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

Kalil Ali¹, H.A. Eyada², Mohamed T. Abd El-Rahman², Mohamed Hamdy Helal², Mohamed Sayed Abd-Elal. El-Gaby³ and Gameel Ahmed Mohamed El-Hag Ali²

¹. Chemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt
². Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo, Egypt
³. Chemistry Department, Faculty of Science, Al-Azhar University, Assuit, Assuit, Egypt

Received: March 04, 2011 / Accepted: March 25, 2011 / Published: September 25, 2011.

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].

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

Corresponding author: Gameel Ahmed Mohamed El-Hag Ali, professor, research field: heterocyclic compounds. E-mail: Elhag1970@yahoo.com.
Synthesis of New Biologically Active Sulphur Containing Compounds Incorporating Diphenyl Ether Moiety

Scheme 1  Synthesis of thiosemicarbazone derivative.

and spectral data. Its infrared spectrum showed absorption bands characteristic for NH2 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 ¹HNMR 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, NH₂ 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). Cycloalkylation 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 ¹HNMR 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 OC₆H₄CH=NNH moiety (Chart 1). Cyclocondensation of compound (2) with ethylchloroacetate (3c) furnished thiazolidinone derivative (6). Its ¹HNMR 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 ¹HNMR 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_{4}O_{5}S (Scheme 2).

Bisheterocyclic compounds were reported to furnish antibacterial, antifungicidal, tuberculostatic, 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,

\[ R \rightarrow CH \rightarrow Y \]
3a: X=Cl, Y=COCH_{3}, R=H  
3b: X=Br, Y=CO_{6}H_{5}, R=H  
3c: X=Cl, Y=H, R=CO_{2}C_{2}H_{5}  
3d: X=Cl, Y=COCH_{3}, R=CO_{2}C_{2}H_{5}  
3e: X= Cl, Y=H, R=CN  
3f: X=Br, Y= R=CN  

Scheme 2  Synthesis of thiazole derivatives.
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 OC₆H₄CH=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
in the presence of sodium acetate. A molecular ion peak was found in the mass spectrum at m/z = 450 (8.02%). Reaction of compound (13) with ethyl α-chloroaetoacetate (3d) in acetic acid in the presence of sodium acetate afforded bis (ethoxycarbonylthiazole) derivative (18). Its mass spectrum revealed a molecular ion peak at m/z = 592 (0.3) (Chart 3).

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/NH₂), 2,950 (CH-aliph.), 1,604 (C=N); ¹HNMR (DMSO-d₆) δ 7.16-7.29 (m, 6H, Ar-H + NH₂), 7.91, 8.31(2d, 4H, Ar-H), 8.23 (s, 1H, CH=N), 11.48 (s, 1H, NH). Anal. for C₁₄H₁₂N₄O₃S (316): Calc.: C, 53.16; H, 3.79; N, 17.72. Found: C, 53.10; H, 3.70; N, 17.60.

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 \(\nu\) (cm\(^{-1}\)): 3,178 (NH), 3,082 (CH-arom.), 2,924 (CH-aliph.), 1,604 (C= N); \(^1\)HNMR (DMSO-\(d_6\)) \(\delta\) 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\(_4\)O\(_3\)S (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 \(\nu\) (cm\(^{-1}\)): 3402 (NH), 3010 (CH-arom.), 1624 (C= N); \(^1\)HNMR (DMSO-\(d_6\)) \(\delta\) 7.16-7.29 (m, 16H, Ar-H + CH=N+ NH), Anal. for C\(_{22}\)H\(_{16}\)N\(_4\)O\(_3\)S (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 \(\nu\) (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-\( d_6 \)) \( \delta \) 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\(_4\)O\(_4\)S (356) Calc.: C, 53.93; H, 3.37; N, 15.73. Found: C, 53.90; H, 3.30; N, 15.70.
Synthesis of New Biologically Active Sulphur Containing Compounds Incorporating Diphenyl Ether Moiety

Chart 3  Fragmentation pattern of compound 18.

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

Yellow crystals (benzene), m.p. 283-85 °C, (82%); IR \( \nu \) (cm\(^{-1}\)): 3,382(NH), 2,926 (CH-aliph.), 1,700(C=O), 1,606 (C=N). \(^1\)HNMR (DMSO-\(d_6\)) \( \delta \) 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\(_4\)O\(_5\)S (426): Calc.: C, 56.33; H, 4.22; N, 13.14. Found: C, 56.30; H, 4.20; N, 13.10.

3.9  \( N-(4\text{-amino-thiazol-2-yl})-n'-(4\text{-nitro-diphenylether}) \) 4-methylene Hydrazine (9)

Yellow crystals (benzene), m.p. 234-35 °C, (63%); IR \( \nu \) (cm\(^{-1}\)): 3,450, 3,432, 3,100 (NH/NH\(_2\)), 1,636 (C=N); \(^1\)HNMR (DMSO-\(d_6\)) \( \delta \) 3.79 (hump, 2H, NH\(_2\)), 3.89 (hump, 2H, NH\(_2\)), 7.10-8.38 (m, 9H, Ar-H + CH=N), 11 .43 (s, 1H, NH).
3.10 \( N-(4\text{-amino-5-cyano-thiazol-2-yl})-n'-(4'\text{-nitro-diphenylether})-4\text{-methylenehydrazine} \) (10)

Yellow crystals (benzene), m.p. > 300 °C, (73%); IR \( \nu (\text{cm}^{-1}) \): 3,336, 3,271, 3,365 (NH/NH\( \text{2} \)), 2,926 (CH-aliph.), 1,702 (C=O), 1,634 (C=N); \( ^1\text{HNMR} \) (DMSO-\( \text{d_6} \)) \( \delta \) 3.99 (hump, 4H, 2NH\( \text{2} \)), 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\( _{8} \)O\( _{2} \)S\( _{2} \) (450) Calc.: C, 53.09; H, 3.53; N, 18.58 Found: C, 52.90; H, 3.60; N, 18.70.

3.16 \( 4,4'\text{-bis\[n-(4-amino-5-cyano-thiazol-2-yl)-hydrazonemethylene\]Diphenylether} \) (15)

Yellow crystals (benzene), m.p. > 300 °C, (70%); IR \( \nu (\text{cm}^{-1}) \): 3,484, 3,420, 3,365 (NH /NH\( \text{2} \)), 2,926 (CH-aliph.), 1,702 (C=O), 1,634 (C=N); \( ^1\text{HNMR} \) (DMSO-\( \text{d_6} \)) \( \delta \) 3.99 (hump, 4H, 2NH\( \text{2} \)), 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\( _{8} \)O\( _{2} \)S\( _{2} \) (450) Calc.: C, 52.80; H, 3.20; N, 28.10 Found: C, 52.70; H, 3.10; N, 28.10.

3.17 \( 4,4'-\text{bis\[n-(4-amino-thiazol-2-yl) hydrazonemethylene\]Diphenylether} \) (17)

Yellow crystals (benzene), m.p. > 300 °C, (60%); IR \( \nu (\text{cm}^{-1}) \): 3,484, 3,420, 3,365 (NH /NH\( \text{2} \)), 2,926 (CH-aliph.), 1,702 (C=O), 1,634 (C=N); \( ^1\text{HNMR} \) (DMSO-\( \text{d_6} \)) \( \delta \) 3.99 (hump, 4H, 2NH\( \text{2} \)), 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\( _{8} \)O\( _{2} \)S\( _{2} \) (450) Calc.: C, 52.80; H, 3.20; N, 28.10 Found: C, 52.70; H, 3.10; N, 28.10.

3.18 \( 4,4'-\text{bis\[n-(4-amino-thiazol-2-yl) hydrazonemethylene\]Diphenylether} \) (17)

Yellow crystals (benzene), m.p. > 300 °C, (60%); IR \( \nu (\text{cm}^{-1}) \): 3,484, 3,420, 3,365 (NH /NH\( \text{2} \)), 2,926 (CH-aliph.), 1,702 (C=O), 1,634 (C=N); \( ^1\text{HNMR} \) (DMSO-\( \text{d_6} \)) \( \delta \) 3.99 (hump, 4H, 2NH\( \text{2} \)), 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\( _{8} \)O\( _{2} \)S\( _{2} \) (450) Calc.:
Synthesis of New Biologically Active Sulphur Containing Compounds Incorporating Diphenyl Ether Moiety

### Table 1  Biological activity of some synthesized compounds.

| Comp. NO. | Gram positive bacteria | Gram negative bacteria |
|-----------|------------------------|-----------------------|
|           | Staphylococcus aureus (NCTC-7447) | Bacillus Cereus (NCTC-14579) | Cereus Serratia (IMRU-70) | Marcesens Proteus (NCTC-289) | Mirabilis |
| 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 μg·mL⁻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-thiazol-2-yl)-hydrazonomethylene]Diphenyl Ether (18)

Yellow crystals, (benzene), m.p. > 260-62 °C, (78%); IR ν (cm⁻¹): 3,438, 3,210 (2NH), 2,926 (CH-aliph.), 1,702 (C=O), 1,624 (C=N). 1HNMR (DMSO-d6) 1.23(t, 6H, 2CH₃), 2.48(s, 6H, 2CH₃), 4.19(q, 4H, 2CH₂), 7.11-7.70 (2d, 8H, Ar-H) 8.10 (s, 2H, 2 CH=N), 12.41 (s, 2H, 2NH). Anal. for C₂₈H₂₈N₆O₅S₂ (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·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 active than thiazoles (8) and (11). Bisthiazoes (14) and (17) having biologically active amino and phenyl moiety were found to possess highest antibacterial towards Staphylococcus aureus (NCTC-7447), Serratia marcesens (IMRU-70), and Bacillus cereus (NCTC-14579), respectively.

### References

[1] A. Covaci, A. Gheorghe, S. Voorspoels, J. Maervoet, E. St. Redeker, R. Blust, et al., Polybrominated diphenyl ethers, polychlorinated biphenyls and organochlorine pesticides in sediment cores from the Western Scheldt river (Belgium): analytical aspects and depth profiles, Environmental International 31 (2005) 367.

[2] D.J. Faulkner, M.D. Unson, C.A. Bewely, The chemistry of some sponges and their symbionts, Pure & Appl. Chem 66 (1994) 1983.

[3] M.P. Divya, G.B. Mahajan, V.P. Kamat, C.G. Naik, R.R. Parab, N.R. Thakur, et al., Antibacterial activity of 2-(2′,4′-dibromophenoxy)-4,6-dibromophenol from Dysidea granulose, Mar. Drugs 7 (2009) 464.

[4] J. Quiroga, P. Hernandez, B. Insuasty, R. Abonia, J. Cobo, A. Sanchez, et al., Control of the reaction between 2-aminobenzothiazoles and Mannich bases, Synthesis of pyrido[2,1-b][1,3]benzothiazoles versus [1,3]
benzothiazolo[2,3b]quinazolines, J. Chem. Soc. Perkin. Trans. 1 (4) (2002) 555.

[5] I. Hutchinson, S. Jennings, B. Vishnuvajjala, A. Westwell, M. Stevens, Synthesis and pharmaceutical properties of antitumor(2-(4-aminophenyl)) benzothiazole amino acid prodrugs, J. Med. Chem. 45 (2002) 744.

[6] K. Hargrave, F. Hess, J. Oliver, N-(4-Substituted -thiazolyl) oxamic acid derivatives, new series of potent, orally active antiallergy agents, J. Med. Chem. 26 (1983) 1158.

[7] W. Patt, H. Hamilton, M. Taylor, M. Ryan, J. Taylor, D.C. Connolly, et al., Structure-activity relationships of a series of 2-amino-4-thiazole-containing rennin inhibitors, J. Med. Chem. 26 (1983) 890.

[8] R. Sharma, F.P. Xavier, K. Vasu, S. Chaturvedi, S. Pancholi, Synthesis of 4-benzyl-1,3-thiazole derivatives as potential anti-inflammatory agents, an analogue-based drug design approach, J. Enz. Inhib. Med. Chem. 24 (2009) 890.

[9] J. Jaen, L. Wise, B. Caprathe, H. Teacle, S. Bergmeier, C. Humblet, et al., 4-(1,2,5,6-Tetrahydro-1-alkyl-3-pyridinyl) -2-thiazonealimines: a novel class of compounds with central dopamine agonist properties, J. Med. Chem. 33 (1990) 311.

[10] K. Tsuji, V. Ishikawa, Synthesis and anti-pseudo-monal activity of new 2-isocephems with a dihydroxy-pyridone moiety at C7, Bioorg. Med. Chem. Lett. 4 (1994) 1601.

[11] F. Bell, A. Cantrell, M. Hogberg, S. Jaskunas, N. Johansson, C. Jordon, et al., Pheethylthiazolethiourea (PETT) compounds, a new class of HIV-1 reverse transcriptase inhibitors: Part 1. Synthesis and basic structure activity relationship studies of PETT analogues, J. Med. Chem. 38 (1995) 4929.

[12] N. Ergenc, G. Capan, N. Gunay, S. Ozkirimli, M. Gungor, S. Ozbey, et al., Synthesis and hypnotic activity of new 4-thiazolidinone and 2-thioxo-4,5-imidazolidinone derivatives, Arch. Pharm. Med. Chem. 332 (1999) 343.

[13] J. Carter, S. Kramer, J. Talley, T. Penning, P. Collins, M. Graneto, et al., Synthesis and activity of sulfonamide substituted 4,5-diaryl thiazoles as selective cyclooxygenase-2-inhibitors, Bioorg. Med. Chem. Lett. 9 (1999) 1171.

[14] A. Badorc, M. Bordes, D. Cointet, P.P. Savi, A. Bernat, A. Lale, et al., New orally active nonpeptide fibrinogen receptor (GpIIIb-IIIa)antagonists identification of ethyl 3-[N-4-[4-N-aminophoxyxarbonyl]limino]methylphenyl]-1,3-thiazole-2-yl]-N-1-(ethoxyxarbonyl)methylpropionate(SR121787) as a potent and long acting antithrombotic agent, J. Med. Chem. 40 (1997) 3393.

[15] J. Rudolph, H. Theis, R. Hanke, R. Endermann, L. Johannsen, F. Geschke, New concise synthesis, inhibitory activity towards bacteria and human DNA topoisomerases, and antibacterial properties, J. Med. Chem. 44 (2001) 619.

[16] R.O. Lamphon, M.S.A. El-Gaby, M.M. Khafagy, G.A.M. El-Hag Ali, A.A. ElMaghraby, H.A. Eyada, et al., Study on thiazolopyridines: Part 5. Synthesis of hithertounkown 4- thiazolidinone and thiazolo[3,2-a] pyridines having in their structures the morpholine-4-yl moiety, Phosphorus, Sulfur and Silicon 179 (2004) 1279.

[17] M.S.A. El-Gaby, M.M. Khafagy, G.A.M. El-Hag Ali, A.A. El-Maghrraby, M.H.M. Helal, Study on thiazolopyridines: Part 4. Synthesis of hithertounkown 1,4-bis(thiazolopyridine)benzene derivatives, Phosphorus, Sulfur and Silicon 178 (2003) 1681.

[18] G.A.M. El-Hag Ali, A. Khalil, A.H.A. Ahmed, M.S.A. El-Gaby, El-Hag Ali, A.A. El-Maghrraby, et al., Study on thiazolopyridines: Part 2. Synthesis and antimicrobial activity of novel-4-thiazolidinone and thiazolo[3,2-a] pyridines and thiazolo [3,2-a] [1,8] napththyridines derivatives having in two different aryl moieties, Acta. Chim. Slov. 49 (2002) 365.

[19] A.A. El-Maghrraby, G.A.M. El-Hag Ali, A.H.A. Ahmed, M.S.A. El-Gaby, Study on thiazolopyridines: part 1, Antimicrobial activity of some novel fluorinated thiazolo [3,2-a] pyridines and [2,3:-1,6] pyrimidines, Phosphorus, Sulfur and Silicon 177 (2002) 293.

[20] M.S.A. El-Gaby, Synthesis of hitherto unkown thiazole, ylidene and pyridine thione derivatives having aipiperdin -1-ylmoietey and their uses as antimicrobial agents, J. Chinese Chem. Soc. 51 (2004) 125.

[21] S.A. Shiba, A.A. El-Khamrry, M.E. Shaba, K.S. Atia, Interaction of oral anticoagulants with methyl xanthines , Pharmazie 52 (1997) 946.

[22] N.C. Desai, Synthesis and antimicrobial activity of some dithiocabamates, 2-arylamino-4-oxothiazoles and their 5-arylidine derivatives, Indian J. Chem. Soc. B. 32 (1993) 343.

[23] M.E. Azab, G.A.M. El-Hag Ali, A.A.F. Abdelwahab, M.S El-Gaby, Studies on thiazolopyridines, Anovel synthesis of bisthiazolo pyridines as promising antimicrobial agents, Acta. Pharm. 53 (2003) 213.

[24] S.R. Pattan, R.L. Hullolikar, N.S. Dighe, B.N. Ingalagi, M.B. Hole, Synthesis and evaluation of some new phenyl thiazole derivatives for their anti-inflammatory activities, J. Pharm. Sci. Res. 4 (2009) 96.

[25] E. Massaranı, D. Nardi, L. Mauri, G. Cavallini, Derivatided difenile, stilbene defeniletano e difeniletere a presumibile attivita antiinfiammatoria, IL Farmaco. 18 (8) (1963) 582.

[26] W. Hewitt, S. Vincent, Theory and Application of Microbiological Assay, Academic Press, New York, 1989.