

## Synthesis, Characterization and Thermal Stability Study of New Heterocyclic Compounds Containing 1,2,3-Triazole and 1,3,4-Thiadiazole Rings

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### ABSTRACT

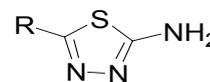
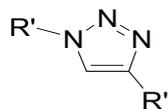
In the current study, a new series of 1,2,3-triazole derivatives was synthesized via copper (I) catalyzed azide-alkyne cycloaddition reaction using a series of synthesised p-substituted phenyl azides and propiolic acid. In addition, a new series of heterocyclic compounds containing 1,2,3-triazole and 1,3,4-thiadiazole ring combined in one molecule was synthesised via a condensation reaction of the synthesised 1,2,3-triazole derivatives and thiosemicarbazide in the presence of  $\text{POCl}_3$ . Furthermore, the thermal behavior of these newly synthesised compounds was studied by TGA and DTG techniques.

**Keywords:** CuAAC, 1,2,3-triazole, 1,3,4-thiadiazole, Click reaction, Thermal stability.

### INTRODUCTION

Heterocyclic compounds are a major class of organic compounds that are identified by the fact that their structures composed of at least one ring system contains at least one non-carbon atom such as oxygen(O), nitrogen(N) and sulpher(S) as heteroatoms<sup>1-3</sup>. Azoles ring system containing heterocyclic compounds have a special importance due to a wide range of different applications<sup>4,5</sup>. Azole is a five-membered ring containing nitrogen atom and at least one other non-carbon atom of either nitrogen, sulphur, or oxygen<sup>6-8</sup>. Among many different azole structures, 1,4-disubstituted-1,2,3-triazole and 2-amino-1,3,4-thiadiazole derivatives (Fig. 1) have a

great interest due to their promising biological and industrial applications<sup>9-14</sup>.



R,R',R''= phenyl or alkyle group

Fig. 1. General structure of triazole and thiadiazole ring system

Thus, the synthesis and study of new 1,4-disubstituted 1,2,3-triazole and 2-amino-1,3,4-thiadiazole derivatives have been attracting the chemists over the recent years<sup>15-17</sup>. Currently, the copper (I) catalysed azide-alkyne cycloaddition

(CuAAC, also known as click reaction) that was introduced by Sharpless and *et al.*, in 2002 is the method choice for the synthesis of 1,4-disubstituted-1,2,3-triazole derivatives<sup>18-20</sup>. While for the synthesis of 2-amino-1,3,4-thiadiazole ring system, many approaches have been reported and most of them proceed via a cyclization reaction of the intermediates such as acylthiosemicarbazide<sup>21-24</sup>. The combination of two or more pharmacophores in one molecule is a powerful strategy in the search for discovering new applications of heterocyclic compounds<sup>25</sup>. Thus, we planned to synthesize a series of new 1,4-disubstituted-1,2,3-triazole derivatives and then combine its 1,2,3-triazole ring system with 1,3,4-thiadiazole ring in one molecule to obtain a novel heterocyclic compounds. In the current work, the retrosynthetic pathway shows that 1,2,3-triazole and 1,3,4-thiadiazole rings are linked together directly via a covalent C-C bond at positions C4 and C5 of their structures, respectively.

## EXPERIMENTAL

### Chemicals and Instruments

All starting materials and solvents that are necessary for the synthesis of the target compounds were purchased from available sources and were directly used without further purification. FT-IR spectra were recorded on an FT-IR-8400S plus spectrometer operating from (4000–400  $\text{cm}^{-1}$ ) as a KBr disc. <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra were recorded at 500 MHz and 125 MHz, respectively on a Bruker AC400 spectrometer. The spectral data are mentioned using the following abbreviations for peak patterns: s-singlet, m-multiplet. The mass spectra (MS) were recorded using an Agilent 1100 Ion trap mass spectrometer operating at 70eV. TG-DTG analysis was performed by using a Perkin Elmer TG 4000 at a temperature range 39-400°C in a heating rate 40°C/min under nitrogen.

### Procedures

#### Synthesis of p-substituted phenyl azide compounds (1-5)

All phenyl azide compounds that were used in the current work were synthesized according to the modified procedure that was described in the literature<sup>26</sup>.

#### General procedure for the synthesis of 1,2,3-triazole derivatives (6-10)

An aqueous solution of sodium ascorbate

(0.8 g, 4.0 mmole) was dissolved in water 2.0 ml) was added to a stirred aqueous solution containing  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (0.65 g, 3.0 mmole) dissolved in water 2.0 ml). To the resulting solution, a mixture of tert-butanol:water (15.0 ml 2:1), propionic acid (2.1 ml, 30.0 mmole) and an appropriate p-substituted-phenyl azide 1-5 (30.0 mmole) were added, sequentially. The resulting reaction mixture was slowly heated up to 50°C and stirred for overnight. The reaction mixture was allowed to cool into room temperature before being treated with water (100 ml). The formed precipitate was collected by vacuum filtration, washed with diethyl ether and dried to obtain the target compounds as solid products.

#### Synthesis of 1-(4-methoxyphenyl)-1H-[1,2,3]-triazolyl-4-carboxylic acid 6

It was prepared by using compound 1 (4.47 g, 30.0 mmole): Yield (5.0 g, 75 %) as a brown solid. FT-IR (KBr disc,  $\text{cm}^{-1}$ ): 3293-2500 (OH, COOH), 3151 (CH-aromatic), 2930 (CH-aliphatic), 1730 (C=O), 1610 (C=C, triazole), 1564 (C=C, Ar) and 1437 (N=N). <sup>1</sup>H-NMR (500 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ = 3.8 (s, 3H,  $\text{OCH}_3$ ), 7.1-7.8 (m, 4H, Ar-H) and 9.2 (s, 1H, C=CH, triazole ring). HPMS-El<sup>+</sup> (m/z): Calc. for  $\text{C}_{10}\text{H}_9\text{N}_3\text{O}_3$  = 219.0, Found = 219.1.

#### Synthesis of 1-(4-methylphenyl)-1H-[1,2,3]-triazol-4-yl carboxylic acid 7

It was prepared by using compound 2 (3.9 g, 30.0 mmole): Yield (3.5 g, 50 %) as a pale brown solid. FT-IR (KBr disc,  $\text{cm}^{-1}$ ): 3332-2560 (-OH, COOH), 3134 (CH-aromatic), 2883 (CH-aliphatic), 1720 (C=O), 1640 (C=C, triazole), 1606 (C=C, Ar) and 1471 (N=N, triazole). <sup>1</sup>H-NMR (500 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ = 2.3 (s, 3H,  $\text{CH}_3$ ), 7.3-7.7 (m, 4H, Ar-H) and 8.7 (s, 1H, C=CH triazole). HPMS-El<sup>+</sup> (m/z): Calc. for  $\text{C}_{10}\text{H}_9\text{N}_3\text{O}_2$  = 203.2, Found = 203.0.

#### Synthesis of 1-(4-hydroxyphenyl)-1H-1,2,3-triazol-4-yl-carboxylic acid 8

It was prepared by using of compound 3 (4.0 g, 30.0 mmole): Yield (6.3 g, 76 %) as a black precipitate. FT-IR (KBr disc,  $\text{cm}^{-1}$ ): 3500-2800 (-OH, COOH), 3134 (CH-aromatic), 2970 (CH-aliphatic), 1727 (C=O), 1608 (C=C, triazole), 1573 (C=C, Ar) and 1470 (N=N). <sup>1</sup>H-NMR (500 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ = 9.5 (s, 1H, OH-phenol), 6.9- 7.7 (m, 4H, Ar-H) and 8.7 (s, 1H, C=CH, triazole). HPMS-El<sup>+</sup> (m/z): Calc. for  $\text{C}_9\text{H}_7\text{N}_3\text{O}_3$  = 205.0, Found = 205.1.

**Synthesis of 1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl carboxylic acid 9**

It was prepared by using compound 4 (5.9 g, 30.0 mmole): Yield (7.5 g, 93 %) as a brown precipitate. FT-IR (KBr disc,  $\text{cm}^{-1}$ ): 3475-2400 (OH, COOH), 3028 (CH-aromatic), 2930 (CH-aliphatic), 1695 (C=O), 1614 (C=C, triazole), 1585 (C=C, Ar), 1402 (N=N) and 734 (C-Br).  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ = 7-8.3 (m, 4H, Ar-H), 8.9 (s, 1H, C=CH, triazole ring). HPMS-El<sup>+</sup> (m/z): Calc. for  $\text{C}_9\text{H}_6\text{N}_3\text{O}_2\text{Br}$  = 268.0, Found = 267.0

**Synthesis of 1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl carboxylic acid 10**

It was prepared by using compound 5 (4.6 g, 30.0 mmole): Yield (6 g, 89 %) as a white precipitate. FT-IR (KBr disc,  $\text{cm}^{-1}$ ): 3468-2570 (-OH, COOH), 3100 (CH-aromatic), 2852 (CH-aliphatic), 1702 (C=O), 1552 (C=C, triazole), 1500 (C=C, Ar) and 1431 (N=N).  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ = 7.7-8.1 (m, 4H, Ar-H), 8.8 (s, 1H, C=CH, triazole ring). HPMS-El<sup>+</sup> (m/z): Calc. for  $\text{C}_9\text{H}_6\text{N}_3\text{O}_2\text{Cl}$  = 223.02, Found = 223.0.

**General procedure for synthesis of 1,3,4-Thiadiazoles derivatives (11-15)**

An appropriate 1,2,3-triazole derivative 6-10 (20.0 mmole) and thiosemicarbazide (1.8 g, 20.0 mmole) were dissolved in  $\text{POCl}_3$  (30.0 ml). The resulting reaction mixture was refluxed for 7.0 hours. The reaction mixture was then allowed to cool into room temperature before being slowly poured onto crush-ice (200 g). The resulting solution was stirred for 15 min before being treated carefully with an aqueous solution of sodium hydroxide 50%. The precipitate was then collected by filtration under vacuum, washed with water and dried to obtain the target compounds as solid products.

**Synthesis of 2-amino-5-[1-(4-methoxy phenyl)-1H-1,2,3-triazol-4-yl]-1,3,4 thiadiazole 11**

It was prepared by using compound 6 (4.3 g, 20.0 mmole): Yield (5.0 g, 92 %) as a dark green precipitate. FT-IR (KBr disc,  $\text{cm}^{-1}$ ): 3287-3130 ( $-\text{NH}_2$ ), 2962 (CH-aromatic), 2864 (CH-aliphatic), 1665 (C=N-), 1612 (C=C, triazole), 1518 (C=C, Ar) and 1440 (N=N).  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ = 3.8 (s, 3H,  $\text{OCH}_3$ ), 8.1-8.3 (m, 4H, Ar-H) and 8.4 (s, 1H, C=CH, triazole ring).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ = 160, 140, 132, 130, 125, 123, 120, 115 and 56. HPMS-El<sup>+</sup> (m/z): Calc. for  $\text{C}_{11}\text{H}_{10}\text{N}_6\text{SO}$  = 274.0, Found = 274.1.

**Synthesis of 2-amino-5-[1-(4-methylphenyl)-1H-1,2,3-triazol-4-yl]-1,3,4-thiadiazole 12**

It was prepared by using compound 7 (4.0 g, 20.0 mmole): Yield (3.5 g, yield 78 %) as a brown precipitate. FT-IR (KBr disc,  $\text{cm}^{-1}$ ): 3414-3100 ( $-\text{NH}_2$ ), 3144 (CH-aromatic), 2937 (CH-aliphatic), 1647 (C=N), 1610 (C=C, triazole), 1504 (C=C, Ar) and 1440 (N=N- triazole).  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ = 2.4 (s, 3H,  $\text{CH}_3$ ), 6.9-7.7 (m, 4H, Ar-H) and 9.7 (s, 1H, C=CH, triazole ring).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ = 165, 154, 147.5, 134, 132, 120, 115 and 110. HPMS-El<sup>+</sup> (m/z): Calc. for  $\text{C}_{11}\text{H}_{10}\text{N}_6\text{S}$  = 258.0, Found = 258.0.

**Synthesis of 2-amino-5-[1-(4-hydroxyphenyl)-1H-1,2,3-triazol-4-yl]-1,3,4-thiadiazole 13**

It was prepared by using compound 8 (4.1 g, 20.0 mmole): Yield (4.6 g, 88 %) as a black precipitate. FT-IR (KBr disc,  $\text{cm}^{-1}$ ): 3445-3150 ( $-\text{NH}_2$ ), 3306 (-OH), 3010 (CH-aromatic), 2744 (CH-aliphatic), 1643 (N=C-), 1606 (C=C, triazole) and 1512 (C=C, Ar).  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ = 9.4 (s, 1H, OH- phenol), 7.3-8 (m, 4H, Ar-H) and 9.4 (s, 1H, C=CH, triazole).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ = 165, 152, 154.2, 133, 130, 120, 122.3 and 116.2. HPMS-El<sup>+</sup> (m/z): Calc. for  $\text{C}_{10}\text{H}_8\text{N}_6\text{SO}$  = 260.0, Found = 260.0.

**Synthesis of 2-amino-5-[1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl]-1,3,4-thiadiazole 14**

It was prepared by using compound 9 (5.3 g, 20.0 mmole): Yield (5.5 g, 85 %) as a gray precipitate. FT-IR (KBr disc,  $\text{cm}^{-1}$ ): 3400-3320 ( $\text{NH}_2$ ), 3009 (CH-aromatic), 2901 (CH-aliphatic), 1653 (N=C-), 1620 (C=C, triazole), 1552 (C=C, Ar) and 1420 (N=N-).  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ = 7.5-8 (m, 4H, Ar-H), 9.8 (s, 1H, C=CH, triazole ring).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ = 168, 160, 148, 142, 136, 133, 123 and 120. HPMS-El<sup>+</sup> (m/z): Calc. for  $\text{C}_{10}\text{H}_7\text{N}_6\text{SBr}$  = 323.9, Found = 324.0.

**Synthesis of 2-amino-5-[1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl]-1,3,4-thiadiazole 15**

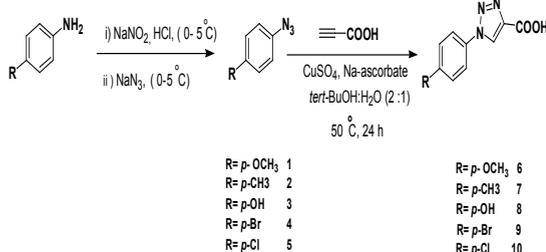
It was prepared by using the compound 10 (5.3 g, 20 mmole): Yield (5.0 g, 90 %) as a dark green precipitate. FT-IR (KBr disc,  $\text{cm}^{-1}$ ): 3466-3120 ( $\text{NH}_2$ ), 2936 (CH-aliphatic), 1676 (N=C-), 1590 (C=C, triazole), 1502 (C=C, Ar) and 1417 (N=N-).  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ ):  $\delta$ = 7.4-8.1 (m, 4H, Ar-H) and 9.3 (s, 1H, C=CH, triazole).  $^{13}\text{C-NMR}$

(125 MHz, DMSO- $d_6$ ):  $\delta$ = 161, 165, 152, 145, 135, 133, 123 and 120. HPMS-El<sup>+</sup> (m/z): Calc. for  $C_{10}H_7N_6O$  = 278.7, Found = 278.0

## RESULTS AND DISCUSSION

### Chemistry

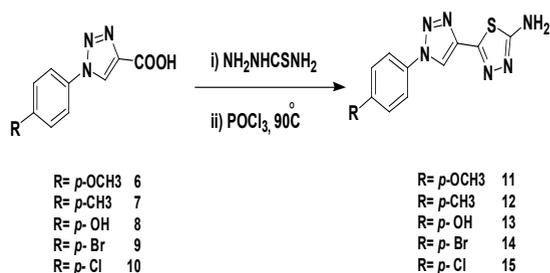
In the current project, a series of rich and poor-electron p-substituted phenyl azide compounds 1-5 was designed as an azido component for CuAAC reaction. Choosing of different substituted phenyl azides is to investigate the effects of a structural variation on their chemical reactivity towards click reaction and the thermal behavior of the synthesized heterocyclic compounds 6-15. The intermediates azide compounds 1-5 were synthesized via reaction of diazonium salts with sodium azide (Scheme 1). Having the target azido compounds 1-5, we turned our efforts to combine them with the commercially available propiolic acid under click reaction conditions. The synthesis route of 1-(4-substituted phenyl)-1H-1,2,3-triazol-4-yl-carboxylic acid derivatives 6-10 is illustrated in Scheme 1. This synthetic route involved addition of propiolic acid and appropriate azide 1-5 to a solution of tert-butanol: water (2:1 v/v) containing  $CuSO_4 \cdot 5H_2O$  and sodium ascorbate. The latter is a reducing agent to generate *in situ* Cu (I) species that are required to perform click reaction.



Scheme 1. Synthesis of 1,2,3-triazole derivatives (6-10)

In this synthetic pathway, the reaction mixture was first left to stir at room temperature for overnight. However, the target compounds were obtained in a very low yield. An attempt to improve this low yield revealed that the standard click reaction solvent tert-butanol: water (1:1) is not enough to dissolve all amounts of the azido components 1-5. Once the ratio of the solvent tert-butanol:water was changed to (2:1 v/v) with heating up to 50°C, the target compounds 6-10 were obtained in relatively high yields. Our synthesis route highlighted a simple work up and the products were pure enough without need

to further purifications by column chromatography. The structures of the newly synthesized compounds were characterized by FT-IR, <sup>1</sup>H-NMR and Mass spectra. Moreover, choosing of propiolic acid as an alkyne component in CuAAC reaction takes advantage that the synthesized 1,2,3-triazole 6-10 containing a carboxyl function group attached directly at C4 position of 1,2,3-triazole ring system. So, it can be exploited to combine 1,2,3-triazole ring system with different structures. In the current work, we are interested in the combination of 1,2,3-triazole ring with 1,3,4-thiadiazole ring in one molecule. The most widely applicable route for the synthesis of 1,3,4-thiadiazole ring system is the thermal acid or base catalyzed dehydro-cyclization of their corresponding acylthiosemicarbazone to construct 2-amino-1,3,4-thiadiazole ring system<sup>27,28</sup>. Therefore, the synthesized 1,2,3-triazole derivatives 6-10 and thiosemicarbazide were the key starting materials for the synthesis of the target compounds 11-15. The cyclocondensation of thiosemicarbazide with 1,2,3-triazole derivatives compounds 6-10 in the presence of  $POCl_3$  under reflux conditions afforded a series of new heterocyclic compounds containing 1,2,3-triazole and 1,3,4-thiadiazole ring systems combined in one molecule 11-15 as described in Scheme 2.



Scheme 2. Synthesis of 1,3,4-thiadiazole derivatives (11-15)

Importantly, the work up of this reaction involved treating the resulting crude solutions with a solution of NaOH (50 %) before being filtered. This step is necessary to remove any remaining unreacted amount of starting materials specially compounds 6-10, thereby leading to give the target compounds 11-15 are pure enough without any need to further purification by column chromatography. The structures of the newly synthesized compounds were characterized by FT-IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and Mass spectra.

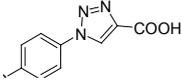
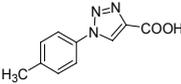
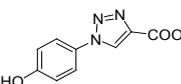
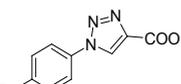
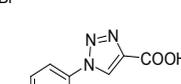
### Thermal stability study of the synthesised compounds (6-15)

Currently, thermal analysis has been

become an important tool to study the thermal stability of important products such as organic compounds, polymers and pharmaceuticals<sup>29</sup>. In the current study, the thermal stability studied by TG and DTG techniques. Thermogravimetry (TG) is one of the basic and useful analytical methods of thermal analysis that are used for recording weight lossing of a tested sample as a function of temperature or time in a heated environment<sup>30</sup>. While, by DTG curve, the area of the peak ( $T_{\text{initial}}$ ,  $T_{\text{final}}$ ) is directly proportional to the mass loss over the same temperature range and the DTG peak high at any temperature gives the rate of mass loss

( $dm/dT$  in  $mg/min$  unit)<sup>31,32</sup>. Therefore, the knowledge of the DTG curve helps to permit the direct application of the rate function of the change in the weight of the target sample to the study of phenomena occurring during thermogravimetric analysis. Practically, depending on the nature of the p-rich or poor-electron substituted phenyl that is attached to N1-position of 1,2,3-triazole ring of compounds 6, 7, 8, 9 and 10. TG-DTG measurements revealed that these compounds are thermally stable up to 250, 240, 275, 205 and 270°C, respectively. Followed a single step decomposition as shown in Fig. 2, 3 and Table 1.

Table 1: TG/DTG data of compounds 6-10

No	Structure	Decomposition temperature range °C		Maximum mass losing temperature °C	Losing weight %
		$T_{\text{initial}}$	$T_{\text{final}}$		
6		253	402	350.7	42.9
7		244	272	259.8	46
8		277	317	290.5	42.4
9		209	278	233.09	29.4
10		271	390	361.2	41.6

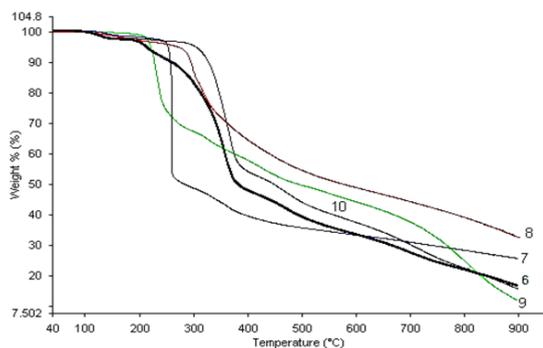


Fig. 2. TG curves for compounds (6-10)

While, TG-DTG measurements that were recorded for compounds 11-15 indicated that these compounds are thermally behaved in the same manner that was described for their precursors

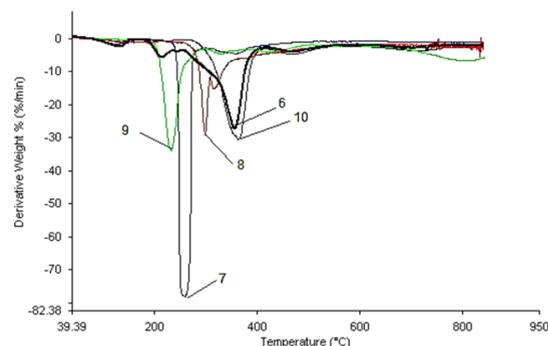
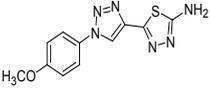
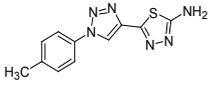
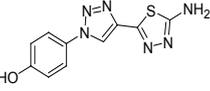
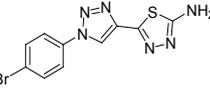
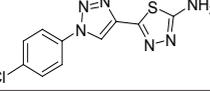
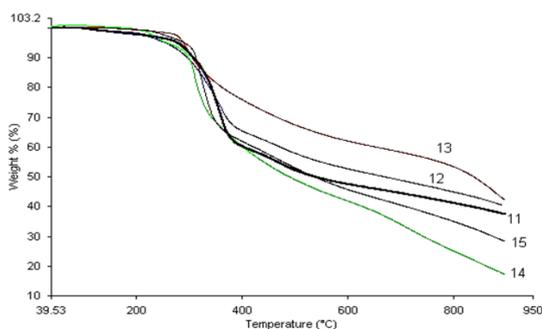
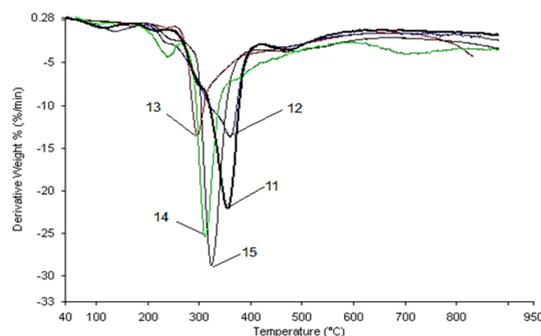


Fig. 3. DTG curves for compounds (6-10)

6-10. All compounds 11, 12, 13, 14 and 15 are thermally stable up to 260, 205, 279, 280 and 274°C, respectively, followed with a single step decomposition as shown in Fig. 4, 5 and Table 2.

**Table 2: TG/DTG data of compounds 11-15**

No	Structure	Decomposition temperature range °C		Maximum mass losing temperature °C	Losing weight%
		T <sub>initial</sub>	T <sub>final</sub>		
11		260	397	355.2	35.8
12		205	410	360.1	25.2
13		279	358	296.5	24.6
14		280	350	313.2	25.2
15		274	384	324.2	31.7

**Fig. 4. TG curves for compounds (11-15)****Fig. 5. DTG curves for compounds (11-15)**

## CONCLUSION

In conclusion, all poor-rich electron phenyl azide compounds were successfully reacted with propionic acid under click reaction conditions. Since the formed compounds containing a carboxyl functional group, it used as a key to synthesise a series of new heterocyclic compounds containing 1,2,3-triazole and 1,3,4-thiadiazole rings in one molecule. Furthermore,

all synthesized heterocyclic compounds displayed a relatively good thermal stability.

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