X-BAND EPR STUDIES OF GAMMA IRRADIATED A NEW ISOQUINOLINE SULFONAMIDE: $C_{17}H_{20}BrNO_3S$

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ABSTRACT: A new epoxyisoquinoline sulfonamide as a fused heterocycle compound (**I**), (4aS,7S,8aR)-8a-bromo-7-methyl-2-tosyl-2,3,4,7,8,8a-hexahydro-1H-4a,7-epoxyisoquinoline was synthesized using green and cascade progress which was then irradiated by ^{60}Co-gamma (γ) ray source with a dose speed of 0.981 kGy/h at the room temperature for 72h. EPR spectra of **I** compound were measured at different orientations in magnetic field with X-band EPR spectrometer along the temperatures between 150-340 K. Isotropic spectrum was obtained without depending on temperature and radical structure, $\dot{C}H_3H$ was observed. Radical was simulated using the Bruker software WinEPR-Simfonia and the experimental isotropic g-value with hyperfine coupling constant of radical was calculated.

Key Words: EPR, Irradiation effects, Radical, Synthesis, Sulfonamide.

Gama Işınları ile Işınlanmış Yeni Bir Isoquinoline Sulfonamide ($C_{17}H_{20}BrNO_3S$) Maddesinin X-Bant EPR Çalışması

ÖZ: Kaynaşık bir heteroksil bileşiği olan yeni epoxyisoquinoline sulfonamide maddesi (**I**), (4aS,7S,8aR)-8a-bromo-7-methyl-2-tosyl-2,3,4,7,8,8a-hexahydro-1H-4a,7-epoxyisoquinoline, yeşil ve kademeli bir süreç ile sentezlendi. Daha sonra doz hızı of 0.981 kGy/h olan ^{60}Co-gama (γ) kaynağı ile oda sıcaklığında 72 saat ışınlandı. **I** bileşiğinin EPR spektrumları, 150-340 K sıcaklık aralığında X-bant EPR spektrometresi kullanılarak manyetik alanda üç farklı yönelimde kaydedildi. Elde edilen sonuçlara göre, örneğe ait izotropik spektrumların olduğu görüldü ve $\dot{C}H_3H$ radikalinin varlığı gözlemlendi. Sonuçlar, Bruker WinEPR-Simfonia programı kullanılarak fit edildi. Radikalin aşırı ince yapı sabiti (A) ile deneysel izotropik spektroskopik değeri (g) hesaplandı.

Anahtar Kelimeler: EPR, Işınlama Etkileri, Radikal, Sentez, Sulfonamide.

1. INTRODUCTION

The Intra Molecular Diels–Alder cycloaddition of Furan, called IMDAF is one of the most widely used synthetic tool for the construction of heterocyclic ring systems since furan's diene character (Padwa and Flick (2013), Schindler and Carreira (2009), Takao *et al.* (2005), Brieger and Bennett (1980)). IMDAF process does allow obtaining usually fused heterocycles like isoquinoline which are extremely important in pharmaceutical field (Alonso and Garcia (2013)). Isoquinolines particularly are important heterocyclic

motifs; its derivatives also have been identified as ligands for a variety of receptors and as agents for the treatment of a number of pathologies (Glushkov and Shklyaev (2001), Dieudonne *et al.* (2012), Pettit *et al.* (2003)). On the other hand, sulfonamides are also widely used class of compounds as anti-inflammatory and antiviral agents, therefore general and efficient synthesis of sulfonamides under mild conditions is of continuing interest among pharmacists (Jafarppour *et al.* (2011), Supuran *et al.*(2003), Scozzafava *et al.* (2003), Greenfield and Grosanu (2008)).

Irradiation (gamma, UV, x-ray) has a significant role and widely used in organic and inorganic chemistry (Chatterjee and Mahata (2004), Yarbası *et al.* (2011), Yordanov and Aleksieva (2019)) such as sterilization of drugs, killing the pathogens in contaminated foods, producing free radicals or modification of physical properties etc. (Sayin *et al.* (2012), Asik *et al.* (2004)). The EPR spectroscopy is one of the most powerful methods for identifying irradiation damage centers over molecules containing unpaired electrons (Dereli *et al.* (2011), Usta *et al.* (2011), Karatas and Aras (2012), Eaton and Eaton (2008), Gordy (1980), Pshezhetskii and Kotov (1973), Atherton (1973)). Furthermore, this method has been in preference for a long time to produce paramagnetic centers for Electron Paramagnetic Resonance (EPR) technique in order to identification of paramagnetic defect centers and also provides a detailed description for structures mentioned above (Karatas *et al.* (2016), Yarbası *et al.* (2011), Yordanov and Aleksieva (2019), Sayin *et al.* (2012)). There are known two EPR parameters (g-value and hyperfine constant (A)) giving the most complete and valuable information about the geometry and electronic structure of radical species and centers (Dereli *et al.* (2011), Gordy (1980), Aras *et al.* (2014)).

In this study, we wish to report synthesis of new isoquinoline sulfonamide, N-(2-bromoallyl)-4-methyl-N-(2-(5-methylfuran-2-yl) ethyl) benzenesulfonamide, **I** using environmentally benign and one pot cascade sequence. The free radical was generated on the structure I by EPR using ^{60}Co-gamma (γ) ray source with a dose speed of 0.981 kGy/h for 72 hours at ambient temperature. Simulated EPR parameters were also calculated, compared with experimental result.

2. MATERIAL AND METHOD

2.1. Synthesis of (4aS,7S,8aR)-8a-bromo-7-methyl-2-tosyl-2,3,4,7,8,8a-hexahydro-1H-4a,7-epoxyisoquinoline (I) C17H20BrNO3S

One-pot protocol for the construction of complex heterocycle through furan tethered terminal bromoalkenes was afforded under catalyst free condition during the synthesis of isoquinoline sulfonamide (**I**). Compound **I** was obtained from overall four step reactions; in the first step, Henry reaction was carried out between **II** and nitromethane in the presence of base to give **III** in quantitative yield (Luzzio (2001)). Reduction of the nitrovinyl group from **III** with lithiumaluminum hydride under refluxing in tetrahydrofuran (THF) is the second step and produced **IV** in good yield. Resulting amine **IV** was then treated with 2,3-dibromopropene and potassium carbonate in THFn gave **V** in third step. In the last step, secondary amine, **V**, tosyl chloride and potassium carbonate were stirred in aqueous media and heated at 368 K for four days to afford **I** in 62% yields. This last step is a one pot cascade sequence in which sulfonyl part of the tosyl group attaches to nitrogen **VI** and followed by intramolecular Diels-Alder cycloaddition progress (Scheme 1).
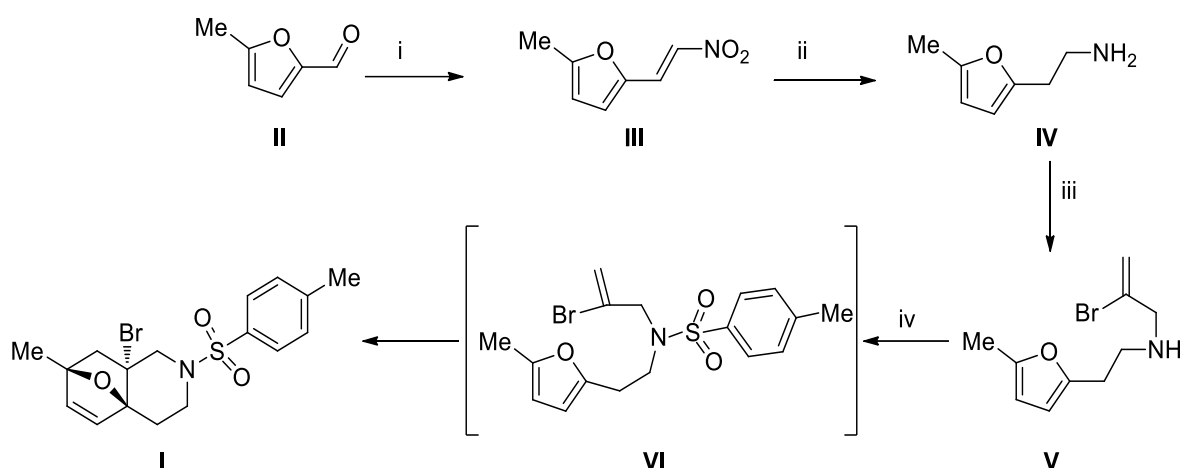
Scheme 1. Synthesis of $C_{17}H_{20}BrNO_3S$: (i. CH_3NO_2, NaOH, Acetone, 273 K, 95%; ii. LiAlH$_4$, THF, reflux, 4h, 72%; iii. 2,3-dibromopropene, K_2CO_3, 4 days, 85%; iv. Tos-Cl, H_2O, K_2CO_3, 4 days, 368 K, 62%).

2.2. Procedure for (4aS,7S,8aR)-8a-bromo-7-methyl-2-tosyl-2,3,4,7,8,8a-hexahydro-1H-4a,7-epoxyisoquinoline ($C_{17}H_{20}BrNO_3S$) I:

Reactions requiring anhydrous conditions were conducted in flame dried or oven dried apparatus under atmosphere of a dry nitrogen except last step. All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise stated. Tetrahydrofuran (THF) was dried by distillation from sodium / benzophenone under an atmosphere of nitrogen and stored over activated 4Å molecular sieves. ChemBioDraw Ultra V12 programme was used for nomenclature of molecules according to IUPAC rules.

IR Spectrum was taken in Niğde Ömer Halisdemir University Research Laboratory on Perkin Elmer BXII, ^{1}H Nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz on a Bruker DPX 400 instrument in Selçuk University. Chemical shifts are reported in parts per million (ppm) relative to residual CHCl$_3$ (δ 7.27ppm) or tetramethylsilane as the internal reference (δ 0.00 ppm). The following abbreviations are used to describe the multiplicity of a given signal: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sex = sextet, m = multiplet, br = broad. Coupling constants, J, are given in Hertz. ^{13}C Nuclear magnetic resonance spectra were recorded either at 100.78 MHz on a Jeol Ex400 FTNMR instrument or at 75.43 MHz, on a Bruker DPX 400 instrument. Chemical shifts are reported in parts per million (ppm) relative to CDCl3 (central line of triplet δ 77.0 ppm).

2-Bromo-N-(2-(5-methylfuran-2-yl) ethyl) prop-2-en-1-amine **V** (0.65g, 2.66mmol, 1equivalent) and Tosyl chloride (0.6g, 3.20 mmol, 1.2 equivalent) were dissolved in 50 mL distilled water. Potassium carbonate (0.46g, 3.2mmol, 1.2 equivalent) were added and the reaction mixture was stirred at 368 K for four days. The reaction mixture was cooled to room temperature then ethyl acetate (100 mL) was added, followed by extraction of aqueous phases using 2x50 mL ethyl acetate. Combined organic phases was evaporated, resulting residue was turned to brown solid phase, which was recrystallized employing dichloromethane, hexane mixture. The titled compound was collected as pale-yellow crystals 0.66g, 62% yield.

IR: υ$_{max}$ (thin film)/cm^{-1} :3014(w,C-H) , 2948(s,C-H), 1585 (w, C=C) ,1479(m,C-N), 708(C-Br), ^{1}H NMR (400 MHz, CDCl$_3$, δ ppm): 7.60(d, J 8Hz, 2H), 7.26 (d, J 8Hz, 2H), 6.23(d, J 5.6 Hz, 1H), 6.07(d, J 5.6 Hz, 1H), 4.07(d, J 2Hz, 1H), 3.85(d, J 2Hz, 1H), 2.64(m, 2H), 2.52(m, 2H), 2.36(s, 3H), 1.95(d, J 12.8Hz, 1H), 1.71(d, J 12.8Hz, 1H), 1.44(s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$, δ ppm): 143.9, 140.1, 138.1, 134.2, 129.9(2xC), 127.8(2xC), 87.4, 87.2, 60.3, 58.8, 48.7, 42.7, 25.4, 21.8, 19.1.

2.3. EPR Measurements

In this study, its polycrystal form was produced, after synthesis of isoquinolin sulfonamide **I**. This polycrystal sample was irradiated at room temperature for 72h using ^{60}Co gamma (γ)-ray source with dose speed of 0,981 kGy/h at Saraykoy Establishment of Turkish Atomic Energy Agency (TAEK) in Ankara. Afterwards, the EPR spectra of isoquinolin sulfonamide **I** were recorded between 150K and 340K in the magnetic fields using Bruker EMX 081 (Germany) X-Band EPR spectrometer. EPR measurements were performed at 150 K in steps of 10º intervals along each of three perpendicular planes (x, y, z) during the experiment using temperature control unit of EPR spectrometer. The spectrometer was set as follows: the microwave power was 4mW, the modulation frequency was 100kHz, and modulation amplitude was 4G. Low and high temperature measurements were performed using variable temperature-control unit of EPR spectrometer. Radical was simulated by using the Bruker software WinEPR-Simfonia and the g value of radical was found by comparison with a DPPH sample (g= 2.0036) (Weil and Wertz (1994), Ceylan *et al.* (2013), Ceylan *et al.* (2015),).

3. RESULTS AND DISCUSSION

EPR signals were not detected on non-irradiated isoquinolin sulfonamide **I** compound, so the sample irradiated for 72h by using ^{60}Co gamma (γ)-ray source and about 71kGy dose have been used for investigating of free radical in isoquinolin sulfonamide **I**. After irradiation, recorded EPR signals showed that free radical was produced over the sample by gamma irradiation. EPR signals of free radical produced by γ-irradiation in **I** compound were able to observe between 150K- 340K temperatures (Figure 2.). The best spectra of isoquinolin sulfonamide **I** was observed at 150K, so we recorded detailed EPR spectra for three mutually perpendicular axes by rotating the crystals around the x, y and z crystallographic axes in steps of 10º at 150K during the experiment using temperature control unit of EPR spectrometer (Figure 1.).
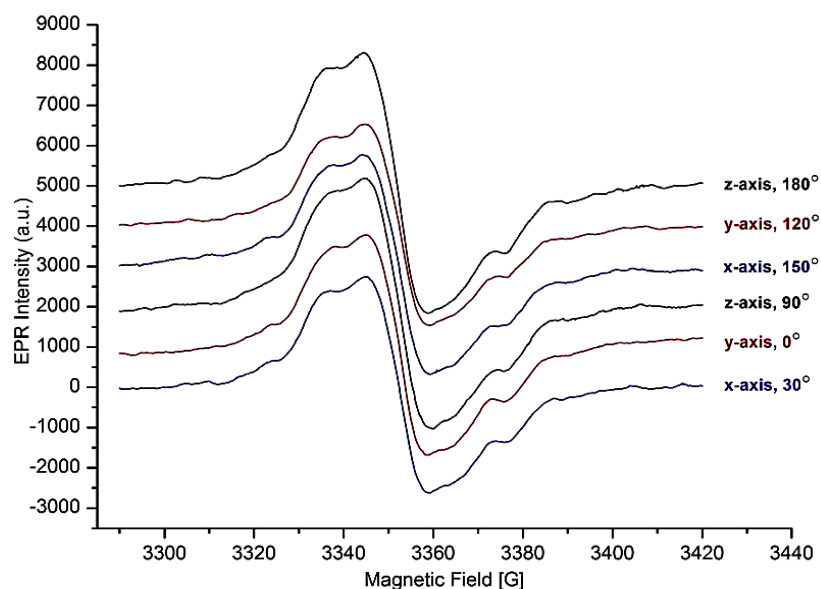
Figure 1. The EPR spectra of gamma (γ)-irradiated isoquinolin sulfonamide **I** at different angles towards the x, y, z axes in magnetic field at 150K.

These measurements showed that only a single peak was observed in these ranges. And also, the distances between the lines were similar and isotropic behaviors were shown in the spectra. It was understood that isotropic properties were observed due to spectra were independent on the magnetic field in the planes which are perpendicular to each other (Figure 1.). In addition to the shapes and intensities

of the lines in the spectra were not changed along with temperature (Figure 1.), so it was deduced that isotropic spectrum was obtained without depending on temperature and radical structure, too.
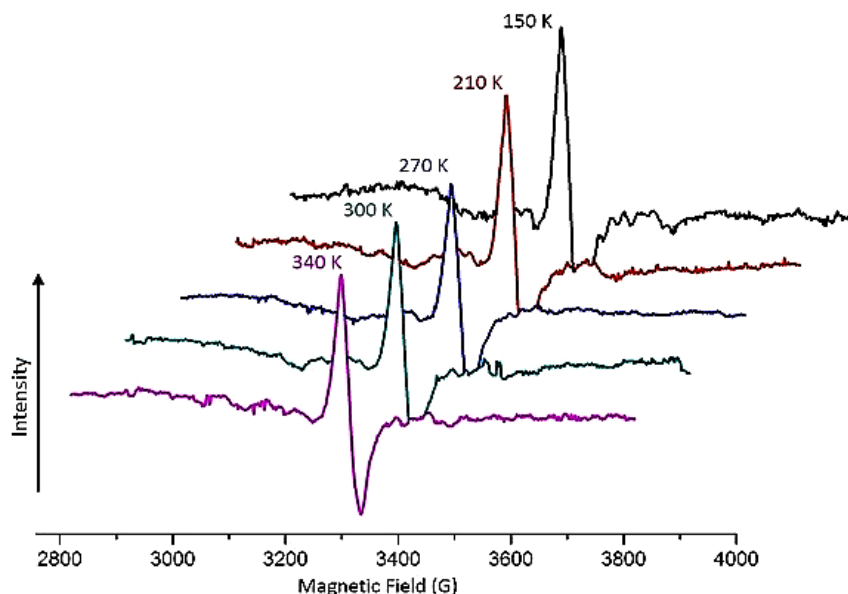
Figure 2. The temperature dependency of EPR spectrum of gamma (γ)-irradiated isoquinolin sulfonamide **I**.

Taking account to recorded EPR spectra and molecular structure, it was deduced that one radical structure was formed under the gamma-rays. The free radical in **I** compound was identified as $\dot{C}H_3H$. After the conduct of an in-depth analysis, it was determined that the spectrum was splitted into 1:3:3:1 intensity ratio from hydrogen atoms in CH_3 ($I_H=1/2$) according to $2nI+1$ formula firstly, because H protons directly attached to the carbon (C). Then each of these lines was splitted into 1:1 intensity ratio due to the other hydrogen atom which is magnetically nonequivalent in CH_3. Therefore spectrum slightly changed due to the overlap and also all splitting were observed 1:4:6:4:1 intensity ratios. As a result, we obtained the computer simulation of spectra (Figure 3.) which gives the best agreement with our experimental values and we attributed these spectra to $\dot{C}H_3H$ radical.
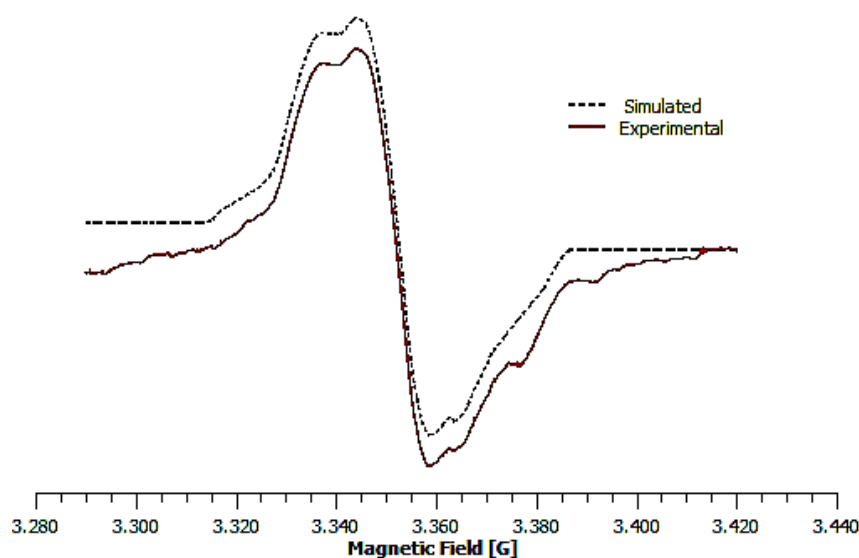
Figure 3. The EPR spectrum of gamma (γ)-irradiated $C_{17}H_{20}BrNO_3S$ polycrystal when the magnetic field oriented to yz plane at angle of 0° and its simulation.

The compound **I** was characterized spectroscopically, well defined and peaks in excellent agreement with the structure which was then taken into EPR analyze. In the most cases the EPR spectra of radical from isoquinolin sulfonamide **I** were poorly resolved, and the hyperfine coupling constants were deduced from the overall width and intensities distributions then verified by computer simulation. Isotropic g-factor was calculated as 2,005841 by resonance equation ($h\nu=g\beta H$) and isotropic hyperfine coupling constants were determined A_{CH3}= 27,12 G, A_H= 15,93 G from the experimental spectra of radical. These parameters were then slightly modified until a reasonable agreement between simulated and experimental spectra was reached (Figure 3.).

4. CONCLUSIONS

A new isoquinoline sulfonamide **I** was efficiently synthesized using an environmentally benign cascade methodology and its radicalic behavior was investigated by EPR. Non-irradiated isoquinoline sulfonamide **I** polycrystal did not give any EPR signal and have stability. The radical generated on isoquinoline sulfonamide **I** and measurement at 150-340 K by gamma irradiation at EPR shows isotropic hyperfine coupling constants and g-factors were determined in this investigation. We observed that the simulation and experimental result are in good harmony. The simulation we used here, promises to be employed more efficiently on different substances as well.

5. ACKNOWLEDGE

REFERENCES

Alonso, R., and N-Garcia, O, 2013, *J. Org. Chem.,* Vol. 78, pp. 2564-2570.

Aras, E., Karatas, O., Meric, Y., Abbass, H.K., Birey, M., and Kılıc, A., 2014, *Radiat. Effects&Defects in Solids,* Vol. 169(9), pp. 754-758.

Asik, B., Aras, E., Caliskan, B., Eken, M., and Birey, M., 2004, *Radiat. Eff. Def. Solids,* Vol. 159, pp. 55-60.

Atherton, N.M., 1973, "Electron Spin Resonance", *John Wiley&Sons,* New York.

Brieger, G., and Bennett, J.N., 1980, *Chem. Rev.,* Vol. 80, pp. 63-97.

Ceylan, Usta, A., Usta, K., Durmaz, F., and Coskun, A.,2013, *J. Mol. Struct.,* Vol. 1050, pp. 69-72.

Ceylan, Y., Usta, K., Usta, A., Aydogmus, H.Y., and Guner, A., 2015, *J. Mol. Struct.,* Vol. 1100, pp. 180-183.

Chatterjee, D., and Mahata, A., 2004, *J. Photochem. Photobiol. A.,* Vol. 165, pp. 19-23.

Dereli, O., Türkkan, e., Özmen, A., and Yüksel, H., 2011, *Radiat. Phys. And Chems.,* Vol. 80, pp. 742-749.

Dieudonne-Vatran, A., Azoulay, M., and Florent, J.-C, 2012, *Org. Biomol. Chem.,* Vol.10, pp. 2683-2691.

Eaton, S.S., and Eaton, G.R, 2008, *R. Soc. Chem.,* Vol. 21, pp. 59-75.

Glushkov, V.A., and Shklyaev, Y.V., 2001, *Chem. Heterocycl. Compd.,* Vol. 37, pp. 663-687.

Gordy, W., 1980, "Theory and Applications of Electron Spin Resonance", *John Wiley&Sons,* New York, Toronto.

Greenfield, A., and Grosanu, C., 2008, *Tetrahedron Lett.,* Vol. 49, pp. 6300-6303.

Jafarppour, M., Rezaeifard, A., and Golshani, T., 2011, *Phosphorus, Sulfur Silicon Relat. Elem.,* Vol. 186, pp. 140-148.

Karatas, O. and Aras, E., 2012, *J. Mol. Struct.,* Vol. 1027, pp. 49-52.

Karatas, O, Aras, E., Karadag, A.H., and Islek, Y., 2016, *Radiat. Effects&Defects in Solids,* Vol. 171(7-8), pp. 651-657.

Luzzio, F.A., 2001, *Tetrahedron,* Vol. 57, pp. 915-945.

Padwa, A. And Flick, A.C., 2013, *Adv. Hererocycl. Chem,* Vol. 110, pp. 1-41.

Pettit, G.R., Meng, Y., Herald, D.L., Graham, K.A.N., Pettit, R.K., and Doubek, D.L., 2003, *J. Nat. Prod.,* Vol. 66, pp. 1065-1069.

Pshezhetskii, S. Ya., and Kotov, A.G., 1973, "EPR of Free Radicals in Radiation Chemistry", *John Wiley&Sons,* New York.

Sayin, U., Dereli, O., and Türkkan, E., 2012, *J. Mol. Struct.,* Vol. 1007, pp. 179-184.

Schindler, C.S. and Carreira, E.M., 2009, *Chem. Soc. Rev.,* Vol. 38, pp. 3222-3241.

Scozzafava, A., Owa, T., Mastrolorenzo, A., and Supuran, C.T., 2003, *Curr. Med. Chem.,* Vol. 10, pp. 925-953.

Supuran, C.T., Casini, A., and Scozzafava, A., 2003, *Med. Res. Rev.,* Vol. 5, pp. 535-558.

Takao, K.-i., Munakata, R. And Tadano, K.-i., 2005, *Chem. Rev.,* Vol. 105, pp. 4779-4807.

Usta, A., Filiz, A., Birey, M., and Ozmen, A., 2011, *Concepts Magn. Reason. Part A,* Vol. 38(3), pp. 102-106.

Weil, J.A., and Wertz, J.R., 1994, Electron Paramagnetic Resonance Elemantary Theory and Practical Applications, *John Wiley&Sons Inc.,* New York.

Yarbası, Z., Karabulut, B., and Karabulut, A., 2011, *Spectrochimica Acta Part A,* Vol. 83, pp. 337-339.

Yordanov, N.D. and Aleksieva, K., 2019, *Radiation. Phys. Chem.,* Vol. 78, pp. 213-216.