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Synthesis of New Biologically Active Sulphur Containing Compounds Incorporating Diphenyl Ether Moiety

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Abstract: The reaction of 4-nitro-4'-carboxaldehyde diphenylether **(1)**, with thiosemicarbazide in ethanol at reflux temperature furnished the novel thiosemicarbazone derivative (**2**). Compound (**2**) was used as a potential starting material for the synthesis of thiazole derivatives (**4-11**) via its reaction with α-halogenated compounds (**3a-f**) and dichloronaphthaquinone , respectively. Bis (carboxaldehyde), (**12**) on refluxing with thiosemicarbazide in ethanol afforded 4,4'-bis thiosemicarbazone)diphenyl ether (**13**). Bis (thiosemicarbazone) diphenyl ether derivative (**13**), on treatment with α-halo compounds (**3a-f**), and dichloronaphthaquinone (1:2 molar ratio), gave bisthiazoles (**14-19**).

Key words: Diphenylether, thiosemicarbazone, thiazole, bisthiosemicarbazone, bisthiazole.

1. Introduction

Diphenylether derivatives has a wide range of applications; Poly brominated diphenyl ether (PBDEs) are used as flame retardants additives to improve fire softy in both commercial and a domestic applications [1], diphenylether derivatives may also exhibit antitubercular properties [2], and 2-(2',4'-Dibromo-phenoxy)-4,6-dibromo isolated from the marine sponge dxsidea granoulas exhibit potent and broad spectrum *in vitro* antibacterial activity [3]. Thiazoles are important class in heterocyclic compounds found in many potent biological active molecules such as sulfathiazole (antimicrobial drug), Ritonavir (antiretroviral), A bafungin (antifungal drug), and Bleomycine (antineoplastic drug) [4, 5]. Recently the applications of thiazoles were found in drug development for the treatment of allergies [6], hypertension [7], inflammation [8], schizophrenia [9], bacterial [10], HIV infections [11], hypnotics [12] and more recently for the treatment of pain [13] , as fibrinogen receptor antagonists with antithrombotic activity [14] and as new inhibitors of bacterial DNA gyrase B [15]. In view of these benefits and in continuation of our program, we report herein the synthesis of newly thiazoles and bisthiazoles having diphenyl ether moiety to improve the biological activity [16-19].

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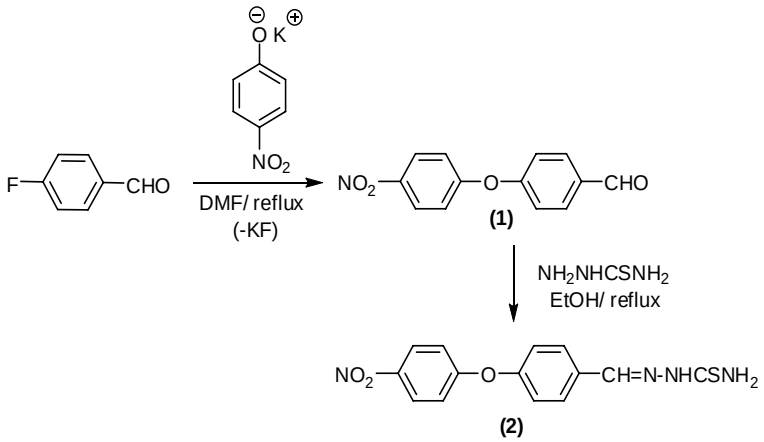
2. Results and Discussion

4-nitro-4'-carboxaldehyde diphenylether **(1)** was readily available by nucleophilic substitution of 4-flourobenzaldehyde with potassium salt of 4-nitrophenol in dimethylsulfoxide under reflux. Condensation of **(1)** with thiosemicarbazide in ethanol at reflux temperature furnished the novel thiosemicarbazone derivative **(2)** in acceptable yield (78%) (Scheme 1). The molecular structure of compound **(2)** was confirmed on the basis of analytical



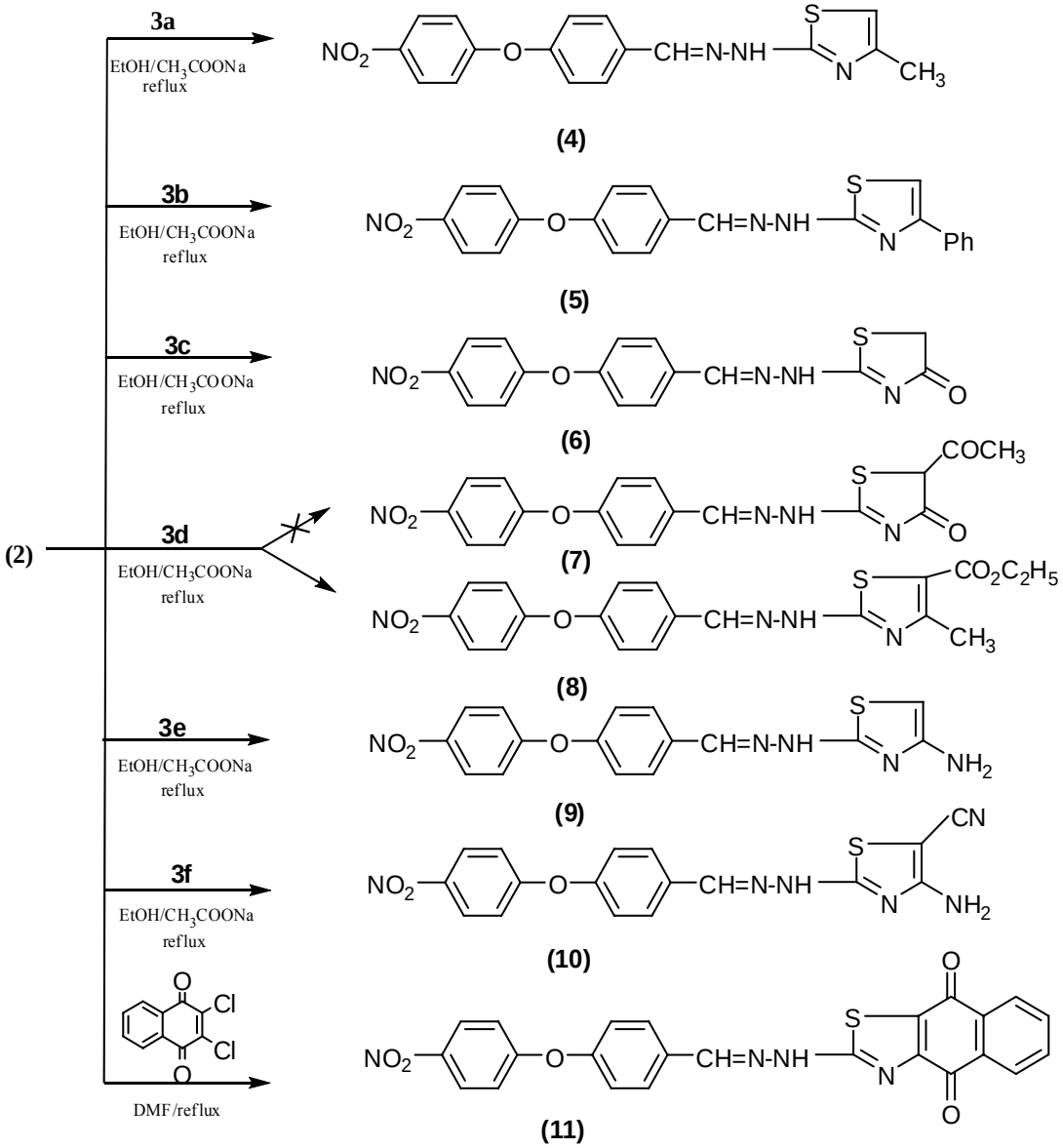
Scheme 1 Synthesis of thiosemiccarbazone derivative.

and spectral data. Its infrared spectrum showed absorption bands characteristic for NH_2 at 3,380, 3,272 cm^{-1} in addition to the presence of CH-aliph. at 2,950 cm^{-1}, and C=N at 1,604 cm^{-1} functional groups. Also, its ^{1}HNMR spectrum revealed a signal characteristic for CH=N at δ 8.23 ppm in addition to the presence of NH at δ 11.48 ppm, and aromatic, NH_2 protons at δ 7.16-7.29 ppm.

Compound **(2)** was used as a potential starting material for the synthesis of thiazole derivatives, via its reaction with α-halo compounds **(3a-3f)**. Cyclo alkylation of thiocarbamoyl function group in compound **(2)** with chloroacetone **(3a)** in ethanol in the presence of sodium acetate at reflux temperature yielded the corresponding thiazole **(4)**. The structure of **(4)** was determined by spectral data and elemental analysis. Its infrared spectrum revealed characteristic bands for NH at 3,178 cm^{-1}, and C=N at 1,604 cm^{-1} functional groups. The ^{1}HNMR spectrum of **(4)** in DMSO-d6 indicated the presence of methyl, thiazole, NH, CH=N, and aromatic protons at δ 2.17, 6.38, 11.85, 8.04, and 7.16-8.29 ppm respectively. The formation of **(4)** is assumed to proceed through initial alkylation by loss of potassium chloride followed by intramolecular cyclization via elimination of water [20]. In a similar manner, thiazole derivative **(5)** was obtained by cyclization of compound **(2)** with phenacyl bromide **(3b)** in refluxing ethanol in the presence of sodium acetate. The mass spectrum of compound **(5)** showed a molecular ion peak at m/z = 416 with a base peak at m/z = 134 which is characteristic for $OC_6H_4CH{=}NNH$ moiety (Chart 1). Cyclocondensation of compound **(2)** with ethylchloroacetae **(3c)** furnished thiazolidinone derivative **(6).** Its ^{1}HNMR spectrum in DMSO-d6 exhibited the presence of methylene group at δ = 3.91 ppm in addition to the presence of NH, CH=N, and aromatic protons. The formation of **(6)** is assumed to proceed through initial alkylation and intramolecular cyclization via elimination of ethanol. 5-Ethoxycarbonyl-4-methylthiazol-2-yl-derivative **(8)** was produced via cyclocondensation of compound **(2)** with ethyl α-chloroacetoacetate **(3d)** in refluxing in ethanol/sod. acetate. The other possible structure **(7)** was discarded on the basis of ^{1}HNMR spectrum which indicated the presence of ethoxycarbonyl, NH, CH = N, and aromatic protons. Cyclization of compound **(2)** with chloroacetonitrile **(3e)** under reflux in ethanol in the presence of triethylamine yielded 4-aminothiazole derivative **(9)**. The mass spectrum of compound **(9)** exhibited a molecular ion peak at m/z = 89. The formation of **(9)** is assumed to proceed via initial alkylation followed by intramolecular nucleophilic cyclization and tautomerization. Also, compound **(2)** was cyclized with bromomalononitrile **(3f)** at reflux temperature in ethanol in the presence of triethylamine to furnish 4-amino-thiazole carbonitrile derivative **(10)**. Refluxing of compound **(2)** with 2, 3-dichloro-naphthoquinone in dimethylformamide

yielded naphtha [2, 3-d] thiazole derivative **(11).** Its mass spectrum revealed a molecular ion peak at m/z = 470 (2.56%) which is characteristic for the molecular formula $C_{24}H_{14}N_4O_5S$ (Scheme 2).

Bisheterocyclic compounds were reported to furnish antibacterial, antifungicidal, tuberculosatic, and plant growth regulative properties [21-23]. In addition, it's observed from the literature that, bishetercyclic compounds displayed much better antibacterial activity than heterocyclic compounds [24]. In the present study,



3a: X=Cl, Y=$COCH_3$, R=H
3b: X=Br, Y=COC_6H_5, R=H
3c: X=Cl, Y=H, R=CO_2C_2H5
3d: X=Cl, Y=$COCH_3$, R=$CO_2C_2H_5$
3e: X= Cl, Y=H, R=CN
3f: X=Br, Y=R=CN

Scheme 2 Synthesis of thiazole derivatives.

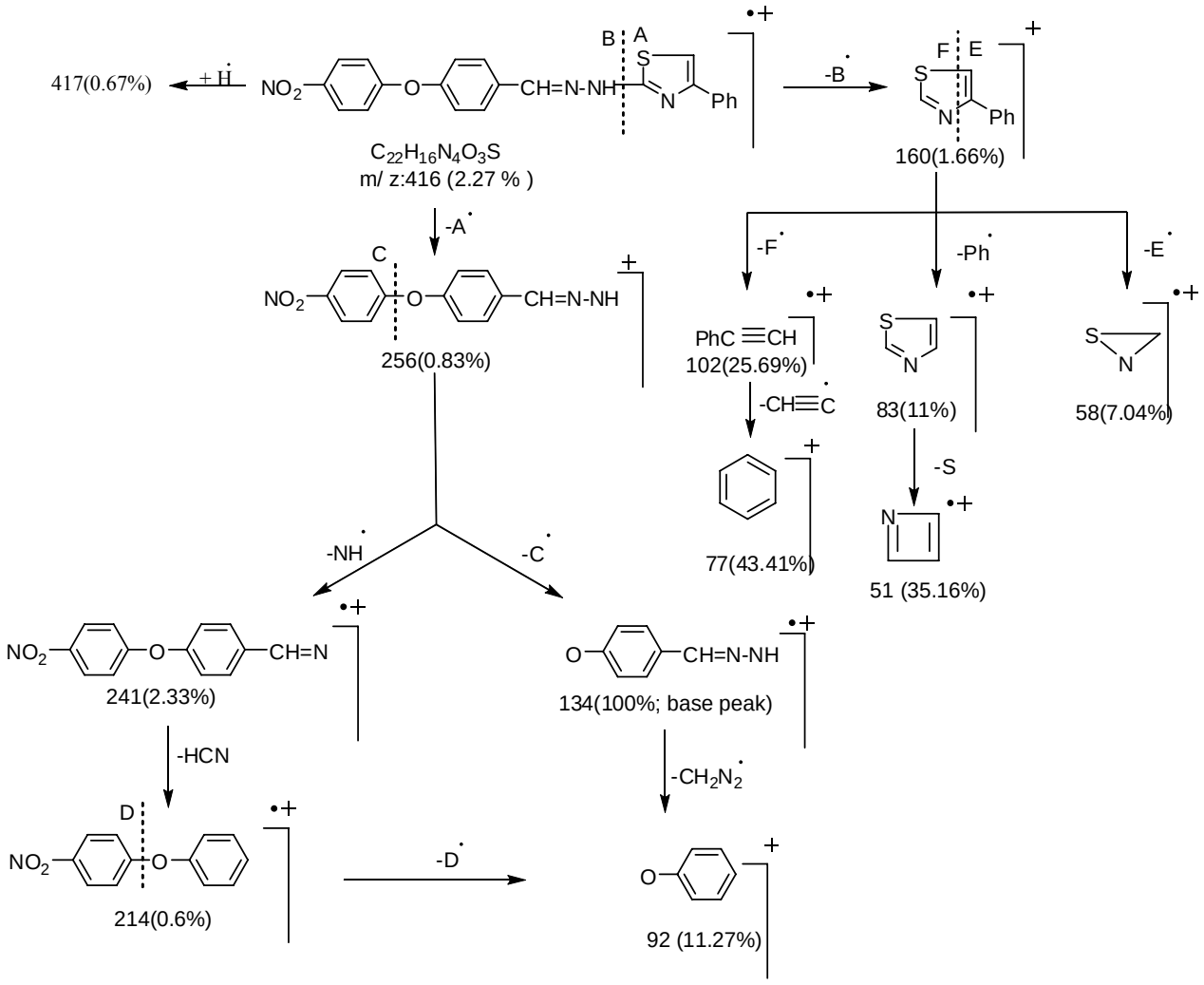
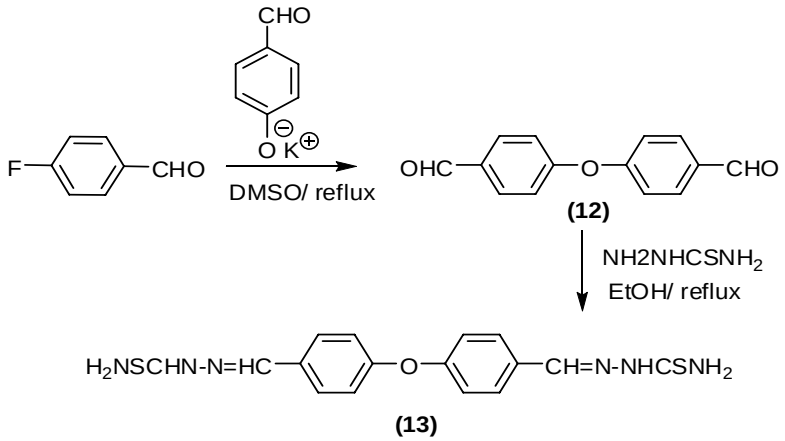


Chart 1 Fragmentation pattern of compound (5).

we report here the synthesis of some novel bisthiazoles from the reaction of 4,4'-bis (thiosemicarbazone) diphenylether (13) with α-halocompounds. Nucleophilic substitution of 4-flourobenzaldehyde with potassium salt of 4-hydroxybenzaldehyde in dimethylsulfoxide at reflux temperature afforded 4,4'-bis (carboxaldehyde) diphenylether **(12)** as stable crystalline solid, in good yield (84%), and readily purified [25]. Bis (thiosemicarbazone) derivative **(13)** was achieved by condensation of bis (carboxaldehyde) (12) with thiosemicarbazide in ethanol under reflux (Scheme 3).

Cyclocondensation of bis (thiosemicarbazone) **(13)** with phenacyl bromide **(3b)** in refluxing acetic acid in the presence of sodium acetate yielded the bis (thiazole) derivative **(14)**. Mass spectrum of compound **(14)** showed a molecular ion peak at m/z = 572 (0.2%) and a base peak was found in the spectrum at m/z = 134, which is characteristic for OC_6H_4CH=N-NH moiety (Chart 2). Compound **(13)** was cyclized with bromomalononitrile **(3f)**, and furnished bis (enaminonitrilethiazole) derivative **(15)**, in high yield. Mass spectrum of compound **(15)** showed a molecular ion peak at m/z = 500 (21.43%) together with a base peak at m/z = 102. Treatment of compound **(15)** with ethylchloroacetate **(3c)** at reflux in acetic acid and sodium acetate afforded bis (thiazolidinone) derivative **(16).** Bis (aminothiazole) derivative **(17)** was obtained in high yield (84%) by cyclization of compound **(13)** with chloroacetonitrile **(3e)** under reflux in acetic acid



Scheme 3 Synthesis of bis thiazole derivatives.

in the presence of sodium acetaete. A molecular ion peak was found in the mass spectrum at m/z = 450 (8.02%). Reaction of compound **(13)** with ethyl α-chloroacetoacetate **(3d)** in acetic acid in the presence of sodium acetate afforded bis (ethoxycarbony-lthiazole) derivative **(18)**. Its mass spectrum revealed a molecular ion peak at m/z = 592 (0.3) (Chart 3). Compound **(13)** was subjected to react with 2,3-dichloronaphthaquinone to yield bis (naphthiazole) derivative **(19)** (Scheme 4). Mass spectrum of compound **(19)** revealed a molecular ion peak at m/z = 680 (24.14%), and a base peak was observed in the spectrum at m/z = 69.

3. Experiment

Melting points are recorded on a Fisher-John melting points apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 470 spectrometer using KBr pellets. ^{1}HNMR spectrum were recorded on a Varian Gemini spectrometer 200 (200 MHz) using TMS as internal standard and mass spectra on a Jeol-JMS-600 mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 micro-analyzer.

3.1 Synthesis of 4-nitro-4'-thiosemicarbazone diphenylether (2) and 4,4'-bis(thiosemicarbazone) diphenylether (13)

To a solution of (**1**) or (**12**) (0.01 mole) in DMF (30 mL) either thiosemicarbazide (0.01 mole) or (0.02 mole) was added. The reaction mixture was refluxed for 0.5 h, the solid products which produced on heating were collected by filtration and recrystallized from the proper solvent**.**

3.2 4-Nitro-4'-thiosemicarbazone Diphenylether (2)

Yellow crystals (ethanol), m.p. 210-211 ºC, (84%); IR ν (cm^{-1}): 3,380, 3,272, 3,150 (NH/NH_2), 2,950 (CH-aliph.), 1,604 (C=N); ^{1}HNMR (DMSO-d_6) δ 7.16-7.29 (m, 6H, Ar-H + NH_2), 7.91, 8.31(2d, 4H, Ar-H), 8.23 (s, 1H, CH=N), 11.48 (s, 1H, NH). Anal. for $C_{14}H_{12}N_4O_3S$ (316): Calc.: C, 53.16; H, 3.79; N, 17.72. Found: C, 53.10; H, 3. 70; N, 17.60.

3.3 4, 4'-bis (thiosemicarbazone) Diphenylether (13)

Yellow crystals (benzene), m.p. > 300 ºC, (88%); IR ν (cm^{-1}): 3,442, 3,248, 3,148(NH/NH_2), 2,980 (CH-aliph.), 1598 (C=N); ^{1}HNMR (DMSO-d_6) δ7.05-7.83 (m, 13H, Ar-H+ CH=N), 8.05(s, 4H, $2NH_2$), 8.20 (s, 2H, 2 CH=N), 11.43 (s, 2H, NH_2).Anal. for $C_{16}H_{16}N_6OS_2$ (372); Calc.: C, 51.61; H, 4.30; N, 22.58. Found: C, 51.50; H, 4.20; N, 22.50.

3.4 Reaction of 2 with α-Halogenated Compounds 3a-3f (General Procedure)

To a solution of compound (**2**) (0.01 mole) in ethanol (30 mL) in presence of fused sodium acetate (2 gm), α-halo compounds 3a-3d (0.01 mole) were added.

The reaction mixture was refluxed for 2 h; the solid products which produced on heating were collected by filtration.

3.5 N-(4-methyl-thiazol-2-yl)-n'-(4-nitro-diphenyl-ether)-methylene Hydrazine (4)

Yellow crystals (benzene), m.p. 225-227 ºC, (64%); IR ν (cm^{-1}): 3,178(NH), 3,082(CH-a-rom.) 2,924 (CH-aliph.), 1,604 (C= N); ^{1}HNMR (DMSO-d_6) 2.17 (s, 3H, CH_3), 6.38 (s, 1H, thiazole-H), 7.16-7.37 (m, 4H, Ar-H), 7.72-8.29 (2d, 4H, Ar-H), 8.04(s, 1H, CH=N), 11.85 (s, 1H, NH). Anal. for $C_{17}H_{14}N_4O_3S$ (354); Calc.: C, 57.62; H, 3.95; N, 15.81. Found: C, 57.50; H, 3.90; N, 15.80.

3.6 N-(4-phenyl-thiazol-2-yl)-n'-(4-nitro-diphenyl ether) Methylen Hydrazine (5)

Yellow crystals (benzene), m.p. 235-236 ºC, (67%); IR ν (cm^{-1}): 3402 (NH), 3010 (CH-arom.), 1624 (C= N); ^{1}HNMR (DMSO-d_6) δ 7.16-7.29 (m, 16H, Ar-H + CH=N+ NH), Anal. for $C_{22}H_{16}N_4O_3S$ (416): Calc.: C, 63.46; H, 3.84; N, 13.46. Found: C, 63.40; H, 3.80; N, 13.60.

3.7 N-(4,5-dihydro-4-oxo-thiazole-2-yl)-n'-(4-nitro-diphenylether) Methylene Hydrazine (6)

Yellow crystals (from benzene), m.p. 266-268 ºC, (74%); IR ν (cm^{-1}): 3,100 (NH), 3,070 (CH-arom.),

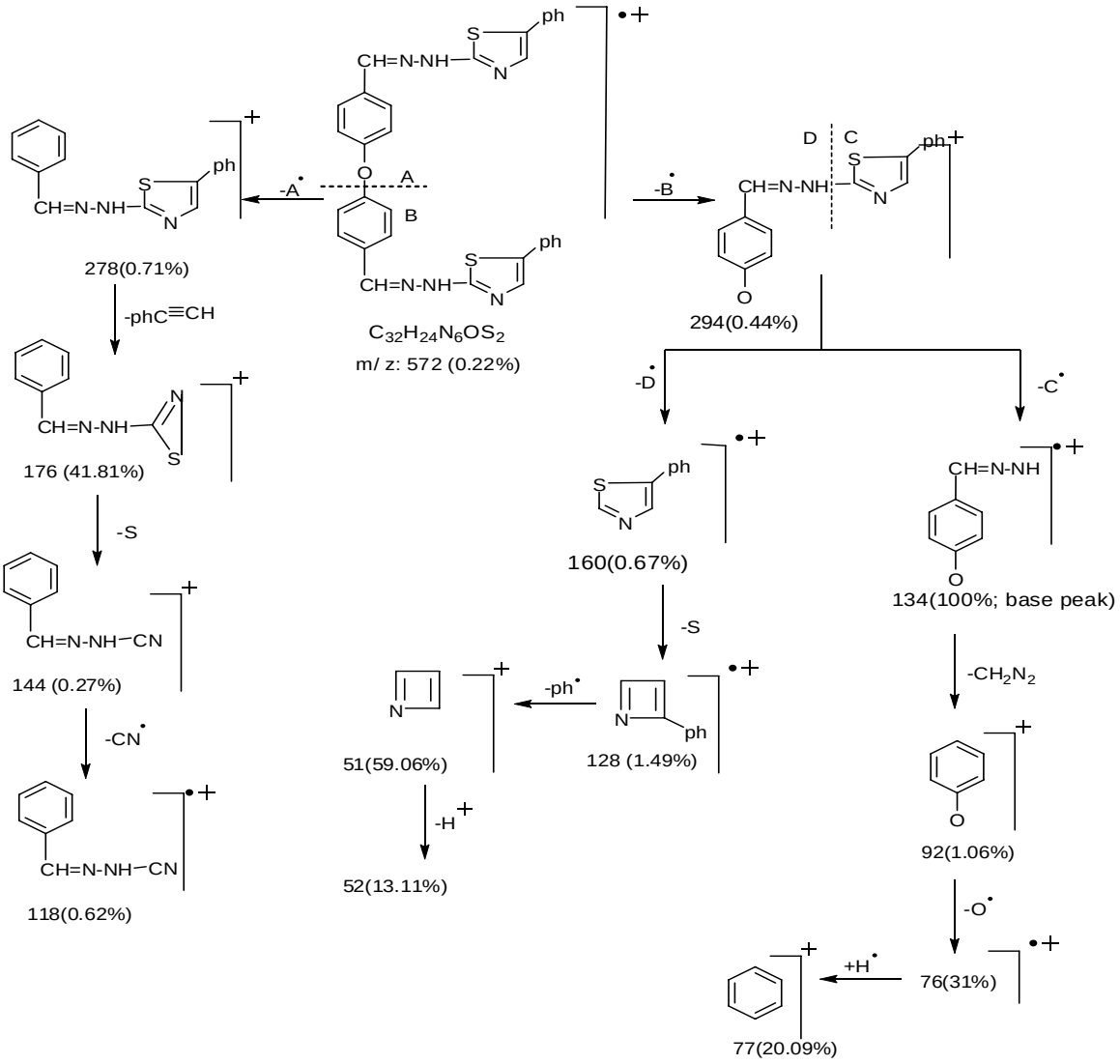
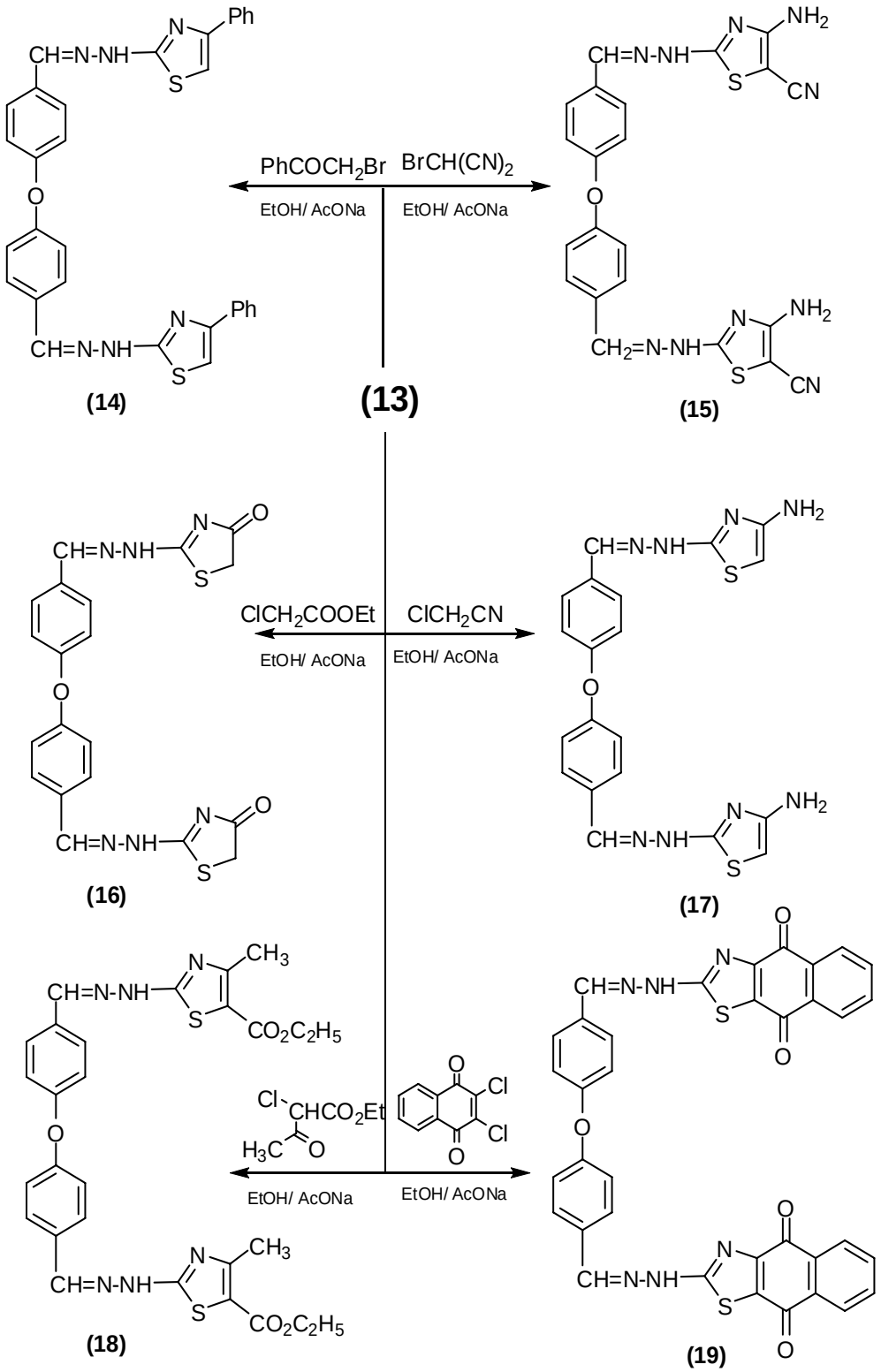


Chart 2 Fragmentation pattern of compound (14).



Scheme 4. Synthesis of bisthiazole derivatives.

2,952 (CH-aliph.), 1,712 (C=O), 1,604 (C=N); ^{1}HNMR (DMSO-d_6) δ 3.91(s, 2H, CH_2), 7.20-7.30 (m, 4H, Ar-H), 7.86-8.26 (2d, 4H, Ar-H), 8.45 (s, 1H, CH=N), 11.98 (s, 1H, NH). Anal. for $C_{16}H_{12}N_4O_4S$ (356) Calc.: C, 53.93; H, 3.37; N, 15.73. Found: C, 53.90; H, 3.30; N, 15.70.

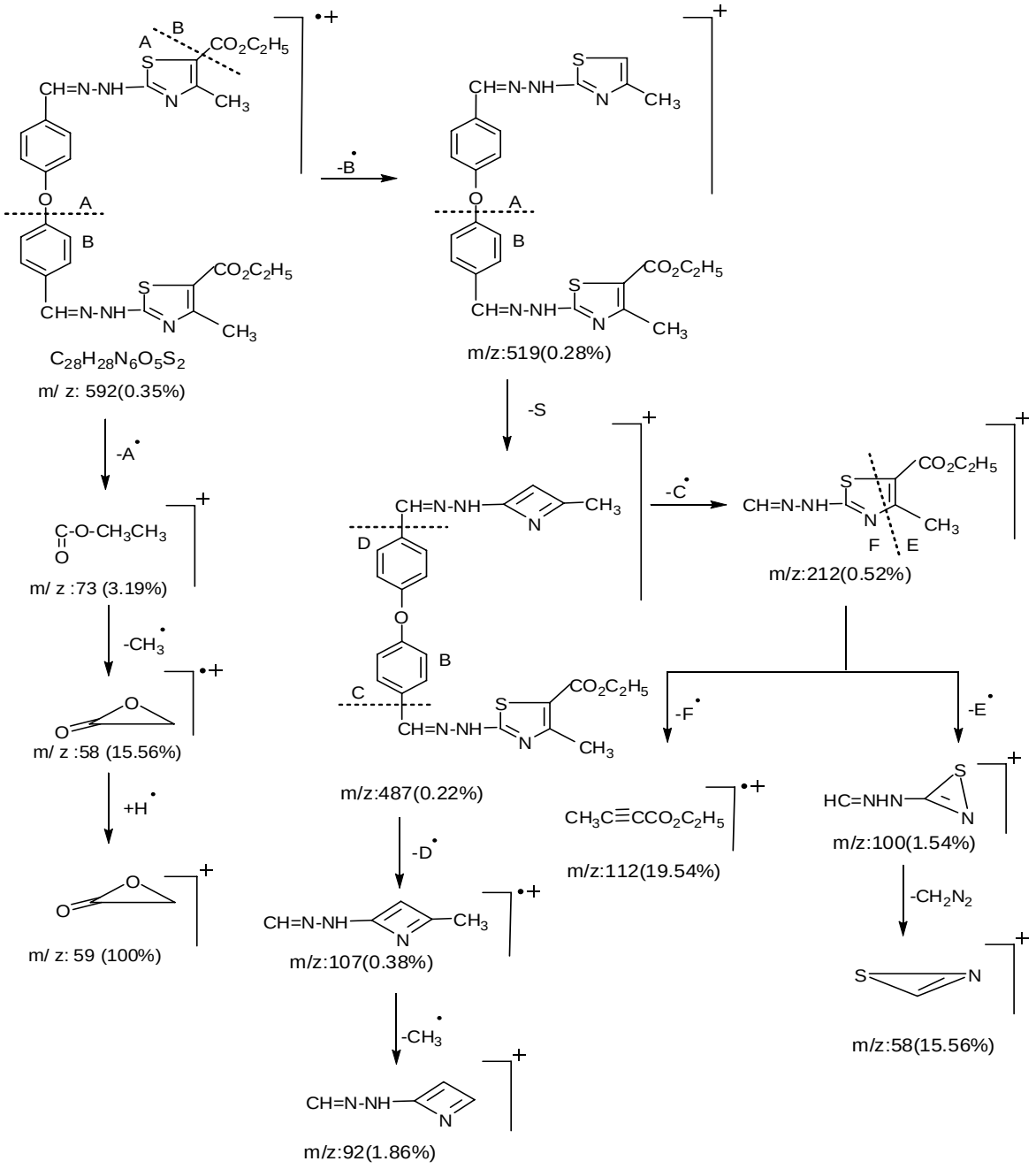


Chart 3 Fragmentation pattern of compound 18.

3.8 N-(5-ethoxycarbonyl-4-methyl-thiazol-2-yl)-n' -(4-nitro-diphenylether) Methylene Hydrazine (8)

Yellow crystals (benzene), m.p. 283-85 ºC, (82%); IR ν (cm^{-1}): 3,382(NH), 2,926 (CH-aliph.), 1,700(C=O), 1,606 (C= N). ^{1}HNMR (DMSO-d_6) δ 1.20 (t, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.15 (q, 2H, CH_2), 7.10-8.38 (m, 9H, Ar-H + CH=N), 11 .43 (s, 1H, NH). Anal. for $C_{20}H_{18}N_4O_5S$ (426): Calc.: C, 56.33; H, 4.22; N, 13.14. Found: C, 56.30; H, 4.20; N, 1310.

3.9 N-(4-amino-thiazol-2-yl)-n'-(4'-nitro-diphenyl-ether)-4-methylene Hydrazine (9)

Yellow crystals (benzene), m.p. 234-35 ºC, (63%); IR ν (cm^{-1}): 3,450, 3,432, 3,100 (NH/NH_2), 1,636 (C=N); ^{1}HNMR (DMSO-d_6) δ 3.79 (hump, 2H, NH_2),

7.17-8.29 (m, 11H, Ar-H + CH=N+ NH). Anal. for $C_{16}H_{13}N_5O_3S$ (355) Calc.: C, 54.08; H, 3.66; N, 19.71. Found: C, 53.90; H, 3.60; N, 19.70.

3.10 N-(4-amino-5-cyano-thiazol-2-yl)-n'-(4'-nitro--diphenylether)-4-methylenehydrazine (10)

Yellow crystals (benzene), m.p. > 300 ºC, (72%); IR ν (cm^{-1}): 3,338, 3,272, 3,179 (NH/NH_2), 3,024 (CH-arom.) 2,201 (C≡N) 1625 (C=N); ^{1}HNMR (DMSO-d_6) δ 5.87 (s, 2 H, NH_2), 7.88-8.01 (m, 9H, Ar-H + CH=N), 10.02 (s, 1H, NH). Anal. for $C_{17}H_{12}N_6O_3S$ (380) Calc.: C, 53.68. H, 3.15; N, 22.10. Found: C, 53.60; H, 3.10; N, 22.00.

3.11 *Reaction of 2, 3-Dichloronaphthaquinone with Either Compound (2) or (13)*

To a solution of **2** or **13** (0.01 mole) in DMF (10 mL) either 2,3-di-chloronaphthoquinone (0.01 mole) or (0.02 mole) was added. The reaction mixture was refluxed for 1h, then allowed to cool and then the products were collected by filtration.

3.12 N-(4, 5-dioxo-naphtho [2, 3-d] thiazol-2-yl) -n'-(4'-nitro-diphenylether)-4 methylenehydrazine (11)

Yellow crystals, (benzene), m.p. 240-42 ºC, (62%); IR ν (cm^{-1}): 3,400 (NH), 1,654(C=O), 1,605 (C=N); ^{1}HNMR (DMSO-d_6) δ 7.22-8.29 (m, 13H, Ar-H + CH=N), 8.50 (s, 1H, NH). Anal. for $C_{24}H_{14}N_4O_5S$ (470) Calc.: C, 61.27; H, 2.97; N, 11.91. Found: C, 61.20; H, 2.90; N, 11.80.

3.13 4,4'-bis-[N-(4,9-dioxo-naphtho [2,3-d] thiazol-2-yl) -hydrazonomethylene] Diphenylethr (19)

Yellow crystals (benzene), m.p. > 300 ºC, (63%); IR ν (cm^{-1}): 3,430 (NH), 1,654 (C=O), 1,594(C=N); Anal. for $C_{36}H_{20}N_6O_5S_2$ (680) Calc.: C, 63.52. H, 2.94; N, 12.35. Found: C, 63.50; H, 2.80; N, 12.30.

3.14 Reaction of (13) with α-Halogenated Compounds (General Procedure)

To a solution of (**13**) (0.01 mole) in acetic acid (30 mL) in presence of fused sodium acetate (2 gm), α-halo compound **3a-3e** (0.02 mole) were added. The reaction mixture was refluxed for 6 h, and then allowed to cool. The solid products obtained were collected by filtration**.**

3.15 4,4'-bis[n-(4-phenyl-thiazol-2-yl)-hydrazonome thylene]Diphenylether (14)

Yellow crystals, (from benzene), m.p. 270-271 ºC, (73 %); IR ν (cm^{-1}): 3,304 (NH), 3,048 (CH-arom.) 2,920 (CH-aliph.), 1,598 (C= N); ^{1}HNMR (DMSO-d_6) δ 7.10-8.07 (m, 22H, Ar-H + 2NH), 8.10 (s, 2H, 2 CH=N). Anal. for $C_{32}H_{24}N_6OS_2$ (572) Calc.: C, 67.13; H, 4.19; N, 14.68 Found: C, 67.00; H, 4.30; N, 14.60.

3.16 4,4'-bis[n-(4-amino-5-cyano-thiazol-2-yl) -hydrazonomethy lene]Diphenylether (15)

Yellow crystals (benzene), m.p. > 300 ºC, (70%); IR ν (cm^{-1}): 3,336, 3,271, 3,177 (NH/NH_2), 2,201 (C≡N), 1592 (C=N); ^{1}HNMR (DMSO-d_6) δ 6.90-8.01 (m, 14 H, Ar-H+ 2CH=N + $2NH_2$), 9.09-9.98 (2s, 2H, 2 NH). Anal. for $C_{22}H_{16}N_{10}OS_2$ (500) Calc.: C, 52.80; H, 3.20; N, 28.00 Found: C, 52.70; H, 3.10; N, 28.10.

3.17 4,4'-bis [n-(4,5-dihydro-4-oxo-thiazol-2-yl) hydrazonomethylene] Diphenylether (16)

Yellow crystals (benzene), m.p. > 300 ºC, (76%). IR ν (cm^{-1}): 3454, 3160 (2NH), 1968 (CH-aliph.), 1704 (C=O), 1624 (C=N) .^{1}HNMR (DMSO-d_6) δ 3.91(s, 4H, $2CH_2$), 7.14-7.79 (2d, 8H, Ar-H), 8.42(s, 2H, 2CH=N), 11.99 (hump, 2H, 2NH). Anal. for $C_{20}H_{16}N_6O_3S_2$ (452) Calc.: C, 53.09; H, 3.53; N, 18.58 Found: C, 52.90; H, 3.60; N, 18.70.

3.18 4,4'-bis -[N- (4-amino-thiazolo-2-yl) hydrazonomethylene]Diphenyl ether (17)

Yellow crystals (benzene), m.p. > 300 ºC,(60%); IR ν (cm^{-1}): 3,484, 3,420, 3,365 (NH /NH_2), 2,926 (CH-aliph.), 1,702 (C=O), 1,634 (C=N); ^{1}HNMR (DMSO-d_6) δ 3.99 (hump, 4H, $2NH_2$), 7.18 (s, 1H, thiazole-H),7.20-7.85 (m,10H+ Ar-H+ 2CH=N), 8.50 (hump, 2H, 2 NH). Anal. for $C_{20}H_{18}N_8OS_2$ (450) Calc.:

Table 1 Biological activity of some synthesized compounds.

Comp. NO.	Gram positive bacteria		Gram negative bacteria	
	Staphylococcous aureous (NCTC-7447)	Bacillus Cereeus (NCTC-14579)	Serratia Marcesens (IMRU-70)	Proteus Mirabilis (NCTC-289)
8	++	++	+	+
11	+	++	++	++
14	+++	++	+++	++
17	+	+++	++	++
18	++	++	+	++
19	+	++	++	++
Standard	++++	+++	+++	++++

+: Less active (0.2-0.5 cm; ++: Moderately active (0.6-1.4); +++: Highly active (1.5-3.0); ++++: Very highly active (over 3.0); Standard: For Gram positive and Gram negative bacteria: Ampicillin 25 $\mu g \cdot m \cdot L^{-1}$.

C, 53.33; H, 4.00; N, 24.88 Found: C, 53.90; H, 3.90; N, 24.90.

3.19 4,4'-bis[n-(5-ethoxycarbonyl-4-methyl-thiaz-ol-2-yl)-hydrazonomethylene]Diphenyl Ether (18)

Yellow crystals, (benzene), m.p. > 260-62 ºC, (78%); IR ν (cm^{-1}): 3,438, 3,210 (2NH), 2,926 (CH-aliph.), 1,702 (C=O), 1,624 (C=N). ^{1}HNMR (DMSO-d_6) 1.23(t, 6H, $2CH_3$), 2.48(s, 6H, $2CH_3$), 4.19(q, 4H, $2CH_2$), 7.11-7.70 (2d, 8H, Ar-H) 8.10 (s, 2H, 2 CH=N), 12.41 (s, 2H, 2NH). Anal. for $C_{28}H_{28}N_6O_5S_2$ (592) Calc.: C, 56.75; H, 4.72; N, 14.18; Found: C, 56.70; H, 3.90; N, 4.10.

4. Antimicrobial Activity

Six compounds were screened *in vitro* for their antimicrobial activities against four strains of bacteria: *Staphylococcus aureus* (NCTC-7447), *Bacillus cereus* (ATCC-14579), *Serratia marcesens* (IMRU-70) and *Proteus mirabilis* (NCTC-289) by agar diffusion technique [26]. A 1 mg/mL solution in dimethylformamide (DMF) was used. The bacteria were maintained on nutrient agar media. DMF showed no inhibition zones. The agar media was incubated with different microorganisms culture tested after 24 h. of incubation at 30 °C for bacteria, the diameter of inhibition zone (mm) was measured. A mpicillin in a concentration (25 $ug \cdot mL^{-1}$) used as reference for antibacterial activity. The minimal inhibitory concentration (MIC) of some of the tested compounds was measured by a two-fold serial dilution method. The most of the synthesized compounds exhibited antimicrobial activity towards all microorganisms used (Table 1).

Most of the synthesized compounds were found to possess various antimicrobial activities towards all the microorganisms used (Table 1). Bisthiazoles (**14**), (**17**), (**18**) and (**19**) biologically activite higher than thiazoles (**8**) and (**11**). Bisthiazoes (**14**) and (**17**) having biologically active amino and phenyl moieties were found to possess highest antibacterial towards *Staphylococcus aureous* (NCTC-7447), *Serratia marcesens* (IMRU-70), and *Bacillus cereeus* (NCTC-14579), respectively.

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