm)δ: 5.18 (s, 1H, NH), 5.48 (s, 2H, $CH_2$), 6.64 – 7.82 (m, 10H, ArH). Anal. Calc. for $C_{16}H_{13}N_3S$: C 68.79, H 4.69, N 15.04. Found: C 68.74, H 4.66, N 14.98%.

**2-(piperazin-N-methyl)mercapto-1*H*-benzimidazole (1E)**
Yield 78%; m.p. 184-186$^0$C; $R_f$ 0.7128. IR (KBr, cm$^{-1}$): 3352 (NH), 2996 (ArCH), 2910 (CH), 1616 (C=N), 1457 ($CH_2$), 1339 (C-N). $^1$H NMR (DMSO-d6, ppm)δ: 1.94 (s, 1H, NH), 2.34 (t, 4H, $CH_2$), 2.77 (t, 4H, $CH_2$), 4.31 (s, 2H, $CH_2$), 5.11 (s, 1H, NH), 7.16 – 7.88 (m, 4H, ArH). Anal. Calc. for $C_{12}H_{16}N_4S$: C 58.04, H 6.49, N 22.56. Found: C 58.00, H 6.44, N 22.52%.

**2-(morpholin-N-methyl)mercapto-1*H*-benzimidazole (1F)**
Yield 76%; m.p. 130-132$^0$C; $R_f$ 0.6624. IR (KBr, cm$^{-1}$): 3324 (NH), 3060 (ArCH), 2950 (CH), 1610 (C=N), 1448 ($CH_2$), 1345 (C-N). $^1$H NMR (DMSO-d6, ppm)δ: 2.76 (t, 4H, $CH_2$), 3.70 (t, 4H, $CH_2$), 3.90 (s, 2H, $CH_2$), 5.13 (s, 1H, NH), 7.27 – 7.36 (m, 4H, ArH). Anal. Calc. for $C_{12}H_{15}N_3OS$: C 57.81, H 6.06, N 16.85. Found: C 57.78, H 6.02, N 16.82%.

**2-((4-hydroxy-N-phenylacetamide)-N-methyl)mercapto-1*H*-benzimidazole (1G)**
Yield 68%; m.p. 173$^0$C; $R_f$ 0.4221. IR (KBr, cm$^{-1}$): 3453 (OH), 3283 (NH), 3010 (ArCH), 1750 (C=O), 1226 (ArOH), 1359 (C-N), 1447 ($CH_3$), 1459 ($CH_2$) 1613 (C=N). $^1$H NMR (DMSO-d6, ppm)δ: 2.38 (s, 3H, $CH_3$), 5.22 (s, 1H, OH), 5.65 (s, 2H, $CH_2$), 5.08 (s, 1H, NH), 6.78 – 7.42 (m, 8H, ArH). Anal. Calc. for $C_{16}H_{15}N_3O_2S$: C 61.32, H 4.82, N 13.41. Found: C 61.28, H 4.78, N 13.42%.

**2-(2,4,5-triphenyl-1*H*-imidazol-N-methyl)mercapto-1*H*-benzimidazole (1H)**
Yield 66%; m.p. 189-192$^0$C; $R_f$ 0.6711. IR (KBr, cm$^{-1}$): 3283 (NH), 3063 (ArCH), 1457 ($CH_2$) 1589 (C=N), 1357 (C-N). $^1$H NMR (DMSO-d6, ppm)δ: 5.08 (s, 1H, NH), 5.77 (s, 2H, $CH_2$), 7.12 – 8.28 (m, 19H, ArH). Anal. Calc. for $C_{29}H_{22}N_4S$: C 75.95, H 4.84, N 12.22. Found: C 75.92, H 4.82, N 12.18%.

**2-(N-phenylbenzamide-N-methyl)mercapto-1*H*-benzimidazole (1I)**
Yield 78%; m.p. 118-120$^0$C; $R_f$ 0.6268. IR (KBr, cm$^{-1}$): 3285 (NH), 3019 (ArCH), 1751 (C=O), 1460 ($CH_2$), 1359 (C-N), 1599 (C=N). $^1$H NMR (DMSO-d6, ppm)δ: 4.86 (s, 2H, $CH_2$), 5.75 (s, 1H, NH), 6.92 - 7.98 (m, 14H, ArH). Anal. Calc. for $C_{21}H_{17}N_3OS$: C 70.17, H 4.77, N 11.69. Found: C 70.14, H 4.76, N 11.66%.

**2-(indole-2,3-dione-N-methyl)mercapto-1*H*-benzoimidazole (IJ)**
Yield 72%; m.p. 160$^0$C; $R_f$ 0.3128. IR (KBr, cm$^{-1}$): 3349 (NH), 3012 (ArCH), 1729 (C=O), 1462 ($CH_2$), 1615 (C=N), C-N (1333). $^1$H NMR (DMSO-d6, ppm)δ: 4.88 (s, 1H, NH), 5.32 (s, 2H, $CH_2$), 6.94 - 8.26 (m, 8H, ArH). Anal. Calc. for $C_{16}H_{11}N_3O_2S$: C 62.12, H 3.58, N 13.58. Found: C 62.10, H 3.56, N 13.54%.

**Anticonvulsant Activity**
**Animals**
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 (AKCP/CPCSEA/509/F(1h)/2007).

**Method**
The anticonvulsant activity was carried out by maximal electrical shock induced convulsion method [15]. Mice were treated with control (2% w/v Tween 80), titled compounds (20 mg/mL, ip) and standard drug, phenytoin (5 mg/mL, ip) [16]. After 30 min, the animals were subjected to electro shock through ear electrodes of 150 mA for 0.2 sec by electroconvulsiometer. The duration of time for extensor response was noted. The reduction in the time or abolition of the hind limb tonic extension component of the seizure was defined as protection in the MES test. Similarly readings for control and standard were also noted and the readings are subjected to preliminary statistical analysis and tabulated in Table 1. The anticonvulsant activity was measured in terms of percentage protection of extensor phase.

**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 [17]. The values of $P < 0.01$ and $P < 0.001$ were considered to indicate a significant difference between the groups.

## RESULTS AND DISCUSSION

A series of 10 novel mannich bases of 2-mercaptobenzimidazole derivatives were synthesized using mannich reaction by the reaction between compounds having secondary amine and formaldehyde. The formation of new chemical analogues was indicted by the melting point and $R_f$ value. The structure of the synthesized compounds was established by spectral (IR and $^1$H NMR) as well as elemental analysis data. The NH band (3283 - 3356 cm$^{-1}$) and NH proton signal (4.88 – 5.75 ppm) of 2-mercaptobenzimidazole in IR and $^1$H NMR spectrum respectively in all the synthesized compounds confirmed the reaction was not taken at 1*H* position. The presence of $CH_2$ stretching (1448 - 1463 cm$^{-1}$) and $CH_2$ proton signal (3.70 – 5.78 ppm) in IR and $^1$H NMR spectrum respectively together with the absence of SH proton of 2-mercaptobenzimidazole confirmed the formation of the titled compounds.

**SCHEME-1**

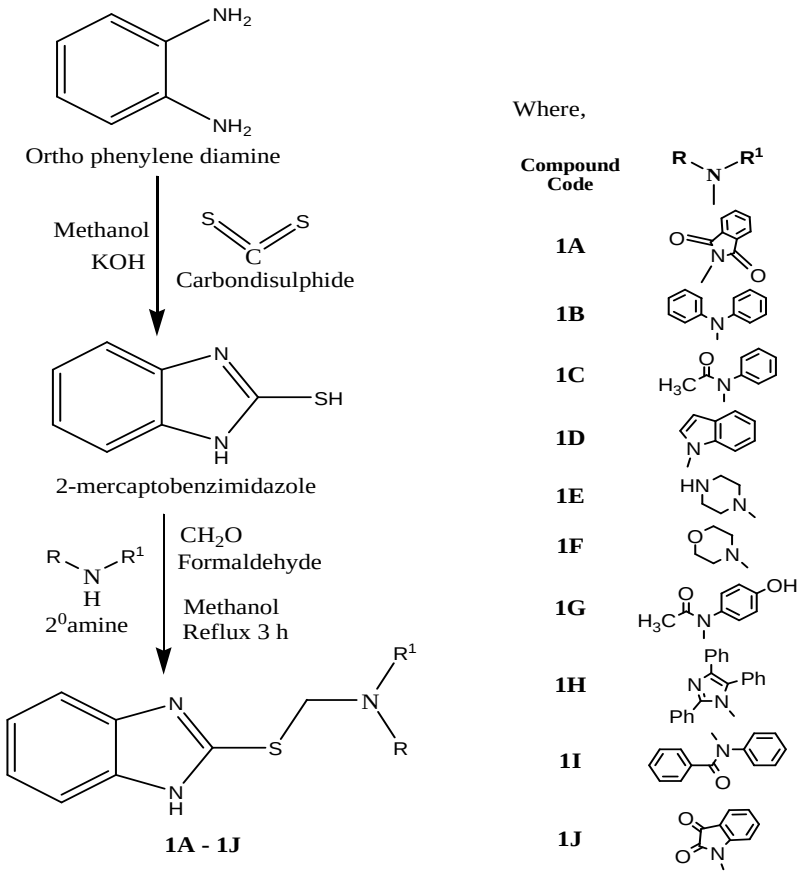


**Table 1: Anticonvulsant activity of titled compounds**

| Compound code | Duration of time of Extensor Phase (Sec) Mean ± SEM | % Protection |
|---|---|---|
| **Control** | 18.47 ± 0.82 | - |
| **Standard** | 2.43 ± 1.23** | 86.84 |
| **1A** | 13.65 ± 1.11* | 26.10 |
| **1B** | 4.44 ± 0.89** | 75.96 |
| **1C** | 11.36 ± 0.18* | 38.49 |
| **1D** | 3.23 ± 1.40** | 82.51 |
| **1E** | 2.59 ± 0.32** | 85.98 |
| **1F** | 3.65 ± 1.11** | 80.24 |
| **1G** | 10.68 ± 0.72** | 42.76 |
| **1H** | 4.76 ± 1.04** | 74.22 |
| **1I** | 3.32 ± 0.62** | 82.02 |
| **IJ** | 5.76 ± 1.04** | 68.81 |

Values are Mean ± SEM, *P < 0.01 and **P < 0.001 statistically significant from control group *(n=6)*

All the synthesized compounds have a tendency to causing a significant reduction in duration of the stimulated extensor phase. All the synthesized compounds at a dose of 20 mg/kg, ip exhibited anticonvulsant activity (26.10 – 85.98 % protection) against maximum electrical shock induced convulsion compared with the standard drug phenytoin (Table 1). Compounds 1E, 1F and 1I exhibited excellent anticonvulsant activity

## CONCLUSION

The present study concluded that the experimental procedures make this methodology a better modesty for the synthesis of the titled compounds for possible anticonvulsant activity. All the tested compounds with structural modifications exhibited promising anticonvulsant activity. From these findings, it can be suggested that the designing of new chemical analogues with 2-mercaptobenzimidazoles lead the necessity for the development of further research.

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