Synthesis and Evaluation of Antibacterial Activities of some Important Bridge-head Nitrogenous Heterocyclic Compounds

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(Received 8/5/2012; Accepted 11/6/2012)

ABSTRACT

The key intermediates in the present study to synthesize the title bridge-head nitrogen heterocycle compounds were N-substituted semicarbazides 2(a-c), which prepared by hydrazinolysis of the ethyl substituted carbamates 1(a-c) with hydrazine hydrate. These carbamates were prepared by the reaction of proper amines and ethylchloroformate.

The reaction of these semicarbazides with ethanolic solution of carbon disulfide under strong basic conditions at room temperature, followed by acidification resulted in the formation of the corresponding potassium (2-arylcarmamoyl)hydrazine carbodithioate 3(a-c), while refluxing the ethanolic solution for three hours afforded 5-(arylamino)-1,3,4-oxadiazole-2-thioles 4(a-c). The potassium salts 3(a-c) were cyclized with hydrazine hydrate to 4-amino-5-arylamino-1,2,4-triazole-3-thiones(thioles) 5(a-c).

Compounds 5(a-c) were excellent precursors for 3-(arylamino)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles 6(a-c) by dehydrative ring closure of the proper triazole with formic acid in benzene in presence of phosphorous oxychloride or using microwave irradiation technique.

Also, refluxing of the proper triazoles with carbon disulfide under basic conditions afforded 3-(arylamino)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-6-thiones 7(a-c). Finally 4-amino-3-(4-(4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-ylamino)-1,3,4-thiadiazol-2-yl)phenylamino)-1H-1,2,4-triazole-5(4H)-thione 5(d) were synthesized by the same procedures that were followed to synthesize its analogs starting from 5-(4-aminophenyl)-1,3,4-thiadiazole-2-amine and duplicated all the scales of the reactants.

The structures of these compounds were confirmed by their physical properties in addition to the IR, UV and NMR spectra. All synthesized compounds were tested for their in vitro growth inhibitory activity against a panel of standard strains of pathogenic microorganism including bacteria Staphylococcus, Streptococcus and Salmonella.

All these compounds were practically inactive against the tested microorganisms.

Keywords: Bridge-head Nitrogen Heterocycles, Ethyl substituted carbamates, N-substituted semicarbazides, amino-1,3,4-oxadiazole-2-thiones.
INTRODUCTION

As part of the continuous program directed toward the synthesis of important heterocyclic compounds, oxygenous and nitrogenous five and six membered rings (Saied et al., 2010), it was became of interest to investigate the preparative routs to synthesize the title fused heterocyclic compounds. All the target analogues heterocyclic compounds have been reported to exert notably antibacterial activity (Subramanian et al., 2009).
Also, new series of 1,3,4-thiadiazole-thione derivatives were synthesized and tested for their antibacterial activities. It was therefore thought worthwhile to incorporate the oxadiazole, thiadiazole and or triazole moieties into the title Bridge-head nitrogen. Semicarbazides were prepared by condensing carbamates with hydrazine hydrate (Mruthunjayaswamy et al., 2009), these carbamate esters were prepared by the reaction of appropriate amines with ethyl chloroformate. It was worthy to mention that semicarbazides converted to carbodithioate salts or cyclized to oxadiazole-2-thiones by the same reagents (carbon disulfide and potassium hydroxide solution in ethanol), but by two different procedures, while the former involved the agitation at room temperature of the reaction mixture which led to precipitate of quantitative yield of potassium salt which was used in the next step without further purification (Joshi et al., 1989). The latter was carried out by heating the reaction mixture until the evolution of hydrogen sulphide was ceased. These procedures were very popular since ease in workup and high yields were consistently observed but with long reaction time (Somani and Shirodkar, 2009).

Bridge-head nitrogen heterocycles were obtained either by cyclization of these salts with hydrazine hydrate in refluxing ethanol then mixing the triazole products with carboxylic acids at room temperature (Hirpara et al., 2003) or by refluxing ethanolic solution of amidothiosemicarbazides with acetyl acetone (Al-Abdullah, 2007). Microwave irradiation was introduced as a useful alternative to the traditional heating for the synthesis of several heterocyclic derivatives with high yields and short reaction times. Some 1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles were recently prepared through the reaction of 4-amino-3-mercapto-1,2,4-triazoles with carboxylic acid or aldehydes under microwave irradiations (Al-Abdullah, 2007).

**EXPERIMENTAL**

All melting points were determined on a Gallen Kamp and Electro thermal 1A9300 Digital-Series (1998) apparatus and were uncorrected. The IR spectra ($\nu$ cm$^{-1}$, KBr disc) were recorded on Perkin – Elmer 590B Spectrophotometer. UV measurements were carried out on Shimadzu UV-160 spectrophotometer using EtOH as a solvent. NMR spectra were obtained on a BRUKER AVANCE DPX 400 MHz. spectrophotometer as d$_6$-DMSO or CdCl$_3$ solutions using TMS as an internal standard at the Department of Chemistry, Donnan and Robert Robinson Laboratories, University of Liverpool, U.K. Finally, microwave irradiation was performed using unmodified domestic Samsung oven (300 MHz).

**Ethyl substituted carbamates 1(a-d):** (Mruthunjayaswamy et al., 2009)

Ethyl chloroformate (10.8gm, 0.01 mole) was added drop-wise to a solution of (0.01 mole) of the proper amine in 15 ml pyridine. The reaction mixture was left aside at room temperature for an hour with occasional shaking. It was then poured on 100 ml ice water and the precipitated carbamate was filtered, washed with water, dilute hydrochloric acid, then water again and crystallized from aqueous ethanol.

Starting from 5-(4-aminophenyl)-1,3,4-thiadiazol-2-amine and duplicated the scales of the reactant ethyl chloroformate afforded ethyl 4-(5-(ethylcarbamate)-1,3,4-thiadiazol-2-yl) phenylcarbamate 1(d).

$^1$H NMR (DMSO-d$_6$, $\delta$ ppm) for ethyl thiazol-5-yl carbamate 1(b) as a representative of these compounds: 11.68 (s, 1H, NH), 7.38 and 7.17 (two s, 2H, thiazole ring), 2.12 (q, 2H, CH$_2$) and 1.25 (t, 3H, CH$_3$), other physical and spectral data were listed in Table (1).
Table 1: Physical and spectral data of compounds 1(a-d).

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>M.P. ºC</th>
<th>Yield %</th>
<th>IR, KBr, v (cm⁻¹)</th>
<th>UV λ_max (nm) MeOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>189-91</td>
<td>66</td>
<td>3162 1727 1636</td>
<td>206</td>
</tr>
<tr>
<td>1b</td>
<td>139-41</td>
<td>66</td>
<td>3184 1728 1596</td>
<td>250</td>
</tr>
<tr>
<td>1c</td>
<td>92-4</td>
<td>57</td>
<td>3186 1722 1620</td>
<td>242</td>
</tr>
<tr>
<td>1d</td>
<td>192-94</td>
<td>44</td>
<td>3190 1728 1620</td>
<td>260</td>
</tr>
</tbody>
</table>

N-substituted semicarbazides 2(a-d), (Mruthunjayaswamy et al., 2009)
A mixture of (0.01 mole) of appropriate carbamate 1(a-c), excess of hydrazine hydrate (80%) and triethyl amine (1 ml.) in ethanol was stirred for an hour, then poured on ice-water and acidified with diluted HCl. The precipitate was filtered and washed with water and crystallized from ethanol.

Starting from compound 1(d) (33.64gm, 0.01 mole) and duplicated the scales of other reactants afforded N-(4-(5-(hydrazinecarboxamido)-1,3,4-thiadiazol-2-yl)phenyl)hydrazine carboxamide 2(d).

1HNMR (DMSO-d₆, δ ppm) for compound 2(b) as a representative of these compounds: 7.90 (s, 2H, thiazol ring), 7.46 (two s, 2H, NHCONH) and 2.25 (s, 2H, NH₂), other physical and spectral data were listed in Table (2).

Table 2: Physical and spectral data of compounds 2(a-d).

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>M.P. ºC</th>
<th>Yield %</th>
<th>IR, KBr, v (cm⁻¹)</th>
<th>UV λ_max (nm) MeOH</th>
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<tr>
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<td>169-71</td>
<td>87</td>
<td>3240 3163 1672</td>
<td>276</td>
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<tr>
<td>2b</td>
<td>150-52</td>
<td>76</td>
<td>3182 3124 1673</td>
<td>254</td>
</tr>
<tr>
<td>2c</td>
<td>188-90</td>
<td>46</td>
<td>3227 3102 1673</td>
<td>238</td>
</tr>
<tr>
<td>2d</td>
<td>219-21</td>
<td>80</td>
<td>3240 3166 1697</td>
<td>280</td>
</tr>
</tbody>
</table>

Potassium (2-arylcarbamoyl) hydrazine carbodithioates 3(a-d).
Carbon disulphide (11.4 g, 0.15 mole) was added dropwise to a solution of proper semicarbazide 2(a-c) (0.1 mole) and potassium hydroxide (8.4 g, 0.15 mole) in ethanol (250 ml). The mixture was stirred at room temperature for 30 minutes. Dry ether (200 ml) was then added to the mixture and the precipitate was filtered, washed with ether and dried to yield the title salts which were used without further purification in the next step.

Starting from 2(d) (0.15 mole) and duplicated the scales of other reactants afforded potassium 2-(4-(5-(2-dithiocarboxylato)hydrazinecarboxamido)-1,3,4-thiadiazol-2-yl) phenyl carbamoyl) hydrazine carbodithioate (3d).
5- Arylamino-1,3,4-oxadiazole-2(3H)-thioles 4(a-c). (Al-Abdullah, 2007)

Carbon disulphide (11.4 g, 0.15 mole) was added dropwise to a solution of appropriate semicarbazide 2(a-c) (0.1 mole) and potassium hydroxide (8.4 g, 0.15 mole) in ethanol (250 ml). The mixture was refluxed for 6hrs, concentrated and acidified with diluted HCl. The resulted solid was collected, washed with water and recrystallized from a mixture of DMF-H$_2$O.

$^1$HNMR (DMSO-d$_6$, δ ppm) for compound 4(a): 12.32 (s, 1H, SH), 7.54-7.92 (m, 5H, Ar) and 4.26 (s, 1H, NH), while that for compound 4(b): 11.96 (s, 1H, SH), 7.16 and 7.37 (s, 2H, thiazole ring) and 4.12 (s, 1H, NH) respectively, other physical and spectral data were listed in Table (3).

### Table 3: Physical and spectral data of compounds 4(a-c).

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>M.P. ºC</th>
<th>Yield %</th>
<th>IR, KBr, v (cm$^{-1}$)</th>
<th>UV $\lambda_{max}$ (nm) MeOH</th>
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<td>75</td>
<td>3155 1600 1280</td>
<td>288</td>
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<tr>
<td>4b</td>
<td>142-44</td>
<td>85</td>
<td>3183 1620 1254</td>
<td>298</td>
</tr>
<tr>
<td>4c</td>
<td>202-04</td>
<td>80</td>
<td>3180 1610 1250</td>
<td>240</td>
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</tbody>
</table>

4-Amino-5-aryl amino-1,2,4-triazole-3-thiones (thioles) 5(a-d). (El-Emam et al., 1993)

A solution of a proper potassium salt 3(a-c) (0.01 mole) in ethanol (150 ml) was refluxed with (0.6 mole) hydrazine hydrate. A precipitate was obtained in 3-5 minutes, and the refluxing of the mixture was continued for 3 hours. On cooling, water (100 ml) was added and the mixture was neutralized with 10% hydrochloric acid and allowed to stand for three hours. The separated product was filtered, washed with water, dried and crystallized from ethanol to yield the title compounds.

Starting from (3d) (0.01 mole) and duplicated the scales of other reactants afforded 4-amino-3-(4-(5-(4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-ylamino)-1,3,4-thiadiazol-2-yl)phenylamino)-1H-1,2,4-triazole-5(4H)-thione (5d).

$^1$HNMR (DMSO-d$_6$, δ ppm) for compound 5(c) as a representative of these series: 9.00 (s, 1H, SH), 7.50-7.92 (m, 5H, ArH and NH) and 4.26 (s, 2H, NH$_2$), other physical and spectral data were listed in Table (4).

### Table 4: Physical and spectral data of compounds 5(a-c).

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>M.P. ºC</th>
<th>Yield %</th>
<th>IR, KBr, v (cm$^{-1}$)</th>
<th>UV $\lambda_{max}$ (nm) MeOH</th>
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<tbody>
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<td>182-83</td>
<td>37</td>
<td>4403 3055 1628 1210</td>
<td>300</td>
</tr>
<tr>
<td>5b</td>
<td>190-92</td>
<td>40</td>
<td>3350 3155 1627 1210</td>
<td>300</td>
</tr>
<tr>
<td>5c</td>
<td>178-80</td>
<td>44</td>
<td>3324 3166 1622 1210</td>
<td>288</td>
</tr>
<tr>
<td>5d</td>
<td>218-20</td>
<td>75</td>
<td>3350 3163 1628 1210</td>
<td>298</td>
</tr>
</tbody>
</table>
Synthesis of authentic sample:

4-amino-5-(3-pyridyl)amino-1,2,4-triazole-3-thiole 5(c). (Farghaly et al., 2007)

A mixture of 5-(pyridin-3-ylamino)-1,3,4-oxadiazole-2(3H)-thione (4c) (0.01 mole) and excess of hydrazine hydrate (80%) in ethanol was refluxed for three hours, then poured on ice-water. The precipitate was filtered, washed with water and crystallized from ethanol. The product has same melting point of compound 5(c) prepared by previous general procedure.

3-( Arylamino)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles 6 (a-c):

Conventional method (A). (Fiona et al., 2008)

A mixture of proper compound 5(a-c) (0.01 mole) and formic acid (0.46 ml, 0.01 mole) in benzene (10 ml) was refluxed for three hours. After evaporating the solvent under reduced pressure, an oily product was obtained which was crystallized from DMF-H_2O (1:1) to afford the title compound. ^1H NMR (DMSO-d_6, δ ppm) for 6(a) as a representative compound of these series: 12.3 (s, 1H, fused thiazole ring), 7.54-7.92 (m, 5H, ArH) and 4.27 (s, 1H, NH), other physical and spectral data were listed in Table (5).

Irradiation method B: (Omprakash et al., 2011)

A mixture of proper compound 5(a-c) (0.01 mole) and formic acid (0.46 ml, 0.01 mole) was placed in 25 ml open round bottom flask and irradiated in the microwave oven for 4 minutes. On cooling, an oily product was obtained which was worked up as in method (A).

Table 5: Physical and spectral data of compounds 6(a-c).

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>M.P. ºC</th>
<th>Yield %</th>
<th>IR, KBr, v(cm⁻¹)</th>
<th>UV λ_max (nm) MeOH</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Method A</td>
<td>Method B</td>
</tr>
<tr>
<td>6a</td>
<td>201-02</td>
<td>37</td>
<td>90</td>
<td>3149</td>
</tr>
<tr>
<td>6b</td>
<td>188-90</td>
<td>40</td>
<td>90</td>
<td>3155</td>
</tr>
<tr>
<td>6c</td>
<td>194-69</td>
<td>44</td>
<td>92</td>
<td>3155</td>
</tr>
</tbody>
</table>

3-(5-Arylamino)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-6-thiones 7(a-c). (Fiona et al., 2008)

To a solution of the proper 4-amino-5-arylamino-1,2,4-triazole-3-thiol 5(a-c) (0.001 mole) in ethanol 20 ml, KOH (0.5 gm) and CS_2 (1 ml) were added and the mixture was refluxed for 2 hours. The solvent was removed under reduced pressure. Ice-water was added to the reaction mixture with stirring. The solid was separated, washed with water and crystallized from ethanol to afford the title compound.

^1H NMR (CDCl_3, δ ppm) for compound 7(a) as a representative of this series: 7.50-7.94 (m, 5H, ArH) and 4.42 (s, 2H, 2NH), other physical and spectral data were listed in Table (6).
### Table 6: Physical and spectral data of compounds 7(a-c).

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>IR, KBr, ν (cm⁻¹)</th>
<th>UV λ_max (nm) MeOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
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<td>3182 1600 1272</td>
<td>326</td>
</tr>
<tr>
<td>7b</td>
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<tr>
<td>7c</td>
<td>186-88</td>
<td>44</td>
<td>3186 1620 1278</td>
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</tr>
<tr>
<td>7d</td>
<td>175-77</td>
<td>75</td>
<td>3186 1620 1278</td>
<td>310</td>
</tr>
</tbody>
</table>

### Biological Test

All the synthesized compounds in the present investigation were screened for their antibacterial activity by subjecting the compounds to a standard procedure. Antibacterial activities were tested on nutrient medium against *Staphylococcus*, *Streptococcus* and *Salmonella*. The antibacterial activity of the compounds was assessed by disc diffusion method. The extent diameter of inhibition after 24 hours was measured as the zone of inhibition in millimeters.

### RESULTS AND DISCUSSION

A convenient synthesis of target compounds were accomplished by the routes outlined in Schemes (1 and 2). Ethyl substituted carbamates 1(a-c) were prepared from ethylchloroformate and a suitable amines. The IR spectra of these compounds showed broad bands at around 3190 – 3162 cm⁻¹ due to NH bond stretching while a strong bands at 1722 – 1728 cm⁻¹ was attributed to C=O bond stretching carbonyl group and at 1596-1636 cm⁻¹ related to aromatic heterocyclic C=N. (Table 1). The ¹H NMR spectra were supporting the presence of two thiazole protons around δ7.17 and 7.38 ppm, while the NH proton appeared as a singlet signal at δ11.68. The CH₂ protons appeared at δ2.12ppm and the CH₃ appeared as triplet at δ2.12ppm.

The key intermediates N-substituted semicarbazides 2(a-d) were prepared by hydrazinolysis of carbamates 1(a-c) with hydrazine hydrate (Varvounisa and Giannopoulos, 1996). The IR spectra showed broad stretching vibrations at around 3240 – 3182 cm⁻¹ due to NH₂ and a strong band at 1697 – 1672 cm⁻¹ attributed to amide carbonyl and at 1639-1610 cm⁻¹ due to aromatic heterocyclic C=N, (Table 2). The ¹HNMR spectra were introducing an evidence to the presence of the two thiazole protons appeared around δ7.90 ppm, and the NHCONH protons appeared multiplet at δ7.46 ppm, the semicarbazide terminal nitrogen protons appeared doublet at δ2.25 ppm.

Refluxing the ethanolic solution of these intermediates with ethanolic solution of carbon disulfide afforded 5-arylamino-1,3,4-oxadiazole-2(3H)-thioles 4(a-c) (Varvounisa and Giannopoulos, 1996). The IR spectra showed broad stretching band at (3155-3186 cm⁻¹) for NH, (1600-1620 cm⁻¹) for C=N and at(1280-1254 cm⁻¹) of C=S, Table (3). The ¹HNMR (d₆DMSO) of compound 4(a) was characterized by the presence of the one SH proton appeared as a singlet signal at δ12.32 ppm, five aromatic protons appeared as multiplet at 7.16-7.37 ppm, two thiazole protons appeared around δ7.16 and 7.37 ppm, while the NH proton appeared as singlet at δ4.26ppm. The ¹HNMR (DMSO-d₆, δ ppm) for
compound 4(b) proves the presence of the one SH proton appeared as singlet at $\delta 11.96$ ppm, two thiazole protons appeared around $\delta 7.16$ and 7.37 ppm, while the NH proton appeared as a singlet signal at $\delta 4.12$ ppm. Changing these conditions to strong basic conditions at room temperature, followed by acidification with dilute hydrochloric acid resulted in the formation of the corresponding potassium (2-arylcarbamoyl) hydrazine carbodithioates 3(a-c). These salts were cyclized with hydrazine hydrate to 4-amino-5-arylaminoo-1,2,4-triazole-3-thioles 5(a-d) (El-Emam et al., 1996).
These compounds were present in thione-thiol tautomeric forms, (Scheme 2). The ultraviolet spectra of methanolic solution of these triazoles showed absorption bands at 288-300 nm due to the presence of the chromophoric C=S group (Fiona et al., 2008). The IR spectran disclosed the presence of C=S at (1210 cm⁻¹) which was responsible to those thiones in addition to C=N bands at (1678-1672 cm⁻¹), NH (3166-3055 cm⁻¹) and of a primary amine bands at (3440-3324 cm⁻¹) with no absorbance at (2600-2400 cm⁻¹) of thiole form, (Table 4) (Almajan et al., 2008). These results did not agree with the ¹HNMR (DMSO-d₆, δ ppm) for compound 5(c) which was characterized by presence of the one SH proton appeared as singlet at δ12.30 ppm and four aromatic protons with NH proton appeared as multiplet around δ7.50-7.92 ppm, while the NH₂ proton appeared as singlet at δ4.26 ppm, indicated that the thiole tautomer was existed predominantly in DMSO solution. This result was due to solvent effects (Looker et al.,1978). (Scheme 2). Thiol-thione tautomerism exists in compounds 5(a-c), in the ¹HNMR the signal of the SH proton was recorded, and as it has been reported that the crystal structures of these compounds correspond to the thione form, but they showed thiol-thione tautomerism in solution (Koparrir et al., 2005).

As the structural skeleton of compounds 5(a-c) was established spectroscopically, the chemical behavior of these compounds was also used for assigning their structure, as expected it was found that refluxing of compound 4(c) with carbon disulfide under strong basic conditions followed by acidification with dilute hydrochloric acid resulted in the formation of the authentic sample 5(c) (Artemov and Shvaika, 2008).

The formation of the same product from two different compounds indicated the correct assignment for these compounds.

These 4-amino-5-mercapto-3-arylamine-1,2,4-triazoles 5(a-d) were excellent precursors for the synthesis of bridge-head nitrogen heterocyclic and have received much attention during recent years (Omprakash et al., 2011). Thus in this study, 3-(5-aryl-1,3,4-thiadiazol-2-ylamino-[1,2,4] triazolo [3,4-b] [1,3,4] thiadiazoles 6(a-c) were synthesized by dehydrative ring closure through heating of corresponding triazole with formic acid in presence of benzene solution of phosphorus oxychloride (Mathew et al., 2006). The method (A) gave low yield, but can be improved to 95% with short time microwave irradiation to 4 minutes (Omprakash and Anjaneyulu; 2001). The IR, ν(cm⁻¹) of this compound was : 3149 - 3155 (NH) and 1566-1555 (C=N) in addition to the disappearance of the absorption exocyclic of thione (1726 cm⁻¹). ¹HNMR (DMSO-d₆, δ ppm) for compound 6(a) was characterized by the presence of the one thiadazole fused ring proton
appeared as singlet at δ9.00 ppm, five aromatic protons appeared as multiplet around δ7.54 -7.92 ppm, whereas the NH proton appeared as singlet at δ4.27 ppm.

Also, refluxing of triazoles 5(a-c) with carbon disulfide under basic conditions afforded 3-(5-arylmino)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-6-thiones 7(a-c) (Varvounisa and Giannopoulos, 1996). This reaction was very popular since ease in workup and high yields (> 90%) were consistently observed.

The IR spectral data of these compounds confirmed their existence in the thione form. The characteristic absorption peaks at 3186-3155 cm⁻¹ (NH), 1278-1272 cm⁻¹ (C=S) and 1620-1600 cm⁻¹ (C=N) were observed. The ¹H NMR (CDCl₃, δ ppm) for compound 7(a) was characterized by the presence of the five aromatic protons appeared as multiplet around δ7.54 -7.94 ppm, also the two NH groups protons (of fused ring and NH) appeared as singlet at δ4.421 ppm. The two diazole ring protons indicated the thione isomer was the predominate.

Finally, 4-amino-3-(4-(5-(4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-ylamino)-1,3,4-thiadiazol-2-yl)phenylamino)-1H-1,2,4-triazole-5(4H)-thiole 5(d) was synthesized by the same procedures that were followed to synthesize its analogues starting from 5-(4-aminophenyl)-1,3,4-thiadiazol-2-amine and duplicated all the scales of the reactants. (Scheme 3). The UV and IR spectral data of these compounds showed similar patterns to those of triazoles-5-thioles 5(a-c). (Tables 1-6).
All the synthesized compounds were tested for their in vitro growth inhibitory activity against a panel of standard strains of pathogenic microorganism including bacteria *Staphylococcus*, *Streptococcus* and *Salmonella*. All these compounds were practically inactive against the tested microorganisms.

**ACKNOWLEDGEMENTS**

The author wishes to express his gratitude for (the 1H NMR spectra) financial support from COUNCIL FOR ASSISTING REFUGEE ACADEMICS (cara), Iraq Programme and Dr Jonathan Iggo, Senior Lecturer in Inorganic Chemistry, Department of Chemistry, Donnan and Robert Robinson Laboratories, University of Liverpool, Liverpool, L69 7ZD, for their help in 1H NMR analysis. Many thanks to Kate Robertson, Deputy Executive Secretary. He also thanks Dr. Nawal A. Alubaidy, Veterinary Medicinal College of Mosul for her help in the evaluation of antibacterial activities.

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