Thermal properties and decomposition mechanism of disubstituted fused 1,2,4-triazoles considered as potential anticancer and antibacterial agents

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Abstract
Thermal resistance is a very important parameter when assessing the therapeutic usefulness of potential pharmaceutics. Therefore, the thermal behaviour and the decomposition mechanism in the atmosphere of helium and synthetic air of disubstituted fused 1,2,4-triazoles—which may be potential anticancer and antibacterial agents—were studied with a use of simultaneous thermal analysis: thermogravimetry/differential scanning calorimetry (TG/DTG/DSC) coupled online with Fourier transform infrared spectroscopy. It was confirmed that the thermal stability of the tested compounds is directly depended on their structure and thus on the number of chlorine atoms as substituents. The pyrolysis process of disubstituted fused 1,2,4-triazoles in inert conditions runs in two main, non-well-separated stages connected with the emission of NH3, HCN, acetonitrile, aromatics with an OH group, aromatics with a NH2 groups, H2O, CO2 and alkene fragments. However, the thermal stability of those compounds in synthetic air atmosphere is comparable or lower than their thermal stability in helium atmosphere. The decomposition of the tested compounds runs through at least three main stages, resulting in the emission of the same type of volatiles as in inert conditions plus the additional emission of CO and some carbonyl fragments for compounds with no or one chlorine atom as a substituent. The results indicate a simultaneous cleavage of C–N, N–N and C–O bonds during heating of the tested disubstituted fused 1,2,4-triazoles in inert conditions and additional combustion process of pre-formed residues in oxidative conditions.

Keywords Annelated 1,2,4-triazoles · Anticancer agents · Antibacterial agents · Thermal behaviour · Thermal decomposition course · TG/DTG/DSC/FTIR

Introduction
Disubstituted annelated 1,2,4-triazoles (1–9) (Fig. 1) make up an important class of nitrogen heterocycles composed of the 1,2,4-triazole and imidazolidine scaffolds possessing a common N4-C7a bond. They have a pharmacophoric phenoxyethyl moiety at the C3 (without or with R2 on the benzene ring) and the phenyl moiety (without or with R1) at the N7. These nitrogen-rich organic compounds have fully defined molecular structures and determined lipophilicity indices (derived from their retention behaviour on an octadecysyl column in methanol–water, acetonitrile–water and dioxane–water buffered mobile phases) [1]. The investigated small molecules (1–8) are of great pharmaceutical relevance as they exhibit important biochemical and pharmacological activities. In particular, compounds 3 and 7 reveal not only significant anticancer activities against human tumour cells of colon, cervix or breast but also they are less toxic for healthy non-cancerous cells. This antitumour activity is related to the ability to induce DNA damage and apoptosis in cancerous cells as confirmed for molecule 3. Furthermore, compounds 4, 5, 6 and 7 exhibit remarkable anticancer activities in human peripheral blood myeloma cells, and the vast majority of them are less toxic to normal cells. In addition, the molecule 4 reveals antibacterial activity against
**Staphylococcus aureus** ATCC 25,923 comparable to that of ampicillin. However, the compound 8—considered as a possible antibacterial agent—reveals the selective effect on Gram-negative bacterial strains, and its proven activity against *Pseudomonas aeruginosa* ATCC 25,923 is even better than that of chloramphenicol and ampicillin [1].

Despite of the above-mentioned utilities of 1–8 [1], there are no scientific reports on the mechanism of thermal degradation as well as the thermal properties of the title potential drugs—i.e. disubstituted fused 1,2,4-triazoles—as their thermal behaviour has not been investigated so far.

Organic compounds containing a core structural component of 1,2,4-triazole as the extremely good scaffold were reported to possess *inter alia* the important relevance as pharmaceutics in a common use from various therapeutic classes [2, 3] as well as energetic materials [4–17]. There are some scientific papers focussed on the thermal properties of pharmacologically active molecules possessing the 1,2,4-triazole skeleton. Ledeți et al. [18] described the thermal stability as well as kinetic parameters of non-isothermal decomposition for molecules with the privileged template of 1,2,4-triazole (i.e. derivatives of ethyl (methylsulfanyl)acetate and (methylsulfanyl)acetic acid) with significant anti-inflammatory activities. Furthermore, Ledeți et al. [19] published studies concerning the kinetic analysis of solid-state degradation of antimicrobially active 3,4-disubstituted-1,2,4-triazole-5-carboxylic acids and identified the volatile decomposition products emitted during their pyrolysis. Godhani et al. [21] described thermodynamic and kinetic parameters of the degradation process and thermal stability of 1,2,5-trisubstituted-1,2,4-triazole-3(2H)-thiones with potential biological utility. Studies of other researchers [4–13] were mainly focussed on the thermal properties and decomposition processes of various energetic materials with the 1,2,4-triazole skeleton. Another scientific investigations [14–16] were aimed at assessing the range of thermal stability, phase-transition and decomposition temperatures of nitrogen-rich energetic materials bearing in their hybrid structures the 1,2,4-triazole scaffold combined with an additional azole ring such as the 1,2,3-triazole, 1,2,4-triazole or 1,2,4-tetrazole. In turn, Yan et al. [17] investigated the thermal properties of nitrogen-rich 1,2,4-triazole-1,2,4,5-tetrazine-1,2,4-triazole hybrids as highly stable energetic materials and identified their thermolysis products. However, Li et al. [22] disclosed the thermal decomposition mode of tetraiodo-4,4'-bi-1,2,4-triazole—an useful intermediate in the synthesis of an energetic material, *i.e.* tetranitro-4,4'-bi-1,2,4-triazole.

The main purpose of the present study is characterizing the thermal behaviour and assessing the range of thermal stability in helium and synthetic air of all potential small molecule drugs, i.e. disubstituted fused 1,2,4-triazoles. The subsequent objective of this investigation is to show the main thermal properties of molecules subjected to pyrolysis and to select compounds with favourable thermal features as candidates for possible pharmaceutical use. It should be clearly emphasized that the authors—using TG-DSC coupled with FTIR technique—made an attempt to explain, for the first time, the thermal decomposition mechanism of potential drugs, showing pathways of their thermal degradation and identifying the decomposition reactions and volatile decomposition products emitted during all stages of their chemical degradation.

**Experimental**

**Materials**

Disubstituted fused 1,2,4-triazoles (1–9) (Fig. 1) have been synthesized via annelation of the 1,2,4-triazole ring with unsubstituted or substituted phenoxyethyl moiety at the C3 (using phenoxyacetic acid or suitable substituted phenoxyacetic acid derivatives) on the basis of 1-substituted-2-hydrazonoimidazolidines as earlier reported [1]. All the compounds intended to thermal investigations were characterized by sharp melting points; the HPLC peak asymmetry factors within the acceptable ranges found elemental analyses, which agreed with the theoretical...
values within ± 0.4%. Their $^1$H NMR, $^{13}$C NMR (including DEPT-45, DEPT-90 DEPT-135), EI-MS and IR spectra have been found to be consistent with the given structures. All the above characterization data of compounds have been published together in an earlier paper aimed at disclosing inter alia the structural, physico-chemical, biochemical and pharmacological properties of the vast majority of disubstituted fused 1,2,4-triazoles (1–8) [1].

3-(2,4,5-Trichlorophenoxy)methyl)-7-(4-chlorophenyl)-5H-6,7-dihydroimidazo[2,1-c][1,2,4]triazole (9) is an unknown compound which was synthesized for the current thermal research needs following our previously reported procedure [1]. However, the spectroscopic characterisation, which supports its assigned structure, is presented for the first time in this article:

$^1$H NMR (δ, ppm, DMSO-d$_6$, 300 MHz, TMS) for 9: 4.32 (t, 2H, CH$_2$), 4.58 (t, 2H, CH$_2$), 5.38 (s, 2H, OCH$_2$), 7.42 (d, $J$ = 8.9 Hz, 2H, 2CH$_{arom}$), 7.51 (d, $J$ = 8.9 Hz, 2H, 2CH$_{arom}$), 7.70 (s, 1H, CH$_{arom}$), 7.85 (s, 1H, CH$_{arom}$).

$^{13}$C NMR (δ, ppm, DMSO-d$_6$, 75 MHz, TMS) for 9: 41.2 (secondary carbon derived from CH$_2$ which yields negative signal in DEPT-135), 54.6 (secondary carbon derived from CH$_2$ which yields negative signal in DEPT-135), 63.2 (secondary carbon derived from CH$_3$O which yields negative signal in DEPT-135), 117.1 (tertiary carbons derived from 2CH$_{arom}$ which appear as one signal in DEPT-90), 117.6 (tertiary carbons derived from 2CH$_{arom}$ which appear as one signal in DEPT-90), 122.7 (quaternary carbon), 124.8 (quaternary carbon), 125.4 (quaternary carbon), 129.7 (quaternary carbon derived from CH$_{arom}$ which yields signal in DEPT-90), 131.4 (quaternary carbon), 131.6 (tertiary carbon derived from CH$_{arom}$ which yields signal in DEPT-90), 140.0 (quaternary carbon), 144.3 (quaternary carbon), 153.4 (quaternary carbon), 160.9 (quaternary carbon).

IR (ATR) (μ, cm$^{-1}$) for 9: 3102–3035 (aromatic C–H stretching), 2964 (O–CH$_2$ stretching), 2938/2863 (methylene C–H asym./sym. stretching), 1594, 1564 (C=N stretching), 1481–1448 (methylene C–H bend), 1077 (aromatic C–Cl stretching), 870 (1,2,4,5-tetrasubstituted benzene ring), 826 (1,4-disubstituted benzene ring).

**Methods**

The simultaneous TG/DTG/DSC analysis was done with a use of a STA 449 Jupiter F1 instrument Netzsch (Germany) coupled on-line with a FTIR TGA 585 analyser (Bruker, Germany). The TG apparatus was calibrated with standard masses according to the manufacturer proceedings. In order to do the temperature and sensitivity calibrations, the metals (mass ca. 10 mg): In, Sn, Bi, Zn, Al, Au were applied. All the results were checked and confirmed with calcium oxalate monohydrate. The compounds 1–9 were heated from 40 °C to 700 °C in helium atmosphere (a flow rate 40 mL min$^{-1}$) or from 40 to 750 °C in synthetic air atmosphere (a flow rate 100 mL min$^{-1}$). The TG/DTG analyses were done in open Al$_2$O$_3$ crucibles. The samples (ca. 10 mg) were heated with a heating rate 10 K min$^{-1}$. The analysis for each sample was repeated three times. Simultaneously, the FTIR spectra of the emitted volatiles were collected by a FTIR TGA 585 analyser. The FTIR spectrometer with IR cell maintained at 200 °C was connected on-line to a STA instrument by a Teflon transfer line with a diameter of 2 mm and heated to 200 °C in order to avoid condensation process of the volatiles. The FTIR spectra were gathered from 600 to 4000 cm$^{-1}$ with 16 scans per spectrum and with a resolution 4 cm$^{-1}$.

**Results and discussion**

**Melting temperature of compounds 1–9**

The melting temperatures of the compounds 1–9 were evaluated from the TG/DSC method. The melting temperatures were studied in helium and synthetic air atmospheres, Table 1, Fig. 2. All the investigated disubstituted fused 1,2,4-triazoles melt within one temperature range with $T_{peak}$ given in Table 1. As can be seen, the $T_{peak}$ temperatures are independent of the atmosphere used. The melting process of disubstituted fused 1,2,4-triazoles is described by one endothermic peak with the onset temperatures ($T_{onset}$) between 216 and 275 °C (helium) and 214 °C and 273 °C (air) and with the following maximum temperatures ($T_{peak}$) 218–279 °C (helium atmosphere) and 218–276 °C (air atmospheres) and it depends on the structure of the analysed compounds. The highest melting temperature is observed for the compound 8 containing four chlorine atoms as substituents (R$_1$—3,4 C$_2$ and R$_2$—2,4 C$_2$). In turn, the lowest melting temperature is visible for the compound 7.

| Sample | Melting process |
|--------|----------------|
|        | Helium         | Synthetic air |
|        | $T_{onset}^\circ\text{C}$ | $T_{peak}^\circ\text{C}$ | $T_{onset}^\circ\text{C}$ | $T_{peak}^\circ\text{C}$ |
| 1      | 240            | 244             | 240            | 244             |
| 2      | 255            | 259             | 253            | 254             |
| 3      | 243            | 246             | 240            | 244             |
| 4      | 220            | 230             | 225            | 231             |
| 5      | 235            | 239             | 233            | 237             |
| 6      | 226            | 231             | 225            | 229             |
| 7      | 216            | 218             | 214            | 218             |
| 8      | 275            | 279             | 273            | 276             |
| 9      | 240            | 250             | 245            | 250             |
containing three chlorine atoms as substituents (R_1—4Cl and R_2—2,4 Cl_2). On the basis of this, it can be seen that the absence of only one chlorine atom in the structure of the compound 7 (that of the meta position of the phenyl moiety) significantly reduces its melting temperature. (A melting point drop by 60 °C is observed.) Other test compounds containing a chlorine atom as R_2 substituent and in the para position (compounds 2, 3, 4, 5, 6, 9) are characterized by the melting temperatures in the range from 231 (the compound 6) to 259 °C (the compound 2). Among them, the compound 2 which additionally contains the –OCH_3 group in the para position as R_1 showed a melting point at the highest temperature. Its melting temperature is similar to that of the compound 9 containing a chlorine atom in the para position as R_1 and in the meta, ortho and para positions as R_2. However, the parent structure (1) containing no substituents on R_1 and R_2 melts at 244 °C. In general, with an increase in the number of chlorine atoms in the structure of the tested compounds (compounds 2–7), a decrease in their melting points is observed. This behaviour is seen for compounds containing up to three chlorine atoms. Whereas, the introduction of four chlorine atoms as substituents, two as R_1 and two as R_2 (the compound 8) causes a significant increase in the melting point. The exception is the compound 9, which—although contains four chlorine atoms in its structure—melts at a lower temperature than the compound 8. It may be due to the arrangement of chlorine atoms because only one of them is placed in the para position of the phenyl moiety as R_1 and the remaining three chlorine atoms are located in the ortho, meta and para positions of the benzene ring as R_2 in the phenoxy methyl moiety.

Thermal stability of compounds 1–9 (helium atmosphere)

The TG/DTG curves of the tested compounds obtained in inert conditions are presented in Fig. 3. In turn, the following TG/DTG data such as the initial decomposition temperature (T_5%), peak maximum temperatures (T_max), final decomposition temperature (T_final), the mass loss (Δm) and the residual mass at 700 °C (rm) are shown in Table 2. All the tested compounds start to decompose above 230 °C (T_5%).
Fig. 3  The TG/DTG curves of compounds 1–9 (helium atmosphere)
initial decomposition temperature is much higher than ambient conditions, and thus, our compounds (1–9) would not require special storage conditions if they were to be used as medicines in the future [23, 24].

In addition, the presented data indicate that the initial decomposition temperature of the compounds is highly depended on their structure. The highest $T_{5\%}$ value is observed for the compound 8; meanwhile, the lowest $T_{5\%}$ value is detected for the compound 9. The $T_{5\%}$ value for compound 1 (i.e. chlorine-free structure) is 274 °C. The incorporation of one chlorine in the para position of the benzene ring as R$_2$ in the phenoxymethyl moiety causes the decrease in the thermal resistance from 273 (the compound 2) to 265 °C (the compound 4). However, the compounds with two chlorine atoms in the para position, one as R$_1$ substituent and second as R$_2$ substituent (compounds 5 and 6), are described by higher thermal stability (280–298 °C) than compounds with only one chlorine atom. In the case of compound 7 having three chlorine atoms, one as R$_1$ in the para position and the others as R$_2$ in the ortho and para position, the decrease in its thermal stability is visible (263). Its thermal stability is comparable to the thermal stability for compounds 3 and 4 (i.e. molecules with one chlorine atom in the para position as R$_2$). On the other hand, the compound 8 with as many as four chlorine atoms in its structure is the most thermally stable (337). This situation is probably due to the stabilization of the aromatic rings by chlorine atoms.

The pyrolysis process of the tested compounds runs in two main, non-well-separated stages in inert conditions. The first stage of decomposition spreads from $T_{5\%}$ to ca. 335–484 °C with $T_{\text{max}1}$ from 254 to 375 °C. The range of the decomposition temperature and maximum temperatures is obviously dependent on the structure of the analysed molecules. The mass loss ($\Delta m_1$) at this stage of decomposition ranges from 30.4% to 49.4% for most of compounds. Only one compound (8) shows a mass loss of more than 70%.

On the other hand, the second decomposition stage occurs immediately after the first decomposition stage. The $T_{\text{max}2}$ is from 380 to 525 °C and the mass loss ($\Delta m_2$) from 32.4 to 46.1% and 9.8% for compound 8. The decomposition of the compounds is not complete in inert conditions. The residue from 10.6% to 24.3% was observed.

**Decomposition course of compounds 1–9 (helium atmosphere)**

The FTIR spectra collected at temperatures where the maximum DTG peak was observed are shown in Fig. 4. When one looks closely at the FTIR gas spectra, one sees that the emission of most of the volatiles takes place in the first stage of decomposition in a helium atmosphere. At $T_{\text{max}1}$, the emission of NH$_3$ is clearly visible. The characteristic absorption bands for ammonia are appeared as two signals at 931 cm$^{-1}$ and 966 cm$^{-1}$ connecting with the N–H deformation and as the signals at ca. 3350 cm$^{-1}$ derived from the N–H stretching vibrations [25–28]. Apart from the emission of NH$_3$ during the first decomposition stage, the evolution of HCN molecule is also observed. Its presence is confirmed on the basis of the occurrence of the absorption band at 713 cm$^{-1}$ [29, 30]. Moreover, at $T_{\text{max}1}$, the emission of H$_2$O (3450–4000 cm$^{-1}$ and 1300–1950 cm$^{-1}$), small amounts of CO$_2$ (bands at 2300–2365 cm$^{-1}$ (valence vibration) and 669 cm$^{-1}$ (deformation vibration)) and acetonitrile (bands at 2900–2970 cm$^{-1}$ and the stretching vibration characteristic for the nitrile group at 2240 cm$^{-1}$) is also confirmed. Otherwise, the emission of aromatic fragments is well seen in the case of all tested compounds at $T_{\text{max}1}$. The compound 1 is the molecule which does not contain chlorine atoms in its structure. When one looks at the FTIR spectra gathered at $T_{\text{max}1}$ for the compound 1, one can confirm that the aromatic volatiles formed during its heating.

**Table 2** The TG/DTG data for compounds 1–9 (helium atmosphere)

| Sample | Degradation process | First decomposition stage | Second decomposition stage |
|------------------|-------------------|--------------------------|---------------------------|
|                | $T_{5\%}$/°C | $T_{\text{max}1}$/°C | $\Delta m_1$/% | $T_{\text{max}2}$/°C | $\Delta m_2$/% | rm/% |
| 1  | 274   | 314   | 39.4  | 411   | 46.1  | 14.5 |
| 2  | 273   | 301   | 30.4  | 380   | 45.3  | 24.3 |
| 3  | 260   | 307   | 39.0  | 400   | 44.0  | 17.0 |
| 4  | 265   | 320   | 43.8  | 401   | 38.4  | 17.8 |
| 5  | 280   | 326   | 44.2  | 398   | 32.4  | 23.4 |
| 6  | 298   | 325   | 45.0  | 415   | 34.8  | 20.2 |
| 7  | 263   | 288   | 49.4  | 406   | 40.0  | 10.6 |
| 8  | 337   | 375   | 71.3  | 525   | 9.8   | 18.9 |
| 9  | 235   | 254   | 45.8  | 402   | 33.7  | 20.5 |

rm—residual mass at 700 °C
are aniline and phenol. Their presence is confirmed by the OH absorption band at 3646 cm⁻¹, C–H stretching vibrations at 3030–3097 cm⁻¹, N–H deformation vibrations at 1619–1640 cm⁻¹, CAr = CAr stretching vibrations at 1495–1554 cm⁻¹, C–N stretching vibrations at 1268 cm⁻¹, C–O stretching vibrations at 1064 cm⁻¹ and N–H and CAr–H out-of-plane deformation vibrations at 660–846 cm⁻¹ [27, 31, 32]. In addition, the emission of alkene compounds is also possible. This is confirmed by the presence of the bands at 1643–1670 cm⁻¹ (the stretching vibration of C=C).

However, in the case of compounds 2–4 which contain as R₂: one chlorine atom in the para position (compounds 2–4) or –CH₃ group in the ortho position (the compounds 3 and 4), while as R₁: -OCH₃ (the compound 2) or –CH₃ (the compound 4) groups in the para position, the emission of aniline or substituted aromatic amines and aromatic chloro derivatives is well visible.

The obtained FTIR spectra suggest that the pyrolysis of the compound 2 leads to the emission of p-chlorophenol and p-anisidine. The emission of p-chlorophenol is visible as absorption bands at 3648 cm⁻¹ (the stretching vibrations of OH), at 1491 cm⁻¹ (CAr = CAr stretching vibrations) at 1254 cm⁻¹, 1171 cm⁻¹ (C–N stretching vibrations), 1090 cm⁻¹ (C–O stretching vibrations) and below 800 cm⁻¹ (C–Cl stretching vibrations). In turn, the presence of the absorption bands at 1517 cm⁻¹ (CAr = CAr stretching vibrations), at 1254 cm⁻¹ (C–N stretching vibrations), 1090 cm⁻¹ (C–C in-plane deformation vibrations of aromatic) and 821 cm⁻¹ (CAr–H out-of-plane deformation vibrations) indicates the formation of p-anisidine [27].

Fig. 4 The gaseous FTIR spectra were collected in helium.
The pyrolysis of the compound 3 gives aniline and 2-methyl-4-chlorophenol. In turn, the decomposition of compound 4 in inert conditions allows obtaining p-toluidine and 2-methyl-4-chlorophenol as aromatic volatiles. The emission of those volatiles as a result of pyrolysis process of the compound 4 is confirmed on the basis of the presence of the following absorption bands: p-toluidine: at 1623 cm\(^{-1}\) (small band, N–H deformation vibration), 1525 cm\(^{-1}\) (small band, C\(_{Ar}\) = C\(_{Ar}\) stretching vibration), at 1260 cm\(^{-1}\) (N–H stretching vibrations), at 960–650 cm\(^{-1}\) (C\(_{Ar-H}\) and N–H out-of-plane deformation vibrations) and 2-methyl-4-chlorophenol at 3648 cm\(^{-1}\) (OH stretching vibrations), at 1492 cm\(^{-1}\) (C\(_{Ar}\) = C\(_{Ar}\) stretching vibrations), at 1307 cm\(^{-1}\) and 1400 cm\(^{-1}\) (C–H deformation vibrations) and at 1203–1106 cm\(^{-1}\) (C–O stretching vibrations).

The heating of the compounds 5 and 6 which contain two chlorine atoms, one as R\(_1\) substituent in the para position and the second as R\(_2\) substituent in the para position, the emission of p-chloroaniline and p-chlorophenol (for the compound 5) and p-chloroaniline (for the compound 6) is the most possible. The emission of p-chloroaniline is confirmed based on the presence of the following absorption bands: N–H deformation vibration at 1620 cm\(^{-1}\), C\(_{Ar}\) = C\(_{Ar}\) stretching vibration at 1490 cm\(^{-1}\), C–N stretching vibrations at 1274 cm\(^{-1}\), C\(_{Ar-H}\) and N–H out-of-plane deformation vibrations) and below 800 cm\(^{-1}\) (C–Cl stretching vibrations). In turn, the appearance on the gaseous FTIR spectrum of the absorption bands at 1490 cm\(^{-1}\) (C\(_{Ar}\) = C\(_{Ar}\) stretching vibrations), at 1307 cm\(^{-1}\) and 1400 cm\(^{-1}\) (C–H deformation vibrations), at 1199 cm\(^{-1}\), 1157 cm\(^{-1}\) (C–O stretching vibrations), at 862 cm\(^{-1}\) (C\(_{Ar-H}\) out-of-plane deformation vibrations) and below 800 cm\(^{-1}\) (C–Cl stretching vibrations) may indicate the creation of aniline derivative such as 2-methyl-4-chlorophenol.

For the compound 7, which contains three chlorine atoms in its structure, one as R\(_1\) substituent in the para position and the two as R\(_2\) substituents in the ortho and para positions, the most likely pyrolysis products are p-chloroaniline and 2,4-dichlorophenol. The presence of p-chloroaniline among volatiles is found on the basis of the N–H deformation vibrations at 1621 cm\(^{-1}\), C\(_{Ar}\) = C\(_{Ar}\) stretching vibration at 1490 cm\(^{-1}\), C–N stretching vibrations at 1274 cm\(^{-1}\), C\(_{Ar-H}\) and N–H out-of-plane deformation vibrations at 815 cm\(^{-1}\) and the C–Cl stretching vibrations below 644 cm\(^{-1}\). The formation of 2,4-dichlorophenol is visible as the absorption bands characteristic for the OH stretching vibrations at 3581 cm\(^{-1}\), C\(_{Ar}\) = C\(_{Ar}\) stretching vibrations at 1479 cm\(^{-1}\), C–O stretching vibrations at 1187 -1052 cm\(^{-1}\), C\(_{Ar-H}\) out-of-plane deformation vibrations at 850 cm\(^{-1}\) and 815 cm\(^{-1}\) and the C–Cl stretching vibrations at 644 cm\(^{-1}\).

However, when analysing the structure of the compounds 8 and 9 containing four chlorine atoms, the creation of more substituted aromatic derivatives is expected. In the case of compound 8, the emission of 3,4-dichloroaniline and 2,4-dichlorophenol is indicated due to the presence of the absorption bands characteristic for dichlorosubstituted aromatic derivatives at 1620 cm\(^{-1}\) (N–H deformation vibrations), at 1477 cm\(^{-1}\) (C\(_{Ar}\) = C\(_{Ar}\) stretching vibrations), at 1280 cm\(^{-1}\) (C–N stretching vibrations), at 1132–1020 cm\(^{-1}\) (C–O stretching vibrations), at 890–746 cm\(^{-1}\) (C\(_{Ar-H}\) and N–H out-of-plane deformation vibrations) and at 643 cm\(^{-1}\) (C–Cl stretching vibrations). However, for the compound 9, the formation of p-chloroaniline and 2,4,5-trichlorophenol is observed. The absorption bands at 3577 cm\(^{-1}\) (OH stretching vibrations), at 1460 cm\(^{-1}\) (C\(_{Ar}\) = C\(_{Ar}\) stretching vibrations), at 1289 cm\(^{-1}\) (N–H stretching vibrations), at 1186–1072 cm\(^{-1}\) (C–O stretching vibrations), at 873 cm\(^{-1}\) (C\(_{Ar-H}\) and N–H out-of-plane deformation vibrations) and below 800 cm\(^{-1}\) (C–Cl stretching vibrations) are characteristic bands of both products.

The gaseous FTIR spectra collected at \(T_{\text{max}}\) for all compounds tested show mainly the emission of CO\(_2\), H\(_2\)O and CH\(_3\)CN as a result of further reactions of formed residues and intermediate gaseous volatiles.

### Thermal stability of compounds 1–9 (synthetic air atmosphere)

The TG/DTG curves obtained under oxidizing conditions are presented in Fig. 5. The TG/DTG data are placed in Table 3. The thermal stability of the compounds in oxidizing conditions—described as the temperature at which a 5% mass loss is observed—is comparable (compounds 1, 2 and 9) or lower (compounds 3, 4, 5, 6, 7, 8) than their thermal stability in inert conditions. However, all the tested compounds are thermally resistant up to the temperature 230 °C. The decomposition of the compounds in air runs through at least three main stages. The first stage of decomposition spreads from \(T_{5\%}\) to 325–431 °C with one \(T_{\text{max}}\) at 363 °C (the compound 8) or two \(T_{\text{max}}\) (other compounds) at 200–251 °C (low intensity, fuzzy DTG peak, \(T_{\text{max0}}\)) and at 298–318 °C (high-intensity DTG peak, \(T_{\text{max1}}\)). The mass loss (\(\Delta m_j\)) is from 21.4 to 58.2% in this decomposition stage. The second decomposition stage occurs immediately after the first and is visible up to ca. 440–478 °C and with the \(T_{\text{max2}}\) 387–405 °C. The mass loss (\(\Delta m_j\)) varies within limits 14.3–40%. When heating the compounds above 440–478 °C, the third decomposition stage happens. The maximum decomposition temperatures (\(T_{\text{max3}}\)) are from 541 to 659 °C, and the mass loss (\(\Delta m_j\)) is from 29.2% to 57.1%. In addition, as it is well visible heating of the compounds to the temperature 700 °C leads to its full decomposition in oxidizing atmosphere.
**Fig. 5** The TG/DTG curves of compounds 1–9 (synthetic air atmosphere)
Decomposition course of compounds 1–9 (synthetic air atmosphere)

The gaseous FTIR spectra collected at $T_{\text{max}}$ and in oxidizing atmosphere are presented in Fig. 6. As it can be clearly seen, all the tested compounds decompose in three main stages with a poorly developed DTG peak at $T_{\text{max}0}$. The FTIR spectrum for the compound 1 collected at $T_{\text{max}0}$ shows the presence of the signals above 3500 cm$^{-1}$ (OH stretching vibrations), at 2300–2365 cm$^{-1}$ and 669 cm$^{-1}$ (CO$_2$), at 1724 cm$^{-1}$ (C=O stretching vibrations), at 1536–1565 cm$^{-1}$ (CAr = CAr stretching vibrations), at 1400–1420 cm$^{-1}$ (C–H deformation vibrations), and at 1083–1095 cm$^{-1}$ (C–O stretching vibrations). In the case of the compounds 2 and 3, a signal that is clearly visible from the FTIR spectrum at $T_{\text{max}0}$ is the signal at 1725 cm$^{-1}$ (C=O stretching vibrations), and for the compound 4, this signal is visible as a peak with very low intensity at 1715 cm$^{-1}$. The presence of the previously mentioned absorption signals at $T_{\text{max}0}$ for the compounds with one or without chlorine atom as a substituent may indicate the formation of some aromatics with carbonyl group.

For the other test compounds, the FTIR spectra at $T_{\text{max}0}$ indicate the presence of a small amount of H$_2$O and/or CO$_2$ in the analysed gases.

At $T_{\text{max}1}$, for all the tested compounds, the absorption signals responsible for the stretching vibrations of OH in water vapour (above 3500 cm$^{-1}$) and in aromatic compound with OH group (at 3658–3660 cm$^{-1}$) are well visible. In the case of compounds 1–3 and compound 9, the emission of CO$_2$ is present (bands at 2300–2365 cm$^{-1}$ and 669 cm$^{-1}$). At $T_{\text{max}1}$, the volatiles containing aromatic rings are created for all the tested compounds. This is confirmed by the appearance of the following absorption bands: C–H stretching vibrations at 3030–3097 cm$^{-1}$, N–H deformation vibrations at 1619–1640 cm$^{-1}$, C$_{\text{Ar}}$ = C$_{\text{Ar}}$

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Table 3 The TG/DTG data for compounds 1–9 (synthetic air atmosphere)

| Sample | Degradation process |
|--------|---------------------|
|        | First decomposition stage | Second decomposition stage | Third decomposition stage |
|        | $T_{5\%/^\circ C}$ | $T_{\text{max}0}/^\circ C$ | $T_{\text{max}1}/^\circ C$ | $T_{\text{max}2}/^\circ C$ | $\Delta m_1/%$ | $T_{\text{max}3}/^\circ C$ | $T_{\text{final}3}/^\circ C$ | $\Delta m_2/%$ | $T_{\text{final}3}/^\circ C$ |
| 1      | 276 | 238/308 | 21.4 | 405 | 40.0 | 659 | 38.6 | 732 |
| 2      | 274 | 232/300 | 42.8 | 398 | 14.3 | 546 | 57.1 | 688 |
| 3      | 240 | 234/304 | 27.8 | 395 | 34.5 | 644 | 37.7 | 710 |
| 4      | 259 | 220/300 | 41.1 | 397 | 24.8 | 562 | 34.1 | 664 |
| 5      | 257 | 201/318 | 49.7 | 394 | 21.1 | 541 | 29.2 | 698 |
| 6      | 277 | 200/311 | 39.1 | 387 | 23.0 | 575 | 37.9 | 675 |
| 7      | 248 | 202/275 | 42.0 | 387 | 22.5 | 566 | 35.5 | 684 |
| 8      | 308 | 363 | 58.2 | – | – | 573 | 41.8 | 666 |
| 9      | 233 | 251/298 | 45.4 | 387 | 18.1 | 580 | 36.5 | 678 |

$T_{\text{max}0}$—low intensity, “fuzzy” DTG peak before $T_{\text{max}1}$

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Fig. 6 The gaseous FTIR spectra were collected in synthetic air atmosphere.
stretching vibrations at 1491–1554 cm⁻¹, C–N stretching vibrations at 1254–1280 cm⁻¹, C–O stretching vibrations at 1064 cm⁻¹–1203 cm⁻¹ and N–H and CAr-H out-of-plane deformation vibrations at 660–846 cm⁻¹ and below 645 cm⁻¹ (C–Cl stretching vibrations) [27, 31–33]. This indicates the formation of the same structure aromatic compounds as those observed in helium. It follows that each compound melts in one temperature range and at almost the same temperatures both under inert and oxidizing conditions. The values of the melting temperatures of the molecules were closely related to their chemical structure. The thermal stability of these compounds was also depended on their chemical structure and applied analysis conditions, but it proved to be higher than 230 °C in both atmospheres. The most thermally stable compound (T₅% above 300 °C) was the compound 8 containing four chlorine atoms, two each as R₁ and R₂ substituents.

In addition, the conducted research confirmed at least two-stage decomposition process of all the tested compounds in inert conditions and at least three-stage decomposition process in oxidative conditions. The range of temperatures in which the individual decomposition steps of the analysed compounds took place was closely dependent on the amount of chlorine substituents and their position in the phenyl moiety and/or in the benzene ring of the phenoxymethyl moiety.

During the heating and thus decomposition of all the tested compounds in inert conditions, the emission of NH₃, HCN, acetonitrile, aromatics with an OH group, aromatics with a NH₂ group, alkene fragments, H₂O and CO₂ was observed. This indicated a simultaneous cleavage of C–N, N–N and C–O bonds in the structure of the analysed compounds. Similarly, the volatiles such as NH₃, HCN, acetonitrile, aromatics with an OH group, aromatics with a NH₂ group, alkene fragments, H₂O and CO₂ and some amounts of carbonyl fragments and CO were emitted in the presence of the furnace atmosphere containing oxygen. This confirmed that disubstituted fused 1,2,4-triazoles were almost resistant to oxidation under the applied analysis conditions. However, the higher emission of CO₂ and additional emission of CO at third decomposition stage indicated the combustion of the pre-formed residues.

Conclusions

The thermal behaviour and pyrolysis and oxidative degradation course of nine disubstituted fused 1,2,4-triazoles—containing none, one, two, three or four chlorine atoms as a substituent in the phenyl moiety (denoted as R₁) and/or in the benzene ring of the phenoxymethyl moiety (denoted as R₂)—have been evaluated using the simultaneous TG/DTG/DSC/FTIR method. On the basis of the conducted research, it was found that each compound melts in one temperature range and at almost the same temperatures both under inert and oxidizing conditions. The values of the melting temperatures of the molecules were closely related to their chemical structure. The thermal stability of these compounds was also depended on their chemical structure and applied analysis conditions, but it proved to be higher than 230 °C in both atmospheres. The most thermally stable compound (T₅% above 300 °C) was the compound 8 containing four chlorine atoms, two each as R₁ and R₂ substituents.

In addition, the conducted research confirmed at least two-stage decomposition process of all the tested compounds in inert conditions and at least three-stage decomposition process in oxidative conditions. The range of temperatures in which the individual decomposition steps of the analysed compounds took place was closely dependent on the amount of chlorine substituents and their position in the phenyl moiety and/or in the benzene ring of the phenoxymethyl moiety.

During the heating and thus decomposition of all the tested compounds in inert conditions, the emission of NH₃, HCN, acetonitrile, aromatics with an OH group, aromatics with a NH₂ group, alkene fragments, H₂O and CO₂ was observed. This indicated a simultaneous cleavage of C–N, N–N and C–O bonds in the structure of the analysed compounds. Similarly, the volatiles such as NH₃, HCN, acetonitrile, aromatics with an OH group, aromatics with a NH₂ group, alkene fragments, H₂O and CO₂ and some amounts of carbonyl fragments and CO were emitted in the presence of the furnace atmosphere containing oxygen. This confirmed that disubstituted fused 1,2,4-triazoles were almost resistant to oxidation under the applied analysis conditions. However, the higher emission of CO₂ and additional emission of CO at third decomposition stage indicated the combustion of the pre-formed residues.
It is concluded that, for the first time, the thermal properties, thermal decomposition course and the identification of volatile decomposition products of disubstituted fused 1,2,4-triazoles—being candidates for possible pharmaceutical use—were successfully assessed using the TG/DTG/DSC/FTIR technique. Moreover, the obtained results confirmed the suitability of these compounds as potential candidates for pharmaceutical applications due to their favourable thermal properties.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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