Synthesis of New Heterocyclic Nitrogen System Bearing Thiazolopyrazole Moiety as New Biocidal Agents

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Novel heteropolycyclic nitrogen systems as pyrazoles, phthalazines and 1,2,4-triazines bearing a thiazolopyrazole moiety (**4-11**) have been synthesized *via* heterocyclization of 2-hydrazino-thiazolo[5,4-d]pyrazole (**3**) with α,β -bifunctional compounds under different conditions. Structures of the new products established by their elemental analysis and spectral data. Some of these products exhibit moderate-good antibacterial activity towards *E. coli* and *S. aureus* in compare with streptomycin and tetracycline antibiotic.

Keywords: Synthesis, Heterocyclic, Thiazolopyrazoles, Bactericidal agents.

INTRODUCTION

Rhodanine and its derivatives exhibit a wide spectrum in the medicinal, pharmacological, agricultural and also as solar cell applications [1,2]. In addition, arylidene rhodanine, use for removal of Cu(II), Hg(II) and CN^- ions in the industrial wastewater [3]. On the other hand, pyrazoles showed a very important medicinal and pharmacological properties [4]. Various heterocyclic nitrogen systems such as phthalazine [5] and 1,2,4-triazine derivatives reported as antimicrobial, anti HIV, anticancer and molluscicidal agents against snail [6-10]. Upon these observations, the present work tends to combination of these heterocyclic in one novel systems in view of their antibacterial in the compare with antibiotics.

EXPERIMENTAL

Melting point were determined on Gallen-Kamp melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on Perkin-Elmer model RXI-IR 55529. ^1H and ^{13}C NMR spectra were recorded on a Burkert DPX-400 FT NMR spectrometer using tetramethylsilane as the internal standard anm DMSO- d_6 as solvent (chemical shift in δ , ppm). Elemental analysis were performed on 2400 Perkin Elmer series 2 analyzer. Direct MS spectra were carried out using quadruple MS (Electronic ionization mod EI mode with source temperature: 200 °C) at 70 eV.

5-[(2'-Hydroxynaphthalen-1'-yl)methylene]-2-thioxo-thiazolidin-4-one (2**):** A mixture of rhodanine (**1**) (1.33 g, 0.01 mol) and 2-hydroxynaphthalene carboxaldehyde (1.72

g, 0.01 mol) in ethanol (100 mL) with piperidine (few drops) refluxed for 8 h. After cooling the reaction mixture poured onto ice-dilute HCl. The solid produced filtered off and crystallized from AcOH to give compound **2**, yield (2.35g, 82 %): m.p. 295-296 °C. IR (KBr, ν_{max} , cm^{-1}): 3500-3400 (phenolic OH), 3200 (NH), 1690 (C=O), 1600 (CH=CH), 1320 (NCS), 1190 (C=S), 900-850 (substituted aryl). ^1H NMR (DMSO- d_6) δ (ppm): 4 (1H, methine), 8-7.6 (m, 6H, aromatic H), 8.8 (1H, $\alpha\text{-C}_2\text{-H}$), 10.8 (s, 1H, OH). ^{13}C NMR (DMSO- d_6) δ (ppm): 180 (C=S), 168 (C=O), 145 (C=C), 130-120 (aromatic carbons). Analytical data for $\text{C}_{14}\text{H}_9\text{NO}_2\text{S}_2$ (287), Calcd.: C, 58.53; H, 3.13; N, 4.87; S, 22.29 %. Found: C, 58.27; H, 3.11; N, 4.55; S, 22.0 %.

2-Hydrazino-7H-6-(2'-hydroxynaphthalen)thiazolo-[5,4-d]pyrazole (3**):** A mixture of compound **2** (2.87 g, 0.01 mol) and hydrazine hydrate (100 %, 2.5 g, 0.05 mol) in absolute ethanol (100 mL) with piperidine (few drops) refluxed for 8 h. Cooled then poured onto ice. The solid produced filtered off and crystallized from EtOH, to give compound **3**, yield (2.49 g, 84.3 %): m.p. 305-306 °C. UV (DMF): 410 nm. IR (KBr, ν_{max} , cm^{-1}): 3400-3100 (phenolic OH), 3350 (NH_2), 3080 (NH), 1590 (C=N), 880-850 (substituted aryl). ^1H NMR (DMSO- d_6) δ (ppm): 11 (s, 1H, NH), 3.5 (s, 2H, NH_2), 10.5 (s, 1H, OH, aryl), 8.8 (s, 1H, $\alpha\text{-C}_5\text{H}$), 7.63 (s, 1H), 7.5-7.4 (d, 2H), 7.3-7.1 (m, 2H), 7.10-7.01 (d, 2H) aromatic protons. ^{13}C NMR (DMSO- d_6) δ (ppm): 140 (C=N), 130-120 (aromatic carbons). Analytical data for $\text{C}_{14}\text{H}_{11}\text{N}_5\text{OS}$ (297): Calcd.: C, 56.56; H, 3.30; N, 23.56; S, 10.77 %. Found: C, 56.36; H, 3.11; N, 23.22; S, 10.55 %.

2-[3',5'-Diaminopyrazol-1'-yl]-7H-6-(2'-hydroxynaphthalene)thiazolo[5,4-d]pyrazole (4): Equimolar mixture of compound **3** (2.97 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) in abs. ethanol (100 mL) with piperidine (few drops) refluxed for 4 h. Cooled and then poured onto ice. The solid obtained filtered off and crystallized from DMF, to give compound **4**, yield (2.32 g, 78.2 %): m.p. 332-335 °C. UV (DMF): 274 nm. IR (KBr, $\nu_{\max}$, cm^{-1}): 3400-3300 (phenolic OH and NH_2), 1594 ($\text{C}=\text{N}$), 1359 (NCS), 817 (substituted aryl). ^1H NMR ($\text{DMSO}-d_6$) δ (ppm): 10.55 (s, 1H, OH), 8.55 (s, 1H, $\alpha\text{-C}_5\text{H}$), 8.1 (s, 1H, C_4 of pyrazole), 3.8-3.55 (4H, 2NH_2), 7.70-7.10 (m, 6H, aromatic protons). Analytical data for $\text{C}_{17}\text{H}_{13}\text{N}_7\text{OS}$ (366): Calcd.: C, 56.55; H, 3.55; N, 26.77; S, 8.74 %. Found: C, 56.32; H, 3.25; N, 26.40; S, 8.52 %.

2-[3',5'-Dioxo-2',3',4',5'-tetrahydropyrazol-1'-yl]-7H-6-(2'-hydroxynaphthalene)-thiazolo[5,4-d]pyrazole (5): A mixture of compound **3** (2.97 g, 0.01 mol) and malonic acid (1.04 g, 0.01 mol) in glacial acetic acid (50 mL) refluxed for 4 h. Cooled and then poured onto ice. The solid obtained filtered off and crystallized from DMF, to give compound **5**, yield (3.16 g, 86.4 %): m.p. 334-337 °C. UV (DMF): 445 nm. IR (KBr, $\nu_{\max}$, cm^{-1}): 3400-3200 (phenolic OH and NH), 1700-1670 ($2\text{C}=\text{O}$), 1575 ($\text{C}=\text{N}$), 1466 (deformation CH_2), 831 (substituted aryl). ^1H NMR ($\text{DMSO}-d_6$) δ (ppm): 13.14 (s, 1H, NH), 10.82 (s, 1H, OH), 8.14 (s, 1H, $\alpha\text{-C}_5\text{H}$), 7.9-7.07 (m, 6H, aromatic protons), 3.7-3.69 (m, 2H, CH_2). ^{13}C NMR ($\text{DMSO}-d_6$) δ (ppm): 161 ($\text{C}=\text{O}$), 134 ($\text{C}=\text{N}$), 128-118 (aromatic carbons), 108 ($\text{C}-\text{C}$) 40-39.13 (CH_2). M/S (Int. %) 3.66 (1.11), 276 (15.9), 217 (5.6), 143 (100), 89 (12.11), 71 (5.1), 67 (23.0). Analytical data for $\text{C}_{17}\text{H}_{11}\text{N}_5\text{O}_3\text{S}$ (368): Calcd.: C, 56.25; H, 2.98; N, 19.02; S, 8.69 %. Found: C, 56.01; H, 2.70; N, 18.85; S, 8.53 %.

2-[3'-Phenyl-5'-oxo-4',5'-dihydropyrazol-1'-yl]-7H-6-(2'-hydroxynaphthalene)thiazolo[5,4-d]pyrazole (6): A mixture of compound **3** (2.97 g, 0.01 mol) and ethyl benzoyl acetate (1.92 g, 0.01 mol) in absolute EtOH (50 mL) with piperidine (few drops) refluxed for 4 h. Cooled and then poured onto ice. The solid obtained filtered off and crystallized from DMF to give compound **6**, yield (3.6 g, 79 %): m.p. 321-324 °C. IR (KBr, $\nu_{\max}$, cm^{-1}): 3300 (phenolic OH), 1682 ($\text{C}=\text{O}$), 1595 ($\text{C}=\text{N}$), 1447 (deformation CH_2), 817 (substituted aryl). ^1H NMR ($\text{DMSO}-d_6$) δ (ppm): 10.3 (s, 1H, OH), 8.2 (s, 1H, $\alpha\text{-C}_5\text{H}$), 7.9-7.2 (m, 6H, aryl), 7.1-6.9 (m, 4H, phenyl), 4.0 (s, 2H, $\text{CH}_2\text{-C}=\text{O}$). Analytical data for $\text{C}_{23}\text{H}_{15}\text{N}_5\text{O}_2\text{S}$ (425): Calcd.: C, 64.94; H, 3.52; N, 16.47; S, 7.52 %. Found: C, 64.71; H, 3.22; N, 16.25; S, 7.33 %.

2-[3',5'-Diphenyl-4',5'-dihydropyrazol-1'-yl]-7H-6-(2'-hydroxynaphthalene)thiazolo[5,4-d]pyrazole (7): A mixture of compound **3** (2.97 g, 0.01 mol) and benzyl benzoyl acetate (2.54 g, 0.01 mol) in absolute EtOH (50 mL) with piperidine (few drops) refluxed for 4 h. Cooled and then poured onto ice. The solid produced filtered off and crystallized from DMF to give compound **7**, yield (3.7 g, 76 %): m.p. 319-322 °C. UV (DMF): 292 nm. IR (KBr, $\nu_{\max}$, cm^{-1}): 3010 (aromatic CH), 2939 (aliphatic CH), 1595 ($\text{C}=\text{N}$), 1447 (deformation CH_2), 817.83 (substituted aryl). ^1H NMR ($\text{DMSO}-d_6$) δ (ppm): 10.1 (s, 1H, OH), 8.2 (s, 1H $\alpha\text{-C}_5\text{H}$), 8.04-7.25 (m, 16H, aromatic), 4.59 (d, 1H, $\text{C}_5\text{-pyrazole}$), 2.8 (m, 2H, CH_2). ^{13}C NMR ($\text{DMSO}-$

d_6) δ (ppm): 148, 144, 140 ($\text{C}=\text{N}$), 130-125 (aromatic carbons), 68 ($-\text{CH}-$), 42 (CH_2 carbon). Analytical data for $\text{C}_{29}\text{H}_{21}\text{N}_5\text{SO}$ (487): Calcd.: C, 71.45; H, 4.31; N, 14.45; S, 6.57 %. Found: C, 71.20; H, 4.11; N, 14.30; S, 6.25 %.

2-[1',4'-Dioxo-3'-hydrophthalazin-2'-yl]-7H-6-(2'-hydroxynaphthalene)thiazolo[5,4-d]pyrazole (8): A mixture of compound **3** (2.97 g, 0.01 mol) and phthalic anhydride (1.48 g, 0.01 mol) in glacial acetic acid (50 mL) refluxed for 4 h. Cooled and then poured onto ice. The solid produced filtered off and crystallized from DMF, to give compound **8**, yield (3.46 g, 85.2 %): m.p. 341-344 °C. IR (KBr, $\nu_{\max}$, cm^{-1}): 3400-3300 (phenolic OH-NH), 1680 ($\text{C}=\text{O}$), 1556 ($\text{C}=\text{N}$), 1350 (NCS), 830 (substituted aryl). ^1H NMR ($\text{DMSO}-d_6$) δ (ppm): 12.9 (s, 1H, NH), 10.55 (s, 1H, OH), 8.8 (s, 1H $\alpha\text{-C}_5\text{H}$), 8.20-8.02, 7.89-7.72, 7.70-7.65, 7.55-7.22 (each d 10H, aromatic). ^{13}C NMR ($\text{DMSO}-d_6$) δ (ppm): 172, 166 ($2\text{C}=\text{O}$), 140 ($\text{C}=\text{N}$), 132-122 (aromatic carbons). M/S (Int. %) 428 (0.11), 276 (3.18), 161 (25.11), 217 (18.0), 143 (100), 152 (80). Analytical data for $\text{C}_{22}\text{H}_{13}\text{N}_5\text{O}_3\text{S}$ (427): Calcd.: C, 61.55; H, 3.04; N, 16.39; S, 7.49 %. Found: C, 61.55; H, 2.88; N, 16.15; S, 7.29 %.

(Z)-N-((Z)-1-(4'-Chlorophenyl)-3-(7'H-6'-(2''-hydroxynaphthalen)thiazolo[5,4]pyrazol-2'-yl-hydrazinyl)-3-oxoprop-1-en-2-yl)benzimidic acid (10): A mixture of compound **3** (2.97 g, 0.01 mol) and oxazolinone (**9**) (2.84 g, 0.01 mol) in aq. EtOH (100 mL) refluxed for 1 h. Cooled and then poured onto ice. The solid obtained filtered off and crystallized from DMF to give compound **10**, yield (4.56 g, 78.5 %): m.p. 342-346 °C. UV (DMF): 430 nm. IR (KBr, $\nu_{\max}$, cm^{-1}): 3462 (phenolic OH), 2600 (alcoholic OH), 3150 (NH), 1662 ($\text{C}=\text{O}$), 1620 ($\text{C}=\text{C}$), 1579 ($\text{C}=\text{N}$), 831 (substituted aryl), 679 ($\text{C}-\text{Cl}$). Analytical data for $\text{C}_{30}\text{H}_{20}\text{N}_6\text{SO}_3$ (544): Calcd.: C, 66.17; H, 3.67; N, 15.44; S, 5.88 %. Found: C, 65.89; H, 3.51; N, 15.30; S, 5.55 %.

2-(3'-Phenyl-6'-oxo-5'-chlorobenzylidene-1',2'-dihydro-1,2,4-triazin-2'-yl)-7H-6-(2'-hydroxynaphthalene)thiazolo[5,4-d]pyrazole (11): Compound **10** (5.8 g, 0.01 mol) with aq. K_2CO_3 (10 %, 50 mL) refluxed for 2 h. Cooled and then poured onto ice-HCl. The solid produced filtered off and crystallized from DMF, to give compound **11**, yield (4.5 g, 81 %): m.p. 355-356 °C. UV (DMF): 420 nm. IR (KBr, $\nu_{\max}$, cm^{-1}): 3462 (phenolic OH), 3160 (NH), 1663 ($\text{C}=\text{O}$), 1579 ($\text{C}=\text{N}$), 1320 (NSC), 831 (substituted aryl) ($\text{C}-\text{Cl}$). ^1H NMR ($\text{DMSO}-d_6$) δ (ppm): 11.8 (s, 1H, NH), 10.55 (s, 1H, OH), 8.9 (s, 1H, $\text{exo CH}=\text{C}$), 8.55 (s, 1H $\alpha\text{-C}_5\text{H}$), 7.9-7.66 (m, 6H, naphthyl), 7.2-6.7 (m, 4H, phenyl). Analytical data for $\text{C}_{30}\text{H}_{19}\text{N}_6\text{O}_2\text{SCl}$ (561): Calcd.: C, 64.17; H, 3.38; N, 14.97; S, 5.70 Cl, 6.23 %. Found: C, 64.00; H, 3.20; N, 14.71; S, 5.39 Cl, 6.00 %.

Biological evaluation (antibacterial activity): Rhodanine structure contains hydrogen bond acceptor (A), hydrogen bond donor (D), hydrophobic (H), positive ionic center (P), negative ionic center (N). Also, rhodanine structure characterized by a tautomer's generating possible stereoisomers which generating low energy ring conformations. Thus, rhodanine and its analogues have a various pharmacological and biological activities. Based upon these observation, we synthesized a novel heterobicyclic nitrogen systems starting from rhodanine (**1**).

In search for new antibacterial agents, the present work, report a new synthetic of possible targets. All the synthesized compounds were evaluated as anti-bacterial agents, against

Escherichia coli (Gram-negative) and *Staphylococcus aureus* (Gram-positive).

The new compounds used at different concentrations (0.1 and 0.2 %) and the examined for antibacterial activity according to the reported method [11] (a mixture of meat extract, 5.0 g; peptone, 5.0 g; NaCl, 5.0 g and distilled water, 1000 mL). Streptomycin and tetracycline were used as controls for Gram-positive and Gram-negative bacteria, respectively.

The inhibiting zone was measured by the millimeters. The evaluation was based on the following criteria: ≥ 25 mm is very strong; ≥ 20 mm is strong; ≥ 15 mm is medium; ≤ 10 mm is weak anti-bacterial activity.

The results obtained, were reported in the Table-1 and can be conclude that: (i) All the tested compounds have a degree of biocidal activity due to presence of 2-hydroxynaphthalene moiety (as bacterial agents). (ii) Heterocyclic systems containing pyrazole exhibited a very strong antimicrobial activity to wards *E. coli*. (iii) Other tested compounds, recorded a medium activity towards both the tested bacteria. (iv) All the synthesized compounds showed a higher degree of activity towards *E. coli*, in compare with *S. aureus*, which agree with reported results.

TABLE-1
ANTIBACTERIAL ACTIVITY OF THE
SYNTHESIZED COMPOUNDS (mm)

Compd. No.	Concentration (%)	<i>E. coli</i>	<i>S. aureus</i>
4	0.1	18	16
	0.2	20	18
5	0.1	30	26
	0.2	35	28
6	0.1	27	22
	0.2	29	24
7	0.1	16	15
	0.2	18	17
8	0.1	18	16
	0.2	20	20
10	0.1	14	16
	0.2	16	20
11	0.1	12	25
	0.2	14	27

RESULTS AND DISCUSSION

Recently, chemistry and applications of the rhodanine derivatives are reviewed [12,13]. Also, pyrazoles showed an important properties in many fields [4]. In an extension of these attempts, condensation of rhodanine (2-thioxo-thiazolidin-4-one) (**1**) with 2-hydroxynaphthalene carboxaldehyde in boiled ethanol-piperidine yielded the arylidene (**2**) which on refluxed with excess hydrazine hydrate in ethanol-piperidine produced 2-hydrazino-7H-6-(2'-hydroxyaphthalen)thiazolo[5,4-d]-pyrazole (**3**) as starting material for the building of novel heteropolycyclic nitrogen systems as biocidal agents (**Scheme-I**).

Structure of compound **3** was deduced from elemental analysis and spectral data. UV absorption recorded $\lambda_{\max}$ 410 nm due to highly extension heterocyclic conjugation systems formed. IR spectrum showed ν at 3400 and 1600 cm^{-1} attribute to OH and C=N groups. ^1H NMR spectrum recorded the diastereotopic ^1H and ^2H appears as a doublet of doublets (A B system)

Scheme-I: Formation of compound **3** from **1**

at 4 ppm of methane protons, in addition of both NH & NH₂ protons at 11 and 3.5 ppm. ^{13}C NMR spectrum showed a lack of both C=S and C=C carbons.

Cyclocondensation reaction of compound **3** with 1,3-bifunctional reagents such as malononitrile (ethanol-piperidine), malonic acid (glacial acetic acid), ethylbenzoyl acetate (ethanol-piperidine) and chalcone (ethanol-piperidine) via ring closure reaction afforded 1,3,5-trisubstituted pyrazoles (**4-7**), respectively (**Scheme-II**).

The structure of new compounds **4-7** has been established upon correct elemental analysis and spectral data. UV absorption of compound **4** showed $\lambda_{\max}$ at 274 nm. While IR spectrum of compound **5** recorded bands at ν 3287, 1700 and 1695 cm^{-1} NH and 2 C=O. ^{13}C NMR spectrum of compound **5** exhibited a different type of carbons at δ 161 (C=O), 134 (C=N), 128-118 (arom. carbons), 108 (C-C) and 40-39.13 ppm (CH₂) carbons. M/s spectrum of compound **5** showed a molecular ion peak at 366 with m/e at 143 as base peak.

El-Gendy *et al.* [5] reported a synthesis of phthalazine-1,4-dione bearing various heterocyclic systems as antifungal agents. Similarly, refluxed compound **3** with phthalic anhydride in glacial acetic acid isolated 2-[1',4'-dioxo-3'-hydroxyphthalazin-2'-yl]-7H-6-(2'-hydroxynaphthalen)thiazolo[5,4-d]pyrazole (**8**) (**Scheme-III**). Structure of compound **8** deduced from elemental analyses and its spectral measurements. UV absorption showed $\lambda_{\max}$ below that of parent compound **3**, which is due to an inhibition of heteroconjugation system. IR spectrum recorded ν at 3200-3100, 1700-1680 cm^{-1} for NH and C=O groups of phthalazine. In addition ν at 1620-721 cm^{-1} for CH=CH and C-Cl groups. M/s spectrum recorded molecular ion peak at m/z 428 with 143 as a base peak (2-hydroxynaphthalene ion).

Abdel-Rahman *et al.* [10] synthesized various 1,2,4-triazine derivatives as pharmacological, medicinal and antimicrobial agents based upon these results 2-(3'-phenyl-6'-oxo-5'-arylidene-

Scheme-II: Formation of compounds 4-7

Scheme-III: Formation of compound 8

1'-H-1,2,4-triazin-2'-yl)-7H-6-(2'-hydroxynaphthalene)thiazolo[5,4-d]pyrazole (**11**) was synthesized from the interaction between compound **3** with oxazol-5-one (**9**) in aqueous ethanol to give the acid hydrazide **10** followed by ring closure reaction in warmed aqueous K_2CO_3 (Scheme-IV).

Structure of compound **11** was established from elemental analyses and its spectral data. UV absorption spectra recorded λ_{max} 420 nm, which attributed to new heteroconjugation system forward. IR spectrum showed a characteristic bands at ν at

Scheme-IV: Formation of compounds 10 and 11

3100, 1680, 1600, 700 and 3500 cm^{-1} for NH, C=O, C=C, C=Cl and C=OH functional groups, respectively. ^1H NMR spectrum exhibited δ at 11.80, 10.55, 8.9 and 8.55 ppm for NH, OH, exo CH=C and $\alpha\text{-C=H}$ (thiazolopyrazole), respectively as well as at 7.90-7.66, 7.20-6.70 ppm attribute to aromatic protons.

Conclusion

Synthetic routes for new heterocyclic nitrogen systems bearing thiazolopyrazole moiety derived from arylidene rhodanine drug were developed for structure-activity relationship study. The improved potency of these systems was possibly due to an increase in binding interactions of hydroxyphenolic group with an NH_2 or NH residues of the tested microorganism *via* the inter and/or intra H-bonding.

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