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RESEARCH ARTICLE

SYNTHESIS OF NEW HETEROCYCLIC COMPOUNDS DERIVED FROM 3-*P*-TOLYL-2-THIOXO-1, 3-THIAZOLIDINE-4-ONE AND EVALUATION OF THEIR ANTIBACTERIAL ACTIVITY

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ABSTRACT

In an effort to discover new biologically active compounds, a series of new heterocyclic compounds have been synthesized from the 3-p-tolyl-2-thioxo-1,3-thiazolidine-4-one (1) and its brominated derivative 5-bromo-3-p-tolyl-2-thioxo-1,3-thiazolidin-4-one (2). Reaction of 1 with 3-benzyloxybenzaldehyde gave the arylidine 3, which either by the reaction with malononitrile gave the pyrano[2,3-*d*]thiazole 4, or by the reaction with cyanothioacetamide gavethe thiazolo[4,5-*b*]pyridine 5. Condensation of 1 with ethylformate and cyanothioacetamide gave the thiazolopyridine 6. Treatment of 1 with triethylorthoformate gave the 5-ethoxymethylene derivative 7, and with phosphorous pentachloride and dimethylformamide gave the dimethylaminomethylene derivative 8. Condensation of 1 with isatin, tetrachlorophthalic anhydride and pyromellitic dianhydride afforded the corresponding 9, 10 and 11, respectively. Treatment of the 5-bromo-rhodanine 2 with hydrazine hydrate gave the 5-hyrazinoderivative 12, which reacted with ethoxymethylene malononitrile to give the pyrazole derivative 13. Reaction of 2 with amino-compounds such as, 2-amino-5-phenyl-1,3,4-thiadiazole, 3-amino-5,6-diphenyl-1,2,4-triazine, *o*-, and *p*-phenylenediamine afforded 14, 15, 16 and 17, respectively. The reaction of 2 with thioacetamide gave the thiazolothiazole 18. Treatment of 2 with carbon disulfide and *p*-toluidine afforded the corresponding *p*-tolyl-dithiocarbamicester 19, which cyclized in ethanol and pipredine to give the thiazolothiazole 20. The chemical structures of the prepared compounds were characterized by their elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR and Mass spectra. Investigation of the antibacterial activity of these compounds was done by the paper disc technique. Some of the tested compounds showed high and favorable antibacterial activity.

INTRODUCTION

Rhodanine derivatives (2-thioxo-1,3-thiazolidin-4-ones) have been widely investigated for a range of pharmacological activities (Sachin *et al*., 2011), such as antidiabetic (Zask *et al*., 1990), antihyperglycemic (Cantello *et al*., 1994), anticancer (Tokumitsu *et al.,* 2002; Vadla *et al*., 2014), antibacterial (Gualtieri *et al*., 2006; Ming-Xia *et al.,* 2012), antifungal (Sortino et al., 2007; Habib *et al*., 1997), antitubercular (Chandrappa*et al*., 2009; Brooke *et al*., 2003), anti-HIV (Ozkirimli *et al*., 2009), antiviral, anticonvulsant (Verma and Saraf, 2008) and anti-inflammatory effects (Delerive *et al*., 2001). In view of a wide spectrum of biological properties of the rhodanine derivatives, the intention of the present work was the synthesis of new heterocyclic compounds derived from 3-*p*-tolyl-2-thioxo-1,3-thiazolidine-4-one (1) and 5-bromo-3-*p*-tolyl-2-thioxo-1,3-thiazolidin-4-one (2), with the purpose of investigating their possible antibacterial activity against Gram-positive and Gram-negative bacteria.

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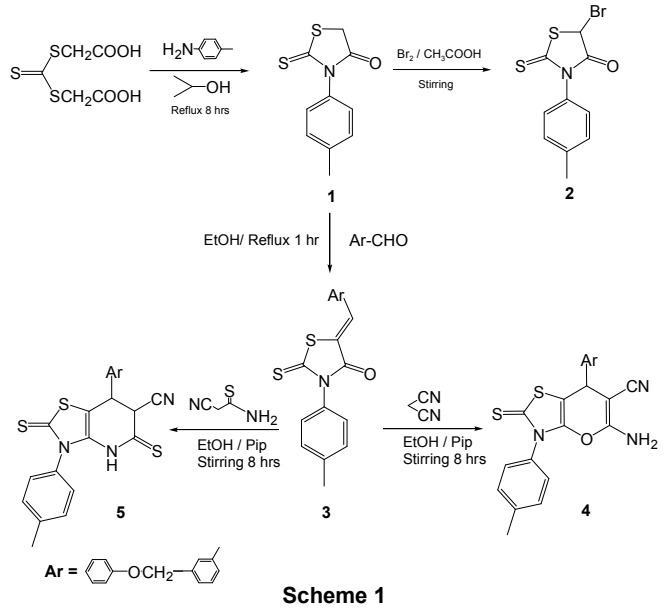
RESULTS AND DISCUSSION

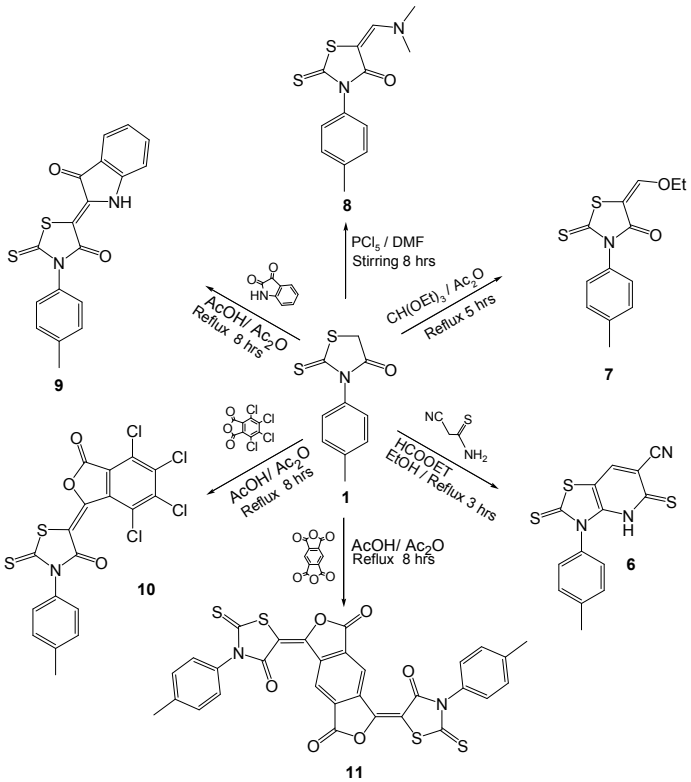
In continuation of the previous studies (Ahmed Abo-Bakr, 2013a; 2014b) in synthesis of some new biologically active heterocyclic compounds, 3-*p*-tolyl-2-thioxo-1,3-thiazolidine-4-one (1) and 5-bromo-3-*p*-tolyl-2-thioxo-1,3-thiazolidin-4-one (2) were used as starting materials for this purpose. Compound 1 was prepared according to *Lesyk et al.* (2009) by reaction of thiocarbonyl-bis-thioglycolic acid and *p*-toluidine in isopropanol, while compound 2 was prepared by bromination of 1 in acetic acid (Gakhar *et al*., 1975) (Scheme 1). In the present work, boiling of compound 1 in ethanolic solution of 3-benzloxy-benzaldehyde in presence of few drops of pipredine afforded the corresponding arylidine 3. The mass spectrum of compound 3 showed molecular ion peak at *m/z*= 417 corresponding to the formula ($C_{24}H_{19}NO_2S_2$). Refluxing of arylidine 3 with malononitrile and/or cyanothioacetamide in ethanolic pipredine solution gave the corresponding pyrano[2,3-*d*]thiazole 4 and thiazolo[4,5-*b*] pyridine 5, respectively (Scheme 1). The IR spectra of 4 and 5 showed absorption bands at 2230 and 2225 cm^{-1} for the (CN) group, respectively. The ^{1}H NMR spectrum of compound 4 exhibited

singlet protons at δ 4.58 corresponding to the (NH_2) group, and the ^{1}H NMR spectrum of 5 showed a singlet proton at δ 10.02 for the (NH) group.



Scheme 1

The multicomponent domino reaction of 1 with ethylformate and cyanothioacetamide afforded the corresponding 2,5-dithioxo-thiazolo[4,5-*b*]pyridine 6. Refluxing of the rhodanine 1 with with triethylorthoformate in acetic anhydride gave the 5-ethoxymethylene derivative 7, and stirring of 1 with phosphorous pentachloride and dimethylformamide for 8 hrs gave the dimethylaminomethylene derivative 8 (Scheme 2).



Scheme 2

The elemental analyses and spectroscopic data are consistent with the assigned structures of 6, 7 and 8 [Experimental part].

Boiling of rhodanine 1 with isatin, tetrachlorophthalic anhydride and pyromellitic dianhydride in acetic acid/ acetic anhydride mixture for 8 hrs afforded the corresponding derivatives of 1,2-dihydro-indol-3-one 9, 3-oxo-3H-isobenzofuran 10 and 3,7-dihydro-benzo[1,2-c;4,5-c']difuran-1,5-dione 11, respectively (Scheme 2).

The chemical structures of 9, 10 and 11 were confirmed from their IR, ^{1}H NMR, MS and elemental analyses. The mass spectra showed molecular ion peak at *m/z*= 352 for compound 9, at *m/z*=491 for compound 10 and at *m/z*=628 for compound 11 which were in agreement with assigned structures. The ^{1}H NMR spectrum of compound 11 indicates the presence of a singlet two identical benzene protons at δ 7.78 in addition to eight aromatic protons at δ 7.46-7.09 (dd, A_2B_2 system), and the ^{13}C NMR spectrum showed thirteen different signals for thirteen different carbon atoms which adds additional confirmation for the proposed structure (Figure 1). On the other hand, stirring of 5-bromo-rhodanine 2 with hydrazine hydrate in ethanol gave 5-hyrazino-2-thioxo-3-*p*-tolyl-thiazolidin-4-one 12, which upon heating with ethoxymethylene malononitrile gave 5-amino-pyrazole-4-carbonitrile derivative 13 (Scheme 3). Elucidation of the chemical structures of compounds 12 and 13 was based on its spectroscopic data [Experimental part].

Hoping to expand the biological activity investigation of these derivatives, compound 2 was next reacted with amino-compounds such as 2-amino-5-phenyl-1,3,4-thiadiazole, 3-amino-5,6-diphenyl-1,2,4-triazine, *o*-, and *p*-phenylenediamine in dioxane/ potassium carbonate to give the corresponding 14, 15, 16 and 17, respectively (Scheme 3). The structures of compounds 14, 15, 16 and 17 were in agreement with their spectral data and elemental analyses. The mass spectra showed molecular ion peak at *m/z*= 380 for compound 14, at *m/z*=451 for compound 15, at *m/z*=311 for compound 16 and at m/z=550 for compound 17. Figure 2 shows the fragmentation pattern for Benzene-1,4-bis(5-amino-2-thioxo-3-p-tolyl-thiazolidin-4-one) (17) which confirms the proposed structure. The ^{1}H NMR spectra of compounds 16 and 17 showed singlet two protons for the two (NH) protons at δ 4.18 ppm for 16 and at δ 4.34 ppm for 17. Also, the ^{1}H NMR spectrum of 17 indicates the presence of a singlet two protons at δ 4.65 for the two thiazolidinone rings protons. When compound 2 was allowed to react with thioacetamide in dioxane/ K_2CO_3, compound 18 assigned as 5-Methyl-3-p-tolyl-3H-thiazolo[4,5-d]thiazole-2-thione was obtained (Scheme 3). The mass spectrum showed molecular ion peak at *m/z*= 278 corresponding to the formula ($C_{12}H_{10}N_2O_2S_3$), and the ^{1}H NMR spectrum exhibited two singlets at δ 2.77 and at δ 2.32 for the two methyles. In dimethylformamide, compound 2 was treated with an equimolar mixture of *p*-toluidine and carbon disulfide in presence of potassium phosphate to give the corresponding 19. A cyclic condensation of compound 19 through losing of water in ethanolic piperidine solution afforded compound 20 assigned as 3,4-di-*p*-tolyl-3H,4H-thiazolo[4,5-*d*]thiazole-2,5-dithione (Scheme 3). The structure of 20 was confirmed from its IR, ^{1}H NMR, MS and elemental analysis. The ^{13}C NMR spectrum of compound 20 showed eight different signals for eight different carbon atoms, which gives a great evidence for the proposed structure [Experimental part].

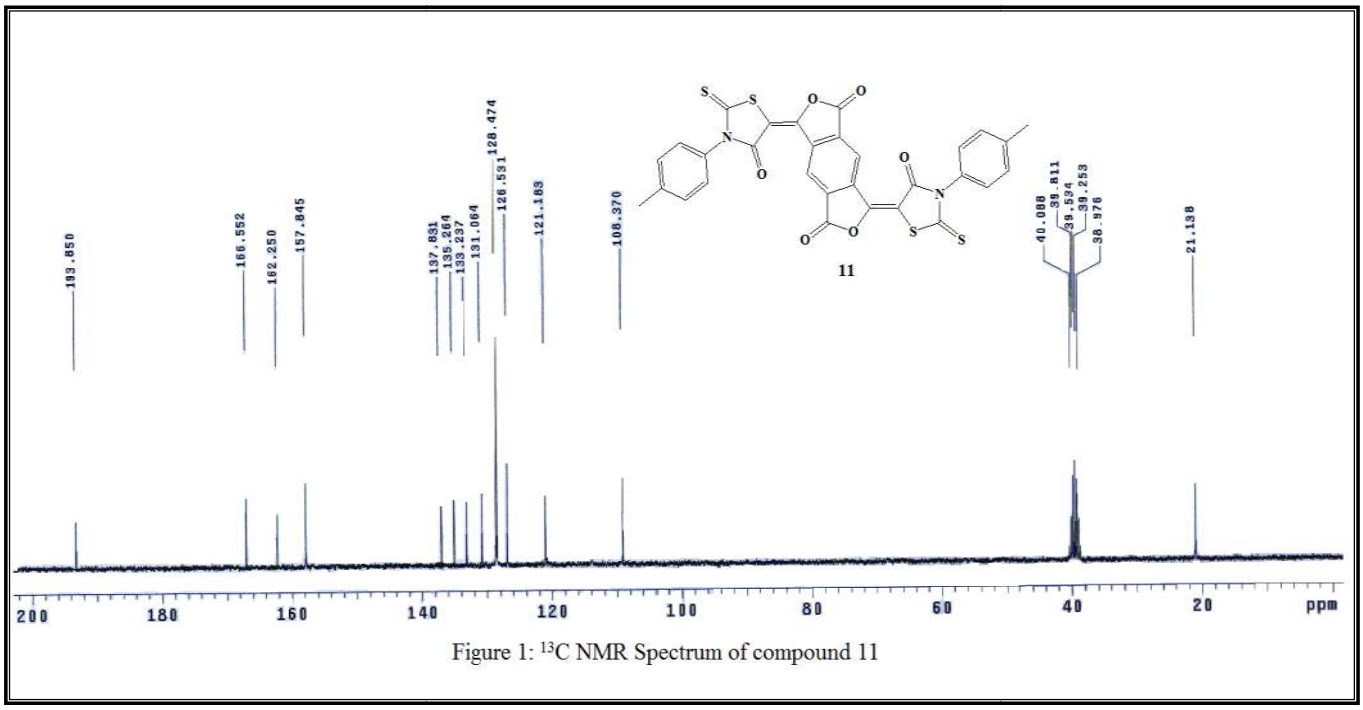


Figure 1: ^{13}C NMR Spectrum of compound 11

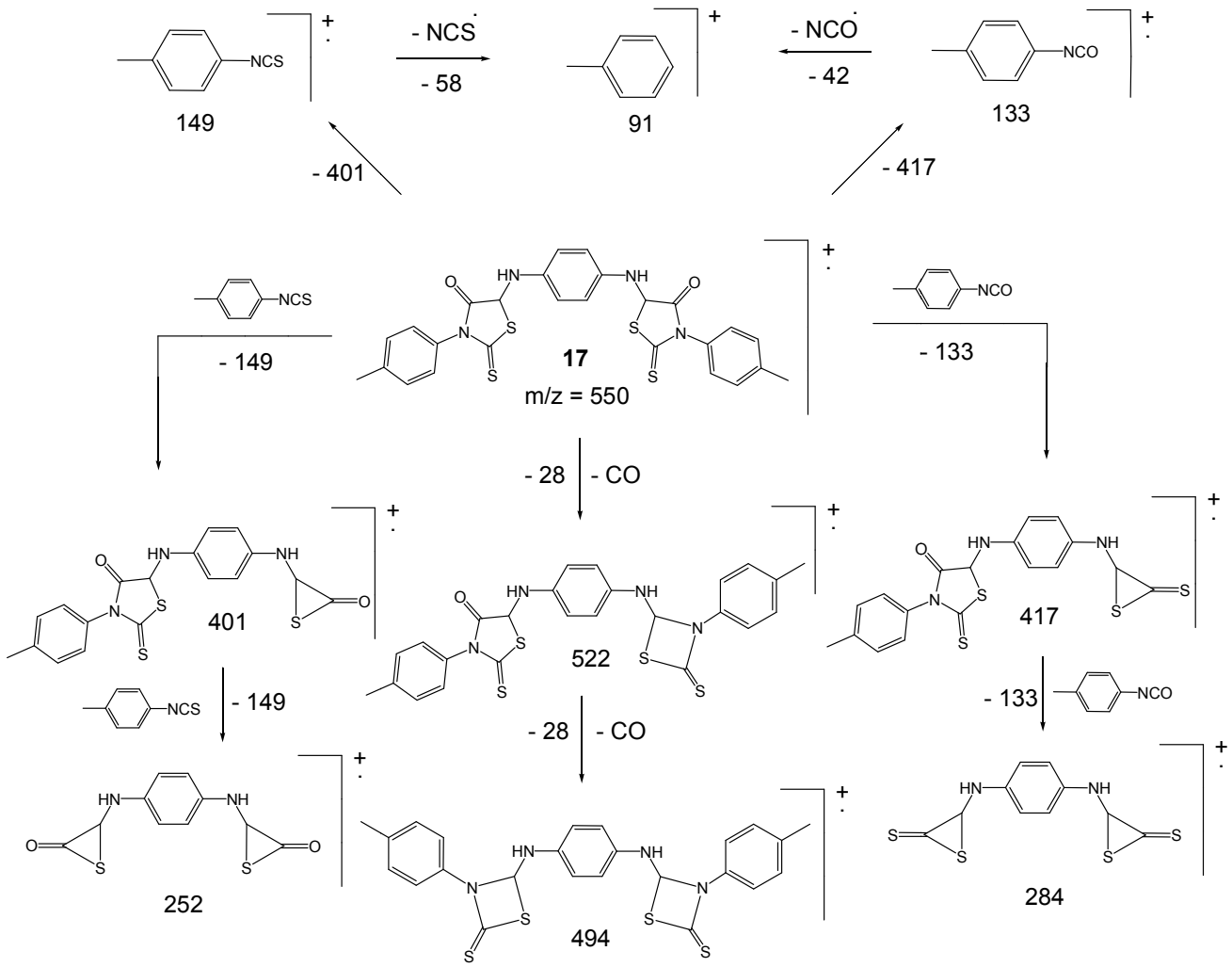
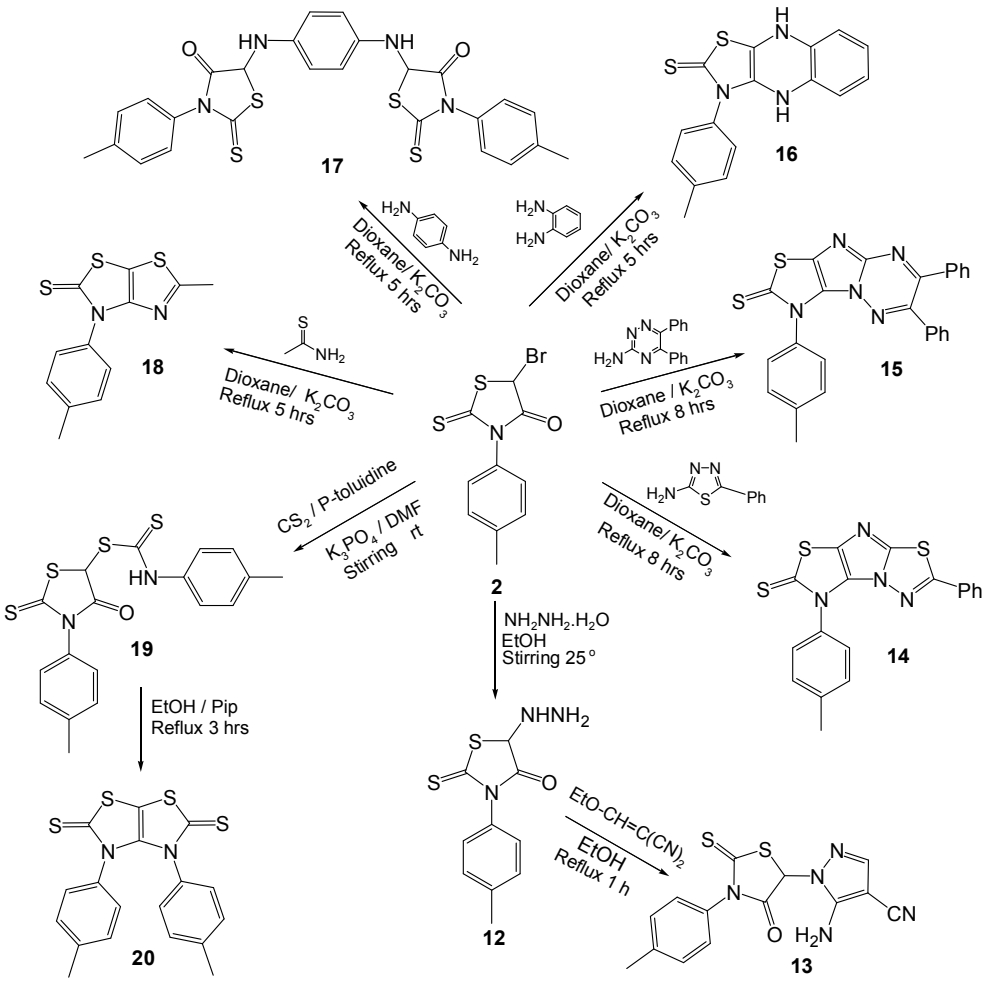


Figure 2



Scheme 3

Antibacterial activity

Bacterial source and culture condition

The used Bacterial strains were Gram negative bacteria including *E. Coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 278223) and Gram positive bacteria *Enterococcus faecalis* (ATCC 29212). Mueller-Hinton Agar was used as culture media (gl^{-1}) (Mueller and Hinton, 1941): Beef extract, 3.0; Peptone, 17.5; Starch, 1.5; Agar, 17, pH= 7.3 ± 0.1. The plates were incubated at 37ºC for 24 – 48 hrs.

Paper disc technique

Antibacterial activity was determined against the above strains using the paper disc assay method (Omenka *et al*., 2000). Whatman number 1 filter paper disc of 6.0 mm diameter was sterilized by autoclaving for 20 min at 121°C. The sterile discs were impregnated with the spaced apart and plates were incubated at 37°C for 24- 48 hrs (Bauer *et al*., 1966). *Chloramphenicol* 50μg/disc was used as a positive control. Diameter of the growth inhibition halos caused by the tested compounds were measured and expressed in millimeter. All the assays were carried out in triplicate. *E. coli* (Escherichia coli) is the name of a germ, or bacterium that lives in the digestive tracts of humans and animals. Many types of *E. coli* can cause bloody diarrhea and urinary tract infections. Some strains of *E. coli* bacteria may also cause severe anemia or kidney failure (Ann Abraham, 2012). *Pseudomonas aeruginosa* cause diseases like mastitis, abortion and upper respiratory complications (Zafer *et al*., 2010).

Table 1. Antibacterial response of compounds 3- 20

Sample No.	Bacterial growth inhibition zone diameter (mm)		
	Gram (-ve) Bacteria *Pseudomonas aeruginosa*	*Gram (-ve)* Bacteria *E. Coli*	*Gram (+ve)* Bacteria *Enterococcus faecalis*
3	7	9	8
4	9	8	-----
5	9	7	8
6	8	7	-----
7	-----	6	-----
8	12	10	16
9	6	7	-----
10	12	9	11
11	-----	8	5
12	14	12	17
13	12	11	7
14	5	-----	7
15	-----	-----	-----
16	7	8	-----
17	11	10	12
18	-----	------	-----
19	12	9	11
20	7	7	9
Chloramphenicol 50 μg (Control)	17	18	21.5

(----) *No bacterial growth inhibition zone.*

P. Aeruginosa is an important and prevalent pathogen among burned patients capable of causing life threatening illness (Vijesh *et al*., 2013). Also, *Enterococci* are Gram-positive *cocci* that often occur in pairs (diplococci) or short chains. The important clinical infections caused by *Enterococcus* include urinary tract infections, bacteremia, bacterial endocarditis, diverticulitis and meningitis (Fisher and Phillips, 2009). The antibacterial activity of the synthesized compounds 3- 20 was carried out on the growth of three pathogenic bacteria (*E. Coli*, *Pseudomonas aeruginosa* and *Enterococcus faecalis*) as shown in Table (1).

The data obtained in Table (1) indicate that 14/20, 15/20 and 11/20 of these compounds have a clear effect on *Pseudomonas aeruginosa*, *E. Coli* and *Enterococcus faecalis* bacteria, respectively. The greater inhibition effect against the three pathogenic bacteria was observed by the 5-hyrazino-rhodanine 12, 5-dimethylaminomethylene-rhodanine 8 and Benzene-1,4-bis(5-amino-rhodanine) 17 and showed high inhibition (10- 17 mm). Compounds 10, 13 and 19 showed moderate inhibition effect (9- 12 mm). The inhibition effect of compounds 3, 4, 5, 6, 7, 9, 11, 14, 16 and 20 was decreased on the three pathogenic bacteria (5- 9 mm). Also, it can be seen from Table (1) that the synthesized compounds 15 and 18 had no effect against the three kinds of bacteria.

Conclusion

In summary, 3-*p*-tolyl-2-thioxo-1,3-thiazolidine-4-one (1) and 5-bromo-3-*p*-tolyl-2-thioxo-1,3-thiazolidin-4-one (2) were used as precursors to synthesize some new biologically active heterocyclic compounds 3- 20. The structures of all synthesized compounds have been confirmed by elemental analyses, FT-IR, ^{1}H ^{13}C NMR and mass spectral data. The newly synthesized compounds were screened for *in vitro* antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa* and *Enterococcus faecalis*.

Compound 12 was found as a potent compound against the three kinds of bacteria. The antimicrobial activity screening revealed that compounds 8, 10, 13, 17 and 19 have significant high inhibition effect against *gram (-ve)* and *gram (+ve)* bacteria. Compounds 3, 4, 5, 6, 9, 11, 14, 16 and 20 showed moderate activity. The results are promising and show that the structures 8, 10, 12, 13, 17 and 19 can lead to some new antibacterial agents in treating infection of *E. coli*, *P. aeruginosa and E. faecalis*.

Experimental

Melting points (uncorrected) were recorded on an Electrothermal melting apparatus. The IR spectra were recorded on a Shimadzu FT-IR 8101 PC spectrometer. The ^{1}H and ^{13}C NMR spectra were determined in DMSO-d_6 at 300 MHz on a Varian Mercury VX 300 NMR spectrometer; Chemical shifts are reported in ppm with TMS as an internal standard and are given in δ units. Electron impact mass spectra were obtained at 70 eV using a GCMS-QP 1000 EX spectrometer. Elemental analyses, mass and NMR spectra were carried out at the Microanalytical Center of Cairo University.

***Synthesis of 5-(3-benzyloxy-benzylidene)-2-thioxo-3-p-tolyl-thiazolidin-4-one* (3)**

A mixture of compound 1 (2.2 gm, 10 mmol) and 4-benzyloxybenzaldehyde (2.1 gm, 10 mmol) in 30 ml absolute ethanol in presence of few drops of pipredine was refluxed for 1 h. After cooling, the solid obtained was filtered off and crystallized from acetic acid as yellowish white crystals. Yield 3.3 g (81%); mp 144-146°C; IR (KBr): 3023 (CH-aromatic), 2880 (CH-aliphatic), 1720 (C=O) cm^{-1}; ^{1}H NMR (DMSO-*d6*): δ 8.48 (s, 1H, =CH), 7.76-7.05 (m, 13H, Ar'H), 5.15 (s, 2H, O-CH_2Ph), 2.23 (s, 3H, CH_3); Ms: *m/z* 417 (M^{+}), 327, 241, 178, 150, 91; Anal. Calcd. for $C_{24}H_{19}NO_2S_2$: C, 69.06; H, 4.59; N, 3.35; S, 15.36. Found: C, 69.21; H, 4.46; N, 3.22; S, 15.45.

***Synthesis of 5-amino-7-(3-benzyloxy-phenyl)-2-thioxo-3-p-tolyl-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6 carbonitrile* (4) *and 7-(3-benzyloxy-phenyl)-5-mercapto-2-thioxo-3-p-tolyl-2,3,4,7-tetrahydro-thiazolo[4,5-b] pyridine-6-carbonitrile* (5):**

General procedure: To a solution of Compound **3** (4.1 gm, 10 mmol) in 30 ml ethanol, malononitrile and/or cynanothioacetamide (10 mmol) was added in presence of few drops of piperedine and the reaction mixture was stirring for 8 hrs. The precipitate was filtered off and crystallized from ethanol to give compound **4** and/or **5** respectively.

***5-amino-7-(3-benzyloxy-phenyl)-2-thioxo-3-p-tolyl-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile* (4)**

This compound was obtained as yellowish white crystals. Yield 3.4 g (72%); mp 202-204°C; IR (KBr): 3545, 3450 (NH_2), 3050 (CH-aromatic), 2850 (CH-aliphatic), 2230 (CN) cm^{-1}; ^{1}H NMR (DMSO-*d6*): δ 7.65-7.01 (m, 13H, Ar'H), 5.22 (s, 2H, O-CH_2Ph), 4.58 (s, 2H, NH2), 3.85 (s, 1H, CH), 2.25 (s, 3H, CH_3); Ms: *m/z* 483 (M^{+}), 412, 366, 190, 160, 118. Anal. Calcd. for $C_{27}H_{21}N_3O_2S_2$: C, 67.06; H, 4.38; N, 8.69; S, 13.26. Found: C, 67.12; H, 4.27; N, 8.50; S, 13.49.

***7-(3-benzyloxy-phenyl)-5-mercapto-2-thioxo-3-p-tolyl-2,3,4,7-tetrahydro-thiazolo[4,5-b]pyridine-6-carbonitrile* (5)**

This compound was obtained as yellow crystals, Yield 3.3 g (68%); mp 192-194°C; IR (KBr): 3314 (NH), 3020 (CH-aromatic), 2225 (CN), 1581 cm^{-1}; ^{1}H NMR (DMSO-*d6*): δ 10.02 (s, 1H, NH), 7.71-7.03 (m, 13H, Ar'H), 5.19 (s, 2H, O-CH_2Ph), 4.76 and 4.40 two (s, 1H, CH), 2.27 (s, 3H, CH_3); Ms: *m/z* 499 (M^{+}), 345, 196, 154, 133, 104. Anal. Calcd. for $C_{27}H_{21}N_3OS_3$: C, 64.90; H, 4.24; N, 8.41; S, 19.25. Found: C, 64.81; H, 4.32; N, 8.54; S, 19.13.

***Synthesis of 2,5-dithioxo-3-p-tolyl-2,3,4,5-tetrahydro-thiazolo[4,5-b]pyridine-6-carbonitrile* (6)**

To a solution of compound **1** (2.2 gm, 10 mmol) in 30 ml ethanol, ethyl formate (0.7 ml, 10 mmol) and freshly prepared cyanothioacetamide (1 gm, 10 mmol) was added in presence of few drops of pipredine and the reaction mixture was refluxed for 3 hrs. After cooling, the solid crystals were filtered off and crystallized from ethanol as yellow crystals. Yield 2.2 g (69%); mp 188-190°C; IR (KBr): 3320 (NH), 3028 (CH-aromatic), 2850 (CH-aliphatic), 2220 (CN), 1290 (C=S) cm^{-1}; ^{1}H NMR

(DMSO-*d6*): δ 10.11 (s, 1H, 1NH), 7.68 (s, 1H, =CH-C), 7.55-7.10 (dd, A_2B_2 system, 4H, Ar'H), 2.30 (s, 3H, CH_3); Ms: *m/z* 315 (M^+), 307, 272, 224, 154, 98; Anal. Calcd. for $C_{14}H_9N_3S_3$: C, 53.31; H, 2.88; N, 13.32; S, 30.50. Found: C, 53.37; H, 2.96; N, 13.23; S, 30.44.

***Synthesis of 5-Ethoxymethylene-2-thioxo-3-p-tolyl-thiazolidin-4-one* (7)**

A mixture of compound **1** (2.2 gm, 10 mmol) and 3 ml triethylorthoformate in 10 ml acetic anhydride was refluxed for 6 hrs, and then evaporated under reduced pressure. The residue was treated with ethanol, and the solid product formed was collected by filtration, washed with ethanol and crystallized from ethanol as yellowish white crystals. Yield 2.14 g (77%); mp 122-124°C; IR (KBr): 3030 (CH-aromatic), 2985 (CH_2), 1690 (C=O) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 8.12 (s, 1H, =CH-O), 7.41-7.08 (dd, A_2B_2 system, 4H, Ar'H), 3.98 (q, 2H, CH_2), 2.28 (s, 3H, CH_3), 1.32 (t, 3H, CH_3); Ms: *m/z* 279 (M^+), 205, 190, 177, 106, 95. Anal. Calcd. for $C_{13}H_{13}NOS_2$: C, 55.89; H, 4.69; N, 5.01; S, 22.95. Found: C, 55.77; H, 4.74; N, 5.13; S, 22.91.

***Synthesis of 5-dimethylaminomethylene-2-thioxo-3-p-tolyl-thiazolidin-4-one* (8)**

To a solution of compound **1** (2.2 gm, 10 mmol) in 20 ml dimethylformamide, phosphorous pentachloride (2 gm, 10 mmol) was added gradually with stirring and the stirring was continued for 8 hrs. The color of the reaction mixture changed from yellow to red. The reaction mixture was poured onto crushed ice. The solid obtained was filtered off washed with water, dried and crystallized from ethanol as pale yellow crystals. Yield 2.6 g (68%); mp 110-112°C; IR (KBr): 3025 (CH-aromatic), 2930 (CH_2), 1680 (C=O) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 7.99 (s, 1H, =CH-N), 7.49-7.01 (dd, A_2B_2 system, 4H, Ar'H), 3.27 (s, 6H, $(CH_3)_2$), 2.29 (s, 3H, CH_3); ms: *m/z* 278 (M^+), 263, 235, 181, 148, 100. Anal. Calcd. for $C_{13}H_{14}N_2OS_2$: C, 56.09; H, 5.06; N, 10.06; S, 23.04. Found: C, 56.00; H, 5.02; N, 10.11; S, 23.12.

Condensation of compound 1 with isatin, tetrachlorophthalic anhydride and pyromellitic dianhydride

General procedure; A mixture of compound **1** (2.2 gm, 10 mmol) and isatin, tetrachlorophthalic anhydride (10 mmol) and/or pyromellitic dianhydride (5 mmole) in 30 ml acetic acid/ acetic anhydride mixture (1:1) was refluxed for 8 h. After cooling, the reaction mixture was gradually poured onto crushed ice. the solid precipitate was filtered off, dried and crystallized from dimethylformamide to give compound **9**, **10** and **11** respectively.

***2-(4-oxo-2-thioxo-3-p-tolyl-thiazolidin-5-ylidene)-1,2-dihydro-indol-3-one* (9)**

This compound was obtained as yellow crystals, Yield 3.02 g (86%); mp 288-290°C; IR (KBr): 3216 (NH), 3045 (CH-aromatic), 1718, 1689 (C=O's) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 12.2 (s, 1H, indole-NH), 7.65-6.98 (m, 8H, Ar'H), 2.33 (s, 3H, CH_3); Ms: *m/z* 352 (M^+), 324, 280, 266, 174, 152. Anal. Calcd. for $C_{18}H_{12}N_2O_2S_2$: C, 61.34; H, 3.43; N, 7.95; S, 18.20. Found: C, 61.22; H, 3.49; N, 7.87; S, 18.34.

***5-(4,5,6,7-tetrachloro-3-oxo-3H-isobenzofuran-1-ylidene)-2-thioxo-3-p-tolyl-thiazolidine-4-one* (10)**

This compound was obtained as golden yellow crystals, Yield 3.3 g (81%); mp > 300°C; IR (KBr): 3005 (CH-aromatic), 1746, 1680 (C=O's) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 7.40-7.06 (dd, A_2B_2 system, 4H, Ar'H), 2.32 (s, 3H, CH_3); Ms: *m/z* 491 (M^+), 314, 242, 212, 149, 91. Anal. Calcd. for $C_{18}H_7Cl_4NO_3S_2$: C, 44.01; H, 1.44; Cl, 28.87; N, 2.85; S, 13.06. Found: C, 44.14; H, 1.50; Cl, 28.75; N, 2.68; S, 13.16.

***3-(3-oxo-4-p-tolyl-dihydro-thiophen-2-ylidene)-7-(4-oxo-2-thioxo-3-p-tolyl-thiazolidin-5-ylidene)-3,7-dihydro-benzo [1,2-c;4,5-c']difuran-1,5-dione* (11)**

This compound was obtained as reddish yellow crystals, Yield 2.4 g (80%); mp > 300°C; IR (KBr): 3015 (CH-aromatic), 1764, 1690 (C=O's) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 7.78 (s, 2H, two identical benzene protons), 7.46-7.09 (dd, A_2B_2 system, 8H, Ar'H), 2.28 (s, 6H, $2CH_3$); ^{13}C NMR (DMSO-*d6*): δ= 21.13 (CH_3), 108.37 (S-C=), 121.18, 126.53, 128.47, 131.06, 133.23, 135.26, 137. 81 (Ar-C), 157.84 (O=C-), 162.25 (C=O), 166.55 (C=O) and 193.85 (C=S); Ms: *m/z* 628 (M^+), 407, 293, 238, 149, 91. Anal. Calcd. for $C_{30}H_{16}N_2O_6S_4$: C, 57.31; H, 2.57; N, 4.46; S, 20.40. Found: C, 57.25; H, 2.51; N, 4.59; S, 20.38.

***Synthesis of 5-hyrazino-2-thioxo-3-p-tolyl-thiazolidin-4-one* (12)**

To a solution of compound **2** (3 gm, 10 mmol) in 30 ml ethanol, hydrazine hydrate (1 ml, 95%) was added dropwise, and the reaction mixture was stirred at 50°C for 3 hrs. After cooling the precipitate formed was filtered off, washed with water, dried and crystallized from ethanol as yellowish white crystals. Yield 1.6 g (66%); mp 284-286°C; IR (KBr): 3440-3150 ($NHNH_2$), 3050 (CH-aromatic), 2936 (CH- aliphatic), 1695 (C=O) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 7.50-7.10 (dd, A_2B_2 system, 4H, Ar'H), 4.47 (s, 1H, CH) 3.98 (s, 2H, NH_2), 3.28 (s, 1H, NH), 2.33 (s, 3H, CH_3); Ms: *m/z* 253 (M^+), 222, 208, 198, 144, 91. Anal. Calcd. for $C_{10}H_{11}N_3OS_2$: C, 47.41; H, 4.38; N, 16.59; S, 25.31. Found: C, 47.66; H, 4.30; N, 16.46; S, 25.26.

***Synthesis of 5-amino-1-(4-oxo-2-thioxo-3-p-tolyl-thiazolidin-5-yl)-1H-pyrazole-4-carbonitrile* (13)**

A mixture of compound **2** (3 gm, 10 mmol) and ethoxymethylene malononitrile (1.2 gm, 10 mmol) in 30 ml ethanol was refluxed for 1 hr. After cooling the solid formed was collected by filtration and crystallized from methanol as yellow crystals. Yield 2 g (62%); mp 220-222°C; IR (KBr): 3400, 3350 (NH_2), 3008 (CH-aromatic), 2950 (CH-aliphatic), 2215 (CN), 1685 (C=O), 1590 (C=N) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 7.72 (s, 1H, pyrazole-H), 7.55-7.03 (dd, A_2B_2 system, 4H, Ar'H), 5.53 (s, 2H, NH_2), 4.39 (s, 1H, CH), 2.30 (s, 3H, CH_3); Ms: *m/z* 329 (M^+), 214, 202, 188, 164, 91. Anal. Calcd. for $C_{14}H_{11}N_5OS_2$: C, 51.05; H, 3.37; N, 21.26; S, 19.47. Found: C, 51.18; H, 3.29; N, 21.33; S, 19.34.

Condensation of 5-bromo-rodanine* (2) *with 2-amino-5-phenyl-1,3,4-thiadiazole,3-amino-5,6-diphenyl-1,2,4-triazine, o-phenylenediamine, p-phenylenediamine and acetamide

General procedure: A mixture of compound **2** (3 gm, 10 mmol) and (10 mmol) of 2-amino-5-phenyl-1,3,4-thiadiazole, 3-amino-5,6-diphenyl-1,2,4-triazine, *o*-phenylenediamine, *p*-phenylenediamine (5 mmol) and/or acetamide in 30 ml dioxane in presence of potassium carbonate (2 gm, 15 mmol) was refluxed on water bath for 8 hrs.

The reaction mixture was allowed to stand overnight at room temperature and then it was gradually poured onto crushed ice. The precipitate formed was filtered off and crystallized from a proper solvent to give **14**, **15**, **16**, **17** and/or **18**, respectively.

***3-(4-methylphenyl)-6-phenyl[1,3]thiazolo [5',4':4,5] imidazo [2,1-b][1,3,4]thiadiazole-2(3H)-thione* (14)**

This compound was obtained as red crystals from benzene, Yield 2.3 g (63%); mp 216-218°C; IR (KBr): 3033 (CH-aromatic), 2985 (CH-aliphatic), 1322 (C=S) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 7.74-7.02 (m, 9H, arom-H), 2.29 (s, 3H, CH_3); Ms: *m/z* 380 (M^+), 307, 264, 223, 181, 115. Anal. Calcd. for $C_{18}H_{12}N_4S_3$: C, 56.82; H, 3.18; N, 14.72; S, 25.28. Found: C, 56.71; H, 3.23; N, 14.64; S, 25.42.

***3-(4-methylphenyl)-6,7-diphenyl[1,3]thiazolo [5',4':4,5] imidazo [1,2-b][1,2,4]triazine-2(3H)-thione* (15)**

This compound was obtained as yellow crystals from xylene, Yield 2.7 g (60%); mp 256-258°C; IR (KBr): 3055- 3012 (CH-aromatic), 2885 (CH-aliphatic), 1310 (C=S) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 7.78- 6.99 (m, 14H, Ar'H), 2.29 (s, 3H, CH_3); Ms: *m/z* 451 (M^+), 374, 297, 223, 166, 91. Anal. Calcd. for $C_{25}H_{17}N_5S_2$: C, 66.49; H, 3.79; N, 15.51; S, 14.20. Found: C, 66.53; H, 3.86; N, 15.44; S, 14.17.

***Synthesis of 3-p-tolyl-4,9-dihydro-3-H-thiazolo[4,5-b] quinoxaline-2-thione* (16)**

This compound was obtained as yellow crystals from methanol, Yield 2 g (67%); mp 205-207°C; IR (KBr): 3235 (NH), 3013 (CH-aromatic), 2880 (CH-aliphatic), 1297 (C=S) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 7.65- 7.12 (m, 8H, Ar'H), 4.18 (s, 2H, 2NH), 2.33 (s, 3H, CH_3); Ms: *m/z* 311 (M^+), 284, 226, 208, 164, 91. Anal. Calcd. for $C_{16}H_{13}N_3S_2$: C, 61.71; H, 4.21; N, 13.49; S, 20.59. Found: C, 61.87; H, 4.28; N, 13.35; S, 20.50.

***Synthesis of Benzene-1,4-bis-(5-amino-2-thioxo-3-p-tolyl-thiazolidin-4-one)* (17)**

This compound was obtained as brownish yellow crystals from dioxane, Yield 1.8 g (70%); mp 236-238°C; IR (KBr): 3320 (NH), 3018 (CH-aromatic), 2898 (CH-aliphatic), 1330 (C=S) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 7.58- 6.98 (m, 12H, Ar'H), 4.65 (s, 2H, 2CH), 4.34 (s, 2H, 2NH), 2.35 (s, 6H, $2CH_3$); Ms: *m/z* 550 (M^+), 436, 292, 228, 176, 91.

Anal. Calcd. for $C_{26}H_{22}N_4O_2S_4$: C, 56.70; H, 4.03; N, 10.17; S, 23.29. Found: C, 56.63; H, 4.13; N, 10.22; S, 23.21.

***Synthesis of 5-Methyl-3-p-tolyl-3H-thiazolo[4,5-d]thiazole-2-thione* (18)**

This compound was obtained as pale yellow crystals from ethanol, Yield 1.6 g (58%); mp 182-184°C; IR (KBr): 3033 (CH-aromatic), 2885 (CH-aliphatic), 1295 (C=S) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 7.54-7.04 (dd, A_2B_2 system, 4H, Ar'H), 2.77 (s, 3H, CH_3), 2.32 (s, 3H, CH_3); Ms: *m/z* 278 (M^+), 244, 218, 188, 176, 91. Anal. Calcd. for $C_{12}H_{10}N_2O_2S_3$: C, 51.77; H, 3.62; N, 10.06; S, 34.55. Found: C, 51.64; H, 3.48; N, 10.14; S, 34.74.

***Synthesis of p-tolyl-dithiocarbamic acid 4-oxo-2-thioxo-3-p-tolyl-thiazolidin-5-yl ester* (19)**

Carbon disulfide (1.2 ml, 15 mmol) was added dropwise to a solution of p-toluidine (1.07 gm, 10 mmol) and potassium phosphate (2.1 gm, 10 mmol) in 20 ml dimethylformamide with stirring at 0^oC. After complete addition, a solution of 5-bromo-rodanine 2 (3 gm, 10 mmol) in 20 ml dimethylformamide was added gradually to the first solution. The reaction mixture was stirred at room temperature for 3 hrs. The reaction mixture was allowed to stand overnight at room temperature and then it was gradually poured onto crushed ice. The precipitate formed was filtered off, washed with hot water and ethanol and crystallized from ethanol as yellow crystals, Yield 2 g (51%); mp 210-212°C; IR (KBr): 3150 (NH), 3058 (CH-aromatic), 1705 (C=O), 1320 (C=S) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 9.42 (s, 1H, NH), 7.54-7.04 (dd, A_2B_2 system, 4H, Ar'H), 7.22-6.82 (dd, A_2B_2 system, 4H, Ar'H), 4.55 (s, 1H, CH), 2.33 (s, 6H, $2CH_3$); Ms: *m/z* 404 (M^+), 382, 256, 134, 112, 91. Anal. Calcd. for $C_{18}H_{16}N_2OS_4$: C, 53.43; H, 3.99; N, 6.92; S, 31.70. Found: C, 53.55; H, 3.91; N, 6.98; S, 31.61.

***Synthesis of 3,4-di-p-tolyl-3H,4H-thiazolo[4,5-d]thiazole-2,5-dithione* (20)**

Compound 2 (3 gm, 10 mmol) in 30 ml ethanol in the presence of few drops of piperidine was refluxed for 3 hrs. After cooling, the solid formed was filtered off, washed with ethanol, dried and crystallized from dioxane as yellow crystals, Yield 2.7 g (72%); mp 195-197°C; IR (KBr): 3035 (CH-aromatic), 2970 (CH-aliphatic), 1325 (C=S) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 7.51-7.02 (dd, A_2B_2 system, 8H, Ar'H), 2.35 (s, 6H, $2CH_3$); ^{13}C NMR (DMSO-*d6*): δ= 20.54 (CH_3), 87.73 (S-C=), 122.44, 127.63, 133.18, 135.18 (Ar-C), 155.43(N-C=) and 190.94 (C=S); Ms: *m/z* 386 (M^+), 310, 289, 237, 149, 91, 88. Anal. Calcd. for $C_{18}H_{14}N_2S_4$: C, 55.92; H, 3.65; N, 7.25; S, 33.18. Found: C, 55.87; H, 3.59; N, 7.33; S, 33.21.

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