SYNTHESIS OF SOME NOVEL THIAZOLES, BISTHIAZOLES, THIAZOLIN-4 ONES AND 1,3,4 THIADIAZOLINE COMPOUNDS STARTING FROM 5-ACETYL-2-PHENYL-4-METHYL-THIAZOLYL-THIOSEMICARBAZONE

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Abstract

A new series of 5-thiazolyethylidene-hydrazinyl-thiazoles 3a-g, 5-thiazolil-ethylidene-hydrazinyl-thiazolin-4-ones 5 and 6a-i was synthesized starting from 5-acetyl-2-phenyl-4-methyl-thiazolyl-thiosemicarbazone 2 by the reaction with various α-halocarbonyle compounds or ethyl-α-chloroacetate. The 5-thiazolyl-1,3,4-thiadiazoline 4 was synthesized by cyclisation of the same thiosemicarbazone 2 with acetic anhydride in the presence of pyridine. The newly synthesized compounds were characterized by ¹H-NMR and mass spectral studies.

Keywords: thiosemicarbazones, hidrazinyl-thiazoles, thiazolin-ones

Introduction

Thiazoles and thiazolin-4-one compounds have attracted continuing interest over the years because of their various biological activity such as antibacterial, antifungal, anti-inflammatory, anti-HIV, antihypertensive, anticonvulsant, antihelmintic. Synthesis of thiazole derivatives by various methods and their biological evaluation have been described by many
researchers [2-6,11]. Similarly, Schiff bases have gained importance because of physiological and pharmacological activities associated with them [1,14-16,18,19]. Prompting by the observed biological activities of the above mentioned derivatives and in continuation of our ongoing studies of novel biological active molecules [8-10], we decided to synthesize compounds with the thiazole nucleus linked with a Schiff base as possible antimicrobial agents. Furthermore, because 1,3,4-thiadiazole nucleus is present in some biological active molecules including antibacterial and antifungal agents, [7,12,17] we also obtained one 5-thiazolyl-1,3,4-thiadiazoline compound.

**Materials and Methods**

The melting points were determined in open capillary tubes, on an Electrothermal melting point apparatus and are uncorrected. The $^1$HNMR spectra were recorded at room temperature on a Bruker Avance NMR spectrometer operating at 500 MHz. Chemical shift values were reported relative to tetramethylsilane (TMS) as internal standard. The samples were prepared by dissolving the synthesized powder of the compounds in DMSO$_d$6 ($\delta$H= 2.51ppm) as solvent and the spectra were recorded using a single excitation pulse of 12 µs. GC-MS analyses were performed with an Agilent gas chromatograph 6890 equipped with an apolar Macherey Nagel Permabond SE 52 capillary column. Elemental analysis was performed with a Vario El CHNS instrument. All the compounds gave satisfactory CHNS quantitative elemental analysis results. The purity of the synthesized compounds was verified by thin layer chromatography (TLC) and was carried out on precoated Silica Gel 60F254 sheets using heptan – ethyl-acetate 1:1 like developpant and UV absorption for visualization.

The synthetic strategies adopted to obtain the target compounds are depicted in the figures 1-3. The key intermediate 2 was prepared in two steps as shown in figure 1. The first step was the condensation of the benzothioamide with 3-chloropentane-2,4-dione to result the 5-acetyl-2-phenyl-4-methyl-thiazole 1. The second step consists in the condensation of 1 with thiosemicarbazide in absolute ethanol, in the presence of concentrated sulphuric acid as catalyst, to obtain the 5-acetyl-2-phenyl-4-methyl-thiazolyl-thiosemicarbazone 2 which is a versatile compound and it was used as an intermediate for the synthesis of all the desired compounds.
Figure 1
Synthesis of 5-acetyl-2-phenyl-4-methyl-thiazolyl-thiosemicarbazone 2

**Synthesis of compound 2**

0.05 mol (10 g) of 5-acetyl-2-phenyl-4-methyl-thiazole dissolved in 25 mL absolute ethanol, was treated with 0.05 mol of thiosemicarbazide dissolved in 25 mL ethanol, followed by adding 5 drops of concentrated sulfuric acid. The mixture was refluxed for 3 hours, cooled, after which the resulted precipitate was filtered and recrystallised from ethanol.

Through Hantzsch condensation reactions between 5-acetyl-2-phenyl-4-methyl-thiazolyl-thiosemicarbazone 2 and various α-halocarboxylic compounds it was obtained a new series of 5-thiazolyl-ethylidene-hydrazinyl-thiazoles 3a-f various substituted in the 4 and 5 positions of the thiazole ring. If the α-halocarboxylic compound was 5-bromoacetyl-2-phenyl-4-methyl-thiazole 7 [13], we obtained the 5-thiazolyl-ethylidene-hydrazinyl-4,5'-bithiazole 3g (Figure 2).
Figure 2
Synthesis of 5-thiazolyl-ethylidene-hydrazinyl-2-thiazoles 3a-f and 5-thiazolyl-ethylidene-hydrazinyl-4-5'-bithiazole 3g

General procedure for the synthesis of compounds 3a-g

0.005 mol of 2 were suspended in 20 mL absolute ethanol with 0.005 mol α-halocarbonylic compound (3-chloro-acetylacetone, 2-chloro-ethyl acetoacetate, 4-chloro-ethyl acetoacetate, α-chloroacetophenone, chloropropanone, 1,3-dichloroacetone, 5-bromoacetyl-2-phenyl-4-methyl-thiazole). The mixtures were refluxed for 2 hours, cooled, after which the resulted precipitates were filtered, washed with water in order to transform them in bases. The resulted compounds were recrystallized from ethanol.

The reaction of the thiosemicarbazone derivative 2 with ethyl chloroacetate in refluxing ethanol in the presence of anhydrous sodium acetate led to the compound 5 (Figure 3). The structure of 5 was identified as 2-(2-(1-(4-methyl-2-phenylthiazol-5-yl)-ethylidene) hydrazinyl) thiazol-4(5H)-one on the basis of its spectral data. Furthermore this structure was derivatized by chemical transformation, where it was condensed with several aldehydes by refluxing in acetic acid containing anhydrous sodium acetate as basic catalyst to give the corresponding arylidene derivatives 6a-i (Figure 3).
In addition, refluxing of thiosemicarbazone derivative 2 with pyridine and acetic anhydride gave the 5-thiazoly-2(1,3,4-thiadiazoline) 4 (Figure 3).

![Synthesis of 5-thiazolyl-2(1,3,4-thiadiazoline) 4 and 5-arildene-2-(5-thiazolyl-ethyldene)-hydrazinyl-thiazolin-4-ones 6 a-i](image)

**Figure 3**

**Synthesis of compound 4**

A mixture of 0.005 mol (1.5 g) of 2, 5 mL pyridine and 5 mL acetic anhydride was refluxed 1 hour. After cooling, the mixture was poured in cold water and the solid obtained was filtered out, washed with water and recrystallized from ethanol.

**Synthesis of compound 5**

A mixture of 0.01 mol of 2 (3g), 0.01 mol ethyl-α-chloroacetate and 0.04 mol anhydrous sodium acetate in absolute ethanol was heated under reflux for 8h. The mixture was left to cool; the solid was filtered out, washed with water and recrystallized from ethanol.

**General procedure for the synthesis of compounds 6a-i**

A mixture of 0.001 (0.3 g) mol of 5, 0.001 mol of carboxylic compounds (4-bromobenzaldehyde, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, 3-nitrobenzaldehyde, 4-hydroxybenzaldehyde, 2-hydroxybenzaldehyde, 2-metoxylbenzaldehyde, 2,4-dichlorobenzaldehyde,
2,6-dichlorobenzaldehyde) and 0.004 mol of anhydrous sodium acetate in glacial acetic acid was refluxed for 24 h. After cooling the mixture, the precipitated solid was filtered off, washed with water and recrystallised from acetic acid to give the compounds 6a-i.

**Results and Discussion**

The target compounds were synthesized with good yields, following the aforementioned procedure. The results for elemental analysis data for the new compounds were within ± 0.4% of theoretical values and are in agreement with the proposed chemical structure. The structures of the newly synthesized compounds were elucidated by spectral data. The MS and $^1$H NMR spectra show all the expected signals.

2: (2-(1-(4-methyl-2-phenylthiazol-5-yl-ethylidene-hydrazine-carbothioamide): $C_{13}H_{14}N_4S_2$ (290.41), Yellow crystals, Yield = 75%, M.p.: 207-210°C, $^1$HRMN (DMSO): $\delta$ppm = 2.40 (s, 3H, Thiazole-4CH$_3$), 2.48 (s, 3H, CH$_3$-C=N), 7.4-7.9 (m, 5H, phenyl), 7.94 (s, 1H, NH), 8.62 (s, 2H, NH$_2$), Elemental Analysis: Calc.: C, 53.77; H, 4.86; N, 19.29; S, 22.08, Found: C, 53.72; H, 4.9; N, 19.4; S, 22.02

Mass spectra of the compounds 3a-g showed intense molecular ion peaks at m/z in agreement with their molecular formulae. The most important fragmentations are the fragmentation of N-NH bound with the formation of ion peaks (m/z=M$^+$-N=C(CH$_3$)-Thiazolyl (4-CH$_3$)-phenyl) and the fragmentation of the 5-thiazolyl-C bound with the formation of ion peaks (m/z=Thiazolyl (4-CH$_3$)-phenyl).

The exhibited chemical shifts obtained from $^1$H NMR spectra of the compounds 3a-g supported the proposed structures of the compounds. The chemical shift of the NH proton (hydrazinyl group) appeared in the form of singlet peak at $\delta$ 7.9-8.3 ppm. The aromatic protons signals were registered in the $\delta$ 7.4-8.1 ppm region in the form of multiple peaks (doublet, double doublets or multiplet). The signal of the proton in the 5 position of thiazole ring appeared at the range of $\delta$ 6.8-7.1 ppm as singlet peak for the compounds 3a, 3b, 3e, 3f, 3g. The chemical shift of the methyl groups (thiazole nucleus and ethylidene-hydrazinyl group) appeared at $\delta$ 2.4-2.7 ppm in the form of a singlet peaks and for the compounds 3b, 3c, 3d, 3g appeared a supplementary singlet signal (3H, methyl group) in the same range.

3a: $C_{16}H_{15}ClN_4S_2$ (362.90), Green crystals, Yield = 70%, M.p.: 243-246°C, MS: m/z = 362, 259, 215, 201, 174, 71; $^1$HRMN (DMSO): $\delta$ppm = 2.45 (s, 3H, Thiazole-4CH$_3$), 2.66 (s, 3H, CH$_3$-C=N), 4.7 (2H CH$_2$Cl), 6.8
(s, 1H, Thiazole-H5), 7.4-7.9 (m, 5H, phenyl), 7.9 (s, 1H, NH) Elemental Analysis: Calc: C, 52.95; H, 4.17; N, 15.44; S, 17.67; Found: C, 53.03; H, 4.14; N, 15.49; S, 17.7

3b: \( C_{16}H_{16}N_4S_2 \) (328.46), Yellow crystals, Yield = 68%, M.p.: 181-184\(^\circ\)C, MS: m/z =328, 225, 215, 201, 174, 71; \(^1\)HRMN (DMSO): δ ppm = 2.41 (s, 3H, CH\(_3\)-Thiazole), 2.43 (s, 3H, CH\(_3\)-Thiazole) 2.65 (s, 3H, CH\(_3\)-C=N), 7.0 (s, 1H, Thiazole-H5), 7.4-7.9 (m, 5H, phenyl), 7.96 (s, 1H, NH) Elemental Analysis: Calc.: C, 53.01; H, 4.91; N, 15.44; S, 17.76; Found: C, 53.01; H, 4.91; N, 15.44; S, 17.76

3c: \( C_{18}H_{18}N_4OS \) (370.49), Green crystals, Yield = 72%, M.p.: 196-199\(^\circ\)C, MS: m/z = 370, 267, 215, 174, 71; \(^1\)HRMN (DMSO): δ ppm = 2.41 (s, 3H, CH\(_3\)-Thiazole), 2.43 (s, 3H, CH\(_3\)-Thiazole), 2.50 (s, 3H, COCH\(_3\)), 2.65 (s, 3H, CH\(_3\)-C=N), 7.4-7.9 (m, 5H, phenyl), 7.96 (s, 1H, NH); Elemental Analysis: Calc.: C, 58.35; H, 4.90; N, 15.12; S, 17.31; Found: C, 58.39; H, 4.87; N, 15.08; S, 17.36

3d: \( C_{19}H_{20}N_4O_2S_2 \) (400.52), Orange crystals, Yield = 65%, M.p.: 187-190\(^\circ\)C, MS: m/z = 400, 354, 215, 200, 174, 71; \(^1\)HRMN (DMSO): δ ppm = 1.28 (3H CH\(_3\)-CH\(_2\)-O-CO), 2.41 (s, 3H, CH\(_3\)-Thiazole), 2.45 (s, 3H, CH\(_3\)-Thiazole), 2.66 (s, 3H, CH\(_3\)-C=N), 4.22 (2H, CH\(_3\)-CH\(_2\)-O-CO), 7.4-7.9 (m, 5H, phenyl), 7.94 (s, 1H, NH); Elemental Analysis: Calc.: C, 56.98; H, 5.03; N, 13.99; S, 16.01; Found: C, 57.02; H, 4.99; N, 14.02; S, 16.05

3e: \( C_{18}H_{18}N_4O_2S_2 \) (400.52), Brown crystals, Yield = 71%, M.p.: 95-100\(^\circ\)C, MS: m/z = 400, 354, 327, 215, 100, 174, 71; \(^1\)HRMN (DMSO): δ ppm = 1.28 (3H CH\(_3\)-CH\(_2\)-O-CO), 2.41 (s, 3H, CH\(_3\)-Thiazole), 2.45 (s, 3H, CH\(_3\)-Thiazole), 2.66 (s, 3H, CH\(_3\)-C=N), 4.0 (2H, CH\(_3\)-COOC\(_2\)H\(_5\)), 4.22 (2H, CH\(_3\)-CH\(_2\)-O-CO), 7.0 (s, 1H, Thiazole-H5), 7.4-7.9 (m, 5H, phenyl), 8.0 (s, 1H, NH) Elemental Analysis: Calc.: C, 56.98; H, 5.03; N, 13.99; S, 16.01; Found: C, 56.96; H, 5.05; N, 14.03; S, 15.97

3f: \( C_{21}H_{18}N_4S_2 \) (390.52), Orange crystals, Yield = 72%, M.p. 230\(^\circ\)C, MS: m/z = 390, 287, 246, 215, 174, 71; \(^1\)HRMN (DMSO): δ ppm = 2.41 (s, 3H, Thiazole-4CH\(_3\)), 2.49 (s, 3H, CH\(_3\)-C=N), 7.0 (s, 1H, Thiazole-H5), 7.4-7.9 (m, 10H, phenyl, phenyl), 8.2 (s, 1H, NH) Elemental Analysis: Calc.: C, 64.59; H, 4.65; N, 14.35; S, 16.42; Found: C, 64.64; H, 4.67; N, 14.39; S, 16.39

3g: \( C_{25}H_{21}N_5S_3 \) (487.66), Red crystals, Yield = 61%, M.p.: 246-248\(^\circ\)C, MS: m/z = 487, 364, 312, 271, 215, 174, 71; \(^1\)HRMN (DMSO): δ ppm = 2.50 (s, 3H, CH\(_3\)-Thiazole), 2.54 (s, 3H, CH\(_3\)-Thiazole) 2.67 (s, 3H, CH\(_3\)-C=N), 6.9 (s, 1H, Thiazole-H5), 7.4-7.9 (m, 10H, phenyl, phenyl), 8.2 (s, 1H, NH) Elemental Analysis: Calc.: C, 61.57; H, 4.34; N, 14.36; S, 19.73; Found: C, 61.63; H, 4.32; N, 14.32; S, 19.69
4: (N-(4-acetyl-5-methyl-5-(4-methyl-2-phenylthiazol-5-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide): C_{17}H_{18}N_{4}O_{2}S_{2} (374.48), White crystals, Yield = 69%, Mp: 148-150, m/z=374, 333, 290, 174, 71; \(^{1}\)HRMN (DMSO): \(\delta_{ppm} = 2.0\) (s, 3H, CH\(_{3}\), NH-COCH\(_{3}\)), 2.16 (s, 3H, CH\(_{3}\) N-COCH\(_{3}\)), 2.2 (s, 3H, CH\(_{3}\), thiadiazol), 2.4 (s, 3H, CH\(_{3}\), thiazole), 7.4-7.9 (m, 5H, phenyl), 11.0 (s, 1H, NH-COCH\(_{3}\)), Elemental Analysis: Calc.: C, 54.52; H, 4.84; N, 14.96; S, 17.13, Found: C, 54.57; H, 4.8; N, 15; S, 17.1

The mass spectrum of compound 5, identified as 2-(2-(1-(4-methyl-2-phenylthiazol-5-yl)ethylidene)hydrazinyl)thiazol-4(5H)-one on the basis of its spectral data showed a molecular peak at m/z 330 and the \(^{1}\)HRMN spectra showed a signal at 3.8 ppm attributed to 5-CH\(_{2}\) protons from thiazolin-one ring.

5: C\(_{15}\)H\(_{14}\)N\(_{4}\)O\(_{2}\)S\(_{2}\) (330.43), Yellow crystals, Yield = 70%, M.p.: 210-215\(^{0}\)C, m/z=330, 215, 200, 174, 71, \(^{1}\)HRMN (DMSO): \(\delta_{ppm} = 2.44\) (s, 3H, CH\(_{3}\)-Thiazole), 2.68 (s, 3H, CH\(_{3}\)-C=N), 3.8 (s, 2H, Thiazole-H5), 7.4-7.9 (m, 5H, phenyl), 11.8 (s, 1H, NH), Elemental Analysis: Calc: C, 54.52; H, 4.27; N, 16.96; S, 19.41, Found: C, 54.48; H, 4.2; N, 16.91; S, 19.4

The mass spectra of the compounds 5-arylidene-2-(1-(4-methyl-2-phenylthiazol-5-yl)-ethylidene)-hydrazinyl)-thiazol-4(5H)-ones 6a-i showed all the molecular peaks in agreement with their molecular formulae. The lack of signals due to C-5 protons of thiazole ring in their \(^{1}\)HRMN spectra and the apparition of singlet signals in range 7.8-8.4 corresponding to the CH= (position 5 thiazole) protons provided a firm support for the formations of the compounds 6a-i.

6a: C\(_{22}\)H\(_{17}\)BrN\(_{4}\)O\(_{2}\)S\(_{2}\) (497.43) Yellow crystals, Yield = 61%, M.p.: 237-240\(^{0}\)C, MS: m/z=498 (M+1), 330, 215, 200, \(^{1}\)HRMN (DMSO): \(\delta_{ppm} = 2.52\) (s, 3H, CH\(_{3}\)-Thiazole), 2.75 (s, 3H, CH\(_{3}\)-C=N), 7.99 (1H, CH=), 7.4-7.9 (m, 9H, phenyl, p-Br-phenyl), 11.8 (s, 1H, NH), Elemental Analysis: Calc: C, 53.12; H, 3.44; N, 11.26; S, 11.26; Found: C, 53.16; H, 3.48; N, 11.26.

6b: C\(_{22}\)H\(_{17}\)ClN\(_{4}\)O\(_{2}\)S\(_{2}\) (452.98) Yellow crystals, Yield = 66%, M.p.: 233-238\(^{0}\)C, MS: m/z= 453, 330, 215, 200; \(^{1}\)HRMN (DMSO): \(\delta_{ppm} = 2.48\) (s, 3H, CH\(_{3}\)-Thiazole), 2.68 (s, 3H, CH\(_{3}\)-C=N), 8.04 (1H, CH=), 7.4-8.02 (m, 9H, phenyl, p-Cl-phenyl), 11.4 (s, 1H, NH), Elemental Analysis: Calc.: C, 58.33; H, 3.78; N, 12.37; S, 14.16, Found: C, 58.37; H, 3.73; N, 12.41; S, 14.12.

6c: C\(_{22}\)H\(_{17}\)N\(_{5}\)O\(_{3}\)S\(_{2}\) (463.53), Orange crystals, Yield = 71%, M.p.: 252-255\(^{0}\)C, MS: m/z= 463, 330, 215, 200; \(^{1}\)HRMN (DMSO): \(\delta_{ppm} = 2.51\) (s, 3H, CH\(_{3}\)-Thiazole), 2.60 (s, 3H, CH\(_{3}\)-C=N), 8.24 (1H, CH=), 7.4-8.04 (m, 9H, phenyl, p-NO\(_{2}\)-phenyl), 11.6 (s, 1H, NH), Elemental
6d: C_{22}H_{21}N_{4}O_{3}S_{2} (463.53) Orange crystals, Yield = 69%, M.p.: 245-248°C, MS: m/z = 463, 330, 215, 200; \(^1\)HRMN (DMSO): \(\delta_{ppm} = 2.47\) (s, 3H, CH\textsubscript{3}-Thiazole), 2.62 (s, 3H, CH\textsubscript{3}-C=N), 8.04 (1H, CH=), 7.4-8.04 (m, 9H, phenyl, m-NO\textsubscript{2}-phenyl), 11.4 (s, 1H, NH), Elemental Analysis: Calc.: C, 57.00; H, 3.70; N, 15.11; S, 13.84, Found: C, 56.96; H, 3.74; N, 15.16; S, 13.81

6e: C_{22}H_{18}N_{4}O_{2}S_{2} (434.52), Orange crystals, Yield = 72%, M.p.: 256-260°C, MS: m/z = 434, 330, 215, 200; \(^1\)HRMN (DMSO): \(\delta_{ppm} = 2.47\) (s, 3H, CH\textsubscript{3}-Thiazole), 2.62 (s, 3H, CH\textsubscript{3}-C=N), 8.04 (1H, CH=), 7.4-8.04 (m, 9H, phenyl, m-NO\textsubscript{2}-phenyl), 11.4 (s, 1H, NH), Elemental Analysis: Calc.: C, 60.81; H, 4.18; N, 12.89; S, 14.76, Found: C, 60.77; H, 4.2; N, 12.91; S, 14.72

6f: C_{23}H_{20}N_{4}O_{2}S_{2} (448.56), Yellow crystals, Yield = 78%, M.p.: 205-208°C, MS: m/z = 448, 330, 215, 200; \(^1\)HRMN (DMSO): \(\delta_{ppm} = 2.45\) (s, 3H, CH\textsubscript{3}-Thiazole), 2.61 (s, 3H, CH\textsubscript{3}-C=N), 8.7 (1H, CH=), 7.4-8.04 (m, 9H, phenyl, o-OCH\textsubscript{3}-phenyl), 11.6 (s, 1H, NH), Elemental Analysis: Calc.: C, 61.59; H, 4.49; N, 12.49; S, 14.30, Found: C, 61.62; H, 4.45; N, 12.53; S, 14.28

6g: C_{22}H_{16}Cl_{2}N_{4}O_{2}S_{2} (486.42), Yellow crystals, Yield = 71%, M.p.: 239-242°C, MS: m/z = 486, 330, 215, 200; \(^1\)HRMN (DMSO): \(\delta_{ppm} = 2.43\) (s, 3H, CH\textsubscript{3}-Thiazole), 2.5 (s, 3H, CH\textsubscript{3}-C=N), 8.8 (1H, CH=), 7.2-7.9 (m, 8H, phenyl, 2,4-di-Cl-phenyl), 11.2 (s, 1H, NH), Elemental Analysis: Calc.: C, 54.21; H, 3.31; N, 11.49; S, 13.16, Found: C, 54.26; H, 3.26; N, 11.54; S, 13.1

6i: C_{22}H_{16}Cl_{2}N_{4}O_{2}S_{2} (486.48), Yellow crystals, Yield = 76%, M.p.: 235-238°C, MS: m/z = 486, 330, 215, 200; \(^1\)HRMN (DMSO): \(\delta_{ppm} = 2.46\) (s, 3H, CH\textsubscript{3}-Thiazole), 2.55 (s, 3H, CH\textsubscript{3}-C=N), 8.9 (1H, CH=), 7.2-7.9 (m, 8H, phenyl, 2,6-di-Cl-phenyl), 11.1 (s, 1H, NH), Elemental Analysis: Calc.: C, 54.21; H, 3.31; N, 11.49; S, 13.16, Found: C, 54.22; H, 3.35; N, 11.43; S, 13.20
Conclusions

In order to obtain new compounds with improved antimicrobial activity, new 5-thiazolyl-ethylidene-hydrazinyl-thiazoles and 5-thiazolil-ethylidene-hydrazinyl-thiazolin-4-ones were synthesized. The newly synthesized derivatives were characterized by 1H NMR, MS and elemental analysis.

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