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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF ALKYL THIOARYL SUBSTITUTED BENZIMIDAZOLE DERIVATIVES

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ABSTRACT

A new series of 2-substituted alkyl thioarylbenzimidazole derivatives were synthesized by condensing o-phenylenediamine with aryl and naphthyl thioglycolic acid. All these compounds were characterized by means of their melting point, HPLC, IR and ^{1}H NMR spectroscopic data. The synthesized compounds **(i to l)** have been screened for *in vitro* antibacterial activity against a variety of bacterial strains. Gram-negative strain of bacteria used were *Klebsiella* and *E. Coli* while gram-positive bacterial strain used was *S. aureus* and *E. fecalis* The activity was determined using MIC. Ciprofloxacin was used as standard (2 µg/mL). The compounds have shown varying degree of antibacterial and antifungal activity.

Key words: Thioaryl, Benzimidazole, Thioglycolic, Naphthyl thioglycolic.

INTRODUCTION

Compounds bearing benzimidazole moiety are reported to possess a number of interesting biological activities such as antitubercular[1], anticancer[2,3], anthelmintic[4], antiallergic[5,6], antioxidant[7–9], antihistaminic[10] and antimicrobial[11,12]. In addition, some thiourea derivatives have been reported as antimycobacterial[13] and antimicrobial[14].

A wide variety of benzimidazole derivatives have been described for their broad-spectrum pharmaceutical applications. We made efforts in order to make new 2-substitued derivatives of benzimidazole[15] by condensing o-phenylenediamine with aryl and naphthyl thioglycolic acids. This provides a process for the preparation of benzimidazole derivatives exhibiting excellent pharmaceutically useful properties. The development of new and different antimicrobial agent has been a very important step and much of the research programs are directed towards the design of new and available drugs, because of the

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unsatisfactory status of present treatment of microorganisms, drug side effects and the acquisition by the infecting organisms of resistance to the present drug[16].

A review of the literature reveals that many effective antimicrobial agents have heterocyclic system in their molecule[17]. Thiabendazole has been found to be effective in the treatment of helmintic diseases with good clinical efficiency in topical therapy of dermatophytic infections[18] and several benzimidazoles derivatives have been reported for antimicrobial activity[19].

EXPERIMENTAL

Chemicals and solvents were reagent grade and used without further purification. The part of the input chemicals were obtained from M/S Gharda Chemicals Ltd. Mumbai. Melting points were determined on a LABINDIA MR.VIS visual melting range apparatus and are uncorrected. Purity of the compounds was checked by reverse phase system using Shimadzu SPD 10AV HPLC. Solvent system (mobile phase) used was acetonitrile–methanol-water (70:15:15 v/v) and 240 nm. HPLC column used was C-18 and flow rate maintained was 1 mL/min. IR spectra in KBr (cm^{-1}) were recorded on Schimidzu FTIR-410 series spectrophotometer and ^1H NMR spectra were recorded on Bruker 200 MHz (DMSO-d_6) using TMS as internal standard (chemical shifts are expressed in δ ppm.)

General procedure for the preparation of aryl thioglycolic acid (e-g)

The aryl thioglycolic acids were prepared as per the literature for the experiments. A mixture of 0.1 mole of aromatic amine (**a** or **b** or **c**) and 100 mL of 5 N HCl was taken together in a 4 neck round bottom flask and heated to 50-55°C and maintained for 1 hr. This was then cooled to zero to below 0.0°C and slow addition of 0.1-0.11 moles of $NaNO_2$ was done below surface and maintaining above temperature. The obtained diazotised mass was filtered to remove some insoluble particles and to clear solution, 100 mL of tetrachloro ethylene solvent was added. This mixture was kept under stirring and 0.1-0.11 moles of thioglycolic acid solution was slowly added at 0.0-5.0°C. Then temperature was slowly brought up to 30°C over 3 hrs. and maintained for 2-2.5 hour till complete evolution of nitrogen. The product precipitated out as pale yellow fluffy slurry. This was then cooled to 0.0-5.0°C and the slurry was filtered. The solid cake was washed with 100 mL of tetrachloro ethylene followed by water. The crude product obtained was crystallized with 40 mL of toluene.

The isolated product (s) were analyzed by HPLC.

Purity obtained = 96- 98 %

Product (s) isolated were having melting points matching with literature values.

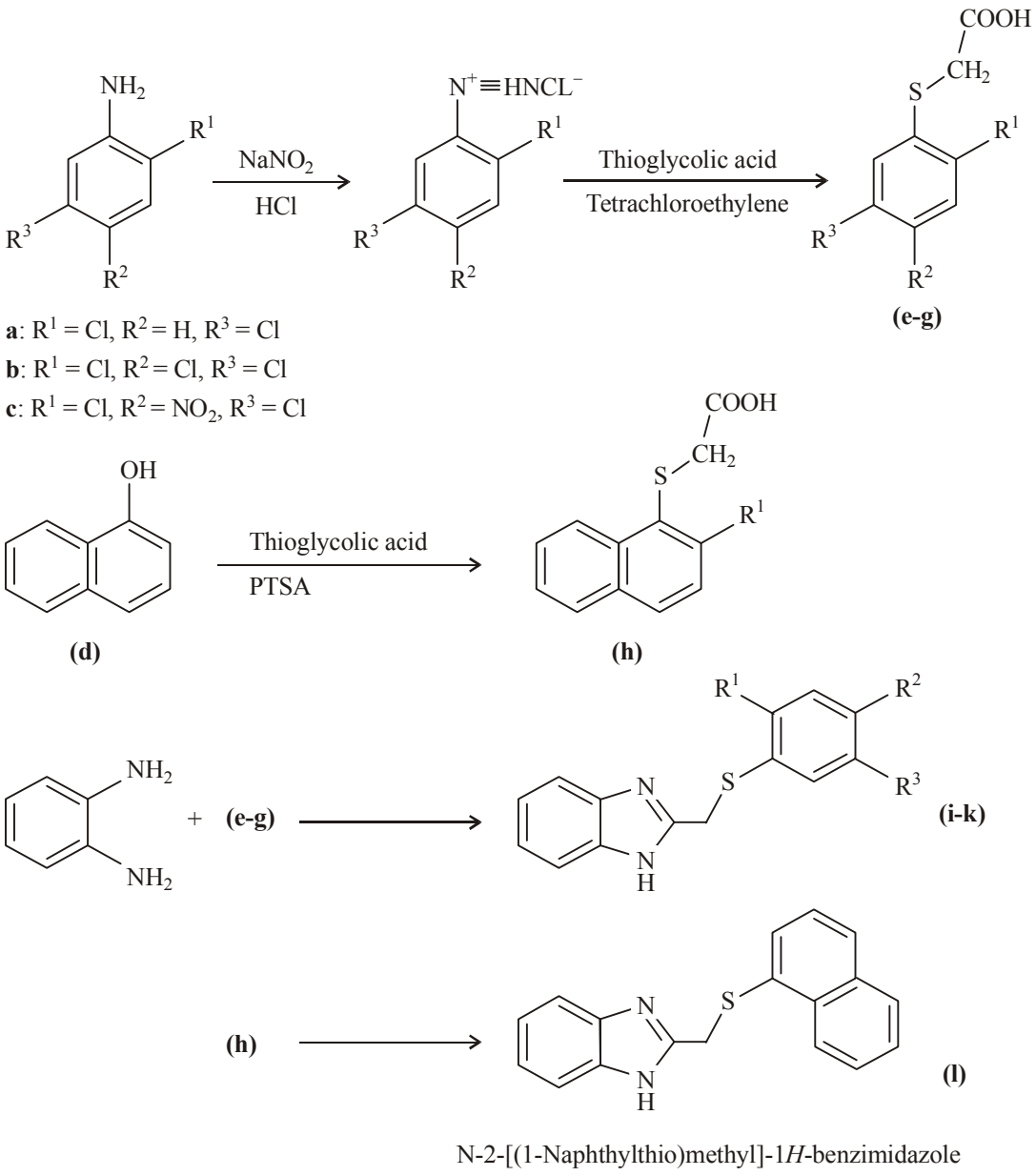

Fig. 1: General scheme for the synthesis of 2-substitued alkyl thioaryl and naphthylthio methyl-1H-benzimidazole.

Preparation of (1-naphthylthio) acetic acid (h)

In a 1.0 L 4 neck round bottom flask, 1.0 g mole of α-naphthol, 0.3 moles of p-toluenesulphonic acid and 1.1 moles of 80.0 % thioglycolic acid were taken. This mixture was heated to 108-110°C under nitrogen atmosphere for 15 hrs. This was cooled to 80°C and further, 500 mL water was added. The mass was filtered and washed with water to displace any unreacted thioglycolic acid.

Crude yield = 85.0 %.

Crude material was further crystallized from aqueous methanol.

Melting point = 106°C. (Literature: 106-107°C)

General procedure for the preparation of 2-[(arylthio) methyl]-1H–benzimidazole (i-k)

A mixture of 0.025 mole of o-phenylenediamine, 50 mL water and 0.029 mole of arylthioacetic acid (**e** or **f** or **g**), was taken in 250 mL 3 neck round bottom flask with magnetic stirring and reflux system. It was refluxed for 4 hrs at 98-100°C. Reaction mass was blue –violet in color with oily mass at bottom under reflux condition. It was cooled to 35°C and on cooling, a solid precipitated out. The mass was filtered and washed with water. A slurry was prepared of this solid mass with 50 mL water and $NaHCO_3$ was added to neutralize unreacted (excess) acid. Again it was filtered and washed with water. Crude product was crystallized with 40 mL methanol. Product was light grey to pale white crystals.

Preparation of 2-[(1-naphthylthio) methyl]-1H-benzimidazole (l)

A mixture of 0.025 mole of o-phenylenediamine, 50 mL water and 0.03 mole of 1-naphthylthioacetic acid **(h)**, was taken in 250 mL, 3 neck round bottom flask with magnetic stirring and reflux system. It was refluxed for 3 hrs at 98-100°C. Reaction mass was blue – violet in color with oily mass at bottom under reflux condition. It was cooled to 35°C and on cooling, a solid precipitated out. The mass was filtered and washed with water. A slurry was prepared of this solid mass with 100 mL water and $NaHCO_3$ was added to neutralize unreacted (excess) acid. This was again filtered and washed with water. Crude product was crystallized with 20 mL methanol. The product was yellowish solid.

Biological activity study: Antibacterial and antifungal activity

The synthesized compounds (**i** to **l**) have been screened for *in vitro* antibacterial activity against a variety of bacterial strains. Gram-negative strain of bacteria used were *Klebsiella* and *E. Coli,* while gram-positive bacterial strain used was *S. aureus* and *E. fecalis*

The activity was determined using MIC. Ciprofloxacin was used as standard (2 µg/mL). The compounds have shown varying degree of antibacterial activity. The synthesized compounds (**i** to **l**) have also shown varying degree of antifungal activity.

Table 1: Chemical data of the compounds (i-l)

Comp.	R^1	R^2	R^3	Formula	m.p. (°C)	Yield (%)
i	-Cl	-H	-Cl	$C_{14}H_{10}Cl_2N_2S$	161	62
j	-Cl	-Cl	-Cl	$C_{14}H_9Cl_3N_2S$	123	78
k	-Cl	$-NO_2$	-Cl	$C_{14}H_9Cl_2N_3O_2S$	157	48
l				$C_{18}H_{14}N_2S$	158	26

Table 2: Spectral data of the compounds (i-l)

Comp.	IR (KBr, cm^{-1})	^{1}H NMR (DMSO-d_6, ppm)
i	3424 (N-H str.), 1622 (C=N str.), 810, 740 (C-Cl str.)	4.02 (2H,s–CH_2), 5.0 (-NH), 7.2-7.1 (3H, Ar-H), 7.4-7.5 (4H, Benzimidazole)
j	3372 (N-H str.), 1630 (C=N str.), 896 (C-Cl str.)	4.03 (2H, s, -CH_2), 4.6 (N-H), 7.8 (4H, Benzimidazole), 7.5 (2H, Ar-H)
k	3390 (N-H str.), 1621 (C=N str.), 1503 (C-NO_2str.) 747, 731 (C-Cl str.)	3.4 (2H, s, -CH_2), 5.0 (N-H), 6.9-6.8 (2H, Ar-H), 7.0 (4H, Benzimidazole)
l	3453 (N-H str.), 1621 (C=N str.)	3.9(2H, s,-CH_2), 5.0 (N-H), 7.6-7.3 (7H) 7.7-7.2 (4H Benzimidazole)

str. – stretching, s - singlet

Table 3: *In vitro* antibacterial activities of benzimidazole derivatives; Standard: Ciprofloxacin: 2 µg/mL

Compound	*S. aureus*	*E. fecalis*	*Kleb.*	*E. Coli*
i	<100	50	<100	100
j	6.25	6.25	50	100
k	50	50	50	100
l	<100	100	<100	50

[a]MIC, µg/mL. Abbrevations : *S. aureus. Staphylococcus aureus; E. fecalis, Enterococcus fecalis ; Kleb., Klebsiella ; E.coli., Enterococcus coli*

Table 4: ***In vitro* antifungal activities of benzimidazole derivatives; Standard: Fluconazole: 2 µg/mL**

Compound	*Aspargillus*	*Candida*
i	50	50
j	50	50
k	50	50
l	6.25	6.25

[b]MIC, µg/mL

RESULTS AND DISCUSSION

In general, most of the compounds showed significant antibacterial and antifungal activity but some compounds are more specific to particular strains of bacteria and fungi. Compound 2-{[(2, 4, 5-trichlorophenyl) thio] methyl}-1*H*-benzimidazole **(j)** has showed potential activity as antibacterial agent for gram-positive bacteria. Compound 2-{[(2, 5-dichloro-4-nitrophenyl) thio] methyl}-1*H*-benzimidazole **(k)** also showed considerable activity as antibacterial agent. The synthesized compound (s) 2-{[(2, 5-dichlorophenyl) thio] methyl}-1*H*-benzimidazole, 2-{[(2, 4, 5-trichlorophenyl) thio] methyl}-1*H*-benzimida-zole, 2-{[(2, 5-dichloro-4-nitrophenyl) thio] methyl}-1*H*-benzimidazole have showed considerable level of

antifungal activity but 2-[(1-naphthylthio) methyl]-1*H*-benzimidazole **(l)** has showed remarkable activity as antifungal activity. Gram-negative strain of bacteria used were *Klebsiella* and *E. Coli* while gram-positive bacterial strain used was *S. aureus* and *E. fecalis*. The activity was determined using MIC. Ciprofloxacin was used as standard (2 µg/mL). The compounds have shown varying degree of antibacterial activity. These compounds may find use as pharmaceutical intermediate or as insecticide (s) for agrochemical use.

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