

Epr Investigation of Gamma-irradiated Hydrochlorothiazide Medicine Samples

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Milli Eğitim Bakanlığı

Research Article

Keywords: EPR, Dosimetry, Gamma irradiation

Posted Date: July 13th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10219823/v1>

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Additional Declarations: No competing interests reported.

EPR INVESTIGATION OF GAMMA-IRRADIATED HYDROCHLOROTHIAZIDE MEDICINE SAMPLES

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ABSTRACT

In this study, the suitability of gamma-irradiated Hydrochlorothiazide (HCTZ) as a dosimetric material was investigated using EPR spectroscopy. Signal fading, microwave saturation behavior, and the dose-response curve were investigated. Moreover, the medicine sample was also measured at different temperature ranges. The EPR signal was not detected in unirradiated samples. The spectroscopic properties of the radical induced by radiation were also determined by spectrum simulation.

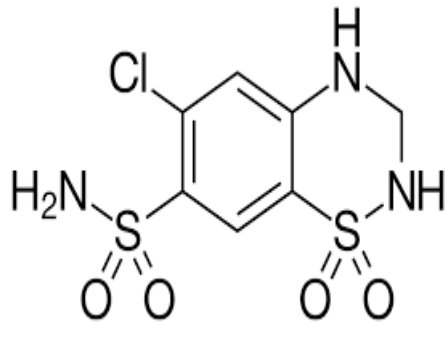
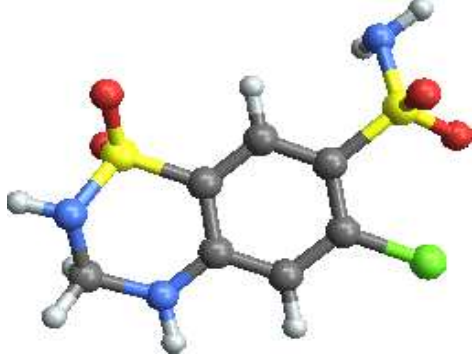
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1. INTRODUCTION

Hydrochlorothiazide (HCTZ), a widely prescribed thiazide diuretic for hypertension and edema, was chosen as the model compound for this EPR study. With the molecular formula $C_7H_8ClN_3O_4S_2$ and a molecular weight of 297.74 g/mol, this sulfonamide derivative is well-known for its therapeutic efficacy. Upon exposure to ionizing radiation, pharmaceuticals often undergo structural changes, leading to the formation of free radicals. EPR spectroscopy provides a direct and sensitive method to detect and characterize these paramagnetic species, revealing the localization of the unpaired electron within the molecular structure. Numerous studies have demonstrated the utility of EPR in analyzing irradiated medicine sample compounds, particularly for understanding radiation-induced degradation pathways and assessing the stability of the final product. Here, a detailed EPR

investigation of gamma-irradiated HCTZ to determine its spectroscopic properties and evaluate its potential as a solid-state dosimeter. "Comprehensive molecular data regarding the investigated Hydrochlorothiazide (HCTZ) matrix is tabulated in Table 1."

Table 1. Chemical structure, ring system, molecular weight, and chemical structure of Hydrochlorothiazide (HCTZ) medicine sample

 	
Hydrochlorothiazide (HCTZ), 2D conformation	
Molecular formula	$C_7H_8ClN_3O_4S_2$
Molecular weight	297.74 g/mol
Chemical names	6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

A maximum radiation dose of 25 kGy was selected, in accordance with the limits recommended by pharmacopoeias (USP XXII, BP 1993) (2,13). The pharmaceutical samples were exposed to gamma radiation at doses of 2, 7, 10, 15, 20, and 25 kGy. The main goal was to characterize the EPR spectral properties of the induced radicals in hydrochlorothiazide (HCTZ) and to obtain dose-response curves at room temperature. This was done to evaluate the compound's potential for use in routine and accidental dosimetry. Further details on EPR in accident dosimetry can be found in Section 1.1.

1.1. Accident Dosimetry

Accident dosimetry aims to precisely measure the radiation dose absorbed during nuclear accidents. This information is essential for the survival of living organisms in affected areas. The International Atomic Energy Agency (IAEA) has recommended biological dosimetry as an independent method for determining radiation doses in such events (IAEA, 1986) (6). Accurate and rapid dose assessment is crucial because it directly guides the medical treatment and influences the overall success of therapy.

2. MATERIALS AND METHODS

Gamma irradiations were performed using a Cobalt-60 source (activity: 370,000 Ci) at the Sarayköy Nuclear Research Center (SANAEM, now TENMAK), which operates under the Turkish Atomic Energy Authority in Kahramankazan. The dose rate was 2 kGy/h. For irradiation, the medicine samples were placed in 1.5 mL Eppendorf tubes and positioned inside the irradiation unit. Process control was maintained using dosimeters placed in the product boxes. Samples were irradiated at five different doses (2, 7, 10, 15, 20, and 25 kGy), each on separate occasions. After irradiation, EPR spectra were recorded at room temperature using a Bruker e-scan X-band spectrometer under the following conditions: center field, 349 mT; scan range, 10 mT; microwave power, ~0.1 mW; microwave frequency, 9.8 GHz; receiver gain, 3.17×10^2 ; modulation frequency, 86 kHz; and modulation amplitude, 2 G.

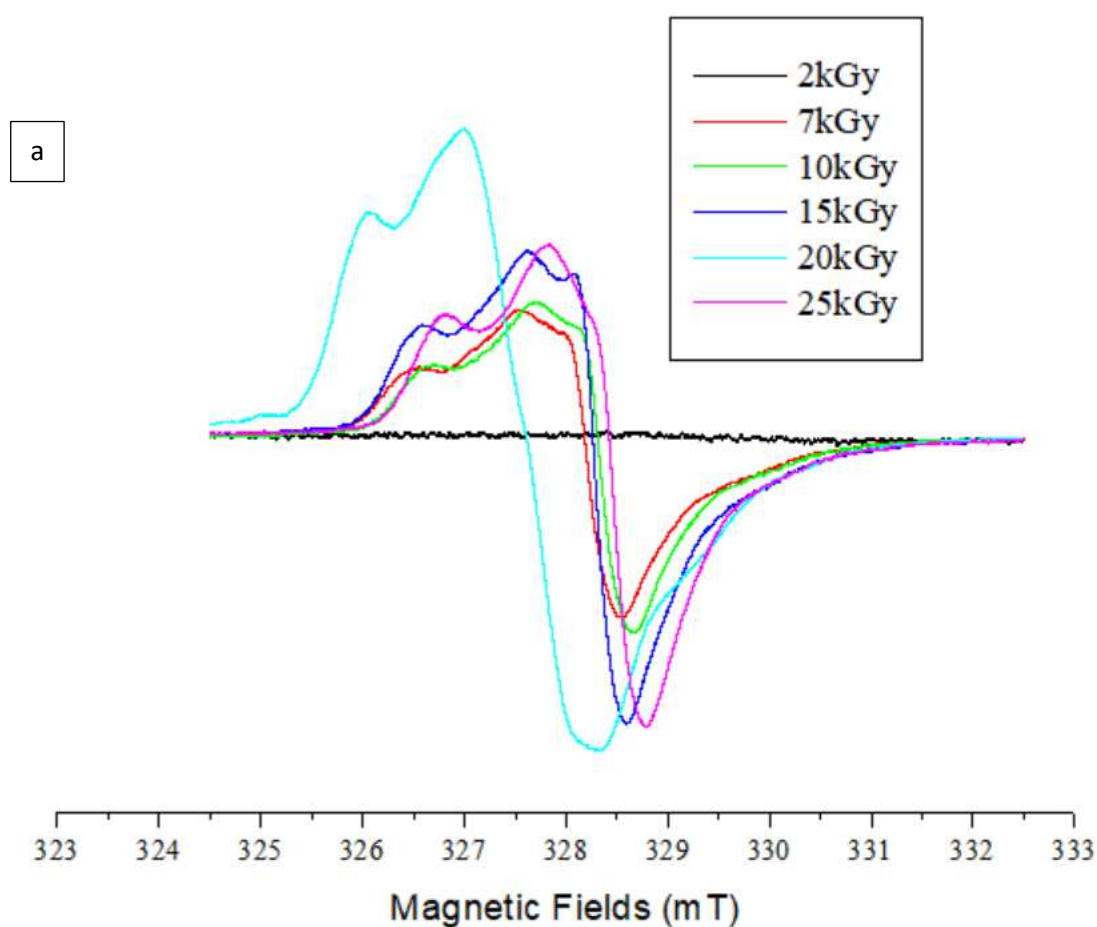
3. RESULTS

3.1. EPR Spectra of Unirradiated and Irradiated Hydrochlorothiazide Samples

Hydrochlorothiazide (HCTZ) was used as received, without any pre-irradiation treatment. The EPR spectra were recorded following gamma exposure at various doses. No EPR signal was detected in the non-irradiated control sample, whereas the irradiated samples exhibited a prominent, dose-dependent increase in signal intensity (Figure 1a) (12). The recorded spectra were centered at an isotropic g -value of 2.0038 ± 0.0005 . Figure 1b displays the experimental spectrum obtained at 20 kGy, and Figure 1c presents its corresponding theoretical simulation performed using the McKelvey software (9).

The simulation successfully resolved the underlying hyperfine interactions, yielding isotropic coupling constants of $a_N = 1.08 \pm 0.03$ mT, $a_C = 0.50 \pm 0.03$ mT, and $a_H = 0.30 \pm 0.03$ mT, with a peak-to-peak line width (ΔB_{pp}) of 0.6 mT. Although the resonance signal grew progressively stronger as the irradiation dose was raised from 2 to 25 kGy, the experimental spectrum manifested as a broadened envelope rather than five distinctly resolved lines. This broad profile is attributed to

the overlapping component peaks spreading across a magnetic field range of approximately 326 mT to 330 mT, which is a common feature in solid-state matrices driven by anisotropic broadening. Structurally, the extracted hyperfine parameters and the underlying quintet configuration strongly point toward a delocalized Nitrogen-Carbon-Nitrogen ($\text{N} - \dot{\text{C}} - \text{N}$ or $\dot{\text{N}} - \text{C} - \text{N}$) radical framework within the heterocycle, where the spin density is shared efficiently across near-equivalent nitrogen nuclei.



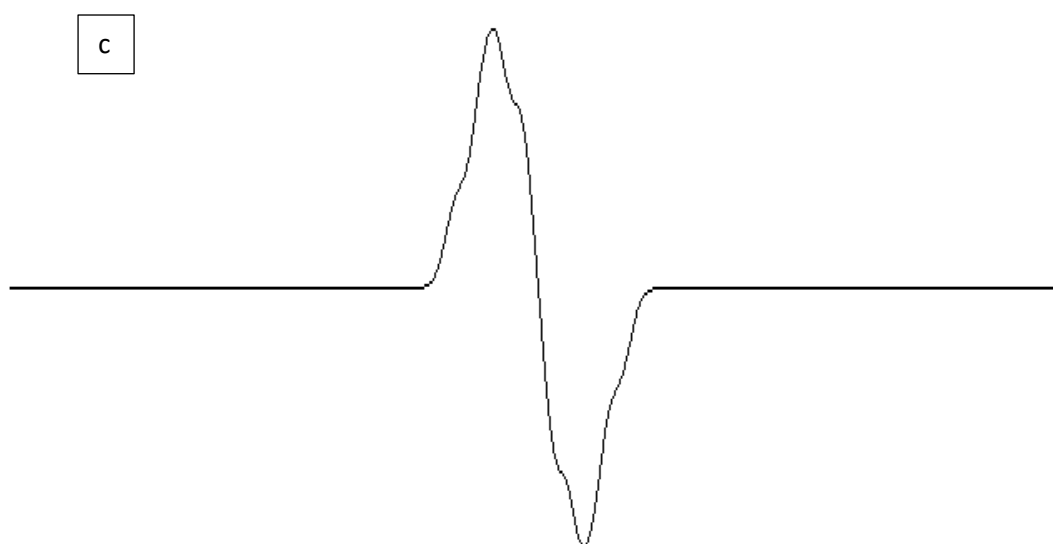
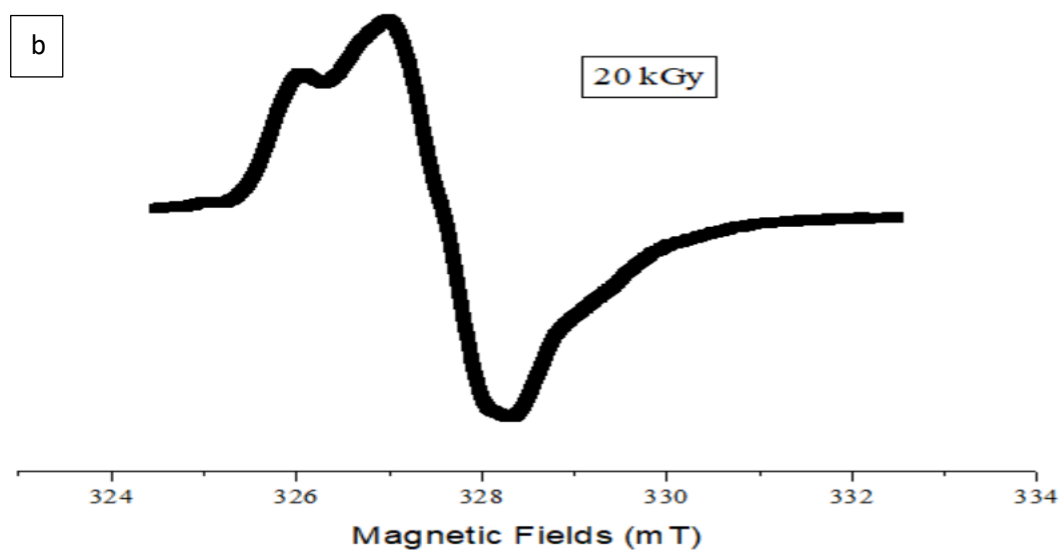


Figure 1a. Spectra obtained from an irradiated Hydrochlorothiazide. Figure 1b. EPR spectrum of Hydrochlorothiazide at 20 kGy dose. Figure 1c. The closest simulation spectrum of the Hydrochlorothiazide obtained at a dose of 20 kGy

3.2. Variation of EPR Signal Intensity with Microwave Power

EPR spectra of the 10 kGy-irradiated HCTZ samples were recorded at various microwave power levels (0.1, 1, 2, 4, 8, 10 and 12 mW). The corresponding $\sqrt{P}(\text{mW})^{1/2}$ values and signal intensities are listed in Table 2. Signal intensities were determined from the peak-to-peak amplitudes of the strongest lines in the spectra, using Origin 6.0

Table 2 Microwave Power $\sqrt{P}(\text{mW})^{1/2}$ and resonance signal intensity. Values of the resonance signal intensity of the Hydrochlorothiazide sample depending on the square root of the applied microwave power.

Microwave Power $\sqrt{P}(\text{mW})^{1/2}$	0.1	1	2	4	8	10	12
Signal Intensity (a.u.)	10.63	17.03	30.43	36.12	44.36	46.23	52.24

Figure 2 shows the variation of the microwave power of the Hydrochlorothiazide medicine sample depending on the signal intensity, and Figure 3 shows the spectra of the irradiated Hydrochlorothiazide medicine sample obtained at 0.1-...-12 mW microwave area values.

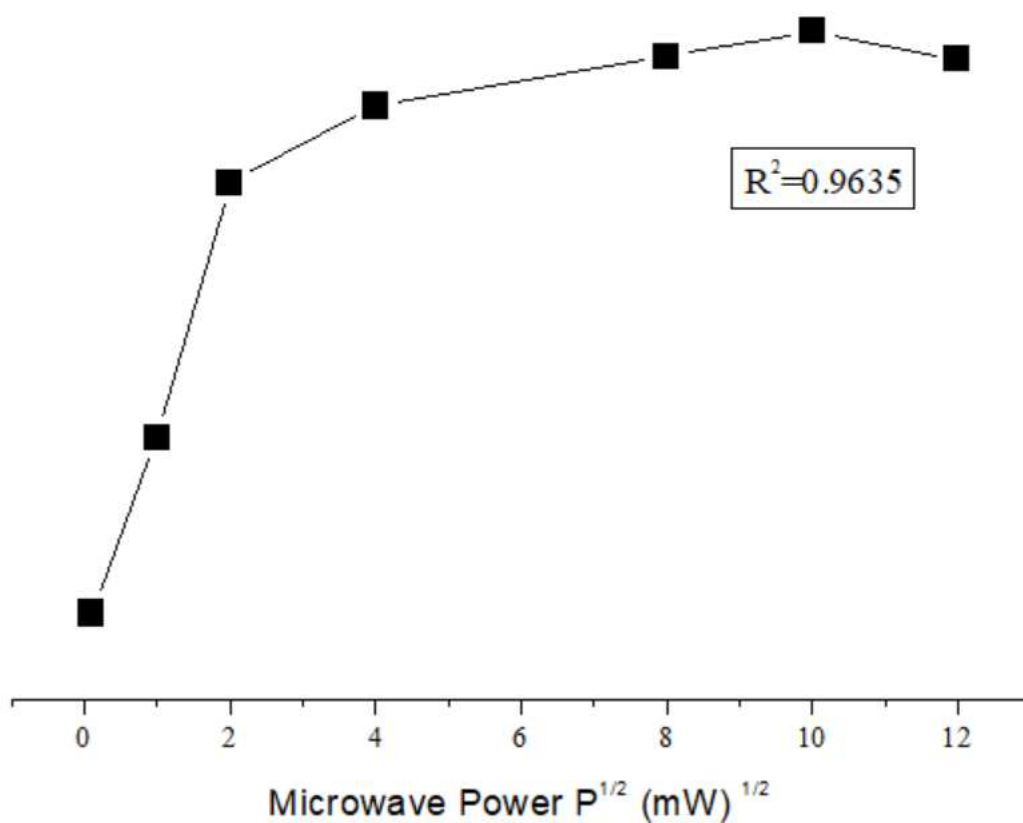


Figure 2. Variation of microwave power of the Hydrochlorothiazide with signal intensity.

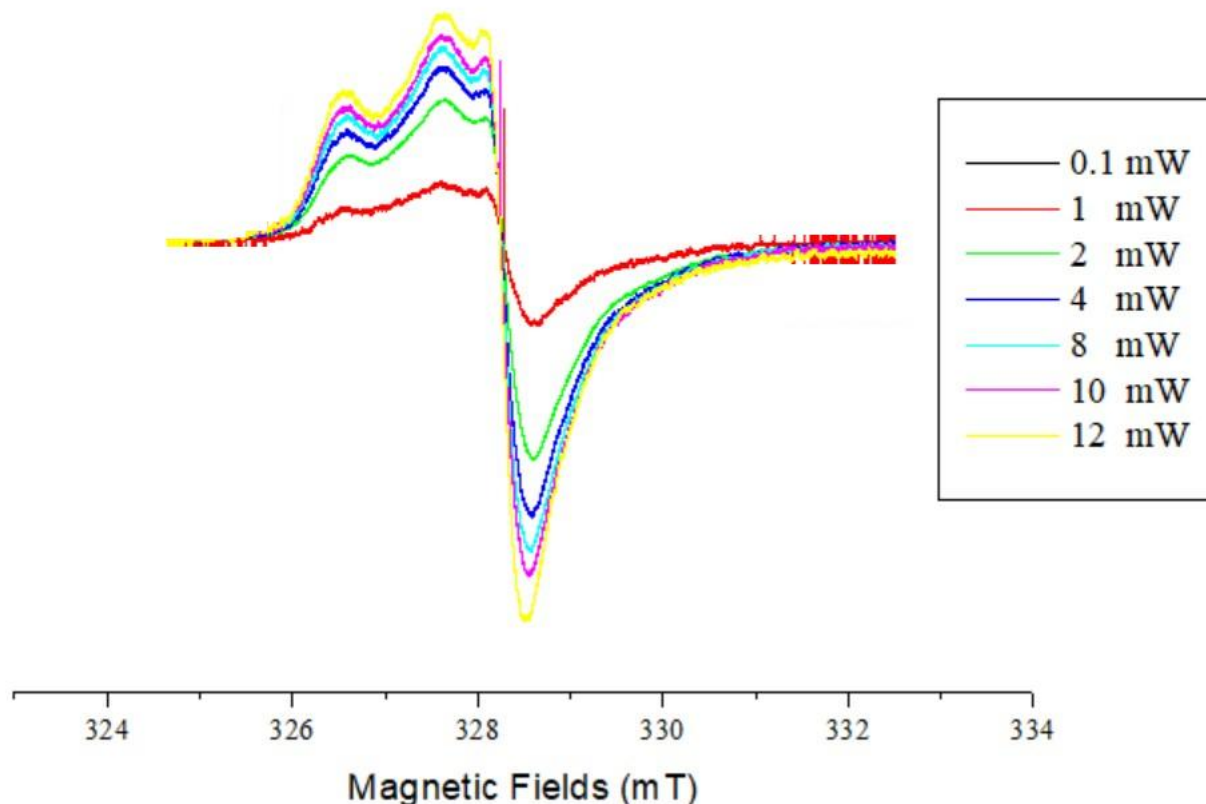


Figure 3. Spectra of irradiated Hydrochlorothiazide obtained with different microwave powers.

3.3. Dose-response curve of Hydrochlorothiazide (HCTZ) sample

In this section, examinations were conducted to determine the dosimetric potential of the Hydrochlorothiazide medicine sample. The most appropriate mathematical functions that can describe the dose-dependent variations of the resonance signal intensity results were determined by the mathematical functions given in the graph. Figure 4 shows the dose-dependent variations in the resonance signal intensity of the irradiated samples.

Table 3. Parameter values and coefficients of concordance were calculated for three different mathematical functions tested using resonance signal intensity (I) values.

Function	Parameters	I
$I(D) = a(D)+b$ (Linear)	A	670.14
	B	147,18
	R^2	0.9867
$I(D) = a \ln(D)+b$ (Logarithmic)	A	203.32
	B	197.89
	C	-4.575
	R^2	0.9916
$I(D) = a+bD+cD^2$	A	242.49
	B	0.7839

(Polynomial)	C	—
	R^2	0.98

Increasing the radiation dose applied to the sample led to no noticeable alteration in either the g-value or the spectral line shape. However, Figure 4 clearly demonstrates that the intensity of the resulting EPR resonance signal grows significantly as the absorbed radiation dose increases. Here, I and D represent the measured EPR signal intensity and the applied radiation dose, respectively, with the square symbols in Figure 4 tracking the experimental data. Various functions listed in Table 3 were evaluated to identify the most accurate mathematical model capturing these dose-dependent shifts. The analysis showed that the dose-response behavior fits well with logarithmic, polynomial, and exponential trends. Nevertheless, the optimal fit for our results was delivered by the logarithmic model ($I = a \cdot \ln(D) + b$), which provided the highest coefficient of determination ($R^2 = 0.9916$). For a material to be viable in dosimetry, it must fundamentally possess a predictable and mathematically modelable dose-response relationship—a requirement successfully met here through this sub-linear framework.

Since the Hydrochlorothiazide sample exhibits a well-defined and consistent response across the investigated dose range, it is considered a promising candidate for use as a dosimetric material.

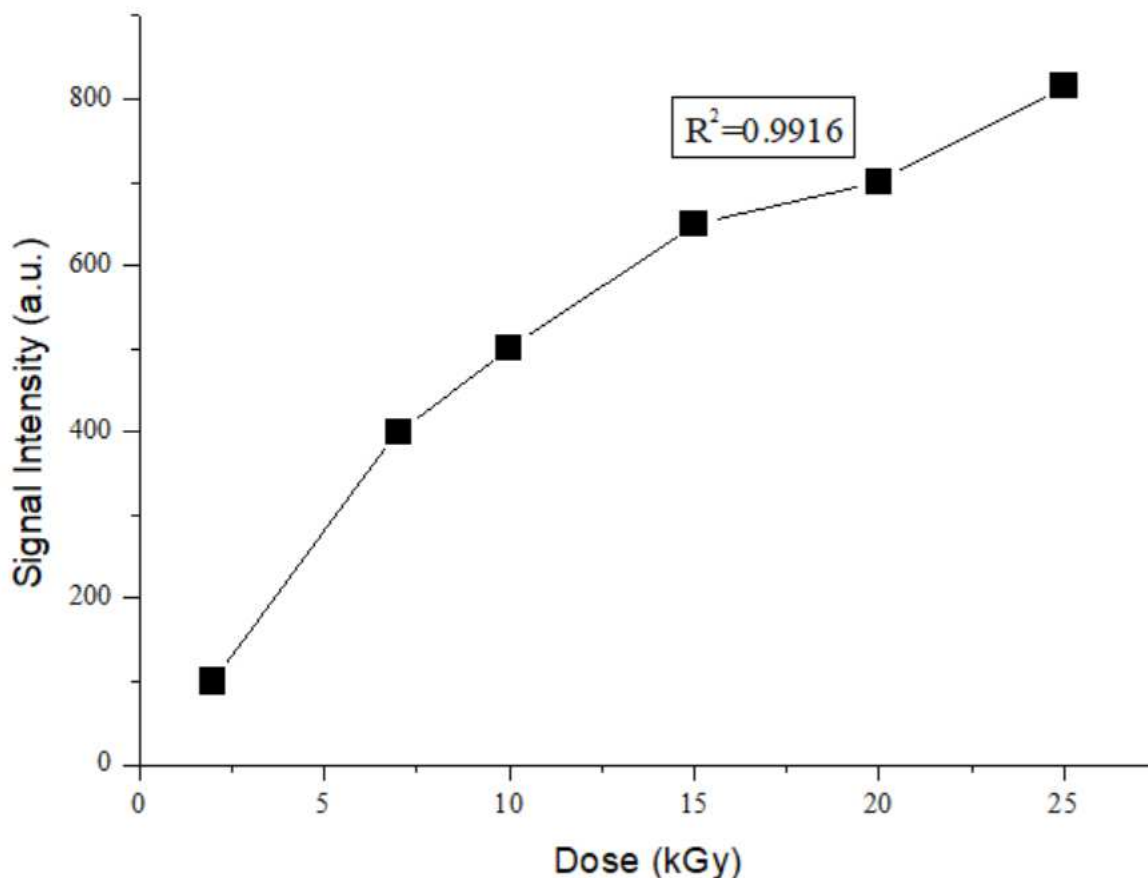


Figure 4. Variation of the signal intensity of the irradiated Hydrochlorothiazide depending on the radiation dose applied.

3.4. Radical Formation Mechanism

The EPR spectra of the irradiated Hydrochlorothiazide (HCTZ) samples exhibited a single dominant radical signal, whose intensity increased monotonically with the increasing irradiation dose while the spectral shape remained essentially unchanged. This observation strongly suggests the formation of a single predominant radiation-induced radical species (12).

A plausible mechanism involves homolytic hydrogen abstraction from the methylene ($-\text{CH}_2-$) carbon at the C(3) position of the heterocycle, or from the adjacent secondary amine nitrogen atoms within the benzothiadiazine ring core. Specifically, hydrogen abstraction from the $-\text{CH}_2-$ bridge generates a stable, carbon-centered α -amino radical.

The resulting unpaired electron is not strictly localized on the carbon atom but undergoes significant spin density delocalization over the adjacent $\text{N}-\text{C}-\text{N}$ fragment via strong interaction with the neighboring nitrogen atoms within the heterocyclic framework. This extensive delocalization imparts considerable resonance stability to the free radical species (3).

Consequently, the unpaired electron interacts with two approximately equivalent ^{14}N nuclei ($I = 1$), giving rise to the characteristic five-line (quintet) EPR hyperfine pattern with a theoretical relative intensity distribution of 1:2:3:2:1 (4, 8). The absence of additional resolved hyperfine splittings from remote functional groups, such as the outer sulfonamide moiety, further supports the strict assignment of the unpaired electron to the delocalized $\text{N} - \dot{\text{C}} - \text{N}$ core. Therefore, the observed EPR spectrum is highly consistent with a carbon-centered α -amino radical stabilized through the benzothiadiazine heterocycle (4, 11). While the formation of alternative nitrogen-centered or sulfur-perturbed radical structures cannot be entirely excluded based solely on powder EPR analysis, the proposed delocalized α -amino carbon-centered radical provides the most plausible and parsimonious interpretation of both the experimental spectrum and the simulation parameters (4,12).

3.5. Fading Characteristics of Gamma-Irradiated Hydrochlorothiazide Medicine Samples

In this section, the EPR spectra of Hydrochlorothiazide (HCTZ) medicinal raw material irradiated at 25 kGy were analyzed dosimetrically both before and after gamma irradiation. To evaluate the fading behavior, assess the stability of the central resonance signal intensities, and obtain the decay curves, the EPR spectra of the gamma-irradiated samples were recorded at regular intervals over a period of approximately 172 days. Simulations of the experimental EPR spectra recorded at room temperature were carried out using the McKelvey simulation software (McKelvey 1987). For a pharmaceutical raw material to be suitable for EPR-based dosimetry, it must meet several essential criteria: high availability, low cost, high radiation sensitivity, the absence of an EPR signal prior to irradiation, and a predictable dose-response relationship over a wide range. These characteristics were systematically evaluated for the Hydrochlorothiazide medicine sample.

The raw material was irradiated using a gamma source up to a dose of 25 kGy. Following irradiation, all samples were stored under identical conditions—sealed and protected from light at room temperature—until their spectra were recorded. This specific dose was selected because 25 kGy is the generally accepted upper limit for pharmaceutical sterilization.

Additionally, many pharmaceutical products are sterilized at lower doses to minimize potential radiation-induced degradation, and the literature suggests that effective sterilization can be achieved at these lower levels. Doses of 5 kGy and below are commonly utilized in the pharmaceutical industry to eliminate microbial contamination in active pharmaceutical ingredients (APIs) and excipients during storage.

The results demonstrated that gamma-irradiated Hydrochlorothiazide produces a distinct EPR signal that remains stable in shape regardless of the applied dose, while its signal intensity increases with the dose. To determine the absorbed radiation dose, the mass-normalized signal intensity was plotted against the irradiation dose. The best fit for the experimental data was achieved with a high correlation coefficient (R^2). In this context, I represents the signal intensity extracted from the EPR spectrum, and D denotes the applied radiation dose. Simulations were also conducted by analyzing the room-temperature decay results. The high correlation between the theoretical spectra—generated using the calculated spectroscopic parameters—and the experimental spectra confirms the success and reliability of the evaluation method. From a dosimetric perspective, the total absence of a baseline EPR signal in Hydrochlorothiazide prior to irradiation, combined with its well-defined dose-response curve over a broad range, offers highly promising results. In conclusion, while Hydrochlorothiazide shows strong potential as a dosimetric material, it is recommended that measurements be performed within the first one or two days following irradiation to ensure maximum accuracy and minimize the effects of signal fading. Nevertheless, the fact that fading does not occur immediately indicates that this medicine sample can successfully be used as a dosimetric material. (Note: The tracking was terminated at day 172 as the signal reached the detection limit / stabilization phase). Exposure to a 25 kGy sterilization dose in the solid matrix induced stable free radicals that became trapped within the crystal lattice (cage effect). Although a time-dependent decay kinetics was observed in signal intensity, the radical concentration did not drop to zero by the end of the monitoring period, indicating the persistence of long-lived radicals.

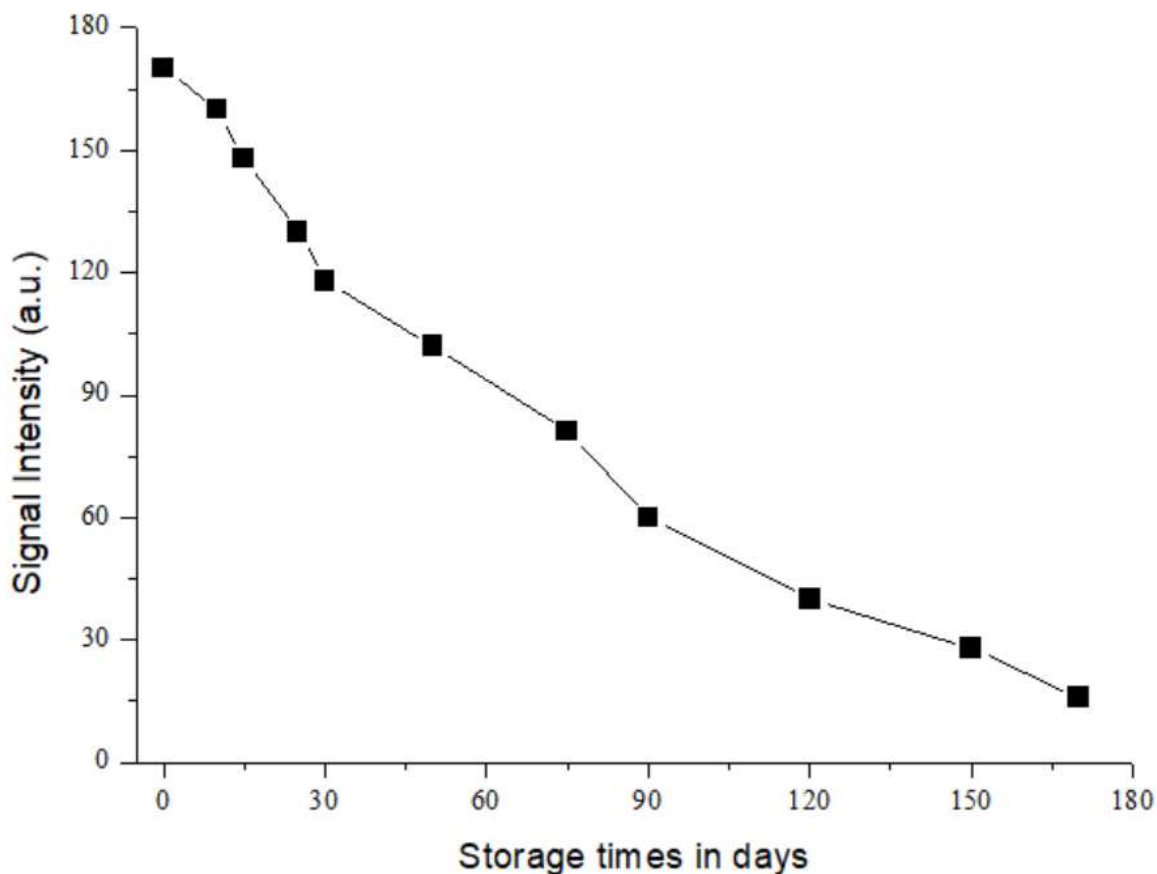


Figure 5. Variation of resonance signal intensity as a function of storage time for the irradiated Hydrochlorothiazide (25 kGy).

4. Temperature Response of the Irradiated Hydrochlorothiazide (HCTZ) Medicine Sample

EPR measurements were performed on Hydrochlorothiazide (HCTZ) drug samples irradiated at a dose of 15 kGy to evaluate the thermal stability and behavior of the radiation-induced paramagnetic centers. The spectra were recorded across six distinct temperatures within the range of 123 K to 423 K with 50 K increments. To avoid any potential microwave power saturation and modulation distortion during the thermal sweeps, the experimental parameters were strictly kept within the linear region, utilizing a low microwave power of 0.05 mW and a modulation amplitude of 1 G. This optimized power setting was deliberately maintained to ensure that the resonance signal intensity accurately reflected only temperature-dependent spins without artificial power broadening.

The temperature dependence of the central resonance signal intensity is illustrated in Figure 6a. The experimental procedure was initiated by positioning the irradiated HCTZ sample into the cavity pre-set at the highest target temperature of 423 K. The cavity temperature was then sequentially decreased in 50 K steps from 423 K to 373 K, and 323 K (heating regime analysis), followed by a further cooling sweep down to 223 K, 173 K, and 123 K (low-temperature regime analysis).

Within the low-temperature regime (123 K – 223 K), the central EPR signal intensity remains relatively stable, exhibiting a slight increase as the temperature decreases. This baseline behavior is primarily governed by the Curie Law ($I \propto 1/T$), where the population difference between the Zeeman energy levels increases at lower temperatures. The observed slight line broadening during the cooling process, shown in Figure 7a, is attributed to the restricted molecular mobility and the freezing of the reorientational dynamics within the crystalline HCTZ matrix at cryogenic states, which consequently enhances spin-spin or spin-lattice relaxation times.

Conversely, an anomalous and prominent sharp increase in the signal intensity is observed in the high-temperature region, specifically between 323 K and 423 K. While typical radical decay due to recombination or thermal destruction is conventionally expected at elevated temperatures, the pronounced enhancement of the signal amplitude indicates a dominant thermal radical generation mechanism. This behavior suggests that high temperatures supply the required activation energy to trigger secondary radical precursors or induce partial thermal degradation products within the HCTZ matrix. These newly generated stable paramagnetic centers superimpose onto the primary radiation-induced radical signal, leading to the substantial boost in intensity shown in Figure 8a. Remarkably, the overall line shapes recorded during both the cooling (Figure 7a) and heating (Figure 8a) cycles remained identical, confirming that the micro environment of the delocalized radical core is structurally preserved across the entire investigated temperature range.

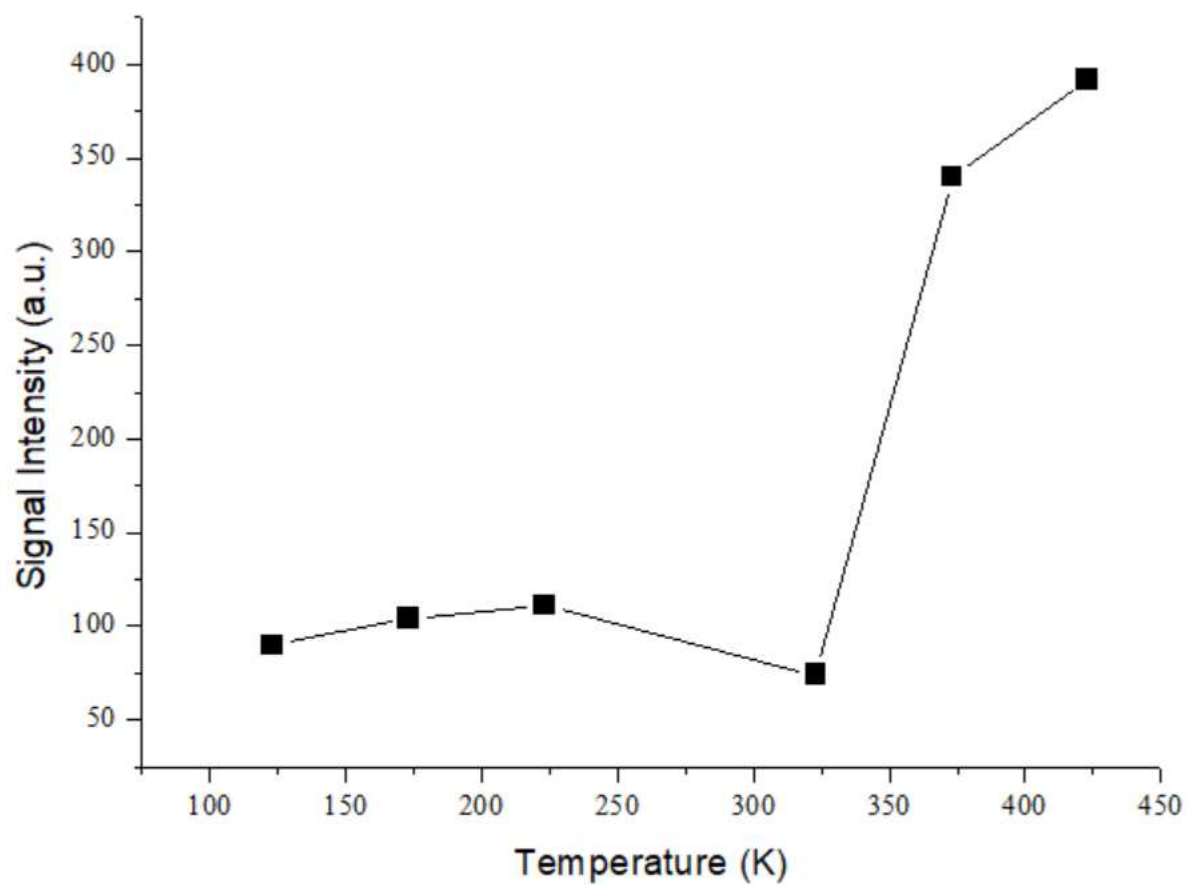


Figure 6a. Temperature-dependent variations of the EPR signal intensity for the Hydrochlorothiazide irradiated at 15 kGy.

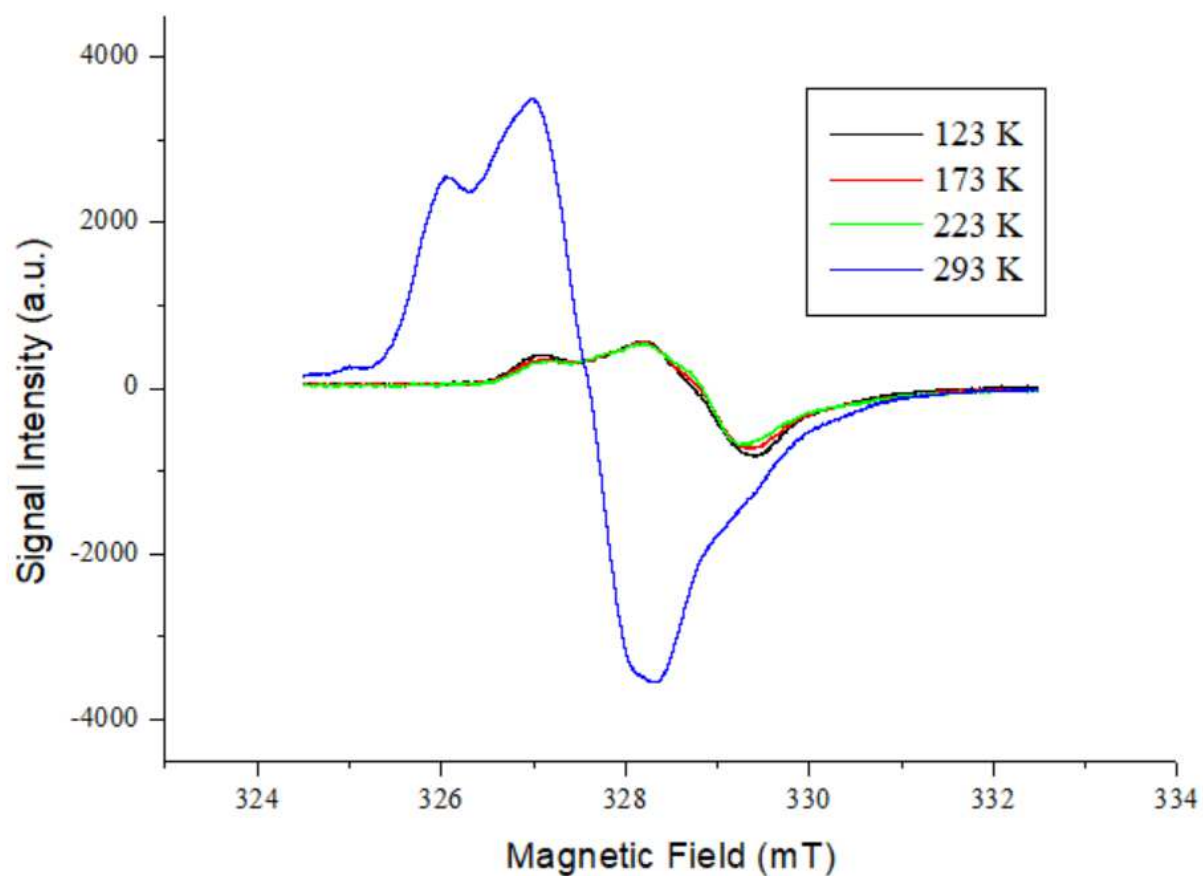


Figure 7a. Low-temperature EPR spectra of irradiated Hydrochlorothiazide recorded during the cooling process (123 K, 173 K, and 223 K) compared with the room-temperature spectrum.

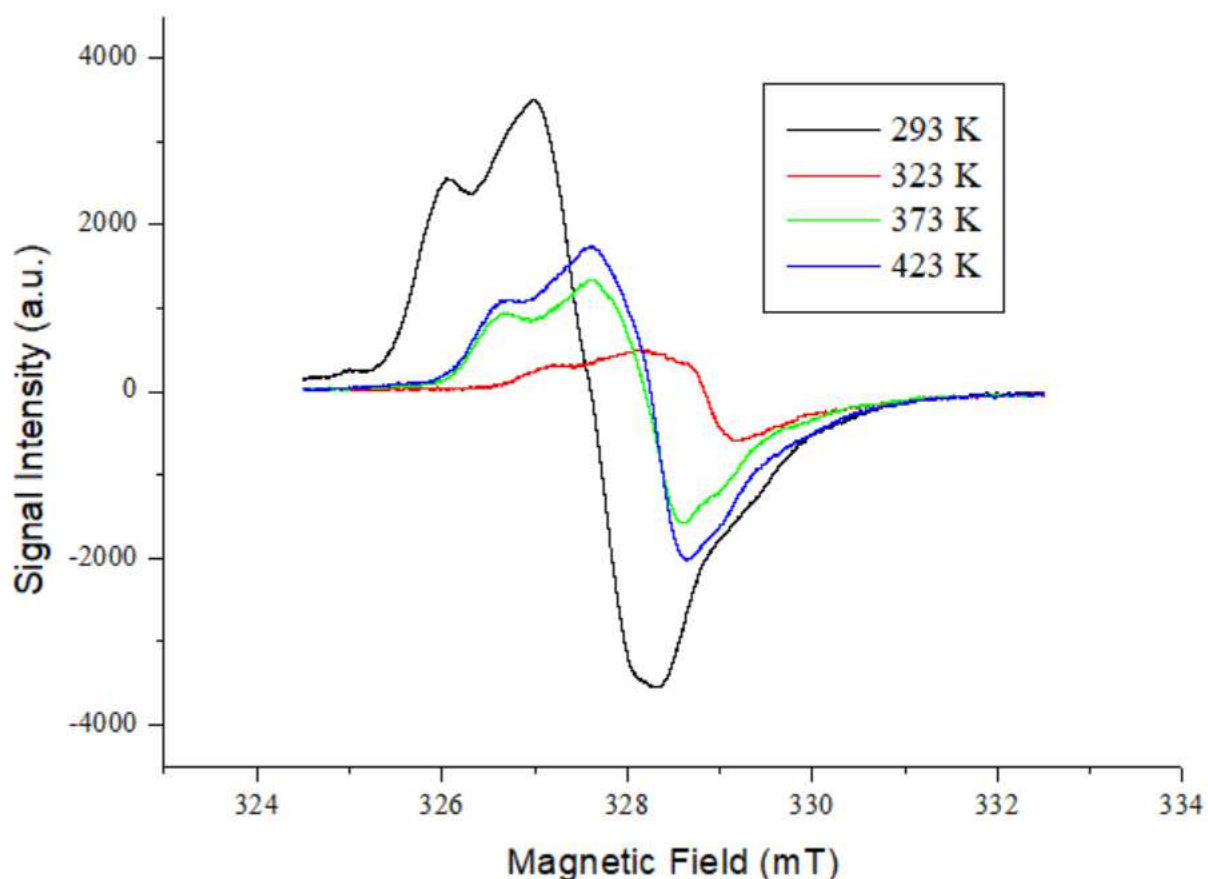


Figure 8a. High-temperature EPR spectra of irradiated Hydrochlorothiazide recorded during the heating process (323 K, 373 K, and 423 K) compared with the room-temperature spectrum.

The consecutive cooling and heating cycles revealed a distinct thermal hysteresis in the signal intensity. As shown in Figure 8b, the signal intensity recorded during the heating cycle (323 K $\rightarrow$ 423 K) was consistently higher than that observed during the cooling cycle (423 K $\rightarrow$ 323 K) at the same intermediate temperatures. This irreversible behavior indicates that the thermally induced radical generation process is not fully reversible within the experimental time frame.

The hysteresis observed in the high-temperature region (323 K–423 K) suggests the presence of a temperature-activated secondary radical formation pathway, likely driven by the thermal degradation or decomposition of the HCTZ matrix upon heating. Once these secondary radicals are formed, they do not recombine or decay completely upon subsequent cooling, leading to a net increase in the overall spin concentration and an irreversible enhancement of the signal intensity. This behavior is consistent with a non-equilibrium, kinetically trapped radical population stabilized within the rigid crystalline lattice.

In contrast, the low-temperature regime (123 K–223 K) exhibited no significant hysteresis, with the signal intensity following the reversible Curie-law behavior ($I \propto 1/T$) during both cooling and heating. The slight line broadening observed at cryogenic temperatures, attributed to restricted molecular motions and prolonged spin-lattice relaxation times, was fully reversible upon warming, indicating that no structural or chemical changes occur in the low-temperature region.

Table 4. Temperature dependence of the EPR signal intensity for the 15 kGy-irradiated Hydrochlorothiazide, recorded at selected temperatures during consecutive cooling and heating cycles. All intensities are normalized to the room-temperature (293 K) signal.

Magnetic Field (mT)	123 K	173 K	223 K	293 K	323 K	373 K	423 K
324	0.05	0.05	0.05	0.05	0.05	0.05	0.05
325	0.05	0.05	0.05	0.05	0.05	0.05	0.05
326	0.05	0.05	0.05	0.05	0.05	0.05	0.05
327	0.05	0.05	0.05	0.05	0.05	0.05	0.05
328	0.05	0.05	0.05	0.05	0.05	0.05	0.05
329	0.05	0.05	0.05	0.05	0.05	0.05	0.05
330	0.05	0.05	0.05	0.05	0.05	0.05	0.05
331	0.05	0.05	0.05	0.10± 0.01	0.05	0.05	0.05
332	0.05	0.05	0.05	0.20± 0.01	0.05	0.05	0.05
333	0.05	0.05	0.05	0.30± 0.01	0.05	0.05	0.05

Magnetic Field (mT)	123 K	173 K	223 K	293 K	323 K	373 K	423 K
334	0.05	0.05	0.05	0.40± 0.01	0.05	0.05	0.05

The temperature-dependent EPR signal intensities of the 15 kGy-irradiated HCTZ sample are summarized in Table 4. In the low-temperature region (123–223 K), the signal intensity remains relatively constant and low (normalized intensity ~ 0.05), consistent with the Curie-law behavior where spin population increases with decreasing temperature. At room temperature (293 K), the signal intensity increases significantly (normalized intensity up to 0.40 at 334 mT), reflecting the expected thermal population of the spin states. In the high-temperature region (323–423 K), the signal intensity shows a further, albeit modest, increase compared to room temperature. This behavior suggests that the primary radical population is already well-established at room temperature, with only minor additional thermal generation or structural relaxation occurring at elevated temperatures.

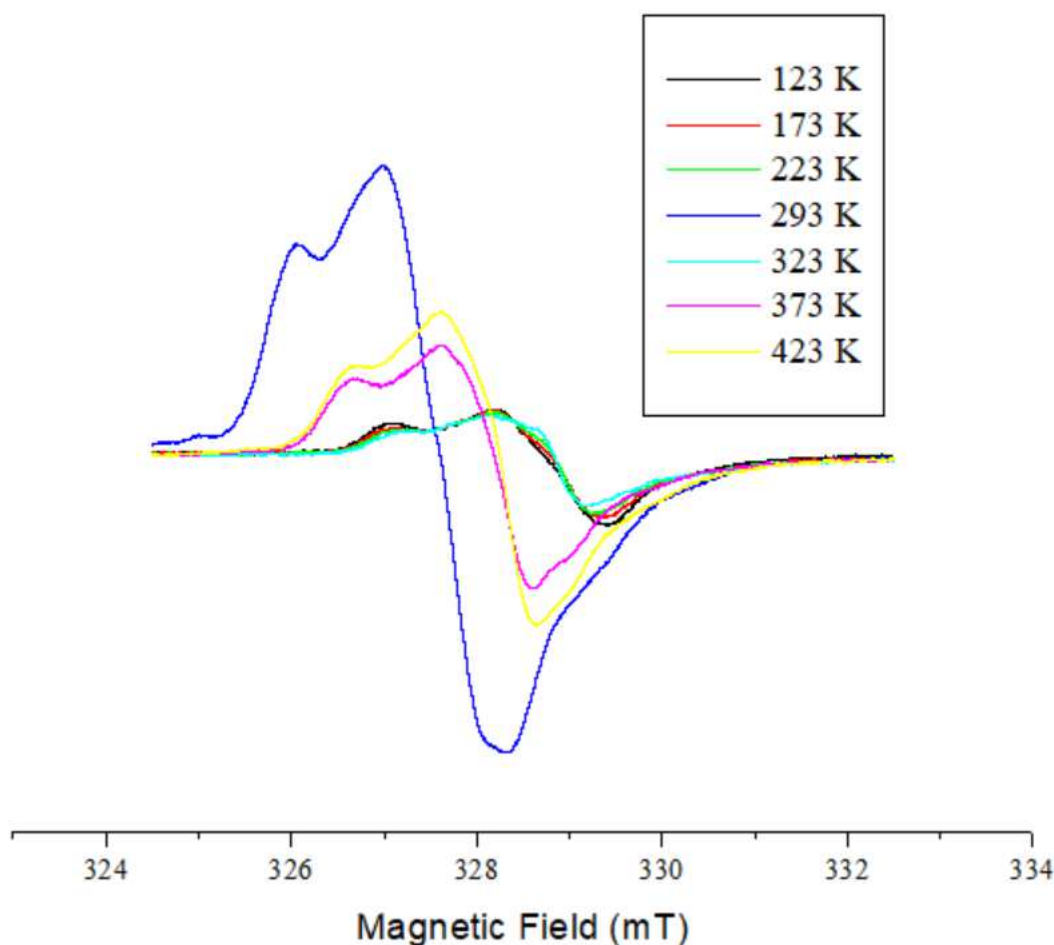


Figure 8b. Thermal hysteresis of the EPR signal intensity for the 15 kGy-irradiated HCTZ sample. The signal intensities recorded during the heating cycle (323 K $\rightarrow$ 423 K, $\circ$) are consistently higher than those recorded during the cooling cycle (423 K $\rightarrow$ 323 K, $\bullet$) at the same intermediate temperatures, indicating irreversible radical formation. The arrow highlights the magnitude of hysteresis at 373 K. Error bars represent the standard deviation from three independent measurements.

5. 5. DISCUSSION AND CONCLUSION

Hydrochlorothiazide (HCTZ) is a widely prescribed thiazide diuretic for hypertension and edema, and its high global usage makes its radiation stability relevant for pharmaceutical quality control [1, 10, 11]. Gamma-irradiated HCTZ samples exhibited a distinct EPR signal, whose intensity increased with dose while the spectral shape remained unchanged. The dose-response data were best described by a logarithmic function $I(D) = a + bD + cD^2$ with a coefficient of determination $R^2 = 0.9916$

Room-temperature fading studies showed a time-dependent decrease in signal intensity, with radical decay persisting up to day 172. The good agreement between the experimental spectra and those simulated using the extracted hyperfine parameters confirmed the reliability of the spectral analysis.

The absence of any EPR signal in non-irradiated samples and the well-defined dose-response curve are favorable results from a dosimetric perspective. For practical use, measurements within the first two days post-irradiation are recommended to minimize fading effects.

Temperature-dependent measurements (123–423 K) revealed that while spectral shapes remained similar, signal intensities varied significantly. At low temperatures (123–223 K), the intensity followed the Curie law ($I \propto 1/T$), while at high temperatures (323–423 K), a pronounced thermal hysteresis was observed, indicating irreversible secondary radical formation upon heating. These findings highlight the thermal stability limits of the HCTZ radical system and provide critical insights for its potential use as a solid-state dosimeter.

Funding The author declare that no funds, grants, or other support were received during the preparation of this manuscript.

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Figures

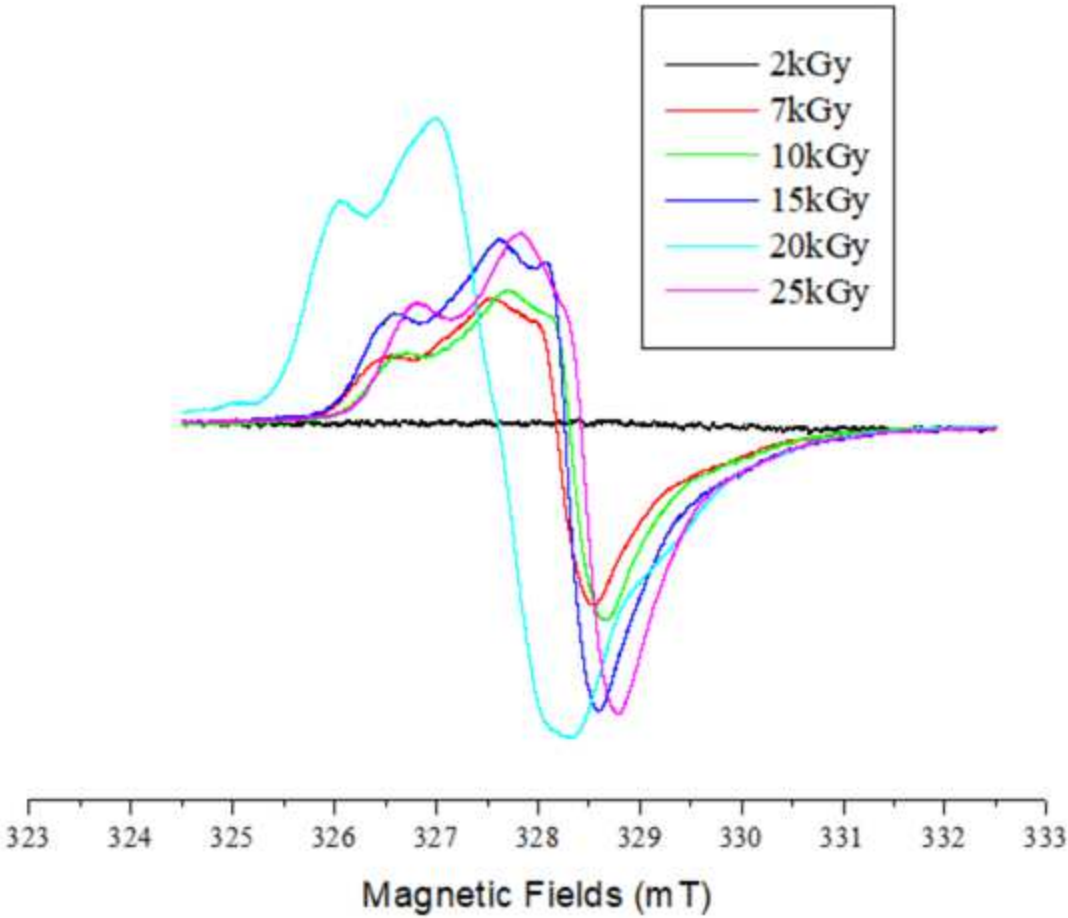


Figure 1

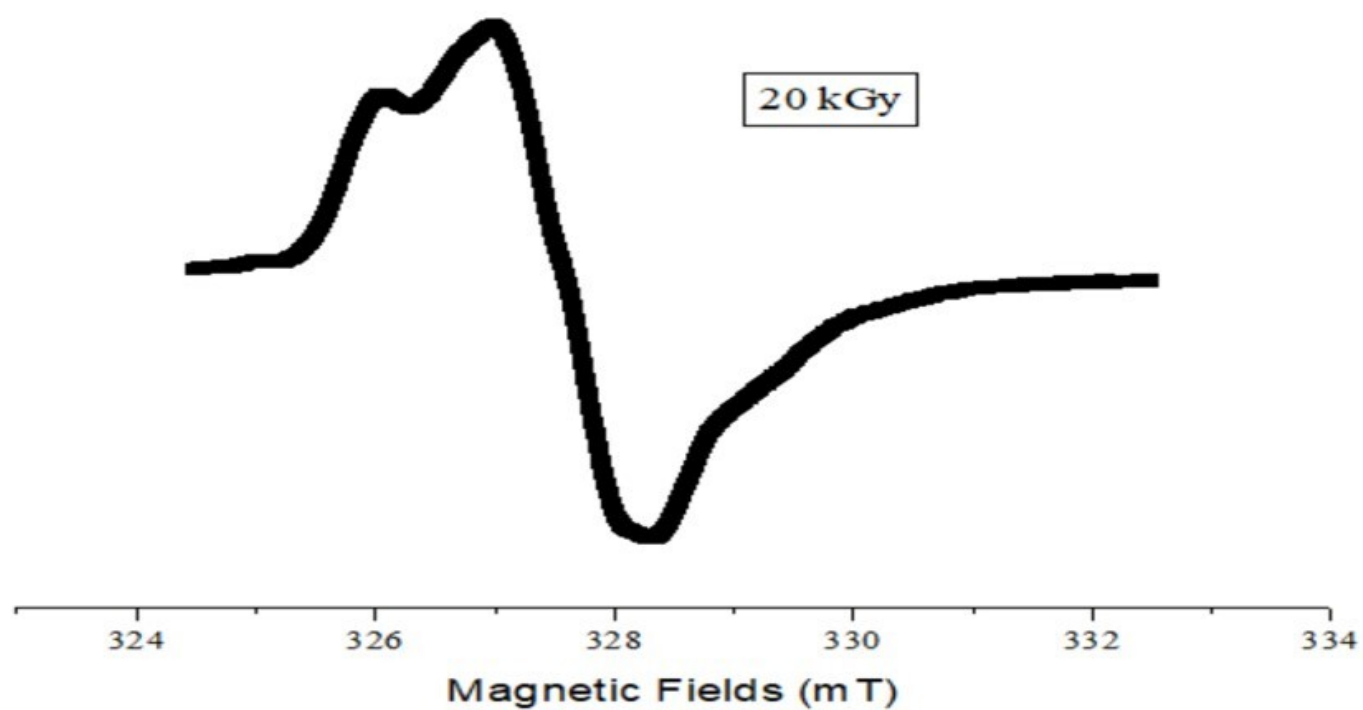


Figure 2

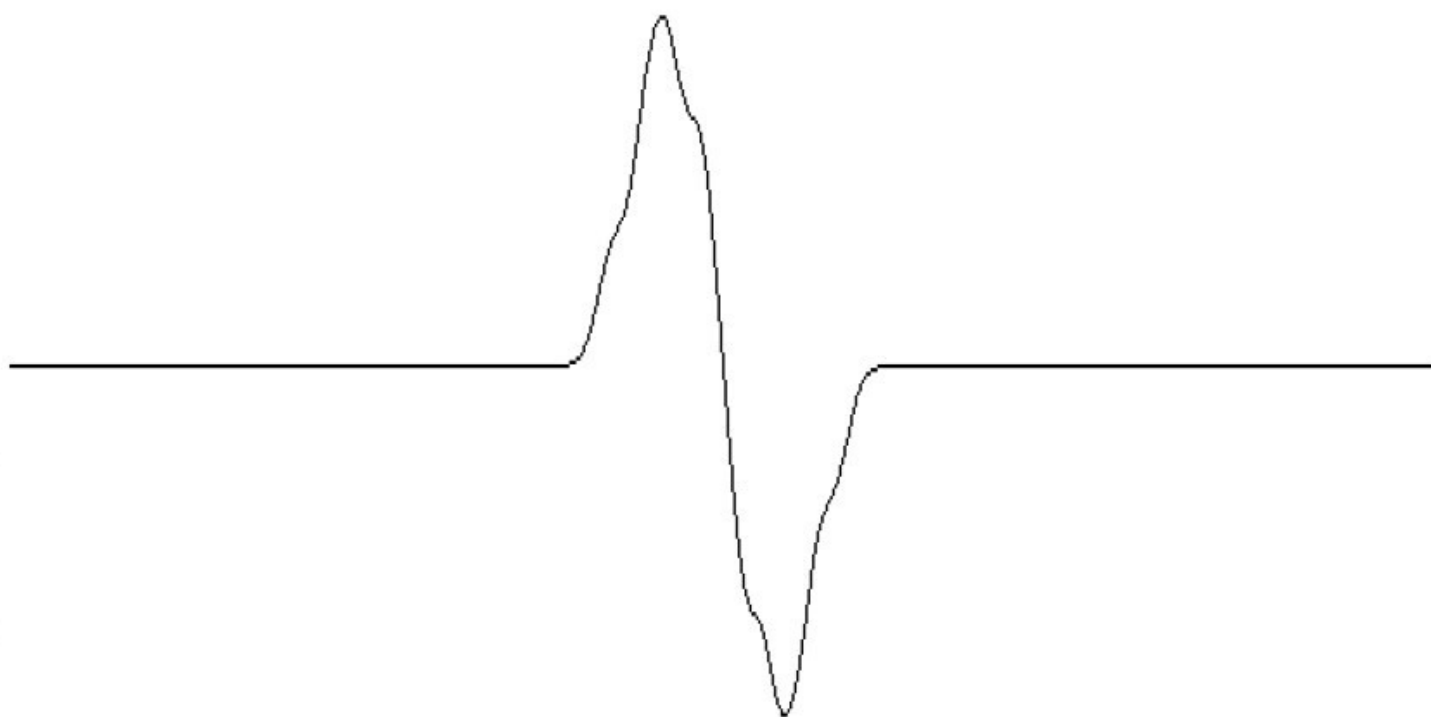


Figure 3

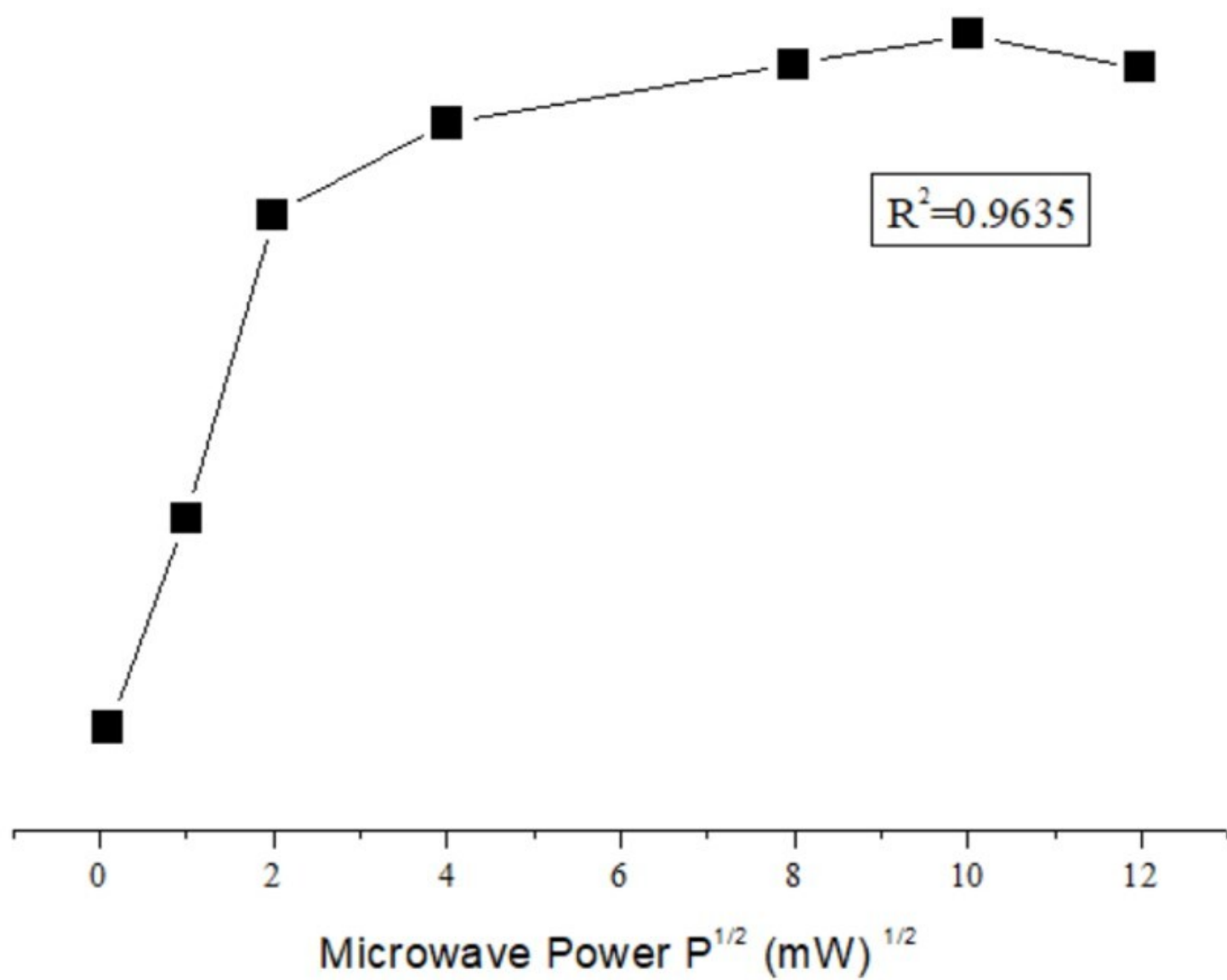


Figure 4

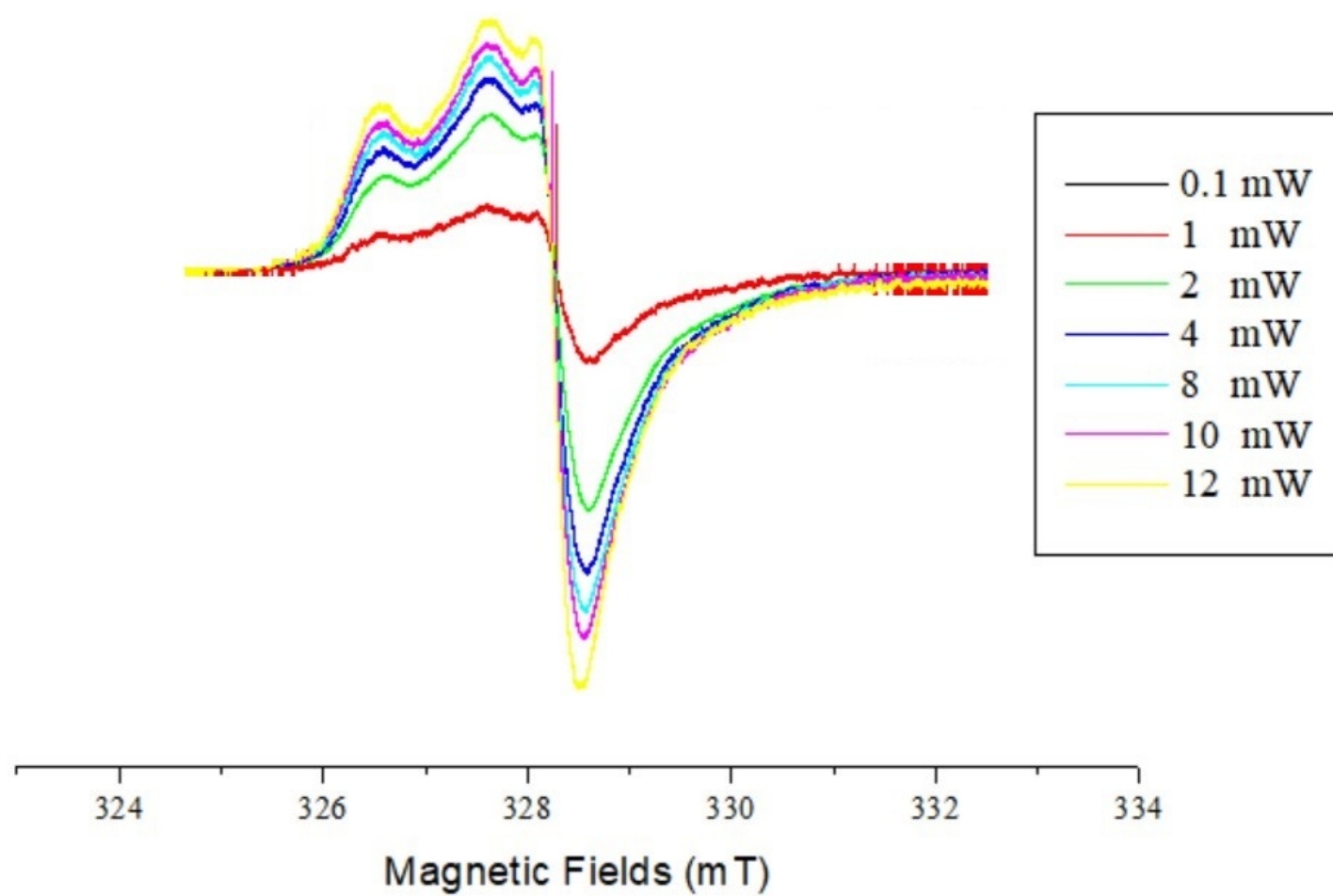


Figure 5

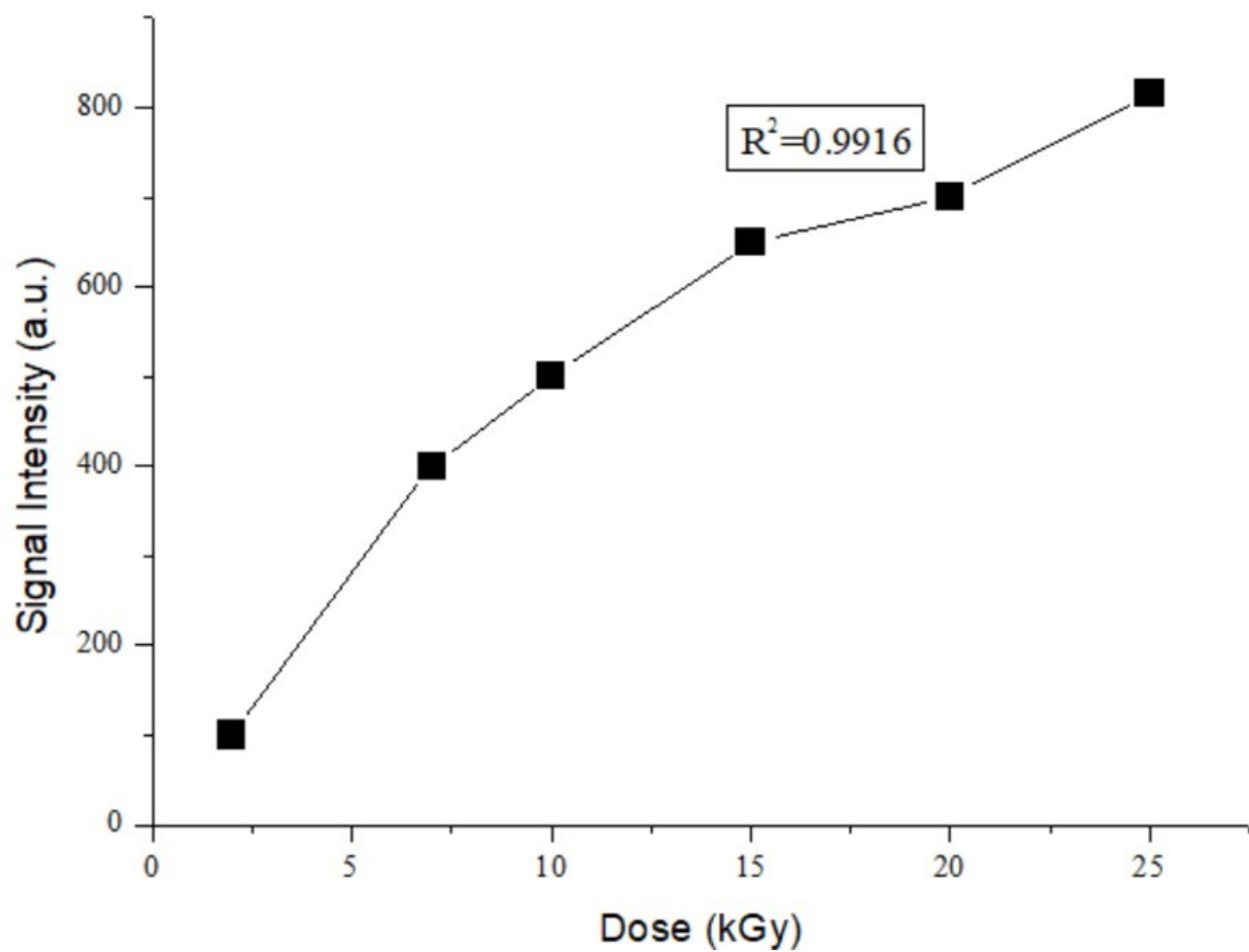


Figure 6

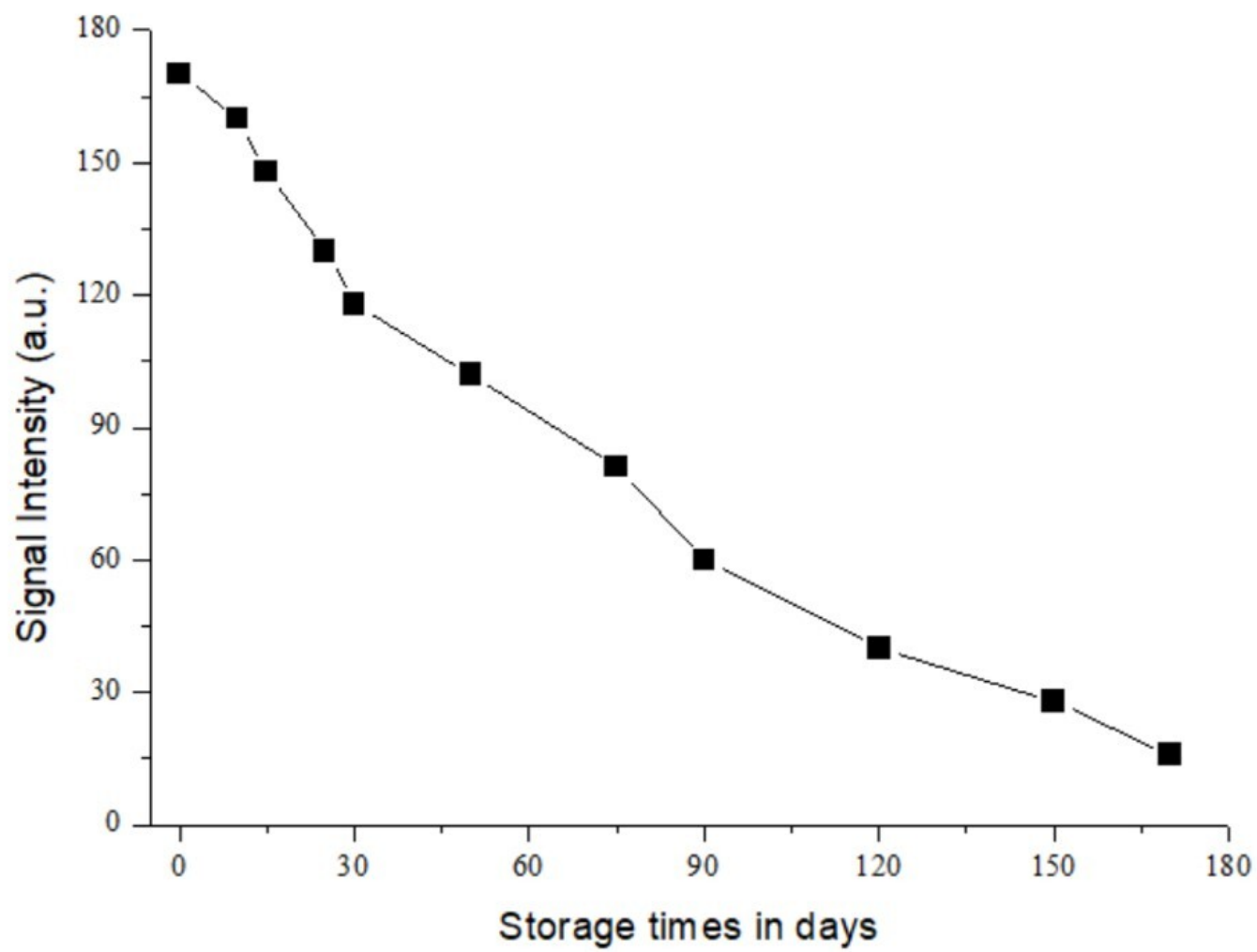


Figure 7

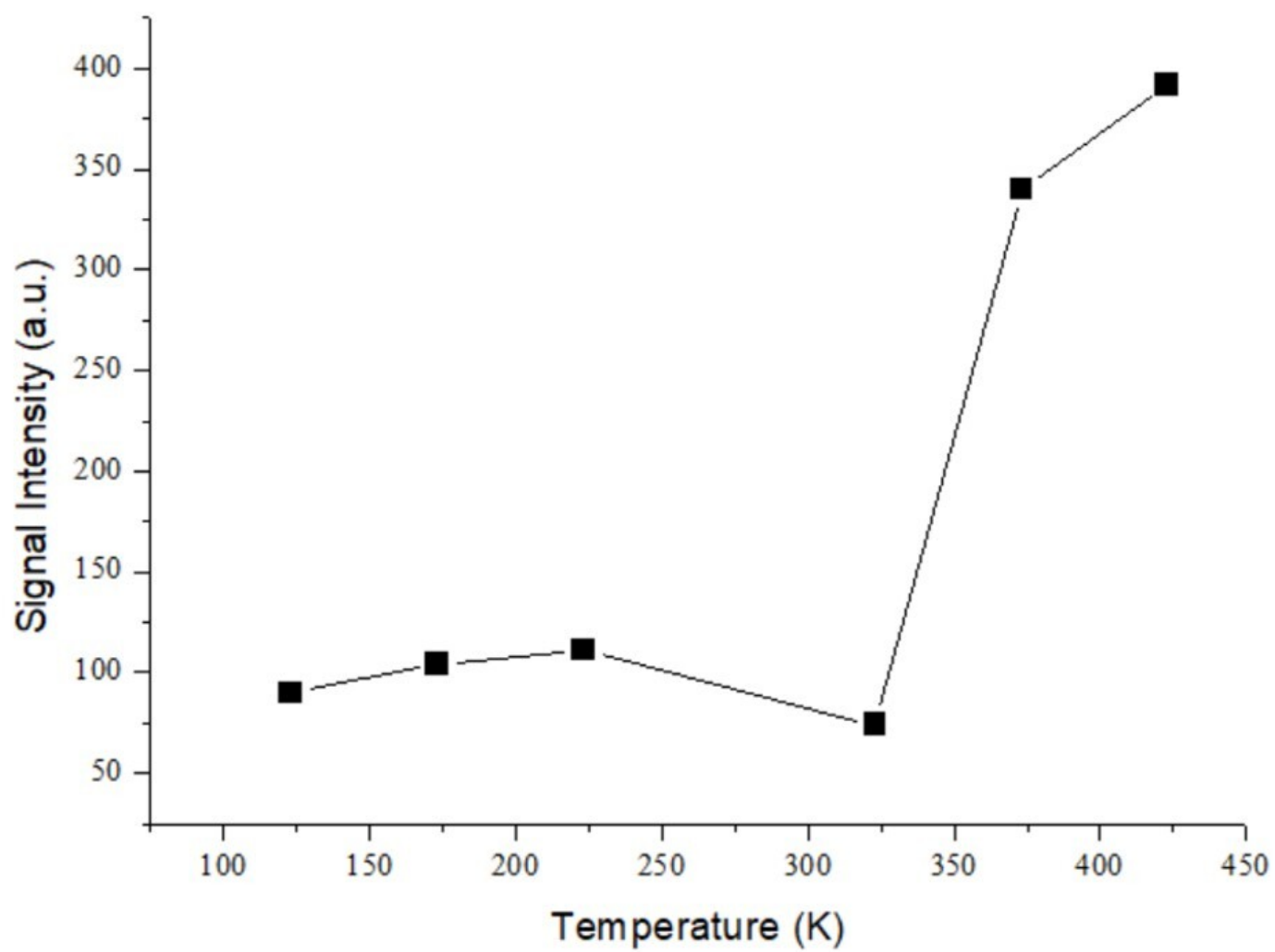


Figure 8

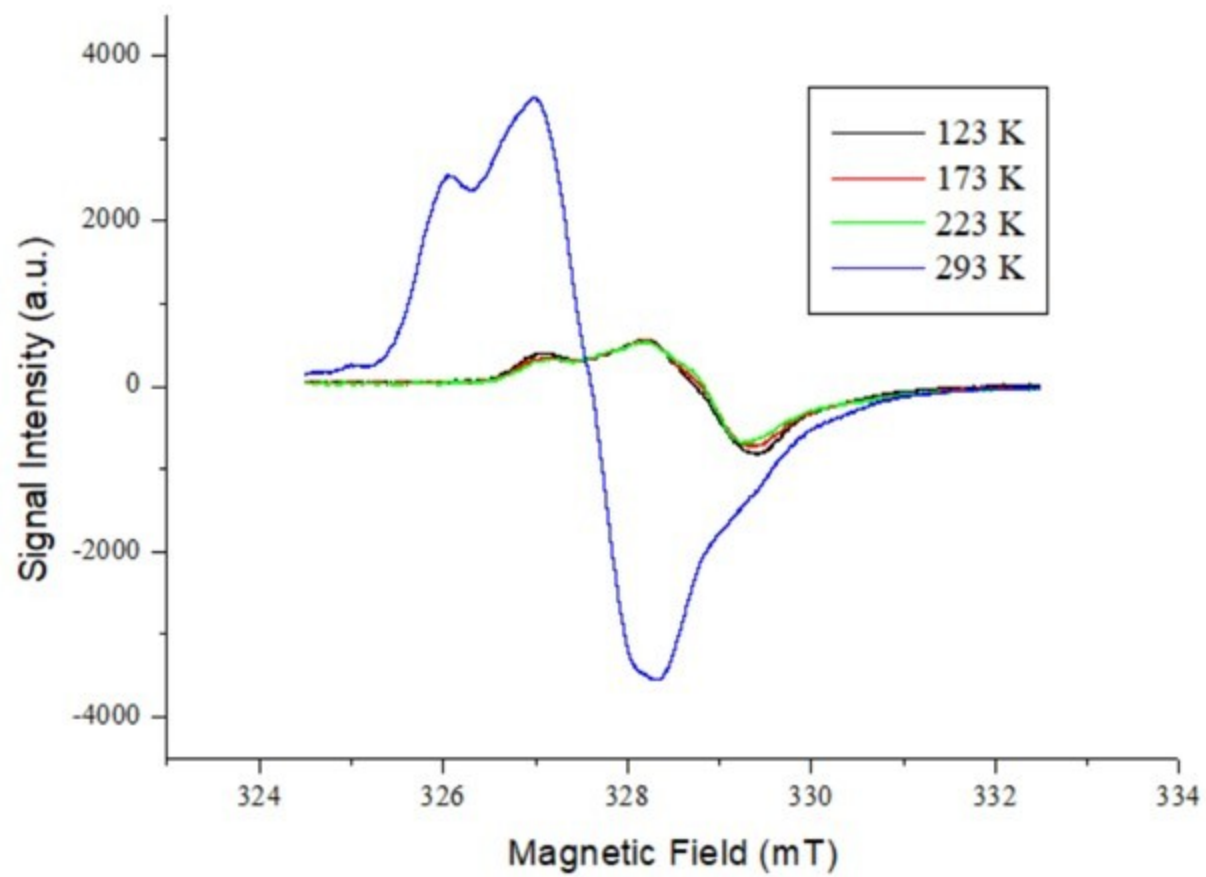


Figure 9

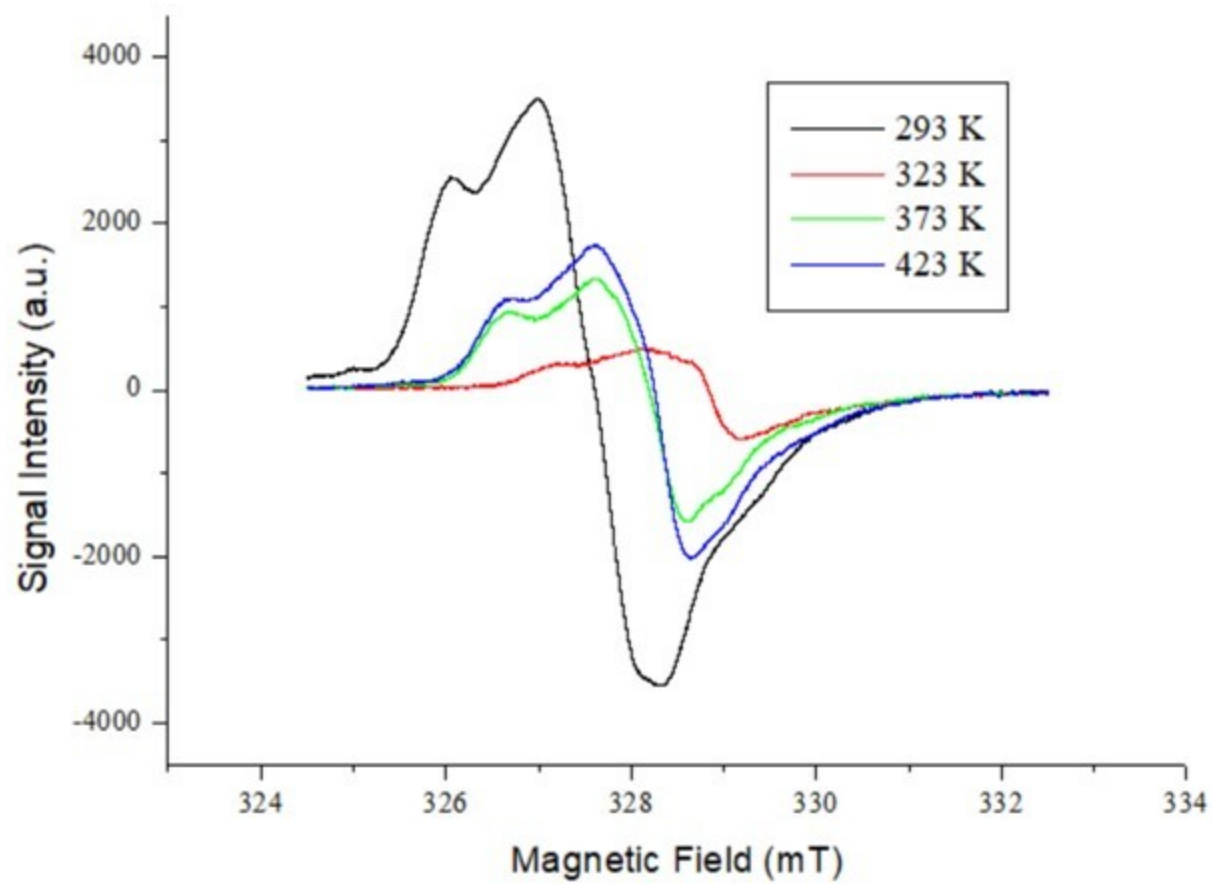


Figure 10

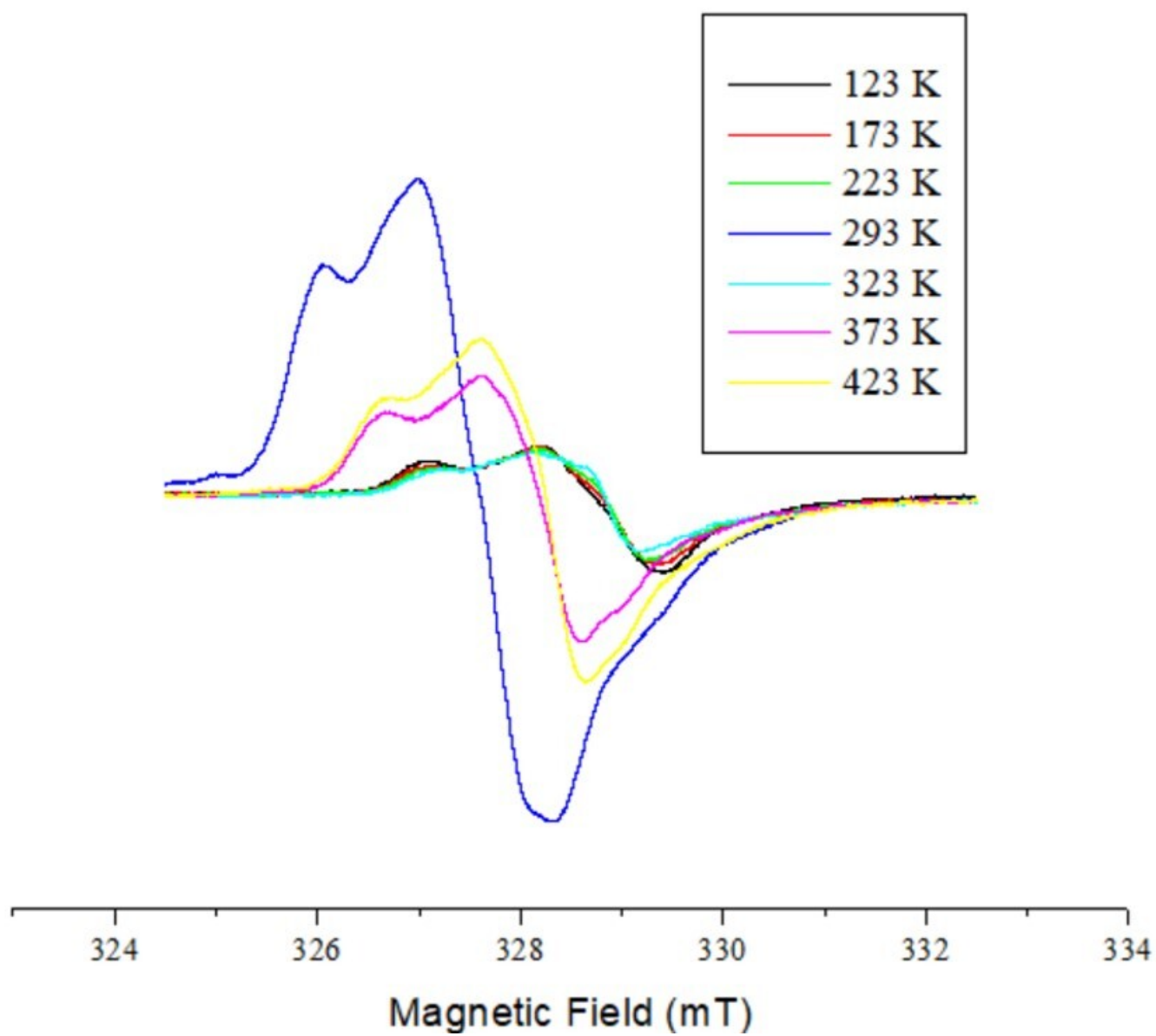


Figure 11

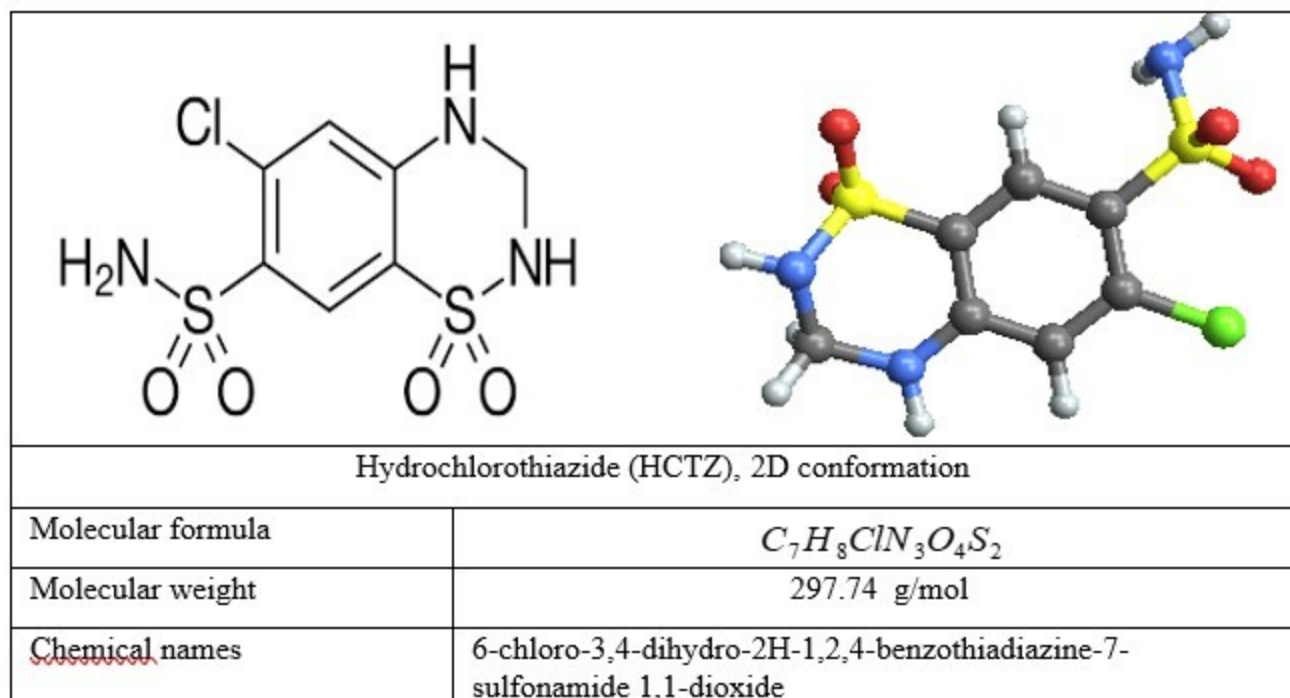


Figure 12

Microwave Power $\sqrt{P}(\text{mW})^{1/2}$	0.1	1	2	4	8	10	12
Signal Intensity (a.u.)	10.63	17.03	30.43	36.12	44.36	46.23	52.24

Figure 13

Function	Parameters	I
$I(D) = a(D)+b$ (Linear)	A	670.14
	B	147,18
	R^2	0.9867
$I(D) = a \ln(D)+b$ (Logarithmic)	A	203.32
	B	197.89
	C	-4.575
	R^2	0.9916
$I(D) = a+bD+cD^2$ (Polynomial)	A	242.49
	B	0.7839
	C	—
	R^2	0.98

Figure 14

~~0.0505~~ Magnetic Field (mT)	123 K	173 K	223 K	293 K	323 K	373 K	423 K
324	0.05	0.05	0.05	0.05	0.05	0.05	0.05
325	0.05	0.05	0.05	0.05	0.05	0.05	0.05
326	0.05	0.05	0.05	0.05	0.05	0.05	0.05
327	0.05	0.05	0.05	0.05	0.05	0.05	0.05
328	0.05	0.05	0.05	0.05	0.05	0.05	0.05
329	0.05	0.05	0.05	0.05	0.05	0.05	0.05
330	0.05	0.05	0.05	0.05	0.05	0.05	0.05
331	0.05	0.05	0.05	0.10± 0.01	0.05	0.05	0.05
332	0.05	0.05	0.05	0.20± 0.01	0.05	0.05	0.05
333	0.05	0.05	0.05	0.30± 0.01	0.05	0.05	0.05

Figure 15

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [table1600dpi.jpg](#)
- [Table2600dpi.jpg](#)
- [Table3600dpi.jpg](#)
- [Table4600dpi.jpg](#)