Organic Compound with Potential for X-ray Imaging Applications

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ABSTRACT: A radiopaque compound, namely, 4,4-bis(4-hydroxy-3,5-diiodophenyl)pentanoic acid, was synthesized by the electrophilic aromatic iodination of 4,4-bis(4-hydroxyphenyl)pentanoic acid using sodium iodide and sodium hypochlorite. The active iodines created by hypochlorite were selectively bound to the ortho positions of the diphenolic acid and obtained a tetraiodo compound. Characterization of this iodinated compound was accomplished by routine methods such as Fourier transform infrared (FTIR) spectroscopy, 1H nuclear magnetic resonance (NMR) spectroscopy, energy-dispersive X-ray spectroscopy, mass spectroscopy, UV−Vis spectroscopy, and thermogravimetry. The iodine content in the compound was as high as 64% by weight and therefore expected to possess substantial radiopacity. A 5% solution of the compound in dimethyl sulfoxide exhibited radiopacity of 885 ± 7 Hounsfield Units when tested with computed tomography (CT) scanner. In vitro cytotoxicity test performed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay demonstrated that the compound was nontoxic to L929 fibroblast cells up to the level of 0.8 mg/mL concentration. Overall results indicate that this highly radiopaque compound has the potential to be used for X-ray imaging in the clinical scenario.

1. INTRODUCTION

Medical imaging plays a crucial role in the diagnosis and treatment of diseases. A myriad of reports in the literature indicates the importance of developing radiopaque compounds for imaging applications.1−17 Radiopaque compounds along with some polymers find applications in imaging body organs,2−9 detection or diagnosis of various diseases, monitoring embolization processes,1,10,11 construction of implants used in surgery,1,12,13 and dental compositions.1,14 Lei et al. reported the development of a radiopaque thermoreversible hydrogel for preventing postoperative adhesions.5 Recently, Wu et al. designed a macromolecular contrast agent with “ultrahigh radiopacity” through the polymerization of iodinated trimethylene carbonate monomer and poly(ethylene glycol).8 Contrast agents used in diagnosis are radiopaque compounds, and they generally fall into two categories: ionic and nonionic.18 The ionic compounds used for intravascular use have a high osmolarity.19 This is responsible for several adverse effects such as pain, endothelial damage, thrombosis, etc. But nonionic compounds are less hyperosmolar solutions. However, they are expensive and exhibit a high rate of adverse events.

Compounds containing multiple iodine atoms, usually three per compound, have been used as radiopaque agents.20−22 A high iodine concentration is used to achieve opacification around 250−300 Hounsfield units (HU) in the thoracic aorta and 300−350 HU in the coronary arteries.23 The radiodensity of iodinated contrast is 25−30 (HU) per milligram of iodine per milliliter at a tube voltage of 100−200 kVp. This substituent is pharmacologically acceptable, which enables the compound to be administered to man or animal. These compounds were found to have sufficient tolerance to the human organ system also. For this purpose, nonionic structures have been suggested, i.e., iodobenzene derivatives possessing nonionic substituent. Iodination involves an electrophilic aromatic substitution in which aromatic constituents that have an electron-donating group can sufficiently activate the carbons on the ring. Therefore phenols, aniline derivatives, or alkyl aniline that contain OH, NH2, or NHR constituents easily undergo iodination. There are different reported techniques for iodination. Edgar and Steinmetz reported an iodination technique for hydroxyl aromatic and amino aromatic compounds using metal iodide and metal hypochlorite.24 Another technique using iodine monochloride was reported by Filimonov et al.25 Reporting new nontoxic compounds with a high level of radiopacity to the scientific literature would pave the way for...

Received: July 12, 2021
Published: September 16, 2021
further advancements in the area of radioimaging and diagnostics. In this work, we report the synthesis of 4,4-bis(4-hydroxy-3,5-diiodophenyl) pentanoic acid (IBHP) by the iodination of 4,4-bis(4-hydroxyphenyl)pentanoic acid (BHP). Four iodine atoms present in the compound would impart a high level of radiopacity to the compound, and the presence of reactive carboxyl functionality enables further modification of the compound through grafting to a polymer or by coupling with other molecules. Bolikal et al. mentioned the use of IBHP as a monomer for the synthesis of biocompatible polymers for medical devices. However, no information is available on the properties of this compound. Patel et al. synthesized chlorine- and bromine-substituted derivatives of 4,4-bis(4-hydroxyphenyl)pentanoic acid and tested their antifungal properties. Here, we report the synthesis of IBHP by adopting a simple process and using inexpensive reagents and mild reaction conditions. The compound was characterized in detail to evaluate its potential for X-ray imaging applications.

2. RESULTS AND DISCUSSION

2.1. Spectral and Thermal Characterization of IBHP. 4,4-Bis(4-hydroxyphenyl)pentanoic acid (BHP) was iodinated by adopting a similar procedure reported by Kiran et al. Here, we used 6 equiv each of sodium iodide and sodium hypochlorite to achieve tetra iodination of BHP (Scheme 1).

Iodination occurred through in situ oxidation of sodium iodide in methanol in the presence of sodium hypochlorite. When 2 g of BHP was reacted with 6 equivalents each of sodium iodide and sodium hypochlorite, the yield of the product was 6 g. This was the expected yield if tetra iodination had taken place. The tetra iodination of BHP was also confirmed by $^1$H nuclear magnetic resonance (NMR) analysis (500 MHz, dimethyl sulfoxide (DMSO)-d$_6$). Since the hydroxyl group is ortho and para directing, the substitution takes place in the ortho position of BHP. Due to the steric hindrance of bulky iodine atoms in the ring, the possibility of further iodination was limited. The NMR spectra of the parent compound (BHP) and product (IBHP) are shown in Figures 1 and 2, respectively. A singlet at 12 ppm corresponds to the carboxylic acid proton. A singlet at 9.18 ppm in BHP corresponds to the phenolic group. Due to iodination, the phenolic peak shifts to a lower field (9.48 ppm) in IBHP. The peaks near 2 ppm in both BHP and IBHP indicate an alkyl group. The chemical shift due to aromatic protons in BHP at $\delta = 6.65$ and 6.9 ppm were absent in IBHP and a new peak at $\delta = 7.45$ ppm was observed in IBHP. This downfield shift in IBHP in comparison to BHP confirmed the presence of four electron-withdrawing iodine atoms at ortho from the $-OH$ group. A similar kind of downfield shift was observed in 4,4′-isopropylidene bis(2,6-bromophenol) and 4,4′-isopropylidenedi(2,6-diiodophenol). These are indications of iodination.

The presence of iodine in the IBHP was elucidated by energy-dispersive X-ray spectroscopy (EDAX) (Figure 3). In the EDAX spectrum of IBHP, the peaks corresponding to carbon, oxygen, and iodine were obtained. The peaks at about 3.5–5 keV confirmed the existence of iodine atoms in the molecule. The weight of iodine obtained (64.9%) from the EDAX spectrum was very close to the theoretically calculated iodine content (i.e., 64% by wt). The atom % of iodine obtained (i.e., 15.5) also suggested the presence of four iodine atoms in the compound.

![Scheme 1. Iodination of 4,4-Bis(4-Hydroxyphenyl) Pentanoic Acid](image)

![Figure 1. $^1$H NMR spectrum of BHP.](image)
IBHP was further characterized by IR spectroscopy, UV–Vis spectroscopy, mass spectroscopy, and thermogravimetric analysis. FTIR spectrum of BHP (Figure 4) showed peaks corresponding to the O–H stretching of the phenolic group at 3296 cm\(^{-1}\), alkane C–H stretching at 2972 cm\(^{-1}\), acid C=O stretching at 1701 cm\(^{-1}\), and aromatic C=C bending at 1512 cm\(^{-1}\). In the FTIR spectrum of IBHP, an increase in the stretching frequency corresponding to the –OH group was observed. All other peaks keep their position with a slight increase in frequency. According to the literature, when the ring substituent becomes more electron-withdrawing, the stretching frequency of the functional groups tends to increase.\(^{30}\) Here, the presence of electron-withdrawing iodine atom adjacent to the –OH group causes an increase in stretching frequency from 3296 to 3415 cm\(^{-1}\). All other frequencies are close to that of BHP but shift toward a higher range. For example, alkane C–H stretching occurs at 2981 cm\(^{-1}\), acid C=O stretching at 1707 cm\(^{-1}\), and aromatic C=C bending at 1529 cm\(^{-1}\). An additional peak observed at 708 cm\(^{-1}\) in IBHP corresponds to C–I stretching. Therefore, FTIR data further confirms the iodination of BHP.

The UV–Vis spectrum of BHP showed primary and secondary absorption bands of the aromatic ring. The primary band falls at 222 nm and the secondary band falls at 280 nm (Figure 5). IBHP shows the primary absorption band at 227 nm and the secondary absorption band at 300 nm (Figure 6). It has been reported that the presence of an electron-donating group in the aromatic ring increases both \(\lambda_{\text{max}}\) and \(\varepsilon_{\text{max}}\) values of the secondary band.\(^{31}\) Even though iodine is electron-withdrawing, it donates electrons to the benzene ring and undergoes conjugation with the benzene ring.\(^{32}\) That is why the secondary absorption band showed a bathochromic shift to 300 from 280 nm.

\[
\begin{align*}
\text{BHP, } \lambda_{\text{max}} \,(\text{MeOH})/\text{nm} & \quad 222 \text{ and } 280 \\
& \quad (\varepsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1} \quad 120{,}000 \text{ and } 30{,}000) \\
\text{IBHP, } \lambda_{\text{max}} \,(\text{MeOH})/\text{nm} & \quad 227 \text{ and } 300 \\
& \quad (\varepsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1} \quad 540{,}000 \text{ and } 32{,}000)
\end{align*}
\]
The formation of IBHP was also confirmed by mass spectroscopy. The mass spectra of BHP and IBHP are shown in Figure 7. The theoretical molecular mass of BHP is 286. On tetra iodination, the molecular weight of the compound becomes 790. The spectral data showed that BHP had a base peak at 309 (M + 23) and a molecular ion peak at 325 (M + 40). However, IBHP had a base peak at 812.69 (M + 23) and a molecular ion peak at 834.67 (M + 40). This is the expected molecular weight if tetra iodination occurs.

\[ \text{BHP, } m/z \ 309 \ (M^+, \ 100\%), \ 227 \ (5), \ 269 \ (6), \ 325 \ (M^+, \ 6%) \]

\[ \text{IBHP, } m/z \ 812 \ (M^+, \ 100\%), \ 834 \ (M^+, \ 18%) \]

The increased molecular weight of BHP was also an indication of tetra iodination, which resulted in the iodine content of 64% ((atomic weight of four iodine atoms/molecular weight of IBHP) \times 100) by weight in the compound.

The thermal stability of IBHP was studied by thermogravimetric analysis. Figure 8 shows the thermogravimetric analysis (TGA) traces of IBHP and its parent compound BHP. Both BHP and iodinated BHP undergo one-stage degradation. The major mass-loss process began at 227.71 °C for BHP, whereas it started at 180.92 °C for IBHP. The thermal stability of BHP decreased on iodination. It has been reported that the volatilization of iodine could take place during the melting of iodocompounds.\(^{33,34}\) Here, it may be assumed that the volatilization of iodine could be a reason for its lower thermal stability. About 50% weight loss was observed for IBHP at 264 °C, whereas the same percentage loss in weight was observed for BHP only at 297 °C.

Therefore, as a consequence of iodination, remarkable changes in thermal stability, molecular weight, and UV absorption maxima were observed in BHP.

### 2.2. In Vitro X-ray Visibility of IBHP

When a compound is radiopaque, it absorbs X-rays and casts a radiological image. The radiopacity was expressed in the Hounsfield units (HU), which is a relative quantitative measurement of radiodensity used by radiologists in the interpretation of CT images. The attenuation observed for cancellous bone was in the range 300–400 HU\(^{35}\) and that for cortical bone was in the range 500–1900 HU.\(^{36,37}\) La Grutta et al. compared the attenuation values of different concentrations of iodixanol and iomeprol contrast agents. The attenuation values increased with the increase in the concentration of iodine load. Iodixanol solutions containing 40, 64, 80, and 160 milligram iodine (mgI) in 10 mL volume showed HU values of 122 ± 6.7, 200.6 ± 6.5, 259.7 ± 6.2, and 473.7 ± 7.3, respectively. Different dilutions of iomeprol containing 50, 80, 100, and 200 mgI in 10 mL volume showed 142.5 ± 8.5, 230.2 ± 7.8, 339.6 ± 7, and 559.8 ± 8.2 HU, respectively.\(^{38}\) Therefore, compounds having attenuation in these ranges were found to be visible under fluoroscopy and can be used for imaging applications.

Figure 9 shows the computed tomographic (CT) images of 5, 10, and 20% solutions of IBHP (solvent: DMSO) along with 20% solution of iodixanol contrast agent (in distilled water) as the control. Iodixanol has an iodine content of 49.1% by wt. On the other hand, IBHP has an iodine content as high as 64% (by wt). This difference in the iodine content was reflected in the attenuation values. The IBHP solutions of concentrations 5, 10, and 20% (iodine load: 321, 643, and 1286 mgI in 10 mL, respectively) showed opacities of 885.15 HU, 1328.8 HU, and 1655.78 HU, respectively. The attenuation value of 10% solution of IBHP (1328.8 HU) was very close to the attenuation value of 20% iodixanol solution (1330.74 HU).
(iodine load: 980 mgI in 10 mL). Therefore, IBHP can provide greater opacity in X-ray imaging due to its higher iodine content.

2.3. In Vitro Cell Culture Cytotoxicity of IBHP. Cytocompatibility studies measure the cell viability and cytotoxicity of the compound through luminescence-based detection methodologies and are critical for the clinical development of safe and effective therapeutics. The cytocompatibility of iodinated BHP was determined by performing colorimetric MTT assay using L929 fibroblast cells. Figure 10 shows the cell viability of different concentrations of IBHP dissolved in DMSO after overnight incubation with L929 cells. Over 90% cell viability was observed for all concentrations tested (concentration range = 0.001–0.8 mg/mL). The results indicate that IBHP exhibits excellent cytocompatibility.

High X-ray opacity resulting from high iodine content in the molecule and its noncytotoxic response to fibroblast cells

Figure 7. Mass spectra of (a) BHP and (b) IBHP.

Figure 8. TGA traces of BHP and IBHP.
indicate that the compound IBHP holds promise in the area of medical imaging and diagnostics.

3. CONCLUSIONS
In this work, we demonstrated that a noncytotoxic organic compound of high radiopacity can be synthesized by iodinating 4,4-bis(4-hydroxyphenyl)pentanoic acid. The compound was characterized by FTIR, $^1$H NMR, EDAX, UV-Vis, mass spectroscopy, and thermogravimetric analysis.

4. MATERIALS AND METHODS
4.1. Materials. All chemicals used were of reagent grade and used as received. Sodium iodide (98.5% purity), sodium hydroxide (99% purity), sodium hypochlorite (EMPLURA, about 4% w/v available chlorine), methanol (99.9% purity), hydrochloric acid (37%, EMSURE, for analysis), and sodium thiosulfate pentahydrate (EMPARTA, for analysis) were purchased from Merck Ltd. (Mumbai, India).

4.2. Methods. 4.2.1. Synthesis of 4,4-Bis(4-hydroxy-3,5-diiodophenyl)pentanoic acid (IBHP). About 2 g of 4,4-bis(4-hydroxyphenyl)pentanoic acid (BHP) was dissolved in 50 mL of methanol. Two equivalents of sodium hydroxide (0.13 g) and 6 equiv of sodium iodide (6.3 g) were added to it. The solution was cooled to 0 °C. Aqueous sodium hypochlorite (3.104 g, 6 equiv) was then added dropwise. As each drop hits the solution, a red color appeared and faded almost instantly, resulting in a yellow solution. The mixture was stirred for 1 h and precipitated by adding 10% sodium thiosulfate pentahydrate and 10% HCl. The compound was purified by washing with water. The yield of the product obtained was 75% (the yield was calculated from the equation (millimole of product/millimole of reactant) × 100).

4.2.2. Material Characterization. IR spectra were recorded on a Nicolet 5700 model FTIR spectrometer with an ATR accessory. Spectrum was taken for powdered sample in KBr pellet and collected in the range of 4000–400 cm$^{-1}$ at a resolution of 4 cm$^{-1}$. $^1$H NMR spectra were recorded using a 500 MHz instrument (Bruker AV 500) using DMSO-$_d_6$ as the solvent. Energy-dispersive X-ray analysis (EDAX) was performed in a scanning electron microscope (ESEM; Quanta 200, The Netherlands). Thermal analysis of the materials was performed using a simultaneous differential thermal analyzer-thermogravimetric analyzer (DTA-TGA) (SDT Q 600) in a nitrogen atmosphere from room temperature to 1000 °C at a heating rate of 10 °C min$^{-1}$. The UV absorbance of BHP and IBHP was measured by preparing 1 × 10$^{-6}$ M solutions in
methanol and recording their spectra in a UV 1800 spectrophotometer (Shimadzu) at a wavelength range of 200–800 nm. The background absorbance of the pure solvent was subtracted from the data. The mass spectra were recorded on a Thermo Scientific Exactive LCMS instrument (Germany).

For radiopacity measurements, the IBHP solutions of concentrations of 5, 10, and 20% (by weight) were prepared in DMSO in polypropylene test tubes. A 20% solution (by weight) of iodixanol was taken as the control. The control solution was prepared from commercially available Visipaque (320 mgI/mL) purchased from M/s. Wipro GE Healthcare Pvt. Ltd. (New Delhi). A computed tomography (CT) scan was performed with a CT scanner (Philips Brilliance 16 Slice) to determine the attenuation values (Hounsfield unit; HU) of all solutions taken in the test tubes. Scan parameters were as follows: 140 kV and 470 mA. The specimens were kept in longitudinal positions (head-to-feet) to obtain the direct cross-sectional images, and the values were recorded. An equal area of 0.107 cm² was selected for all samples.

4.2.3. Cell Viability Assay. Cell culture cytotoxicity of IBHP was determined using a MTT assay. L929 fibroblast cell lines (1 × 10⁴ cells/well, 96-well tissue culture plates) were cultured to 80% confluency in a Dulbecco’s modified Eagle’s medium (DMEM) (supplemented with 10% heat-inactivated fetal bovine serum (FBS), 1× antibiotic–antimycotic solution, and sodium bicarbonate). Different concentrations of IBHP prepared in DMSO were added to cells and incubated overnight at 37 °C in a CO₂ incubator. The culture medium was aspirated and MTT solution (100 μL, 1 mg/mL, serum-free DMEM) was added to the wells of the plate. The plate was incubated for 6 h, and then 150 μL of DMSO was added to solubilize the formazan crystals. One hundred microliters of the supernatant was measured in a UV-Vis plate reader at 595 nm.

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■ ACKNOWLEDGMENTS

The authors thank the Director, SCTIMST and the Head, BMT Wing for the laboratory facilities provided and the kind permission to publish this work. The financial support received from the Technical Research Centre for Biomedical Devices scheme of the Department of Science and Technology, Government of India, is acknowledged. G.V.G. gratefully acknowledges the provision of Ph.D. fellowship offered by SCTIMST, Trivandrum.

■ ABBREVIATIONS

BHP, 4,4-bis(4-hydroxyphenyl)pentanoic acid; IBHP, 4,4-bis(4-hydroxy-3,5-diodophenyl)pentanoic acid; DMSO, dimethyl sulfoxide; EDAX, energy-dispersive X-ray analysis; HU, Hounsfield unit; CT, computed tomography; DMEM, Dulbecco’s modified Eagle’s medium; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

■ REFERENCES

(1) Mottu, F.; Rufenacht, D. A.; Doelker, E. Radiopaque polymeric materials for medical applications. Current aspects of biomedical research. Invest. Radiol. 1999, 34, 323–335.
(2) Torchilin, V. P. PEG-based micelles as carriers of contrast agents for different imaging modalities. Adv. Drug Delivery Rev. 2002, 54, 235–252.
(3) Torchilin, V. P. The Use of Polychelating and Amphiphilic Polymers in Gamma, MR and CT Imaging. In Biomedical Polymers and Polymer Therapeutics, 1st ed.; Chiellini, E.; Sunamoto, J.; Migliaresi, C.; Ottenbrite, R. M.; Cohn, D., Eds.; Springer: Boston, MA, 2002; pp 268–284.
(4) Torchilin, V. P. Polymeric contrast agents for medical imaging. Curr. Pharm. Biotechnol. 2000, 1, 183–215.
(5) Lei, K.; Chen, Y.; Wang, J.; Peng, X.; Ding, J.; et al. Non-invasive monitoring of in vivo degradation of a radiopaque thermoreversible hydrogel and its efficacy in preventing post-operative adhesions. Acta Biomater. 2017, 55, 396–409.
(6) Lei, K.; Chen, Y.; Wang, J.; Peng, X.; Ding, J.; et al. Non-invasive monitoring of in vivo degradation of a radiopaque thermoreversible hydrogel and its efficacy in preventing post-operative adhesions. Acta Biomater. 2017, 55, 396–409.
(7) Ma, Q.; Lei, K.; Ding, J.; Yu, L.; et al. Design, synthesis and ring-opening polymerization of a new iodinated carbonate monomer: a universal route towards ultrahigh radiopaque aliphatic polycarbonates. Polym. Chem. 2017, 8, 6665–6674.
(8) Wu, X.; Wang, X.; Chen, X.; Yang, X.; Ma, Q.; Xu, G.; Yu, L.; Ding, J. Injectable and thermosensitive hydrogels mediating a universal macromolecular contrast agent with radioopacity for noninvasive imaging of deep tissues. Biomater. 2021, 6, 4717–4728.
(9) Qian, M.; Xiaohui, W.; Lin, Y.; Jiandong, D. Design and Synthesis of Novel Iodinated Polycarbonates with Inherent X-Ray Opacity. Chem. J. Chin. Univ. 2019, 40, 2233–2240.
(10) Okamura, M.; Yamanobe, T.; Arai, T.; Uehara, H.; Komoto, T.; Hosoi, S.; et al. Synthesis and properties of radiopaque polymer hydrogels. II. Copolymers of 2,4,6-triiodophenyl- or N-(3-carboxy-2,4,6-triiodophenyl)-acrylamide and p-styrene sulfonate. J. Mol. Struct. 2002, 602−603, 17−28.

(11) Mottu, F.; Rufenacht, D. A.; Laurent, A.; Doelker, E. Iodine-containing cellulose mixed esters as radiopaque polymers for direct embolization of cerebral aneurysms and arteriovenous malformations. Biomaterials 2002, 23, 121−131.

(12) Horak, D.; Metalova, M.; Rypacek, F. New radiopaque poly-HEMA-based hydrogel particles. J. Biomed. Mater. Res. 1997, 34, 183−188.

(13) James, N. R.; Juby, P.; Jayakrishnan, A. Polyurethanes with radiopaque properties. Biomaterials 2006, 27, 160−166.

(14) Davy, K. W. M.; Anseau, M. R. X-ray opaque methacrylate polymers for biomedical application. Polym. Int. 1997, 43, 143−154.

(15) Saralidze, K. S.; Aldenhoff, B. J.; Knetsch, L. W.; Koole, L. H. Injectable polymeric microspheres with X-ray visibility. Preparation, properties, and potential utility as new traceable bulking agents. Biomacromolecules 2003, 4, 793−798.

(16) Vázquez, B.; Ginebra, M. P.; Gil, F. G.; Planell, J. A.; Bravo, A. L.; Roman, J. S. Radiopaque acrylic cements prepared with a new acrylic derivative of iodo-quinoline. Biomaterials 1999, 20, 2047−2053.

(17) Emans, P. J.; Saralidze, K.; Knetsch, L. W.; Gijbels, J. J.; Kuiper, R.; Koole, L. H. Development of new injectable bulking agents: Biocompatibility of radiopaque polymeric microspheres studies in a mouse model. J. Biomed. Mater. Res., Part A 2005, 73, 430−436.

(18) Lucic, H.; Grinstaff, M. W. X-Ray Computed Tomography Contrast Agents. Chem. Rev. 2013, 113, 1641−1665.

(19) Baerlocher, M. O.; Asch, M.; Myers, A. The use of contrast media. Can. Med. Assoc. J. 2010, 182, 697.

(20) Qu, W.; Xia, W.; Feng, C.; Tuo, X.; Qiu, T. Synthesis and characterization of radiopaque poly(ether urethane) with iodine-containing diol as chain extender. J. Polym. Sci., Part A: Polym. Chem. 2011, 49, 2191−2198.

(21) Wang, X.; Geng, X.; Ye, L.; Zhang, A. Y.; Feng, Z. G. Synthesis and characterization of radiopaque iodine-containing methacrylate-based polymers via reversible addition-fragmentation chain transfer (RAFT) polymerization. Front. Mater. Sci. China 2010, 4, 366−375.

(22) Shiralizadeh, S.; Isfahani, H. N.; Keivanloo, A.; Bakherad, M. M. N- and triiodophenyl isocyanate as radiopaque tying agents for methacrylate-based copolymers; biocompatibility and non-toxicity. RSC Adv. 2016, 6, No. 110400.

(23) Solbak, M. S.; Henning, M. K.; England, A.; Martinsen, A. C.; Aaløkken, T. M.; Johansen, S. Impact of iodine concentration and scan parameters on image quality, contrast enhancement and radiation dose in thoracic CT. Eur. Radiol. Exp. 2020, 4, No. 57.

(24) Edgar, K. J.; Steinmetz, G. R. Process for the Iodination of Hydroxyl Aromatic and Amino Aromatic Compounds. European Patent EP0377 638 B11993.

(25) Filimonov, V. D.; Krasnokutskaya, E. A.; Lesina, Y. A. Generation of Electrophilic Iodine from Iodine Monochloride in Neutral Media. Iodination and Protodeiodination of Carbazole. Russ. J. Org. Chem. 2003, 39, 875−880.

(26) Bolikal, D.; Brandom, D. K.; Kabalnova, L.; Baluca, E. G.; Kohn, J. Biocompatible Polymers for Medical Devices. U.S. Patent US8476 399 B22013.

(27) Patel, R. M.; Carew, D. P.; Lach, J. L. Synthesis of halogen substituted derivatives of 4, 4-bis(4-hydroxyphenyl)pentanoic acid and their antifungal properties. J. Pharm. Sci. 1967, 56, 1326−1328.

(28) Kiran, S.; James, N. R.; Joseph, R.; Jayakrishnan, A. Synthesis and characterization of iodinated polyurethane with inherent radiopacity. Biomaterials 2009, 30, 5552−5559.

(29) Pouchert, C. J. The Aldrich Library of NMR Spectra, 2nd ed.; Aldrich Chemical Co.: Milwaukee, 1983; Vol. 1.

(30) Krueger, P. J.; Jan, J. Infrared spectra and the molecular conformations of some aliphatic amines. Can. J. Chem. 1970, 48, 3229−3235.

(31) Kumar, S. Spectroscopy of Organic Compounds. 2021. http://www.uobabylon.edu.iq/eprints/publication_11_8282_250.pdf.

(32) Bird, M. L.; Ingold, C. K. Influence of directing groups on nuclear reactivity in oriented aromatic substitutions. Part IV. Nitration of the halogenobenzenes. J. Chem. Soc. 1938, 918−929.

(33) Moulay, S. Molecular iodine/polymer complexes. J. Polym. Eng. 2013, 33, 389−443.

(34) Goh, S. H.; Lee, S. Y. Effect of iodination on the thermal properties of polystyrene. Thermochim. Acta 1990, 161, 119−123.

(35) Birur, N. P.; Patrick, S.; Gurushanth, K.; Raghavan, A.; Gurudath, S. Comparison of gray values of cone-beam computed tomography with Hounsfield units of multislice computed tomography: An in vitro study. Indian J. Dent. Res. 2017, 28, 66−70.

(36) Fat, D. L.; Kennedy, J.; Galvin, R.; O’Brien, F.; Mc Grath, F.; Mullett, H. The Hounsfield value for cortical bone geometry in the proximal humerus—an in vitro study. Skeletal Radiol. 2012, 41, 557−568.

(37) Aamodt, A.; Kvistad, K. A.; Andersen, E.; Lund-Larsen, J.; Eine, J.; Benum, P.; Husby, O. S. Determination of Hounsfield value for CT-based design of custom femoral stems. J. Bone Jt. Surg., Br. Vol. 1999, 81-B, 143−147.

(38) La Grutta, L.; Galia, M.; Gentile, G.; Lo Re, G.; Grassedonio, E.; Coppolino, F.; Maffeì, E.; Maresì, E.; Lo Casto, A.; Cademartiri, F.; Midiri, M. Comparison of iodinated contrast media for the assessment of atherosclerotic plaque attenuation values by CT coronary angiography: observations in an ex vivo model. Br. J. Radiol. 2013, 86, No. 2012038.