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Synthesis and thermal study of 1,2,4-triazole derivatives

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ABSTRACT

A series of 1,2,4-triazole derivatives ($PM4_{a-c}$) were synthesized and characterized by various analytical tools such as FT-IR, NMR, mass spectrometry and elemental analysis. The thermal stabilities of these compounds ($PM4_{a-c}$) were also investigated by TGA and DSC analysis. Moreover, the kinetic parameters such as order of reaction (n), energy of activation (E_a), pre-exponential factor (A), entropy of activation ($\Delta S^{\#}$), enthalpy of activation ($\Delta H^{\#}$) and Gibbs free energy of activation ($\Delta G^{\#}$) were evaluated using Freeman-Carroll method.

Keywords: Freeman–Carroll method, TGA and DSC analysis, kinetic parameters

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INTRODUCTION

1,2,4-Triazole and their derivatives are significantly one of the most biologically active class of heterocyclic compounds. 1,2,4-Triazole and their derivatives are well known for their antimicrobial activity [1-5]. A literature review revealed that 1,2,4-triazole and their derivatives belong to an important class of heterocyclic compounds that are biologically active as well as pharmaceutically very important. 1,2,4-Triazole and their derivatives are also well known for their anticancer [6], antitubercular [7-9], cytotoxic agent [10], analgesic [11], anti-inflammatory [12], anticonvulsant [13], antioxidant activity [14], antiviral [15], antimalerial [16] and aromatase inhibitor [17] activity.

Thermal gravimetric analysis was used to investigate the thermal behavior of newly synthesized compounds such as presence of intermediates, degradation process and melting. All thermal techniques are simply used to measure the change in specific property of compound as a function of temperature. The thermal techniques have great importance in the field of pharmaceutical sciences because it gives collective information about the behavior of synthesized compounds when it undergoes thermal changes at elevated temperature. Looking to the importance of this field and in continuation to our previous work in the field of thermal analysis of synthesized heterocyclic compounds, the present study focused on synthesis of 1,2,4-triazole derivatives, thermal behavior and evaluate their kinetic parameters.

EXPERIMENTAL SECTION

Melting points were determined by using Gallenkamp melting point apparatus and are uncorrected. Progress of the reaction was checked on thin layer chromatography (TLC) at certain interval of time. TLC was performed during the reaction on Merck silica gel GF_{254} aluminum sheets using benzene: ethyl acetate (8:2 V/V) system as mobile phase and were visualized under ultraviolet (UV) light or iodine vapor. These compounds were purified by combiflash

chromatography using ethyl acetate: hexane as eluent. Elemental analysis (CHN) was carried out by using a Perkin-Elmer 2400 CHN analyzer. FT-IR spectrums of compounds were recorded on Thermo-Nicolet FT-IR-200 spectrophotometer in KBr disc (cm^{-1}). ^1H NMR and ^{13}C NMR spectra have been recorded on Bruker DRX (200 and 50 MHz) spectrometer using $CDCl_3$ as a solvent and TMS as an internal standard. Mass spectra of synthesized compounds ($PM4_{a-c}$) were carried out by using Shimadzu GC-MS (Shimadzu 2010 plus) direct probe method. TGA and DSC of compounds ($PM4_{a-c}$) were scanned on a Perkin Elmer TGA and DSC (model No. Pyris-1) instrument under N_2 atmosphere at heating rate of 10 °C min^{-1}.

1,2,4-Triazole derivatives were synthesized according to reported method [18-19]. Synthesis and characterization for these three derivatives are summarized herein.

Synthesis of the 4- methoxy benzoyl chloride (1) and its spectral data

Synthesis of intermediate step was carried out using standard methods available in the literature. A mixture of 5.0 g 4-methoxy benzoic acid and 7.5 mL thionyl chloride in 250 mL RBF was refluxed for 8 hrs. Excess thionyl chloride was distilled after completion of reaction and allowed the solution at room temperature to get a product of 4-methoxy benzoyl chloride. (**1**). The characterization data are summarized here.

IR (KBr) ν_{max}, cm^{-1}: 3060 (Ar–C–H stretching), 1032 (Ar–C=O stretching), 1468 (Ar–CH_3 stretching), 764 and 834 (C–H out of plane). ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.204 - 8.042 (m, 4H, Ar–H), 3.352 (s, 3H, methoxy, Ar–OCH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) 114.6 - 134.4 (benzene ring, C–H, 4C), 125.5, 167 (attached with benzene ring, C-C and C-O 3C), 55.8 (Ar–OCH_3) ppm. MS: *m/*z (relative intensity. %), M^+ 108 a. m. u. Elemental analysis Calcd (%) for $C_8H_7ClO_2$: C, 56.32; H, 4.14; N, 0.00%; Found: C, 56.31; H, 4.13; N, 0.00%.

Synthesis of the 4-methoxybenzoyl isothiocyanate (2) and its spectral data

0.01mol of 4-methoxy benzoyl chloride (**1**) were dissolved in 50mL of dry acetone and then 0.01mol of ammonium thiocyanate was added to it with constant stirring for an hour at room temperature. The reaction mixture were filtered after completion of the reaction which help to rid the byproduct ammonium chloride formed during reaction, while filtrate contain main product 4-methoxybenzoyl isothiocyanate (2).

IR (KBr) ν_{max}, cm^{-1}: 3053 (Ar–C–H stretching), 1025 (Ar–C=O stretching), 1471 (Ar–CH_3 stretching), 764 and 836 (C–H out of plane), 1653 (Ar–C=N), 1020 (Ar–C=S isothiocynate). ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.180 - 7.783 (m, 4H, Ar–H), 3.341 (s, 3H, methoxy, Ar–OCH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) 114.8 - 130.9 (benzene ring, C–H, 4C), 127.4, 166.4 and 127.6 (attached with benzene ring, C-C and C-O 4C), 55.8 (Ar–OCH_3, 1C) ppm. MS: *m/*z (relative intensity. %), M^+177 a. m. u. Elemental analysis Calcd (%) for $C_9H_7NO_2S$: C, 55.94; H, 4.65; N, 7.25%; Found: C, 55.92; H, 4.63; N, 7.23%.

Synthesis of the 5-(4-methoxyphenyl)-1-phenyl-1H-1,2,4-triazole-3(2H)-thione (3) and its spectral data

0.01mol of phenyl hydrazine was added to round bottom flask containing 0.01mol of 4-methoxybenzoyl isothiocyanate (2). The reaction mixture was refluxed for 5 hr, a solid product was filtered, washed with distilled water and cold acetone, and dried it over night at 60 °C.

IR (KBr) ν_{max}, cm^{-1}: 3056 (Ar–C–H stretching), 1029 (Ar–C=O stretching), 1473 (Ar–CH_3 stretching), 766 and 834 (C–H out of plane), 1655 (Ar–C=N stretching of triazole ring), 1022 (Ar–C=S isothiocynate), 1615 (Ar–NH out of plane in triazole ring).^1H NMR ($CDCl_3$, 200 MHz) δ: 6.940-7.646 (m, 9H, Ar–H), 3.840 (s, 3H, methoxy, Ar–OCH_3), 3.784 (s, 1H, N–H, triazole ring) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) 111.60-129.23 (C–H benzene ring, 10C), 129.12 (Ar–C, attached with triazole ring, 1C), 163.26 (Ar–C=S, triazole ring, 1C), 161.56 (Ar–C–OCH_3, attached with methoxy, 1C), 139.26 (Ar–C=N, triazole ring, 1C), 58.11 (Ar–OCH_3, 1C) ppm. MS: *m/*z (relative intensity. %), M^+228 a. m. u. anal Calcd (%) for $C_{15}H_{13}N_3OS$: C, 66.58; H, 4.62; N, 14.83%; Found: C, 66.56; H, 4.61; N, 14.82%.

Synthesis of the 5-(4-methoxyphenyl)-1-phenyl-2-((m-tolylamino)methyl)-1H-1,2,4-triazole-3(2H)-thione; compound ($PM4_a$) and its spectral data

A reaction media containing 0.01mol of 5-(4-methoxyphenyl)-1-phenyl-1H-1,2,4-triazole-3(2H)-thione (3), 0.01mol of formaldehyde and 0.01mol of 4-chloro aniline in 50mL of 1,4-dioxan was stirred for 22 hrs. After a confirming the completion of the reaction using TLC technique, reaction mixture was neutralized with liquor ammonia solution and then reaction mixture was poured into water. Additionally, ethyl acetate was added to the mixture for extraction

of the final compound ($PM4_a$). The final compound ($PM4_a$) was obtained by distilled out the solvent, and recrystallized it with methanol. Other compounds ($PM4_{a-c}$) of series were prepared by using a similar method and their physico-chemical and thermodynamic data are summarized in Table.1 and Table. 2. The structural formula of compounds ($PM4_{a-c}$) is shown in the figure 1.

IR (KBr) ν_{max}, cm^{-1}: 3060 (Ar–C–H stretching), 1032 (Ar–C=O stretching), 1468 (Ar–CH_3 stretching), 764 and 834 (C–H out of plane), 1665 (Ar–C=N stretching of triazole ring), 1026 (Ar–C=S isothiocynate), 1615 (Ar–NH out of plane in triazole ring).^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.948-7.767 (m, 13H, Ar–H), 3.709 (s, 3H, Ar–OCH_3), 3.783 (s, 1H, N–H, triazole ring), 3.866 (s, 2H, –CH_2, attached with triazole ring) ppm.^{13}C NMR ($CDCl_3$, 50 MHz) 116.92-128.18 (C–H, benzene ring, 13C), 129.86 (Ar–C–N, attached with triazole ring, 1C), 137.40 (Ar–C=S, triazole ring, 1C), 55.85 (Ar–C–OCH_3, attached with methoxy, 1C), 160.40 (Ar–C=N, triazole ring, 1C), 55.70 (Ar–OCH_3, 1C), 127.54 (Ar–C–C, triazole ring, 1C), 145.50 (N–CH_2, attached triazole ring, 1C), 158.20 (Ar–C–NH, attached with secondary amide, 1C), 135.50 (Ar–Cl, benzene ring, 1C) ppm. MS: *m/*z (relative intensity. %), M^+267 a. m. u. anal Calcd (%) for $C_{22}H_{19}ClN_4OS$: C, 62.48; H, 4.53; N, 13.25%; Found: C, 66.47; H, 4.52; N, 13.23%.

Elemental and characterization data of 5-(4-methoxyphenyl)-2-(((4-nitrophenyl)amino)methyl)-1-phenyl-1H-1,2,4-triazole-3(2H)-thione ($PM4_b$).

IR (KBr) ν_{max}, cm^{-1}: 3096 (Ar–C–H stretching), 1032 (Ar–C=O stretching), 1467 (Ar–CH_3 stretching), 765 and 834 (C–H out of plane), 1615 (Ar–C=N stretching of triazole ring), 1032 (Ar–C=S isothiocynate), 1615 (Ar–NH out of plane in triazole ring), 1250 (Ar–N–O benzene ring).^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.842-7.778 (m, 13H, Ar–H), 3.714 (s, 3H, methoxy, Ar–OCH_3), 3.734 (s, 1H, N–H, triazole ring), 3.825 (s, 2H, –CH_2, attached with triazole ring) ppm.^{13}C NMR ($CDCl_3$, 50 MHz) 115.83-129.48 (C–H, benzene ring, 13C), 128.16 (Ar–C–N, attached with triazole ring, 1C), 136.33 (Ar–C=S, triazole ring, 1C), 55.82 (Ar–C–OCH_3, attached with methoxy, 1C), 161.25 (Ar–C=N, triazole ring, 1C), 55.65 (Ar–OCH_3, 1C), 126.45 (Ar–C–C, triazole ring, 1C), 143.52 (N–CH_2, attached triazole ring, 1C), 159.15 (Ar–C–NH, secondary attached with amide, 1C), 134.56 (Ar–C–NO_2, benzene ring, 1C) ppm. MS: *m/*z (relative intensity. %), M^+296 a. m. u. anal Calcd (%) for $C_{22}H_{19}N_5O_3S$: C, 60.96; H, 4.42; N, 16.16%; Found: C, 60.94; H, 4.40; N, 16.15%.

Elemental and characterization data of 2-(((4-fluorophenyl)amino)methyl)-5-(4-methoxyphenyl)-1-phenyl-1H-1,2,4-triazole-3(2H)-thione ($PM4_c$).

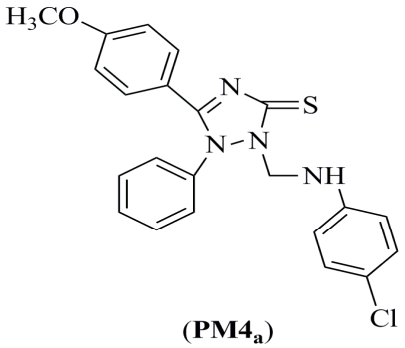
IR (KBr) ν_{max}, cm^{-1}: 3085 (Ar–C–H stretching), 1036 (Ar–C=O stretching), 1472 (Ar–CH_3 stretching), 761 and 831 (C–H out of plane), 1619 (Ar–C=N stretching of triazole ring), 1035 (Ar–C=S isothiocynate), 1628 (Ar–NH out of plane in triazole ring), 1117 (Ar–F benzene ring).^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.652-7.776 (m, 13H, Ar–H), 3.725 (s, 3H, methoxy, Ar–OCH_3), 3.716 (s, 1H, N–H, triazole ring), 3.586 (s, 2H, –CH_2, attached with triazole ring) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) 113.75-129.36 (C–H, benzene ring, 13C), 127.57 (Ar–C–N, attached with triazole ring, 1C), 134.49 (Ar–C=S, triazole ring, 1C), 55.89 (Ar–C–OCH_3, attached with methoxy, 1C), 161.26 (Ar–C=N, triazole ring, 1C), 55.56 (Ar–OCH_3, 1C), 124.77 (Ar–C–C, triazole ring, 1C), 146.78 (N–CH_2, attached triazole ring, 1C), 160.63 (Ar–C–NH, attached with secondary amide, 1C), 133.47 (Ar–C–F benzene ring, 1C) ppm. MS: *m/*z (relative intensity. %), M^+374 a. m. u. anal Calcd (%) for $C_{22}H_{19}FN_4OS$: C, 65.01; H, 4.71; N, 13.78%; Found: C, 65.00; H, 4.69; N, 13.77%.

Table 1. Physico chemical data of compounds ($PM4_{a-c}$) obtained from DSC technique

Compound' Code	Peak Temp /°C (Endo)	On set Temp/°C	End set Temp/°C
$PM4_a$	277.6	272.6	272.5
$PM4_b$	258.75	258.36	261.0
$PM4_c$	258.93	254.19	260.0

Table 2. Thermodynamic data of the thermal decomposition of 1,2,4-triazole compounds ($PM4_{a-c}$)

Compound Code	TGA range/°C	E_a/ kJmol^{-1}	A/S^{-1}	$\Delta S^{\#}$ /Jdeg^{-1}	$\Delta H^{\#}$/ kJ mol^{-1}	$\Delta G^{\#}$/ kJ mol^{-1}	Order of reaction (n)
$PM4_a$	100-650	3.1943	0.0200	-104.70	-1.810	61.221	1.10
$PM4_b$	100-650	2.9392	0.0179	-104.97	-2.024	60.645	1.24
$PM4_c$	100-650	4.6345	0.0397	-103.33	-0.329	61.359	1.69

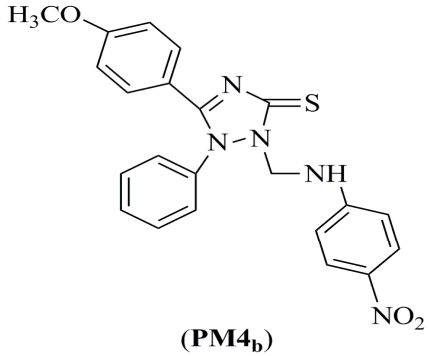


(**PM4$_a$**)

2-(((4-chlorophenyl)amino)methyl)-5-(4-methoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole-3(2*H*)-thione

Chemical Formula: $C_{22}H_{19}ClN_4OS$

Exact Mass: 422.10

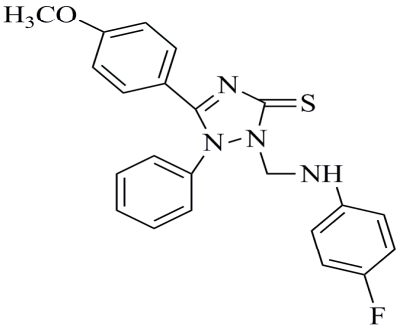


(**PM4$_b$**)

5-(4-methoxyphenyl)-2-(((4-nitrophenyl)amino)methyl)-1-phenyl-1*H*-1,2,4-triazole-3(2*H*)-thione

Chemical Formula: $C_{22}H_{19}N_5O_3S$

Exact Mass: 433.12



(**PM4$_c$**)

2-(((4-fluorophenyl)amino)methyl)-5-(4-methoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole-3(2*H*)-thione

Chemical Formula: $C_{22}H_{19}FN_4OS$

Exact Mass: 406.13

Figure 1. Structure of 1,2,4-triazole derivatives

RESULTS AND DISCUSSION

Thermal behavior of compound PM4$_a$

The thermal behavior of PM4$_a$ was characterized on the basis of TGA and DSC methods. Figure 2 reveals that PM4$_a$ is thermally stable up to about 100°C and follows a single step degradation involving about 92.46% mass loss over the temperature range from 100 to 500°C leaving 7.54 % residue beyond 500 °C. The considerable weight loss was obtained at about 500°C. The characteristic temperatures for the assessment of the PM4$_a$ relative thermal stability of compound PM4$_a$ was done using initial decomposition temperature (T_o), temperature of 10% mass loss (T_{10}),

temperature of maximum mass loss (T_{max}) and temperature of final decomposition (T_f). The T_o, T_{max} and T_f were 215.5, 500 and 650°C respectively.

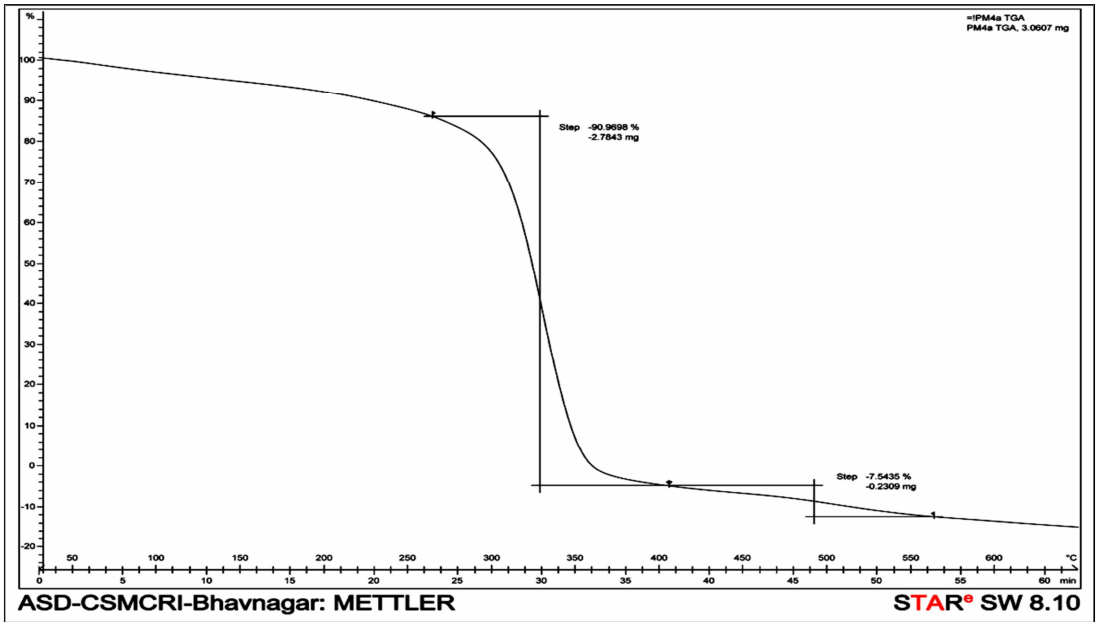


Figure 2. TGA thermogram of 2-(((4-chlorophenyl)amino)methyl)-5-(3-methoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole-3(2*H*)-thione; compound ($PM4_a$) at the heating rate of 10 °C/min in an N_2 atmosphere

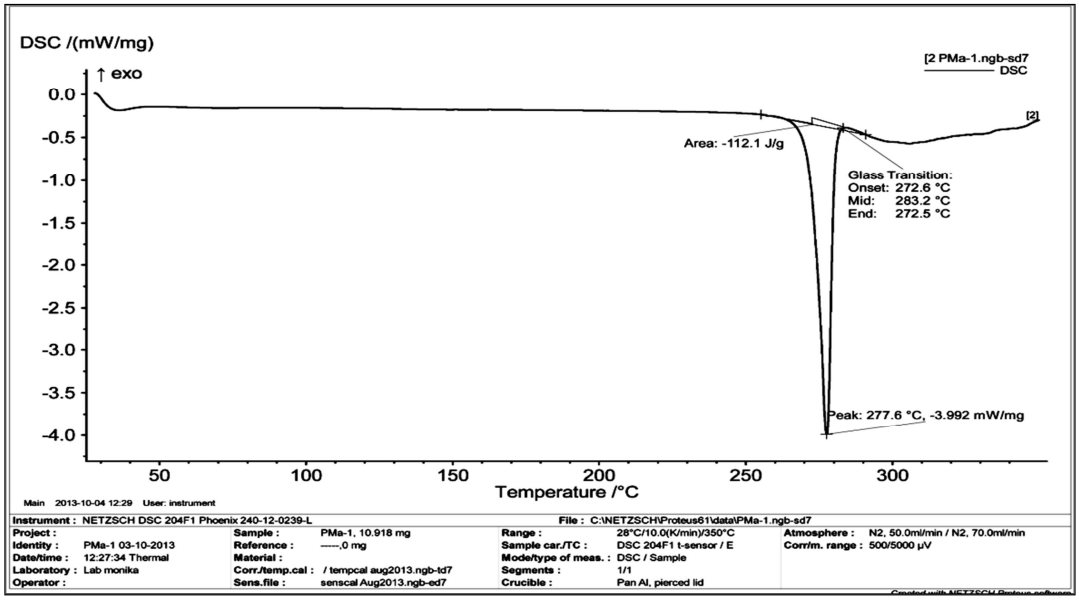


Figure 3. DSC thermogram of 2-(((4-chlorophenyl)amino)methyl)-5-(3-methoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole-3(2*H*)-thione ($PM4_a$) at the heating rate of 10 °C/min in an N_2 atmosphere

The DSC curve of the compound $PM4_a$ shown in figure 3 reveals endothermic transition at 277.6 °C, which was due to melting of $PM4_a$. Figure 4 shows associated Kinetic parameters such as order of reaction (n), energy of activation (E_a), frequency factor (A) and entropy of activation change ($\Delta S^{\#}$) which have been determined according to Freeman- Carroll method. The least square values (R^2= 0.964) of n, E_a, A, $\Delta S^{\#}$, $\Delta H^{\#}$ and $\Delta G^{\#}$ were determined as 1.10, 3.1943 *k*J mol^{-1}, 0.0200 s^{-1}, -104.82 *k*J mol^{-1}, -1.810 *k*J mol^{-1} and 61.221 *k*J mol^{-1} respectively. Degradation

process is linking a variety of reactions such as rearrangement, branching, etc. Negative magnitude of $\Delta S^{\#}$ established that transition state was much in orderly state for compound $PM4_a$.

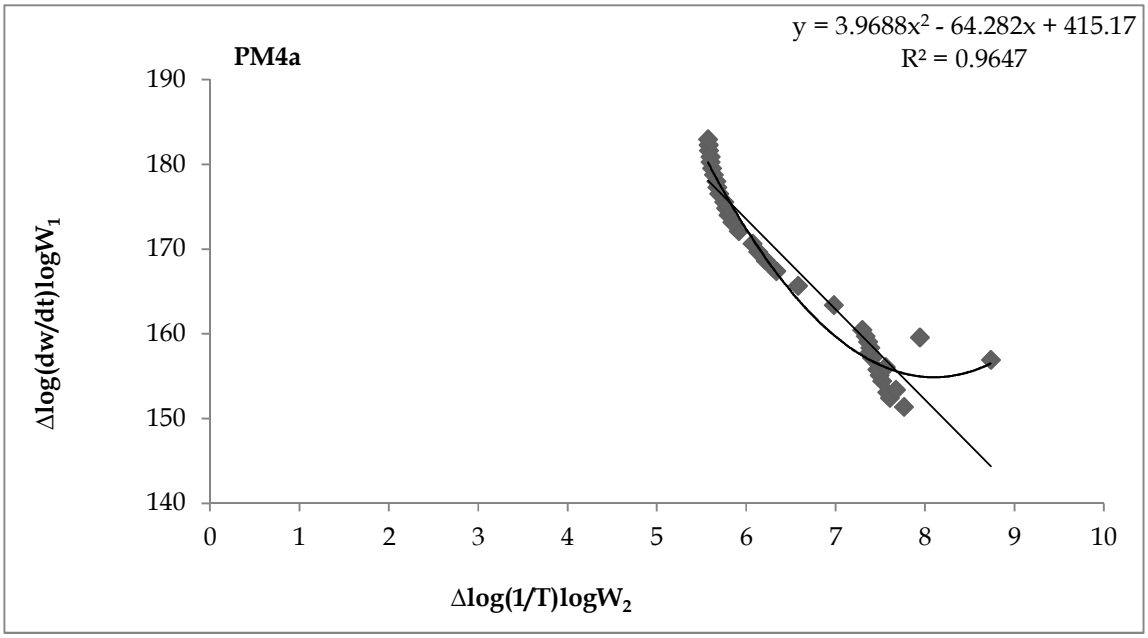


Figure 4. Freeman-Carroll plot for compound ($PM4_a$)

Thermal behavior of compound $PM4_b$

The thermal behavior of the compound **$PM4_b$** was carried out using TGA and DSC. The TGA thermogram of compound $PM4_b$ is shown in figure 5 and it reveals that $PM4_b$ is thermally stable up to about 100°C. After 100°C, it follows considerable single step degradation in the temperature range from 100 to 500°C. The final residue was left beyond 500°C with 6.96%.

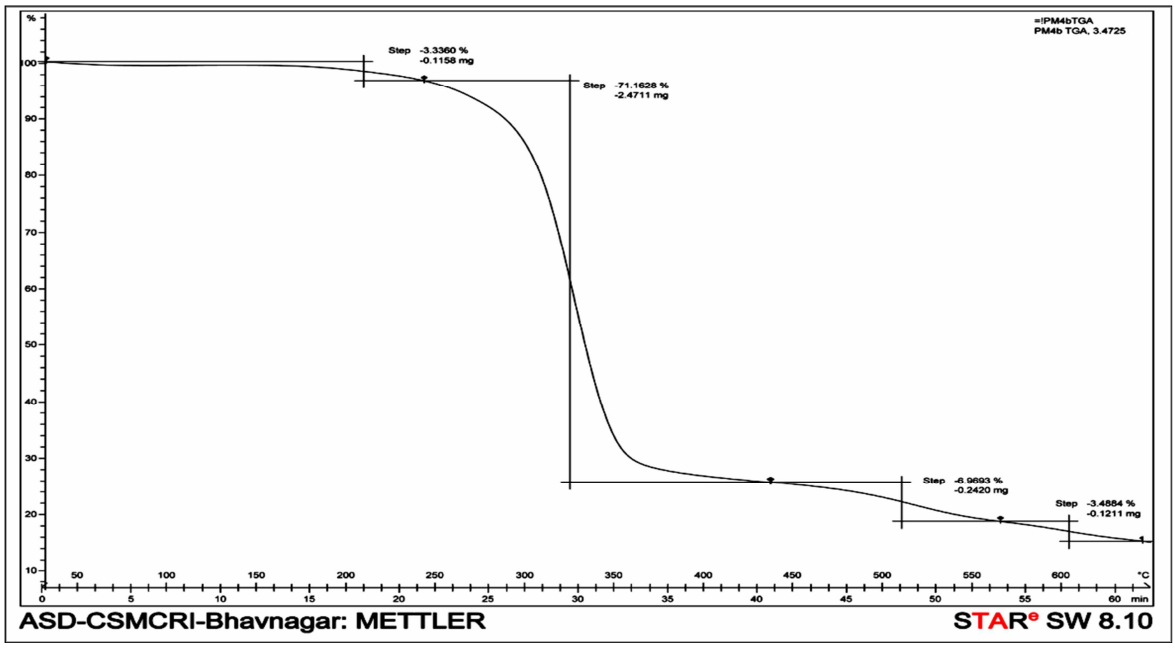


Figure 5. Simultaneous TGA thermogram 5-(4-methoxyphenyl)-2-(((4-nitrophenyl)amino)methyl)-1-phenyl-1*H*-1,2,4-triazole-3(2*H*)-thione ($PM4_b$) at the heating rate of 10 °C/min in an N_2 atmosphere

The DSC curve of compound $PM4_b$ is presented in figure 6. Endothermic transition was found at 258.36 ℃, which is due to melting of $PM4_b$. Figure 7 shows Associated Kinetic parameters such as order of reaction (*n*), energy of activation (E_a), frequency factor (*A*) and entropy of activation change ($\Delta S^{\#}$) have been determined according to Freeman- Carroll method. The least square values (R^2= 0.961) of *n*, E_a, *A*, $\Delta S^{\#}$, $\Delta H^{\#}$ and $\Delta G^{\#}$ were determined as 1.24, 2.9392 *k*J mol^{-1}, 0.0179s^{-1}, -104.97 *k*J mol^{-1}, -2.0241 *k*J mol^{-1} and 60.645 *k*J mol^{-1} respectively.

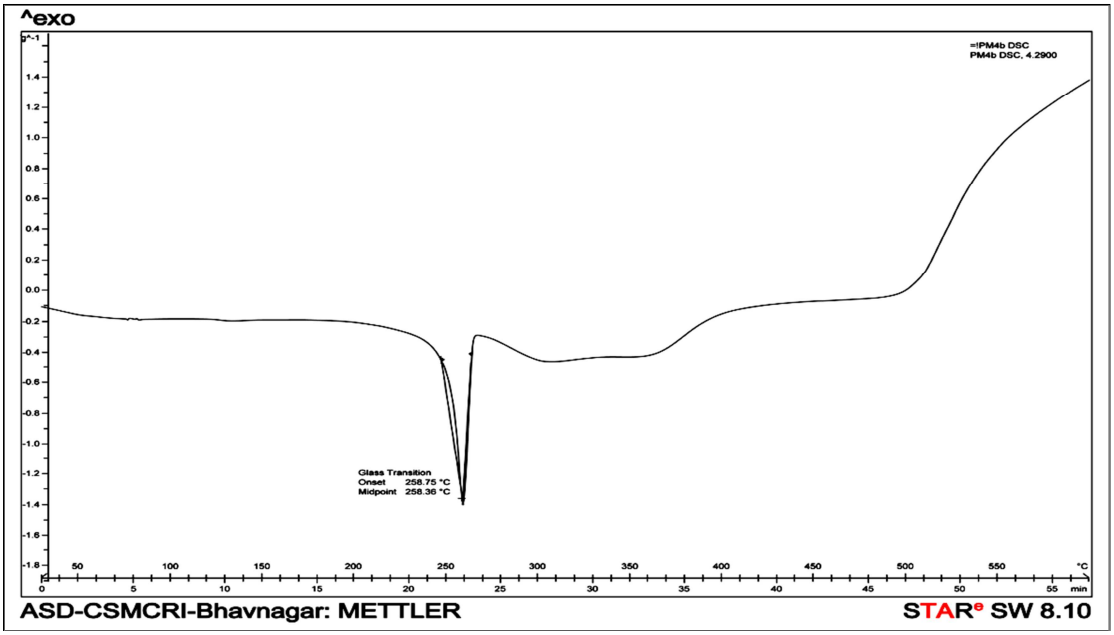


Figure 6. DSC thermogram of 5-(4-methoxyphenyl)-2-(((4-nitrophenyl)amino)methyl)-1-phenyl-1*H*-1,2,4-triazole-3(2*H*)-thione ($PM4_b$) at the heating rate of 10 °C/min in an N_2 atmosphere

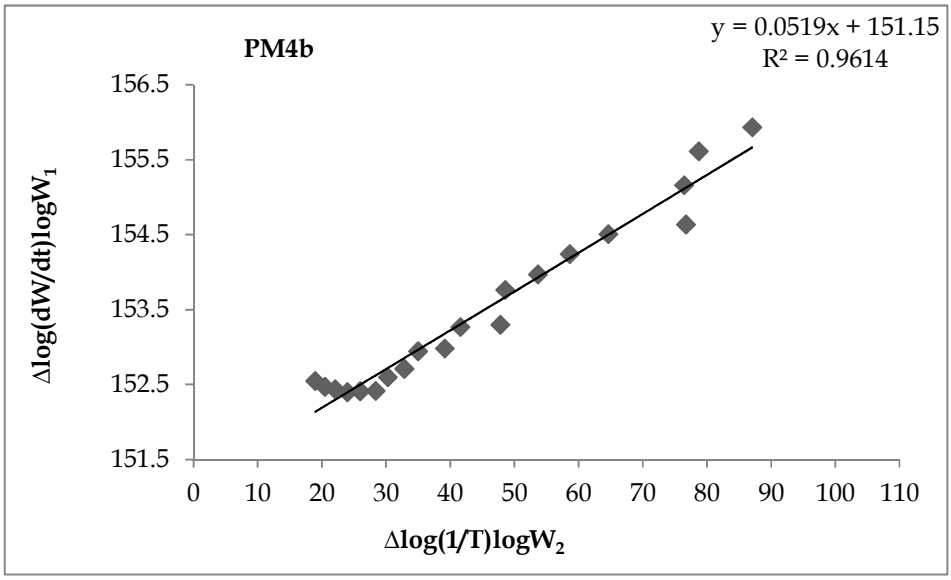


Figure 7. Freeman-Carroll plot for compound ($PM4_b$)

Thermal behaviour of compound PM4$_c$

TGA thermogram of compound PM4$_c$ is presented in figure 8 and it described that PM4$_c$ is thermally stable up to about 100℃ and followed single step degradation beyond 100℃. The considerable mass loss involved in this step the temperature range from 100 to 500°C. The final residue was obtained at 500°C with 6.73%.

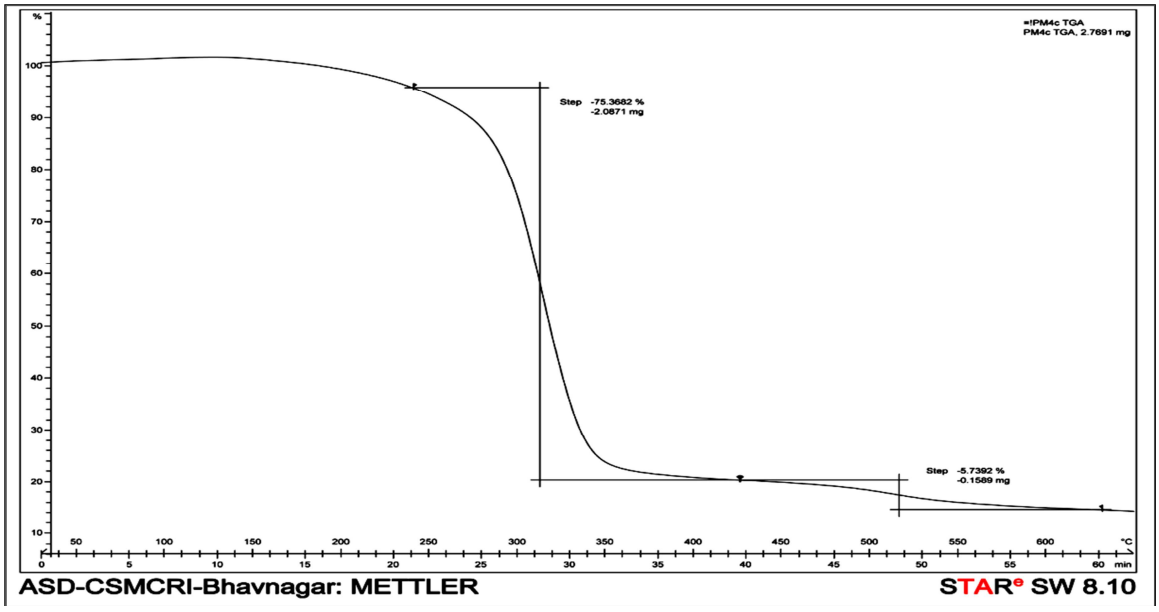


Figure 8. TGA thermogram of 2-(((4-fluorophenyl)amino)methyl)-5-(4-methoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole-3(2*H*)-thione; compound (PM4$_c$) at the heating rate of 10 °C/min in an N_2 atmosphere

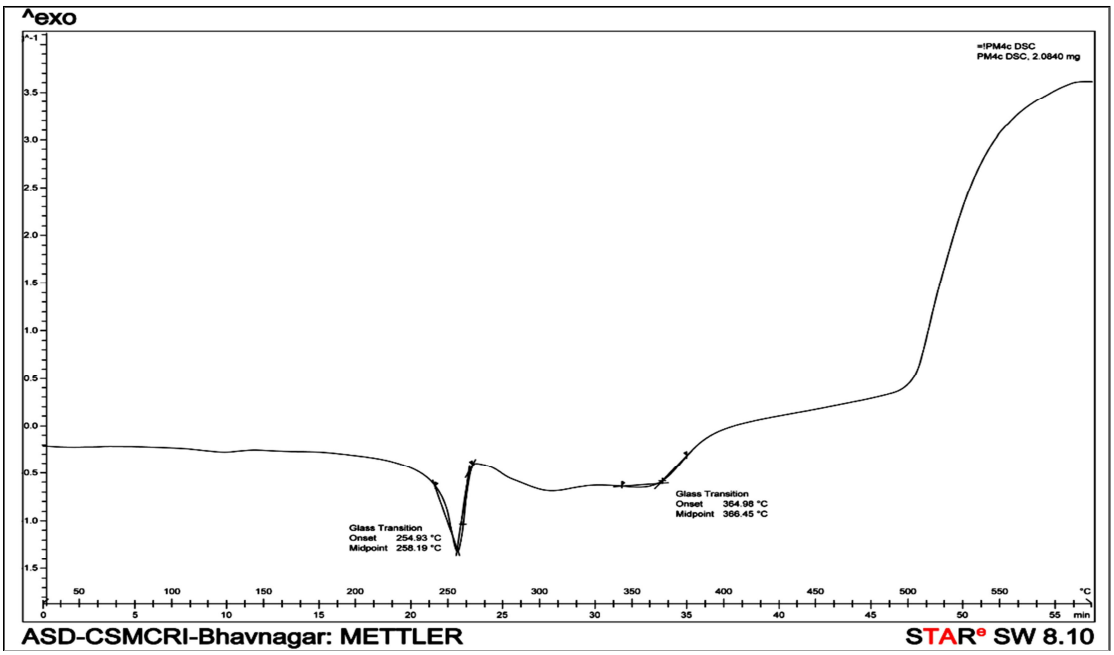


Figure 9. DSC thermogram of 2-(((4-fluorophenyl)amino)methyl)-5-(4-methoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole-3(2*H*)-thione (PM4$_c$) at the heating rate of 10 °C/min in an N_2 atmosphere

The DSC curve of compound PM4$_c$ is depicted in figure 9. Endothermic transition was found at 258.19 ℃, which was due to melting of PM4$_c$. Figure 10 shows Associated Kinetic parameters such as order of reaction (*n*), energy of

activation (E_a), frequency factor (A) and entropy of activation change ($\Delta S^{\#}$) have been determined by using Freeman- Carroll method. The least square values (R^2= 0.997) of n, E_a, A, $\Delta S^{\#}$, $\Delta H^{\#}$ and $\Delta G^{\#}$ were determined as 1.69, 4.6345 kJ mol^{-1}, 0.0397 s^{-1}, -103.33 kJ mol^{-1}, -0.329 kJ mol^{-1}, 61.359 kJ mol^{-1} respectively. Degradation process is covers a variety of reactions such as rearrangement, branching, etc. Negative magnitude of $\Delta S^{\#}$ established that transition state was much in orderly state for compound PM4$_c$.

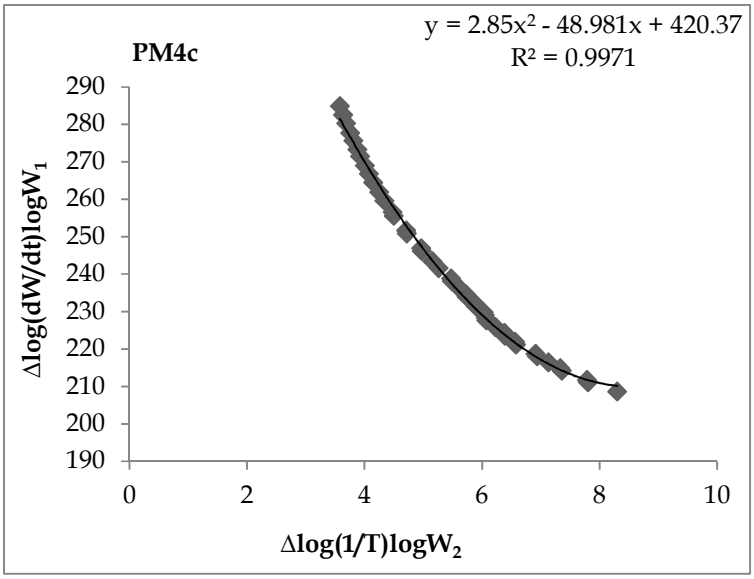


Figure 10. Freeman-Carroll plot for compound (PM4$_c$)

CONCLUSION

1,2,4-triazole derivatives (PM4$_{a-c}$) were prepared successfully and characterized by various spectral techniques.

The thermal behavior of compounds (PM4$_{a-c}$) was carried out using TGA and DSC techniques. In all the three cases, endothermic reaction and one step degradation was observed. Thermodynamic and kinetic parameters were calculated using Freeman-Carroll method; this suggests that degradation process was dominated by first order reaction. The calculation of thermal stability to understand structural relationship of these three synthesized derivatives of 1,2,4-triazole has of great importance looking to the importance of 1,2,4-triazole in pharmaceutical chemistry. Significant variation of thermal stabilities is expected in three derivatives of 1,2,4-triazole due to their structural modification. It has been found that small structural changes of hydrazide moiety can modify substantially the thermal behavior. Approach of this work is to study the thermal behavior of two compounds in non-isothermal system.

Overall, the aim of our present study was achieved successfully and three derivatives of 1,2,4-triazole were prepared. The findings suggest that the compounds possess good thermal stability and hence, can be used further for medicinal use after successful completion of all necessary protocols.

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