



Synthesis and thermal decomposition kinetics of some pyrazolo-quinazoline derivatives

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ABSTRACT

Some new pyrazolo-quinazolines have been synthesized and characterization of the synthesized was done by IR, NMR and mass spectral data. The thermal properties of some synthesized compounds were studied by TGA and DSC methods. From the thermo grams, thermal stability and some kinetic parameters such as energy of activation, frequency factor, order of reaction and entropy of activation were evaluated. It is observed that for all the studied compounds, degradation is single step process. Thermal stability varies slightly according to the nature and position of the substitutions present in the studied compounds.

Keywords: Pyrazolo-quinazolines, thermal gravimetric analysis, differential scanning calorimetry, thermal stability, kinetic parameters, chalcones

1. INTRODUCTION

In recent years, quinazolines and their derivatives have drawn a great attention in the field of pharmacological medicinal chemistry [1]. A vast number of quinazoline derivatives have been synthesized to design highly effective medicines [2]. Literature survey shows that sulphur containing compounds of five-membered and six-membered rings possess various

types of biological activities. The compounds which have quinazoline moiety shows various biological activities such as antidepressant agents [3], antimalarial [4], antibacterial [5-7], anticancer [8,9], anti-inflammatory [10-12], anticonvulsant [13-16], antifungal [17,18] etc.

Thermal analysis is one of the important tools for the study of thermal transformation of materials and finds wide applications in industrial and research fields [19].

Thus, in the present section, thermal analysis of some synthesized compounds was done using Thermo gravimetry and differential scanning calorimeter. The data was used to determine thermal stability of compounds and to evaluate various kinetic parameters such as order of the degradation (n), energy of activation (E), frequency factor (A) and entropy change (ΔS) have also been evaluated.

2. EXPERIMENTAL

Synthesis:

Synthesis of (different chalcones) Int.-I:

Mixture of α -tetralone (0.01 mole) and different substituted benzaldehydes (0.01 mole) in methanol were stirred for 4 h in presence of catalytic amount of potassium hydroxide. The completion of reaction was confirmed by analytical thin layer chromatography (TLC) (Performed on aluminum coated plates Gel 60F254 (E. Merck)) using (7:3-Hexane: Ethyl acetate) as mobile phase. After completion of reaction, the reaction mass was cooled and the resulting solid was filtered, washed with water and dried under vacuum to give crude product. The obtained crude product was purified by adding suitable solvent (diethyl ether) to remove colored, non polar impurity by scratching/stirring. The product was then allowed to settle down and the above solution was decanted. The procedure was repeated 3-4 times to remove impurities. The purity of Int.-I was 99.5 % as determined by gas chromatography.

Synthesis of (5-amino-3-(methylthio)-1H-pyrazole-4-carbonitrile) Int.-II:

A mixture of malonitrile (0.01 mol) and dry K_2CO_3 (0.012 mol) were stirred in dry DMF at room temperature (RT) for 30 min. To this reaction mixture, 0.02 mole of carbon disulphide was added drop wise and the resulting solution was stirred for 2.5 hrs at room temperature. The solution was then cooled at 0 to 50 °C. To this cooled solution, 0.02 mol dimethyl sulphate was added and the solution was again stirred for 5-6 hrs at room temperature. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, it was poured into crushed ice to give solid product. The resulting solid was filtered, washed with cold water and dried under vacuum to give crude product.

Equimolar solution of this crude product and hydrazine hydrate in isopropyl alcohol (IPA) was refluxed for 30 min. The reaction mixture was then poured into crushed ice. The resulting solid was filtered, washed with water and dried under vacuum to give product. The obtained crude product was purified by trituration with hexane and was used in the next step without further purification.

Synthesis of pyrazolo-quinazoline derivatives:

A mixture of Int-I (chalcones) (0.01 mol) and Int-II (5-amino-3-(methylthio)-1H-pyrazole-4-carbonitrile) (0.01 mole) were refluxed in n-butanol for 4-5 hrs. The completion of

reaction was confirmed by Thin Layer Chromatography using (6:4- Hexane: Ethyl acetate) as a mobile phase. The reaction mixture was then allowed to cool and the resulting solid was filtered, washed with diethyl ether to remove impurities. The procedure was repeated 3-4 times to free the product from impurities. All the reaction schemes are given in Figure 1.

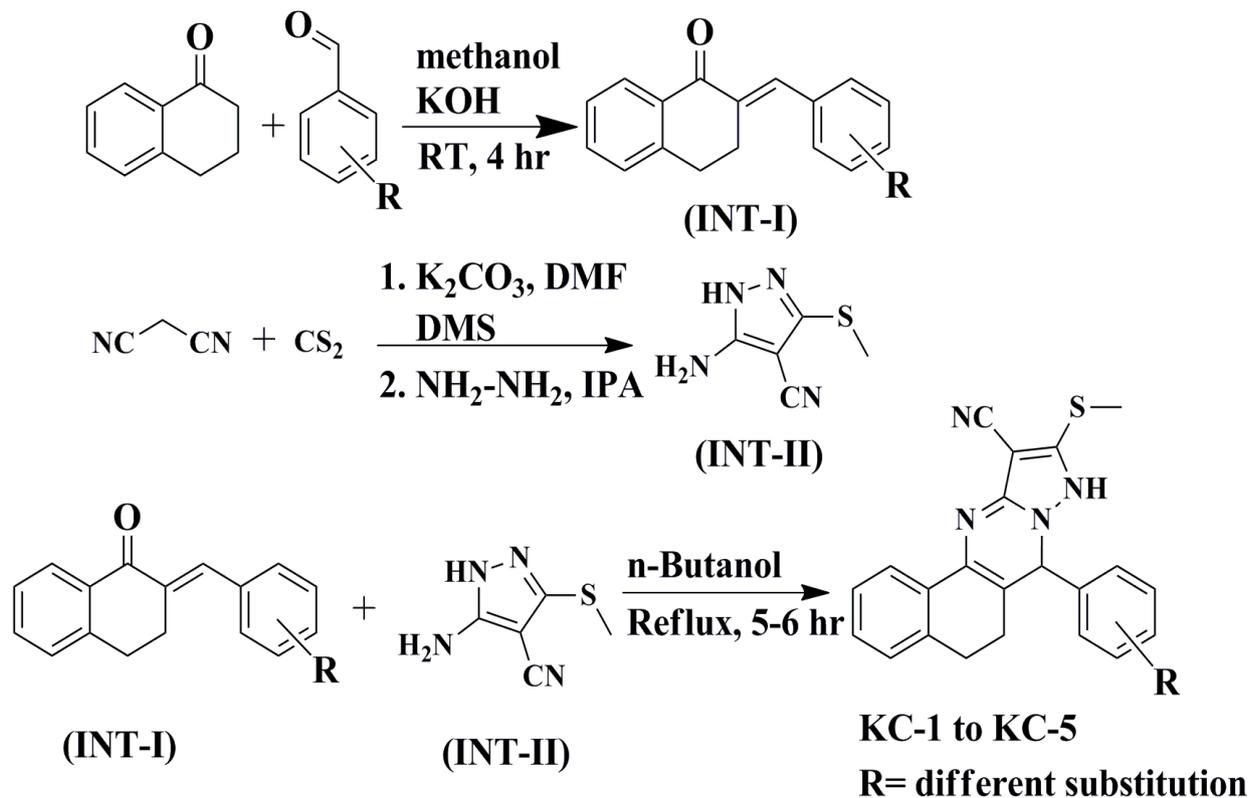


Figure 1. Synthesis scheme of pyrazolo-quinazoline derivatives.

3. RESULTS AND DISCUSSION

The physical constants of the studied compounds are given in Table 1.

Table 1. Physical constant of synthesized compounds.

| Compound Code | Substitution R | M.F. | M.W. | Yield (%) |
|---------------|-------------------------|---|--------|-----------|
| KC-1 | -4-Cl | C ₂₂ H ₁₇ ClN ₄ S | 404.09 | 78 |
| KC-2 | -4-OCH ₃ | C ₂₃ H ₂₀ N ₄ OS | 400.14 | 79 |
| KC-3 | -4-F | C ₂₂ H ₁₇ FN ₄ S | 388.46 | 78 |
| KC-4 | -4-Br | C ₂₂ H ₁₇ BrN ₄ S | 449.37 | 76 |
| KC-5 | -3,4-diOCH ₃ | C ₂₄ H ₂₂ N ₄ O ₂ S | 430.52 | 71 |

3. 1. Spectroscopy study

Spectroscopic study of pyrazolo-quinazoline derivatives has done by IR, ^1H NMR and Mass spectroscopy. IR spectrum was recorded on KBr disc, using FT-IR Model No.-8400 (Shimadzu) spectrophotometer. ^1H -NMR spectra was taken on a Bruker Avance II 400 in DMSO using TMS as an internal standard and NMR signals are reported in δppm . ^{13}C NMR Spectra were also taken on Bruker Avance II 400 MHz in DMSO- d_6 using TMS as an internal standard. Elemental analysis was done by Elemental analyser EURO EA 3000 instrument. Mass spectrum was determined using direct inlet probe on a GCMS-QP-2010 mass spectrometer. Melting point was measured by Differential Scanning Calorimeter (Shimadzu-DSC-60). For calibration of instrument, Indium and Zinc are used as a calibration substance.

Figures 2, 3 and 4 show the IR, ^1H NMR and mass spectra of compound KC-2 respectively.

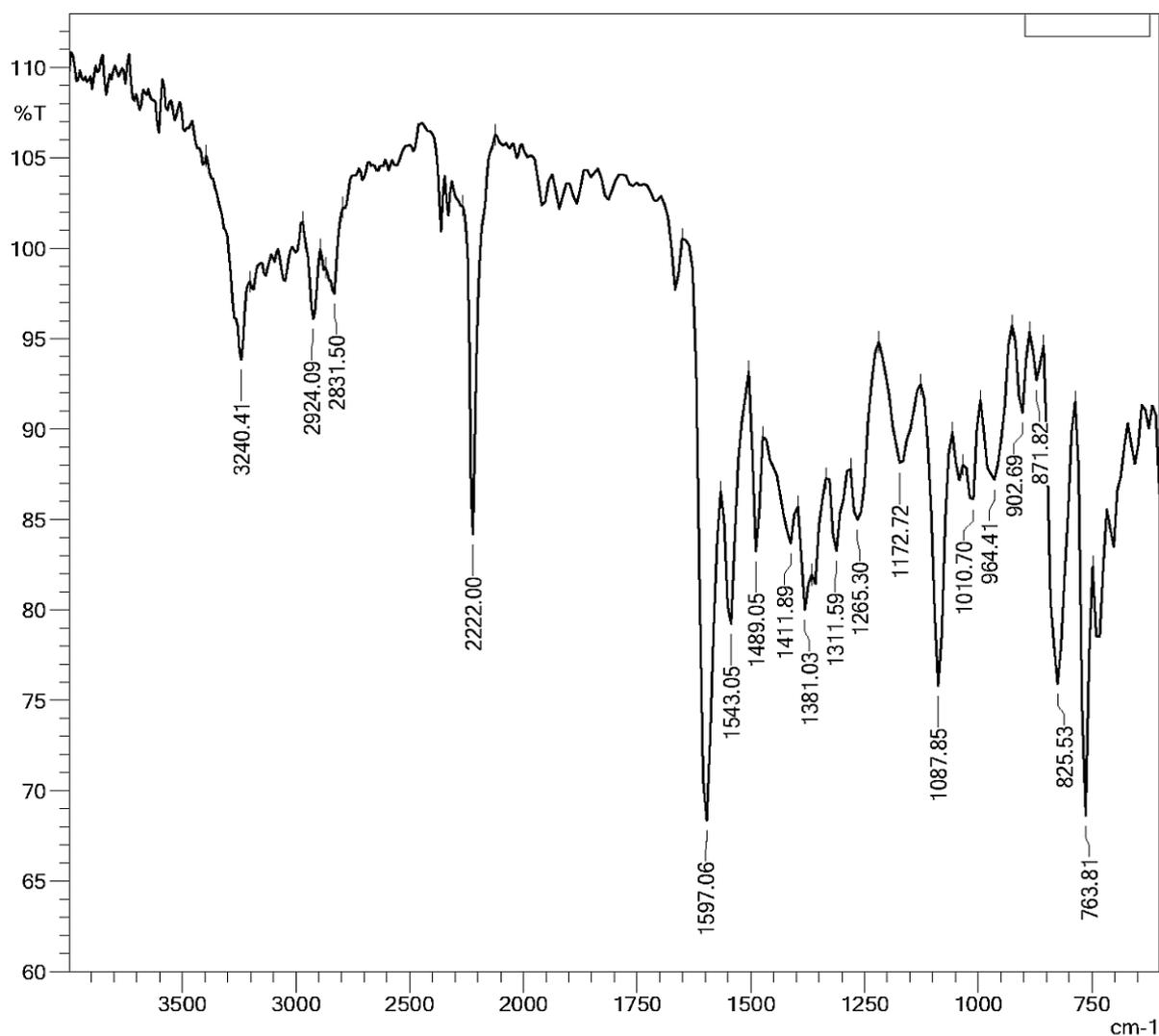


Figure 2 IR spectrum of compound KC-2.

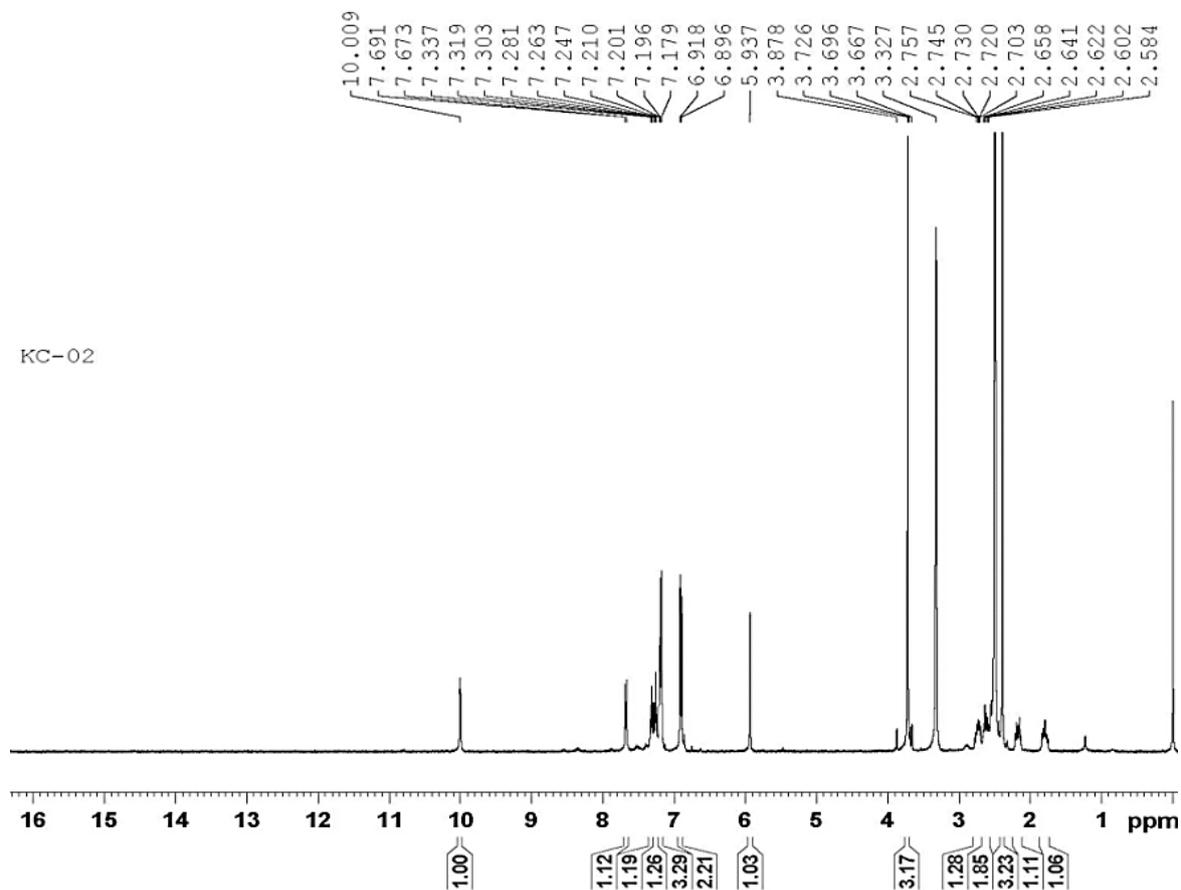


Figure 3. ¹H NMR spectrum of compound KC-2.

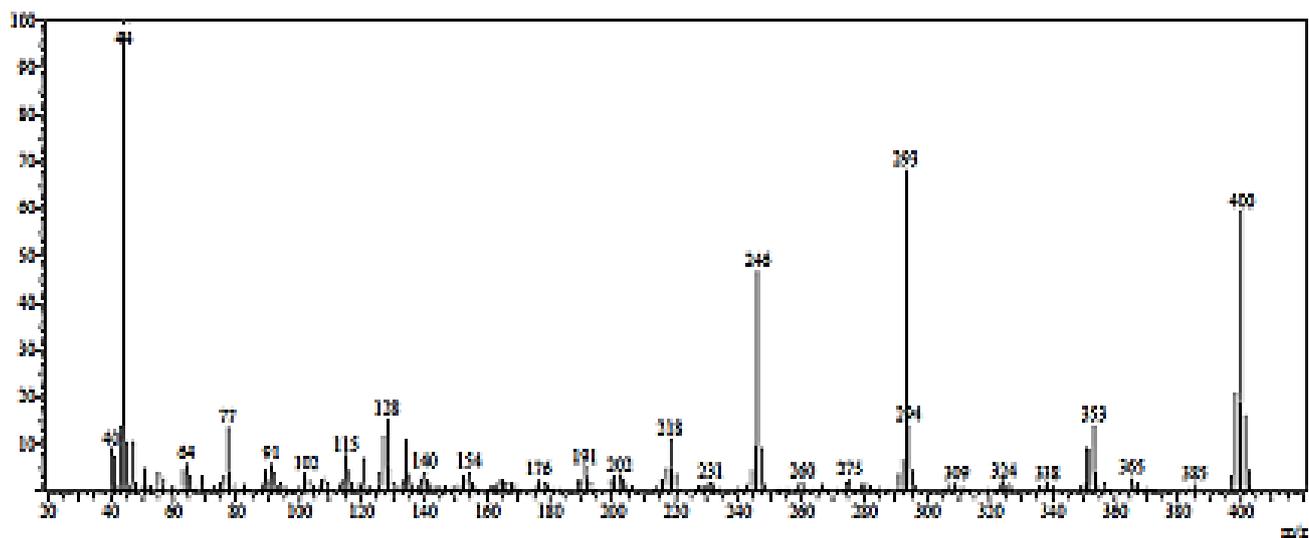


Figure 4. Mass spectra of compound KC-2.

3. 2. Spectral data

KC-1: IR (cm^{-1} , KBr): 3475.85 (-NH (sec.) str.), 3049.56 (Ar-H str.), 2924.18 (-CH₂ sym. str.), 2227.86 (-CN str.), 1664.62(C=C str. α , β unsaturated 6-member ring), 1604.83 (-NH bending vib. Secondary amine), 1381.08 (-CH bending.), 1315.50 (C-N (sec) bending.), 1242-1010 (C-H in plane bending, phenyl ring), 767.69 (C-H str. 5-adjacent carbon atoms), 767.69 (C-Cl str.) **¹H NMR (DMSO-*d*₆) δ (ppm):** 2.400 (3H, singlet, -CH₃), 1.785-2.750 (4H, multiplet, C-H), 6.068 (1H, singlet, C-H), 7.216-7.704 (8H, multiplet, C-H), 10.139 (1H, singlet, -NH). **Elemental analysis:** %C = 65.29 (65.34), %H = 4.21 (4.20), %N = 13.88 (13.86), %S = 7.92 (7.92). **MS: (*m/z*) = 404**

KC-2: IR (cm^{-1} , KBr): 3284.83 (-NH (sec.) str.), 3064.99 (Ar-H str.), 2908.75 (-CH₂ sym. str.), 2225.93 (-CN str.), 1666.55(C=C str. α , β unsaturated 6-member ring), 1604.83 (-NH bending vib. Secondary amine), 1383.01 (-CH bending.), 1336.71(C-N (sec) bending.), 1242-1010 (C-H in plane bending, phenyl ring), 767.69 (C-H str. 5-adjacent carbon atoms), 731.05 (C-H in plane bending), **¹H NMR (DMSO-*d*₆) δ (ppm):** 2.443 (3H, singlet, -CH₃), 3.696 (3H, singlet, -OCH₃), 1.798-2.757(4H, multiplet, C-H), 5.937 (1H, singlet, C-H), 6.896-7.691 (8H, multiplet, C-H), 10.009 (1H, singlet, -NH). **Elemental analysis:** %C = 68.92 (69.00), %H = 5.06 (5.00), %N = 13.97 (14.00), %S = 8.03 (8.00), %O = 4.02 (4.00). **MS: (*m/z*) = 400**

KC-3: IR (cm^{-1} , KBr): 3479.70 (-NH (sec.) str.), 3037.99 (Ar-H str.), 2918.40 (-CH₂ sym. str.), 2227.86 (-CN str.), 1666.55 (C=C str. α , β unsaturated 6-member ring), 1599.04 (-NH bending vib. Secondary amine), 1381.08 (-CH bending.), 1319.08 (C-N (sec) bending.), 1242-1010 (C-H in plane bending, phenyl ring), 1093.67 (C-F str.), 725.26 (C-H str. 5-adjacent carbon atoms). **¹H NMR (DMSO-*d*₆) δ (ppm):** 2.419 (3H, singlet, -CH₃), 1.791-2.767 (4H, multiplet, C-H), 5.987 (1H, singlet, C-H), 7.148-7.684 (8H, multiplet, C-H), 10.251 (1H, singlet, -NH). **Elemental analysis:** %C = 68.07 (68.04), %H = 4.42 (4.38), %N = 14.41 (14.43), %S = 8.25 (8.24). **MS: (*m/z*) = 388.**

KC-4: IR (cm^{-1} , KBr): 3257.88 (-NH (sec.) str.), 3047.63 (Ar-H str.), 2929.97 (-CH₂ sym. str.), 2227.86 (-CN str.), 1653.05 (C=C str. α , β unsaturated 6-member ring), 1604.83 (-NH bending vib. Secondary amine), 1383.01 (-CH bending.), 1315.50 (C-N (sec) bending.), 1242-1010 (C-H in plane bending, phenyl ring), 723.33 (C-H str. 5-adjacent carbon atoms), 582.52 (C-Br str.). **¹H NMR (DMSO-*d*₆) δ (ppm):** 2.422 (3H, singlet, -CH₃), 1.799-2.787 (4H, multiplet, C-H), 5.993 (1H, singlet, C-H), 7.210-7.815 (8H, multiplet, C-H), 10.247 (1H, singlet, -NH). **Elemental analysis:** %C = 58.87 (58.93), %H = 3.79 (3.80), %N = 12.45 (12.50), %S = 7.07 (7.14). **MS: (*m/z*) = 448.**

KC-5: IR (cm^{-1} , KBr): 3236.66 (-NH (sec.) str.), 3007.12 (Ar-H str.), 2929.97 (-CH₂ sym. str.), 2224.40 (-CN str.), 1666.55 (C=C str. α , β unsaturated 6-member ring), 1604.83 (-NH bending vib. Secondary amine), 1383.09 (-CH bending.), 1334.78 (C-N (sec) bending.), 1242-1010 (C-H in plane bending, phenyl ring), 702.11 (C-H str. 5-adjacent carbon atoms), 731.05 (C-H in plane bending), **¹H NMR (DMSO-*d*₆) δ (ppm):** 2.451 (3H, singlet, -CH₃), 3.708 (3H, singlet, -OCH₃), 4.023 (3H, singlet, -OCH₃), 1.798-2.757 (4H, multiplet, C-H), 5.981 (1H, singlet, C-H), 7.002-7.758 (8H, multiplet, C-H), 10.087 (1H, singlet, -NH). **Elemental analysis:** %C = 66.91 (66.97), %H = 5.21 (5.12), %N = 13.08 (13.02), %S = 7.49 (7.44), %O = 7.31 (7.44). **MS: (*m/z*) = 430**

3. 3. Thermal Analysis

Figure 5 show thermo gram for KC-1. The initial degradation temperature, degradation temperature range, weight loss, % weight data are listed in Table 2 for all the compounds. It is observed that for all the studied compounds, degradation is single step process. Looking to the initial decomposition temperature in Table 2, it is clear that there is slight difference in decomposition temperature of the studied compounds. However, KC-4 is most stable whereas KC-3 is least stable compound. The variation in the trend of thermal decomposition might be interpreted by taking into account some interactions (structural as well as electronic) and also because of several experimental factors.

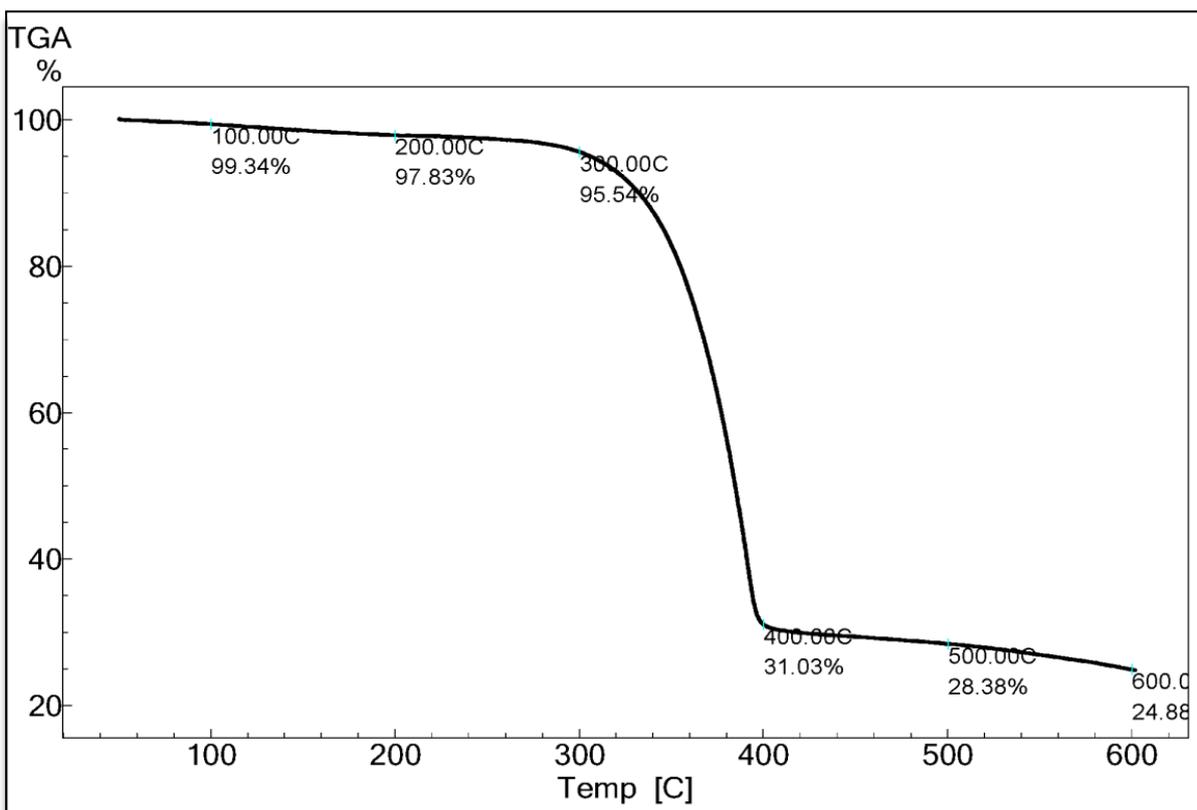


Figure 5. Thermo gram of compound KC-1.

Table 2. TGA data for synthesized compounds.

| Compd. Code | Amount (mg.) | Initial Decomp. Temp. (°C) | Decomp. Range (°C) | % Wt. loss | Residual wt. loss (mg.) |
|-------------|--------------|----------------------------|--------------------|------------|-------------------------|
| <i>KC-1</i> | 3.669 | 290 | 290-600 | 75.12 | 2.7561 |
| <i>KC-2</i> | 3.236 | 295 | 295-500 | 80.86 | 2.6166 |

| | | | | | |
|-------------|-------|-----|---------|-------|--------|
| KC-3 | 4.288 | 287 | 287-450 | 74.56 | 3.1971 |
| KC-4 | 3.034 | 300 | 300-500 | 65.97 | 2.0021 |
| KC-5 | 7.359 | 289 | 289-650 | 62.06 | 4.5669 |

The thermal stability depends on the substitutions. However, in the present case, there is not much significance change in initial thermal degradation temperature for the studied compounds due to substitution. Further, the position of groups also affects stability. KC-4 contain bromo group at para position whereas KC-3 has fluoro group at para position.

The degradation range and % weight loss for the compounds varies considerably. The % weight loss is maximum for KC-2 and minimum for KC-5. Thus, thermal degradation is also affected by different substitutions. From thermo grams, various kinetic parameters, such as order of the degradation (n), energy of activation (E), frequency factor (A) and entropy change (ΔS) have also been evaluated and are reported in Table 3.

Using the Anderson-Freeman plot, energy of activation (E) and order of reaction (n) were evaluated from the slope and intercept respectively. The evaluated kinetic parameters are given in Table 3 along with the correlation coefficients. It is evident from Table 3 that order of reaction is quite different for all the synthesized compounds. The maximum order of reaction is found to be 0.841 for compound KC-1.

Table 3. The kinetic parameters of synthesized compounds.

| Compound Code | n | E (kJmol⁻¹) | A (Sec⁻¹) | $-\Delta S$ (J·mol⁻¹·K⁻¹) | Correlation coefficient |
|----------------------|-----------------------|--|--|---|--------------------------------|
| KC-1 | 0.841 | 166.28 | 1.36×10^{11} | 38.30 | 0.9957 |
| KC-2 | 0.505 | 731.63 | 2.41×10^{03} | 186.68 | 0.9904 |
| KC-3 | 0.706 | 931.17 | 1.65×10^{05} | 151.42 | 0.9898 |
| KC-4 | 0.545 | 698.38 | 1.48×10^{03} | 190.65 | 0.9934 |
| KC-5 | 0.568 | 133.024 | 1.59×10^{08} | 94.61 | 0.9961 |

The energy of activation (E) is found to be maximum for KC-3, while lowest for KC-5 compound. The frequency factor is highest for compound KC-1 (1.36×10^{11}) and lowest for compound KC-4 (1.48×10^{03}).

The entropy (ΔS) values are negative for all the compounds and are quite different for different compounds. The negative entropy corresponds to an increase in the order of transition state than that of individual molecules.

The DSC of compound KC-1 is given in Figure 6. The melting points measured by DSC are reported in Table 4 along with melting points determined by open capillary method. It is observed that there is good agreement between the values evaluated from DSC and those determined by open capillary method.

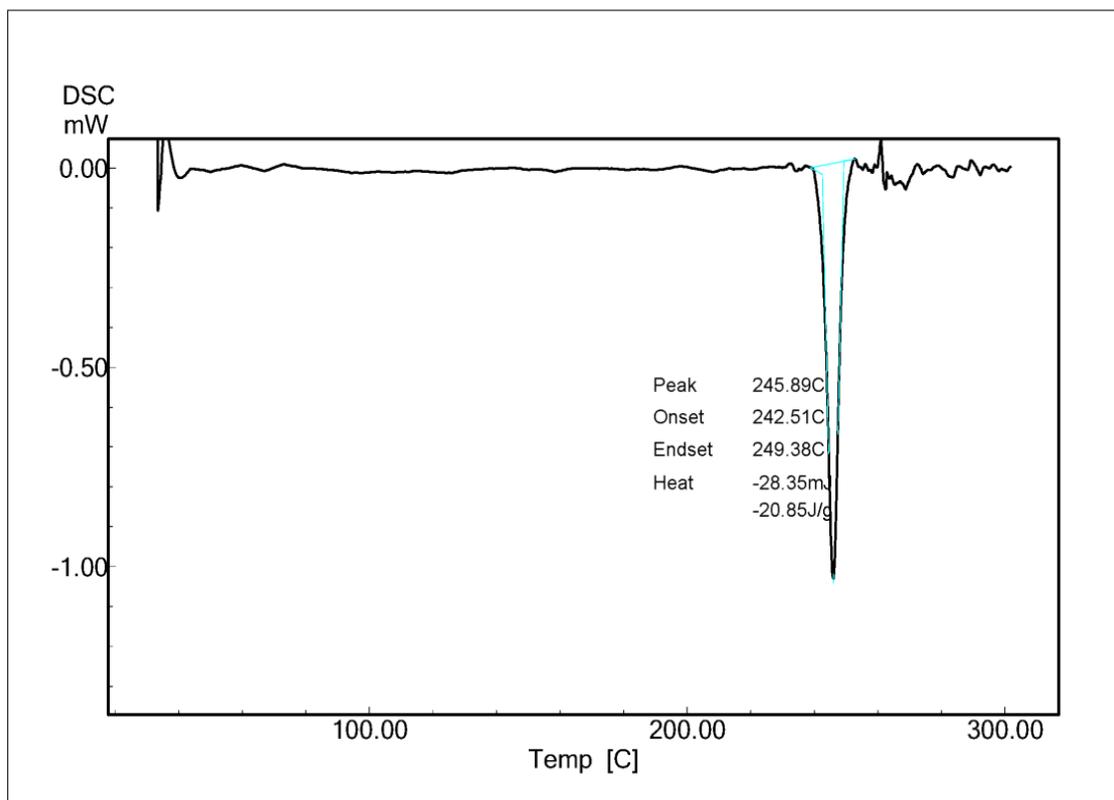


Figure 6. The DSC of compound KC-1.

Table 4. The melting temperatures (°C) of synthesized compounds by DSC and open capillary methods.

| Compound Code | DSC (°C) | Open capillary (°C) |
|---------------|----------|---------------------|
| <i>KC-1</i> | 243 | 240-244 |
| <i>KC-2</i> | 254 | 252-256 |
| <i>KC-3</i> | 250 | 248-252 |
| <i>KC-4</i> | 269 | 268-272 |
| <i>KC-5</i> | 228 | 226-230 |

4. CONCLUSION

It is concluded that for the studied compounds, degradation is single step process. Thermal stability is not much affected by the nature and position of the substitutions present in the studied compounds.

References

- [1] Eweas, A. F.; Nezhawy, A. O. H.; Baiuomy, A. R. and Awad, M. M.; Design, synthesis, anti-inflammatory, analgesic screening, and molecular docking of some novel 2-pyridyl (3H)-quinazolin-4-one derivatives. *Med. Chem. Res.* 22 (2013) 1011-1020
- [2] Dangi, R. R.; Hussain, N.; Joshi, A.; Pemawat, G.; and Talesara, G. L.; Design, facile synthesis and biological evaluation of quinazoline containing pyrazolothiazolyl, triazinone and their ethoxyphthalimide derivatives, *Ind. J. Chem.* 50 (2011) 1165-1172.
- [3] Shehata, A. S.; Faida, H.; Bamanie, A.; Moustafa, M. A. and Mashaly, M. M.; A simple and ecofriendly synthesis in water of fully functionalized pyridines via an efficient one-pot three component reaction, *J. Amer. Sci.* 7 (2011) 240-242
- [4] Verhaeghe, P.; Azas, N.; Gasquet, M.; Hutter, S.; Ducros, C.; Laget, M.; Rault, S.; Rathelot, P. and Vanelle, P. Synthesis and antiplasmodial activity of new 4-aryl-2-trichloromethylquinazolines, *Bioorg. Med. Chem. Lett.* 18 (2008) 396-401
- [5] Dangi, R. R.; Hussain, N.; Joshi, A.; Pemawat, G.; and Talesara, G. Design, facile synthesis and biological evaluation of quinazoline containing pyrazolothiazolyl, triazinone and their ethoxyphthalimide derivatives. *Ind. J. Chem.* 50 (2011) 1165-1172
- [6] Sharma, P.; Rane, N.; Gurram, V. K.; Synthesis and QSAR studies of pyrimido[4,5 d]pyrimidine-2,5-dione derivatives as potential antimicrobial agents, *Bioorg. Med. Chem. Lett.* 14 (2004) 4185-4190
- [7] Elkholy, Y. M.; Morsy, M. A.; Facile Synthesis of 5, 6, 7, 8-Tetrahydropyrimido [4, 5- b]-quinoline Derivatives, *Molecules*, 11 (2006) 890-903
- [8] Joseph, A.; Pai, A.; Srinivasan, K. K.; Kedar, T.; Thomas, A. T.; Jessy, E. M. and Singala, R. K.; Synthesis and anticancer activity of some novel 3-(1,3,4-thiadiazol-2-yl)-quinazolin-4-(3H)-ones, *Orbital Electro. J. Chem.* 2 (2010) 159-167
- [9] Al-Obaid, A. M.; Abdel-Hamide, S. G.; El-Kashef, H. A.; Abdel-Aziz, A. A. M.; El-Azab, A. S.; Al-Khamees, H. A. and El-Subbagh, H. I.; Synthesis, in vitro antitumor activity and molecular modeling study of certain 2-thieno-4(3H)-quinazolinone analogs. *Eur. J. Med. Chem.* 44 (2009) 2379-2391
- [10] Sondhi, S. M.; Singh, N.; Johar, M. and Kumar, A., Synthesis, anti-inflammatory and analgesic activities evaluation of some mono, bi, tricyclic pyrimidine derivatives, *Bioorg. Med. Chem.* 13 (2005) 6158-6166
- [11] Kumar, P.; Chandak, N.; Kaushik, P.; Sharma, C.; Kaushik, D.; Aneja, K. R. and Sharma, P. K.; Synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory –antibacterial agents, *Med. Chem. Res.* 21 (2012) 3396-3405
- [12] Chandrika, P. M.; Ram Rao, A. R.; Narsaiah, B. and Raju, M. B.; Quinazoline derivatives with potent anti-inflammatory and anti-allergic activities, *Int. J. Chem. Sci.* 6 (2008) 1119-1146
- [13] Farghaly, A.; Esmail, S.; Abdel-Zaher, A.; Abdel-Hafez, A. and El-Kashef, H.; Synthesis and anticonvulsant activity of some new pyrazolo[3,4-b]pyrazines and related heterocycles. *Bioorg. Med. Chem.* 22 (2014) 2166-2175

- [14] Abdel Gawad, N. M.; Georgey, H. H.; Youssef, R. M. and El Sayed, N. A.; Design, synthesis and anticonvulsant activity of some novel quinazoline analogues, *Med. Chem. Res.* 20 (2011) 1280-1286
- [15] Kashaw, S. K.; Kashaw, V.; Mishra, P.; Jain, N. K. and Stables, J. P.; Synthesis, anticonvulsant and CNS depressant activity of some new bioactive 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4H-quinazolin-3-yl)-urea, *Eur. J. Med. Chem.* 44 (2009) 4335-4343
- [16] Archana, K.; Sriyastava, V. K. and Kumar, A.; Synthesis of newer derivatives of substituted quinazolinonyl-2-oxo/thiobarbituric acid as potent anticonvulsant agents, *Bioorg. Med. Chem.* 12 (2004) 1257-1264
- [17] Pandey, V. K.; Pathak, L. P. and Mishra, S. K.; Synthesis and characterization of isoquinolinyl quinazolines and a study of their antiviral and antifungal activities, *Ind. J. Chem.* 44 (2005) 1940-1944
- [18] Shivananda, M. K. and Shivarama, B. H.; Antifungal activity studies of some quinazoline derivatives, *J. Chem. Pharm. Res.* 3 (2011) 83-86
- [19] Le Chatelier, H.; Delaction de la chaleur sur les argiles, *Bull. Soc. Franc. Mineral. Cryst.* 10 (1887) 204-211

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