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RESEARCH ARTICLE

Thermal Studies of Some Biological Active Bis[1,2,4]triazolophthalazines: Non Isothermal Kinetic Study of one of the Potent 3,6-*Bis*(4-nitrophenyl) *bis*([1,2,4]triazolo)[3,4-a:4′,3′-c]phthalazine

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Abstract: Thermal decomposition studies of twelve bis-1,2,4-triazolophthalazines (**4a-l**) have been investigated using TG and DSC techniques under argon atmosphere at a heating rate of 10 °C min^{-1}. TG study shows that all halogen substituted compounds (**4e-j**) are thermally most stable except **4f**. Mass percentage residues left at 550 °C lie in the range 29-52%. This shows that compounds are thermally stable at high temperatures. DSC curve shows two peaks except for **4c** and **4d** which are showing three DSC peaks degradation. Second peak of most of the compounds and third DSC peak of **4c-d** shows exothermic decomposition. Activation energy calculated by model free methods for compound **4k** show dependence on conversion value. Activation energy at conversion 0.8 for this compound is around 562.6 kJ mol^{-1}.

Keywords: 1,2,4-Triazoles, Phthalazines, TG, DSC, Activation energy

Introduction

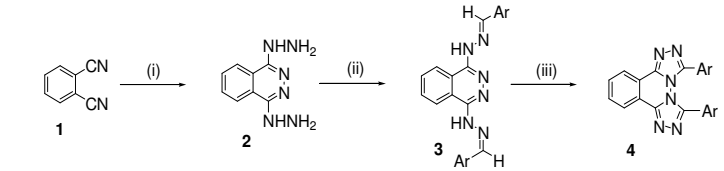
1,2,4-Triazoles derivatives are important class of nitrogen containing heterocyclic compounds because of their diverse biological activity such as antifungal, bactericidal, anxiolytic, anticonvulsant, herbicidal, antidepressants, anti-inflammatory *etc.*[1-7]. Thermal analysis of pharmaceutical/medicinal compounds is a very reliable method for purity control and it is a necessary part of the characterization of new compounds with potential bioactivity. The thermal analysis methods are widely used for the study of the stability and decomposition of the substances used in medicine. The evaluation of the stability of biological active compound in solid dosage form is realized especially by analyzing its decomposition in isothermal and non-isothermal conditions[8]. There are many application of thermal analysis in pharmaceutical industry and is summarized by Giron[9]. It is also a reliable method for study of interaction of active pharmaceutical ingredient (API) or drug with the excipients.

Besides the good biological activity, triazole derivatives are energetic molecules which are suitable for developing energetic materials[10]. Thermal analysis is an important technique to study these molecules also from the energy point of view. In this regard, Sasidharan *et al.*[10]

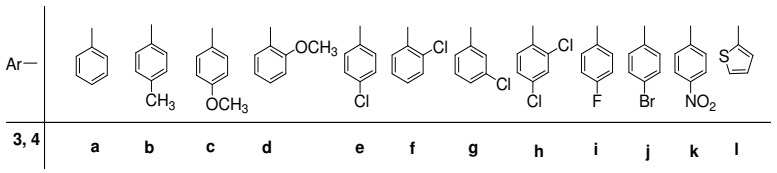
and Yoshino *et al.*[11] reported the thermal behaviour of some triazole derivatives. Keeping in mind the above facts, we hereby report the thermal studies of some biological active bis-1,2,4-triazolophthalzines.

Experimental

3,6-Bis(aryl)bis([1,2,4]triazolo)[3,4-a:4′,3′-c]phthalazines (**4a-l**) used for the study were prepared according to procedure explained in our recently accepted paper[12] and the various steps involved in the synthesis are shown in Scheme 1. All the compounds were studied for their *in vitro* antibacterial and antifungal evaluation against Gram-positive and Gram-negative strains are also described in the paper[12].



(i) $NH_2NH_2.H_2O$, AcOH, Dioxane, reflux 2-3h, (ii) ArCHO, MeOH, reflux 5h, (iii) IBD, DCM, 24h, stirred at rt



Scheme 1. Synthesis of compounds **4a-l**

Thermal analysis

Thermal analysis of compounds **4a-l** was carried out using Perkin Elmer Diamond TG/DTA analyzer. Thermograms were recorded at a heating rate 10 °C min^{-1} from ambient temperature to 600 °C under flowing argon atmosphere at a flow rate of 150 mL min^{-1}. Before starting each run, argon was used to flush out the furnace for 30 minute to create an inert atmosphere so as to avoid unwanted oxidation. Dried alumina powder was used as a reference material and ceramic sample holder was used for taking thermograms. Thermograms of the most potent compound **4k** were recorded at multiple heating rates (β) 5, 10, 15, 20 and 25 °C min^{-1} under similar conditions in order to meet the requirement of multiple heating rate methods. In order to ensure the uniformity of temperature of the sample and good reproducibility, small amounts (2-6 mg) were taken.

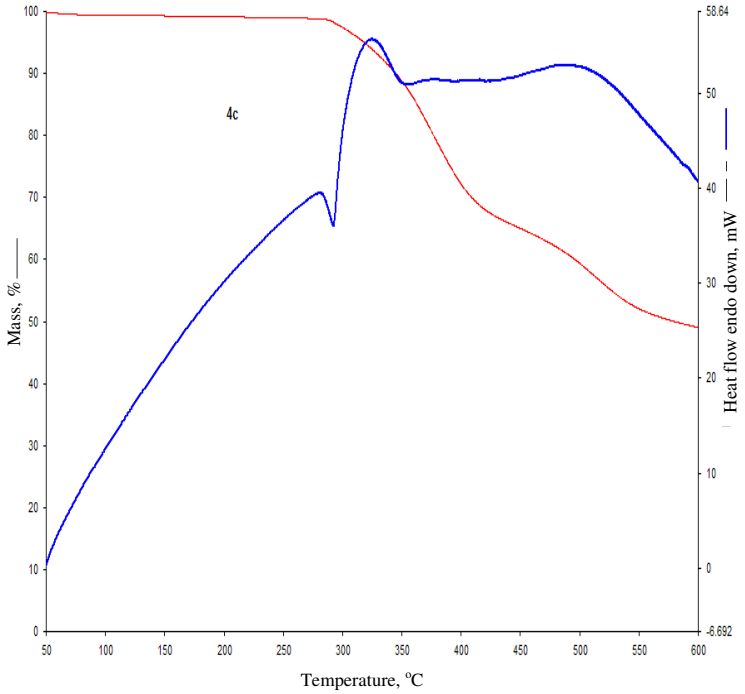
Non-isothermal model free kinetic methods

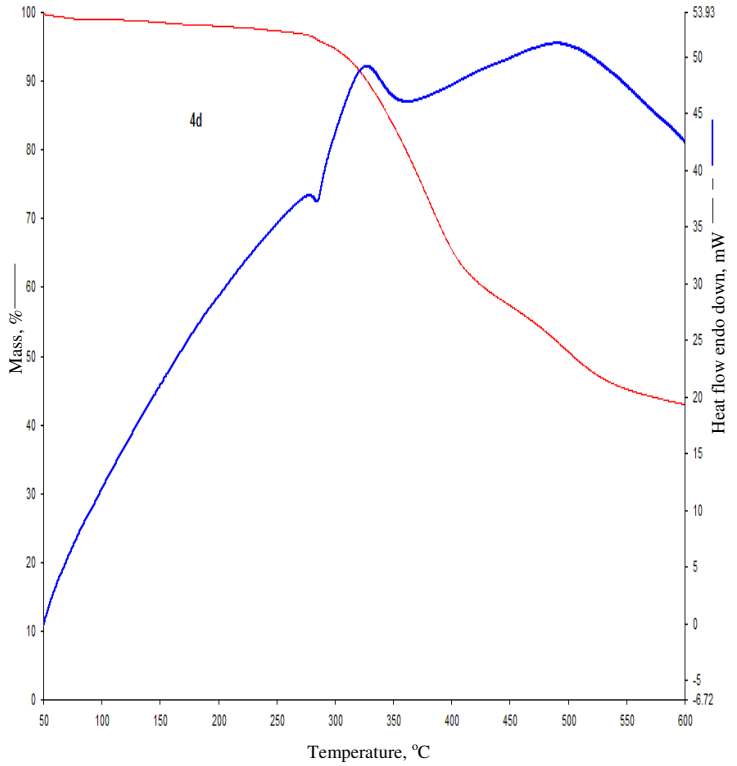
TG data was used in MS Excel software to appraise activation energy (E_a) and correlation coefficient (R^2) of most potent compound **4k**. The E_a values of the most potent compound **4k** was calculated by "model free" methods namely, Ozawa-Flynn-Wall (O-F-W)[13,14], Coats-Redfern (modified)[15] and Friedman[16] as described in our research studies[17,18].

Results and Discussion

Thermal study

TG and DSC curves of compounds **4c-e** and **4l** at a heating rate of 10 °C min^{-1} under argon atmosphere are shown in Figure 1, for illustration. Data taken from TG and DSC curves are summarized in Table 1-2, respectively.


4c
Mass, %
Heat flow endo down, mW
Temperature, °C
100
90
80
70
60
50
40
30
20
10
0
58.64
50
40
30
20
10
0
-6.692
50
100
150
200
250
300
350
400
450
500
550
600


4d
Mass, %
Heat flow endo down, mW
Temperature, °C
100
90
80
70
60
50
40
30
20
10
0
53.93
50
45
40
35
30
25
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200
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450
500
550
600

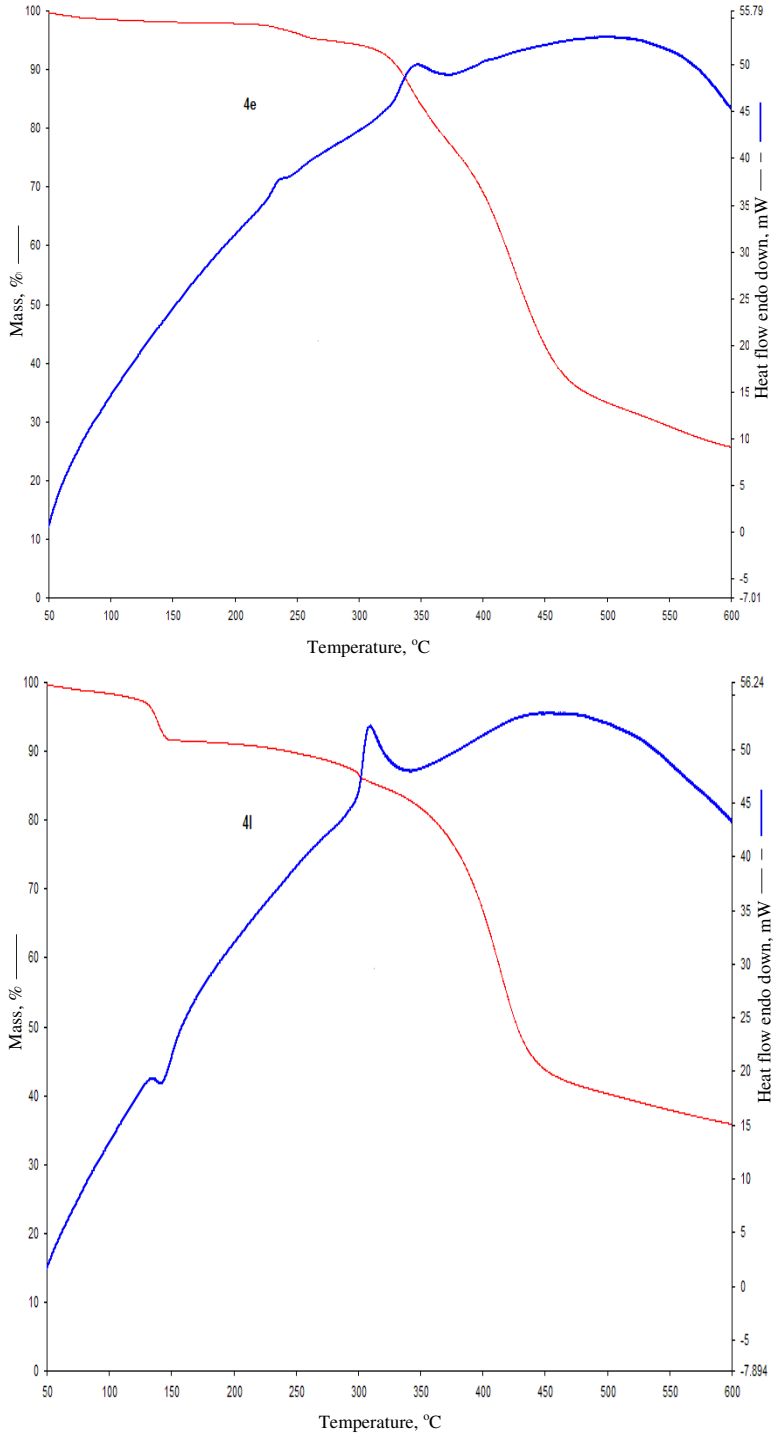

Figure 1. TG and DSC curves of compounds **4c-e** and **4l**

On the basis of initial decomposition temperature (T_i), it has been found that substituted compounds **4b-j** are thermally more stable than unsubstituted **4a** except **4c-d, 4f, 4k-l**. T_i of unsubstituted compound **4a** is 309.6 °C. The thermal stability of compound **4b** having methyl group at *para* position increases ~2 °C and thermal stability of methoxy substituted compounds **4c-d** decreases ~3 °C. All halogen substituted compounds **4e-j** are also thermally more stable than unsubstituted **4a** except **4f** having chloro at *meta* position. Compounds **4k** and **4l** having nitro group at *para* position and thiophene ring as substituent, respectively, are least stable which might be due to early rupture of N-O bond in nitro group and C-S bond in thiophene ring. Higher values of T_i are due to presence of heterocyclic rings enriched with nitrogen[39-40]. Mass loss (ML_i) percentage corresponding to T_i is small for all which lie in the range 1-7%. Mass percentage residues left at 550 °C lie in the range 29-52%. The residues mainly consist of carbonaceous products. High value of char residue shows that compounds are thermally stable at higher temperature (Table 1). It is well known that higher the value of char residue higher will be thermal stability of compounds. The decomposition up to 550 °C may be due to rupture of heterocyclic rings, various polymerization reactions, bond breaking and bond forming, simultaneously[19].

Table 1. TG data of compounds **4a-l**

Compounds	Ti, °C	MLi, %	Residue at 550 °C, %
4a	309.6	2.0	29.0
4b	311.1	2.6	38.9
4c	306.5	1.2	52.1
4d	307.8	4.0	45.2
4e	322.2	6.2	29.2
4f	291.7	2.0	40.3
4g	347.7	5.8	41.3
4h	343.8	6.8	36.2
4i	321.3	3.9	37.7
4j	329.9	3.8	36.3
4k	188.5	1.8	48.2
4l	132	2.7	37.9

DSC curves of all compounds shows two peaks except **4c** and **4d** which shows three peaks (Figure 1). All DSC peaks are corresponding to decomposition of compounds. First peak decomposition is endothermic for all except **4e**, **4j** and **4k** which shows small exotherms. Second and third peak correspond to major decomposition and are exothermic in nature. Peak temperature (T_p) corresponding to first endothermic DSC peak lie in the range 143-330 °C and corresponding enthalpy change (ΔH) lie in the range 18-50 Jg^{-1} (Table 2). T_p values for first exothermic peak of compounds **4e**, **4j** and **4k** lie in the range 235-352 °C and corresponding ΔH values lie in the range -16 to -92 Jg^{-1}. T_p values for second exothermic peak of compounds lie in the range 308-443 °C and corresponding ΔH values lie in the range -506 to -148 Jg^{-1}. T_p values corresponding to third exothermic peak of compounds **4c** and **4d** are 508.8 and 496.6 °C, respectively and corresponding heat release during this stage are -614.5 and -1298.6 Jg^{-1}. Decomposition products in these compounds might be NH_3, HCN, N_2O, NO, CO, CO_2, HCNO *etc*. as observed in earlier cases in the related compounds[19].

Table 2. DSC data of compounds **4a-l**

Compounds	Stages	T_{peak}, °C	Temperature range, °C	Peak nature	ΔH, J g^{-1}
4a	i	317.1	309-320	Endo (small)	+22.0
	ii	327.2	320-365	Exo	-231.3
4b	i	315.0	308-319	Endo (small)	+25.2
	ii	327.2	319-359	Exo	-148.6
4c	i	292.56	281-297	Endo (small)	+37.2
	ii	323.66	297-423	Exo	-505.1
	iii	508.8	423-600	Exo	-614.5
4d	i	285.5	274-294	Endo (small)	+39.8
	ii	323.7	294-407	Exo	-505.8
	iii	496.6	407-600	Exo	-1298.6
4e	i	235.2	226-245	Exo	-19.0
	ii	344.0	245-371	Exo	-173.8
4f	i	270.0	257-279	Endo (small)	+44.5
	ii	317.4	279-369	Exo	-383.7
4g	i	274.1	250-293	Endo (small)	+29.5
	ii	384.7	340-410	Exo	-173.9
4h	i	257.8	237-271	Endo (small)	+38.7
	ii	386.7	356-405	Exo	-153.8
4i	i	330.0	323-334	Endo (small)	+18.8
	ii	339.6	334-369	Exo	-280.6
4j	i	243.0	233-258	Exo (small)	-16.9
	ii	353.3	326-378	Exo	-208.0
4k	i	351.5	321-375	Exo	-91.6
	ii	442.7	375-489	Exo	-486.7
4l	i	143.6	123-160	Endo	+49.5
	ii	308.6	288-345	Exo	-177.6

Activation energy

The compound **4k** was selected to study the kinetics of thermal degradation on the basis of good antibacterial agent as compared to others. TG curves of **4k** were recorded at five multiple heating rates *i.e.* 5, 10, 15, 20 and 25 °C min^{-1} to meet the requirement of model free methods. TG curves at 5, 10, 15, 20 and 25 °C min^{-1} heating rates are given in Figure 2. The TG curves shifts towards higher temperature with increase in heating rates. This might be due to different heat transfer and kinetic rates which delays the decomposition of sample[21]. Iso-conversional plots of O-F-W for **4k** are shown in Figure 3, for illustration. The E_a and R^2 values calculated by iso-conversional model free methods at a constant α value are given in Table 3. The $R^2 > 0.94$ was chosen to calculate E_a at particular α value. Study shows that E_a depend upon that α value and there is no regular trend in the conversion range 0.06-0.3. After this, E_a increases continuously from 138 to 562.6 kJ mol^{-1} up to 0.8 conversion value. High value of E_a values at high α value shows that compounds are stable at high temperatures and support the result elucidated from TG study. The E_a values calculated by Coats-Redfern (modified) method are in good agreement with those of calculated by O-F-W[21].

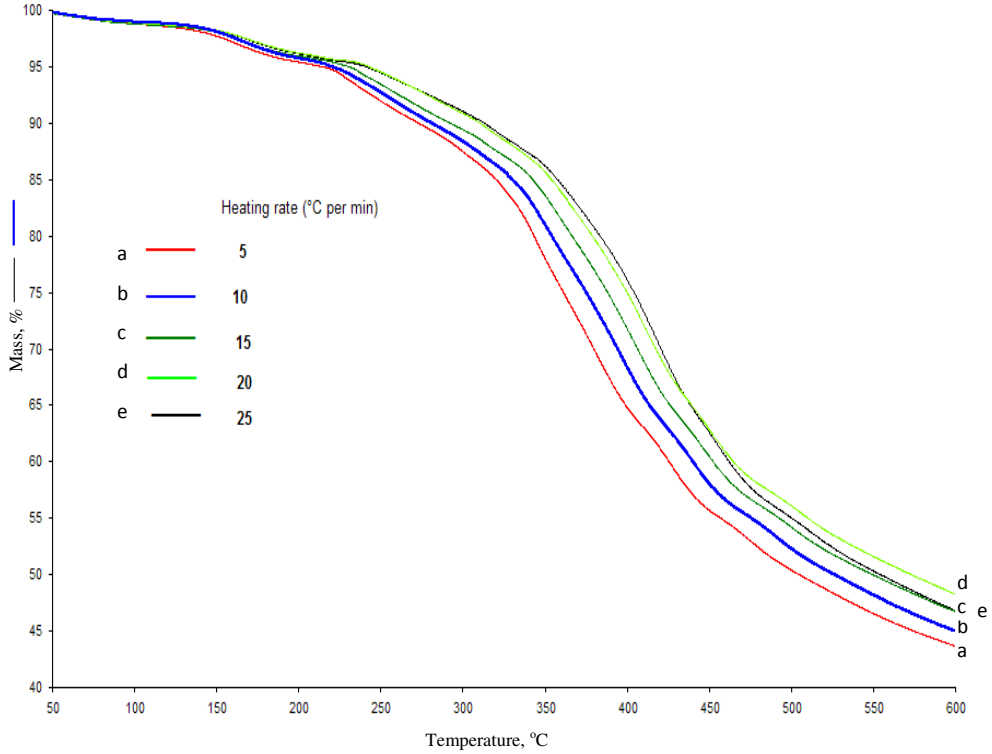

Figure 2. TG curves of **4k** at heating rate 5, 10, 15, 20 and 25 °C in argon atmosphere

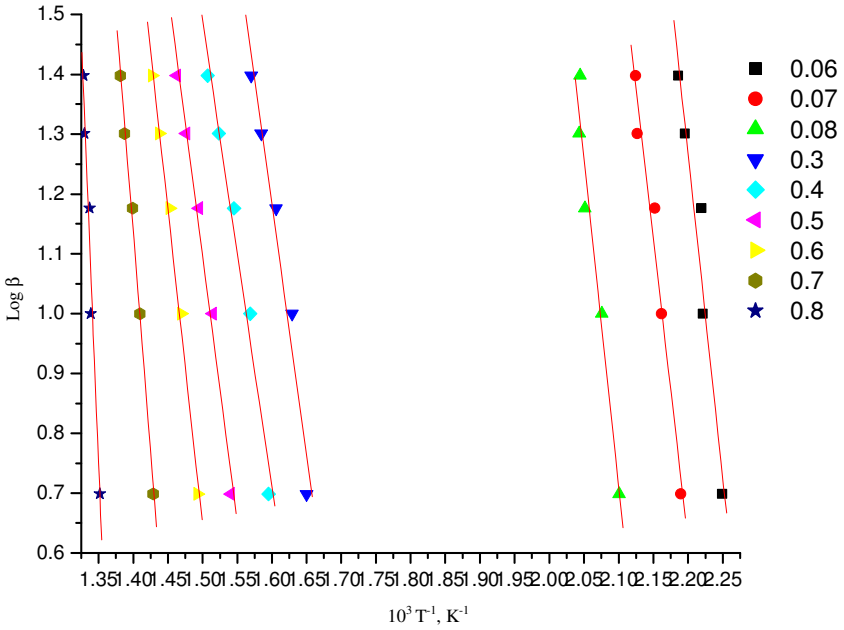

Figure 3. Iso-coversional plot of O-F-W method for **4k**

Table 3. Activation energy and correlation coefficient of compound **4k** at calculated by different methods at different conversional values

α (Conversion values)	O-F-W	R^2	Coats-Redfern	R^2	Friedmann	R^2
0.06	197.5	0.9446	200.4	0.9406	212.6	0.9394
0.07	182.9	0.97	184.7	0.9675	195.4	0.9511
0.08	199.3	0.9589	201.5	0.9557	212.8	0.94
0.3	152.6	0.9467	150.1	0.9589	162.6	0.9425
0.4	141.7	0.977	138.3	0.9732	151.4	0.9592
0.5	161.7	0.9857	159.0	0.9835	173.1	0.9702
0.6	192.2	0.9914	190.8	0.9903	205.9	0.9782
0.7	266.3	0.9954	268.2	0.9949	285.4	0.9831
0.8	522.0	0.9699	536.8	0.9685	562.6	0.968

Conclusions

From the TG study it has been concluded that all the compounds are thermally stable. DSC curves of all shows two peaks except **4c** and **4d** which shows three peaks. Second and third DSC peak of **4c-d** shows major exothermic decomposition. Mass percentage residues left at 550 °C lie in the range 29-52%. Activation energy calculated by model free methods for compound **4k** show dependence on conversion value. Activation energy at conversion 0.8 for this compound is around 562.6 kJ mol^{-1}. High value of residue percentage and activation energy represent that compound is thermally stable at high temperatures. TG and activation energy study for **4k** are in good agreement. High values of Ti, Tp, mass residue percentage and exothermicity shown by compounds lead to conclusions that these compounds are highly thermally stable can be used as a suitable energetic material which is very useful for variety of defence and civilian application[19-22]. As the studied compounds are also good antimicrobial agents, so this thermal study will be helpful in studying the drug-excipient interaction in developing drug in tablet form and it can be used in quality control of the drug and for determination of drug quality via technological parameters[23].

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