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# SYNTHESIS AND EVALUATION OF 2-MERCAPTOTHIAZOLE-PROPIONIC ACID DERIVATIVES OF BIOLOGICAL INTEREST

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## ABSTRACT

The title compounds have been synthesized from 4-phenyl-2-mercaptothiazole **(I)**, which was synthesized by the reaction of phenacyl bromide and ammonium dithiocarbamate. This compound **(I)** on treatment with various N-substituted β-chloropropionamide **(II)** furnishes the title compounds. The structures of these compounds were established on the basis of spectral data. All these compounds were screened for their antibacterial and antifungal activities. These compounds possessed moderate antibacterial and antifungal activities at compared with standard drugs.

**Key words:** 4-Phenyl-2-mercaptothiazoles, Antibacterial activity, Antifungal activity.

## INTRODUCTION

Thiazole nucleus is the centre of attraction over the decades for the development new chemical entities having biological and industrial applications. This is due to its ease of preparation, lipid solubility coupled with hydrophilicity and non-carcinogenic nature[1]. These thiazole derivatives have been employed as an antipsychotics[2], antimalarials[3] and antibacterials[4].

Mercaptothiazole plays a vital role in pharmaceutical practice due to its well built in toxophoric (S-C=N) unit. These compounds were found to possess wide range of biological activities[5] such as fungicidal[6], insecticidal[7], CNS stimulant[8], and anthelementic[9].

Extensive literature survey and these reports led us to synthesize the title compounds and evaluate their antibacterial and antifungal activities.

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The reactions sequence leading to formation of different title compounds is outlined in **Scheme I**. Δ- 4 –thiazoline -2- thione **(I)** was synthesized by using phenacyl bromide and ammonium dithiocarbamate. Later, it was treated with various N-substituted β – chloropropionamides **(II)** to form β – (4-phenyl-2-thiazolyl) mercapto-N-substituted propionamides **(III)**. Phenacyl bromide[1o], ammonium dithocarbamate[11], β-chloropropionyl chloride[12] and β - chloropropionamide[13,14] were prepared by known procedures.

## EXPERIMENTAL

### Materials and methods

All the melting points and boiling points were determined by open capillary method in liquid paraffin bath and uncorrected. All the solvents were used after distillation. Chloropropionic acid, aniline, morpholine, p-chloroanline, benzylamine, n-propylamine, pyrolidine and acetophenone, were purchased from S.D. Fine Chemicals, Mumbai. Liquid bromine was used after drying over conc. $H_2SO_4$. Silica gel G Plates (3 x 8 cm) were used for TLC and spots located by iodine vapors in a chamber. Column chromatography was performed on a neutral alumina column (2.5 x 45 cm) using appropriate eluent.

The IR spectra (KBr/nujol) were recorded on Perkin-Elmer FT-IR spectrometer and the values are expressed in $cm^{-1}$. UV spectra were determined on Shimadzu UV – Visible Recording Spectrometer, UV-160 TCC 240A. $^1H$ NMR spectra ($CDCl_3$) were taken on Brucker AC 200 MHz FT using TMS as an internal reference compound.

### Method of preparation

### Prepration of △-4-thiazoline-2-thione (I)

To a suspension of 24.8 g of ammonium dithiocarbamate in 50 mL of absolute ethanol was added with shaking and cooling a mixture of 20.4 g of phenacyl bromide and 100 mL of absolute ethanol. After the initial reaction had subsided, the flask was stoppered and allowed to stand at room temperature for overnight.

Next day, the reaction mixture was refluxed for 1 hour to complete the reaction and solvent was removed under reduced pressure. The crude solid product was diluted with 200 mL of water, filtered and dried. This product was dehydrated by heating with 150 mL of benzene and collecting the water in a Dean and Stark trap. The residue, obtained by evaporating the benzene, was treated with 150 mL of 5% sodium hydroxide and filtered. The filtrate was cooled in an ice-bath and acidified with dilute hydrochloric acid. The resulting white precipitate was washed with water and dried. It was then recrystallised from aqueous ethanol.

### General preparation of n- substituted –β-chloropropiomnamides (II a-f)

### For primary amines

Appropriate amine (0.05 mol) was dissolved in a mixture of 25 mL of glacial acetic acid and 25 mL of saturated sodium acetate. It was then cooled to 5° C and to this cold solution, chloride (0.06 mol) was added dropwise, with stirring at 0-5° C. Then, it was allowed to stay at room temperature. The crude product that separated was filtered, washed with 50% acetic and water. It was then recrystallised from 50% alcohol.

### For secondary amines

Appropriate amine (0.1 mol), in 20 mL of ether was added at 0-5° C to β-chloropropionyl chloride (0.12 mol) in ether, dropwise with stirring and it was left at room temperature for 1 hr. Then, ether was removed under reduced pressure and crude viscous liquid was washed with petroleum ether. It was used directly in the next reaction.

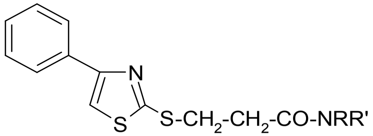
### Preparation of β- (4-phenyl-2-thiazolyl) mercapto-n-substituted propionamides (III a-f)

To solution of metallic sodium, 0.61 g (0.025 moles) in absolute ethanol (50 mL), 5.0 g (0.025 moles) of 4-phenyl-2-mercaptothiazole was added with cooling. Then 0.025 mole of N-substituted β-chloropropionamide was added to this solution at room temperature with stirring. Then the mixture was refluxed for 8-12 hours. It was then cooled and filtered to remove sodium chloride. Then the solvent was removed under diminished pressure and product that obtained was purified by recrystallisation from alcohol. The physicochemical characteristics and spectral data of various compounds **(IIIa-f)** are described in Table 1 and Table 2, respectively.

### Antibacterial activity

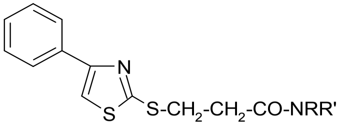
The compounds, **(IIIa-f)** were screened against *P. euroginose*, *E. coli* and *S. aureus* by cup plate method[15]. As compared to the standard drug norfloxacin, these compounds showed moderate activity at concentrations 100 μ/mL and 150 μ/mL (Table 3)

**Table 1. Physicochemical data for (III a-f)**

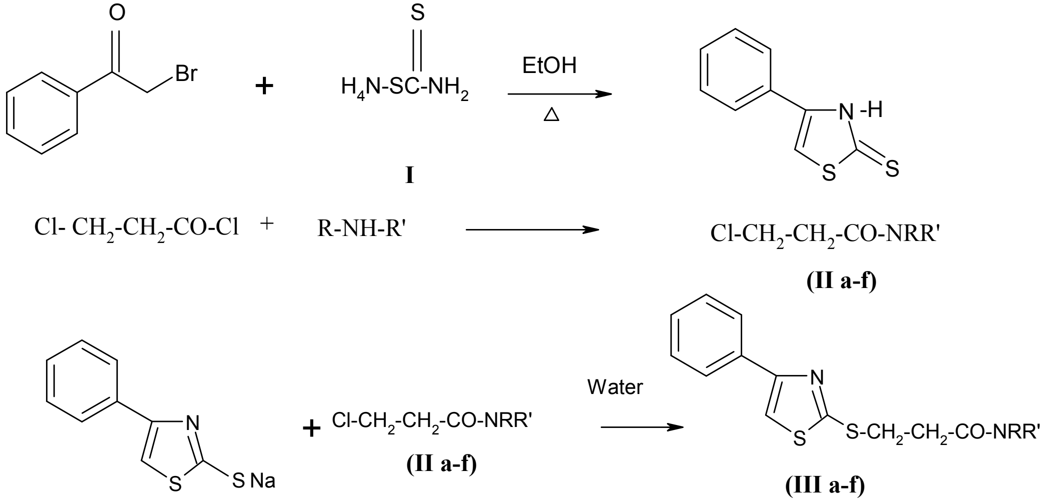


| Comp. | R | R' | M. P. (ºC) | Yield (%) | Nature | Mol. formula | Elemental analysis | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Calc (%)<br>Found (%) | | |
| | | | | | | | C | H | N |
| **III a** | H | $C_6H_5$ | 80 | 73.29 | Pale yellow needles | $C_{17}H_{14}N_2OS_2$ | 63.52 | 4.70 | 8.23 |
| | | | | | | | 63.20 | 4.82 | 8.50 |
| **III b** | H | p- C1$C_6H_5$ | 110 | 76.28 | Pale yellow shining needles | $C_{17}H_{13}N_2OS_2Cl$ | 57.61 | 4.00 | 7.47 |
| | | | | | | | 64.40 | 5.08 | 7.90 |
| **III c** | H | $CH_2C_6H_5$ | 108-109 | 76.5 | Pale yellow shining needles | $C_{18}H_{16}N_2OS_2$ | 64.40 | 5.08 | 7.90 |
| | | | | | | | 64.50 | 5.28 | 7.99 |
| **III d** | H | n-$C_3H_7$ | 92-94 | 81.01 | Pale yellow flakes | $C_{14}H_{16}N_2OS_2$ | 58.82 | 5.88 | 9.15 |
| | | | | | | | 59.11 | 5.66 | 9.00 |
| **III e** | RR' = Pyrolidine-1-yl | | 146-148 | 57.31 | Light yellow granules | $C_{15}H_{16}N_2OS_2$ | 60.37 | 5.66 | 8.80 |
| | | | | | | | 60.30 | 5.61 | 8.86 |
| **III f** | RR' = Morpholine-1-yl | | 168-170 | 53.61 | Pale yellow granules | $C_{15}H_{16}N_2O_2S_2$ | 57.48 | 5.38 | 8.38 |
| | | | | | | | 57.59 | 5.45 | 8.25 |

**Table 2. Spectral data for (III a-f)**



| Comp | R | R' | IR ($cm^{-1}$) KBr | | | | $^1H$ NMR (ppm) $CDCl_3$ |
|---|---|---|---|---|---|---|---|
| | | | vNH | vCO | vC = N | ArH | |
| **III a** | H | $C_6H_5$ | 3272 | 1655 | 1535 | 710 | 7.94-7.05 (m, 12,H, 2X$C_6H_5$H+NH); 3.60 (t, 2H, $COCH_2$); 2.59 (t, 2H,S-$CH_2$); |
| **III b** | H | p-Cl$C_6H_5$ | 3250 | 1655 | 1542 | 718 and 828 | - |
| **III c** | H | $CH_2C_6H_5$ | 3310 | 1646 | 1532 | 705 and 725 | 7.81,7.39-7.24,6.10 (m, 12H, 2x$C_6H_5$ +5-H+NH); 4.40 (s, 2H, $CH_2$,of benzyl); 3.55(t, 2H,$COCH_2$); 2.79(t, 2H,S-$CH_2$). |
| **III d** | H | n-$C_3H_7$ | 3326 | 1647 | 1536 | 684 and 738 | - |
| **III e** | RR' = Pyrolidine-1-yl | | - | 1644 | 1556 | 684 and 738 | - |
| **III f** | RR' = Morpholine-1-yl | | - | - | - | 680 and 744 | - |



Where,

(a) R = H; R' = $C_6H_5$
(b) R = H; R' = p-Cl$C_6H_4$
(c) R = H; R' = $CH_2C_6H_5$
(d) R = H; R' = n-$C_3H_7$
(e) RR1 = Pyrolidine-1-yl
(f) RR1 = Morpholine-1-yl

**Scheme I**

**Table 3. Antibacterial activity of compounds (III a-f)**

| **Comp.** | **R** | **R'** | **Zone of inhibition (mm)** | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | ***P. aeuroginose*** | | ***S. aureus*** | | ***E. coli*** | |
| | | | **100 (µg/mL)** | **150 (µg/mL)** | **100 (µg/mL)** | **150 (µg/mL)** | **100 (µg/mL)** | **150 (µg/mL)** |
| **III a** | H | $C_6H_5$ | 07 | 08 | 14 | 16 | 02 | 03 |
| **III b** | H | p-C1$C_6H_5$ | 09 | 11 | 13 | 15 | 03 | 03 |
| **III c** | H | $CH_2$-$C_6H_5$ | 06 | 07 | 12 | 13 | 01 | 01 |
| **III d** | H | n-$C_3H_7$ | 04 | 05 | 10 | 11 | 01 | 01 |
| **III e** | RR' = Pyrolidine-1-yl | | 08 | 11 | 19 | 20 | 04 | 04 |
| **III f** | RR' = Morpholine-1-yl | | 09 | 12 | 23 | 26 | 05 | 07 |
| **Standard** | Norfloxacin | | 18 | 23 | 45 | 50 | 10 | 15 |

**Table 4. Antifungal activity of compounds (III a-f)**

| Comp | R | R’ | Zone of inhibition in mm | | | |
|---|---|---|---|---|---|---|
| | | | *C. albicans* | | *A. niger* | |
| | | | 100 µg/mL | 150 g/mL | 100 µg/mL | 150 g/mL |
| **III a** | H | $C_6H_5$ | 06 | 06 | 05 | 06 |
| **III b** | H | p-$C1C_6H_5$ | 08 | 09 | 06 | 07 |
| **III c** | H | $CH_2C_6H_5$ | 07 | 08 | 03 | 03 |
| **III d** | H | n-$C_3H_7$ | 07 | 07 | 04 | 04 |
| **III e** | RR’ = Pyrolidine - 1-yl | | 09 | 10 | 08 | 09 |
| **III f** | RR’ = Morpholine - 1-yl | | 10 | 12 | 10 | 10 |
| **Standard** | Griseofulvin | | 34 | 38 | 32 | 36 |

### Antifungal activity

The synthesized compounds were screened for antifungal activity using cup plate method[16] against *C. albicans* and *A. niger*. These compounds showed moderate activity at concentrations 100 µ/mL and 150 µ/mL (Table 4)

## RESULTS AND DISCUSSION

The synthesized compounds were evaluated for both; antibacterial and antifungal activities. These compounds possessed moderate antibacterial and antifungal activities at 100 µg/mL and 150 µg/mL concentrations as compared with norfloxacin and griseofulvin, respectively.

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