Heteroatom/Metal-Doped Carbon Dot-Based Image-Guided Photodynamic Therapy

Subjects: Infectious Diseases

Contributor: Rajkumar Sekar, Nagaraj Basavegowda, Saktishree Jena, Santhoshkumar Jayakodi, Pandian Elumalai, Amballa Chaitanyakumar, Prathap Somu, Kwang-Hyun Baek

Carbon nanodots (CNDs) are advanced nanomaterials with a size of 2–10 nm and are considered zero-dimensional carbonaceous materials. CNDs have received great attention in the area of cancer theranostics.

Keywords: carbon dots ; photodynamic therapy ; cancer theranostics

1. Synthesis Techniques for Doped CNDs for PDT

Doping is an efficient way to alter the essential properties of CNDs. By presenting heteroatoms/metal ions doped into CNDs, their electronic structures can be altered, promoting n- or p-type carriers. Therefore, their optical and electronic characteristics are linked to the HOMO–LUMO band gaps and they are able to change by using dopants. Additionally, current progress in research has shown that doping could largely improve the quantum yield of CNDs [1]. Commonly, there are two types of methods that can be used to prepare the CNDs, namely top-down and bottom-up methods. Recent methodologies for the synthesis of doped CNDs are summarized in **Table 1**. In the top-down process, heavy carbon resources (graphite, coal, ash) are decomposed into CNDs, whereas in the bottom-up process, organic matter is converted and polymerized into CNDs [2].

In the top-down process, sulfuric and nitric (strong) acids are employed to oxidize the carbon bulk materials so the surface of CNDs is surrounded by carboxyl and hydroxyl groups [3][4][5]. The amount of these oxygen-comprising functional groups can be quickly controlled by tuning the pH range of the acids. Moreover, it is very hard to dope heteroatoms/metal ions into CNDs. Additionally, using strong acids may destroy the π-conjugated forms in the CNDs, as it creates low absorption and low-emission wavelengths. Thus, the top-down process is not adaptable for the large-scale preparation of CNDs. However, in the bottom-up process, CNDs are synthesized using the solvothermal method for the organic substances. Commonly, this is an eco-friendly method using non-toxic solvents and produces a high yield compared to the top-down approach; thus, it is fit for bulky synthesis. The surface functional groups on CNDs are majorly dependent on the chemical formula of carbon materials, pH value, pressure, solvents, and temperature. Different kinds of heteroatoms/metal ions can be quickly doped into CNDs [6]. Furthermore, the doping amount and sites are also hard to regularize. The photoluminescence properties of doped CNDs, particularly their emission and absorption wavelengths, are vital for their photodynamic application in cancer therapies. The doped CNDs with strong NIR fluorescence and absorption can be utilized for successful diagnoses and the destruction of tumors in deep tissue [7].

Table 1. Heteroatom/metal-doped CNDs along with their synthesis methods, quantum yields, and colors.

Heteroatom-Doped CNDs					
Synthesis Method	**Doping Agent**	**Precursors**	**Quantum Yield (%)**	**Emission**	**Ref.**
Hydrothermal	N	Folic acid	23	Blue	[8]
	F	PEI 600 Da and 2,2,3,3, 4,4-hexafluoro-1,5-pentanediol diglycidyl ether	5.6	-	[9]
	P	Sodium citrate and phytic acid	3.5	Blue	[10]
	B	Phenylboronic acid	12	-	[11]

Heteroatom-Doped CNDs					
Synthesis Method	**Doping Agent**	**Precursors**	**Quantum Yield (%)**	**Emission**	**Ref.**
Solvothermal	N	Carbon tertrachloride and diamines	9.8–36.3	Blue	[12]
	F	Tetrafluoroterephthalic acid	-	Green	[13]
	P	Hydroquinone and phosphorous tribromide	25.1	Blue	[14]
	B	Hydroquinone and boron tribromide	14.8	Blue	[15]
Microwave	N	citric acid-malonic acid-oxalic acid-succinic acid	90	Blue	[16]
	P	Ethylenediamine/phytic acid	21.65	Green	[17]
	B	Citric acid, urea, and boric acid	15	Green	[18]
Metal-Doped CNDs					
Hydrothermal	Cu	Poly(methacrylic acid) and Cupric nitrate	80	Blue	[19]
	Zn	Glucose oxidase and glucose, zinc chloride	32.3	Blue	[20]
	Mg, N	Citric acid and Magnesium hydroxide	83	Blue	[21]
	Cu, N	citric acid monohydrate, copper acetate monohydrate	50.1	Blue	[22]
Solvo thermal	Zn	Citric acid monohydrate, urea, zinc chloride	51.2	Yellow	[23]
	Mn	Ethylenediaminetetraacetic acid and manganese chloride tetrahydrate	90.79	Blue	[24]
Micro wave	Fe, N	L-Tartaric acid, urea, $FeCl_3.6H_2O$, oleic acid	-	Blue	[25]
	Gd	Diethylene glycol (DEG), sucrose, and Gd_2O_3	5.4	Green	[26]

2. Physicochemical and Biological Properties of Doped CNDs

CNDs as 0D carbon group materials have excellent biocompatibility and their lateral dimensions are typically less than 10 nm [27]. The preparation techniques for doped CNDs are entirely dependent on the approach used (top-down or bottom-up), which have been systemically described [27][28]. Apart from these old-style methods for preparing doped CNDs using carbon sources, currently, many eco-friendly green preparation tactics have been utilized. Well-organized heteroatom/metal-doped CNDs with good hydrophilic properties were prepared by an eco-friendly approach using natural polysaccharides as a precursor [29]. In addition, well-formed heteroatom/metal-doped CNDs have been synthesized with exceptional photoluminescence (optical) and biocompatibility (biological) properties. Furthermore, various advanced techniques in the characterization process have provided a strong underpinning for the usage of doped CNDs in the field of biomedical science.

2.1. Physicochemical Properties of Heteroatom/Metal-Doped CNDs

Most reports confirm that heteroatom/metal doping of CNDs could disturb the pristine electronic structure of CNDs. Thus, the PL properties of doped CNDs are linked to the HOMO–LUMO band gaps that have been changed due to the different types of heteroatom/metal-doped CNDs. The high quantum yield in the doped CNDs enhances the PL properties and also introduces some novel physicochemical properties, namely the magnetic resonance imaging (MRI) relativity rate and catalytic performances.

2.1.1. Photoluminescence in CNDs

The most popular and attractive property of CNDs is its optical (PL) properties since its clear mechanism is still unpredictable. Many proposed mechanisms for CNDs' PL are based on their surface effect, quantum confinement effect, and molecule-like state. In CNDs, a smaller particle size leads to quantum confinement, and many researchers have shown that the energy/band gap of the carbon core energy level increases with the decreasing size of CNDs, subsequently in an emission wavelength with the blue shift of CNDs [30][31]. However, the PL properties arise from the surface effect of the CNDs and develop an improved quantum yield, decay lifetime, and emission wavelength. Many functional groups on CNDs' surface can develop various surface effect energies, which can offer emissive energy levels

and create several PL colors [32][33]. Many reported CNDs show blue and green PL emission wavelengths in the range of 400–500 nm; moreover, some red PL emissions have also been observed [34][35][36]. It is important to note that CNDs with good quantum yields and lifetimes are required in cancer theranostics, particularly to enhance image-guided photodynamic therapy [37].

2.1.2. Photoluminescence in Heteroatom/Metal-Doped CNDs

Heteroatom/metal-doped CNDs showed improved PL properties due to the surface defects via the increasing number of energy traps. Due to this effect, the energy gap of CNDs decreases and the non-radioactive electron transfer has less of an impact and consequently leads to the enhancement of the quantum yield of CNDs [33][38]. In heteroatom doping, the N atom is predominantly used as a dopant and causes a red shift in the emission wavelength of CNDs and an increase in the quantum yield. It can be allocated to the surface energy states created by doping the N onto CNDs, developing a radioactive reunion and reducing the chance of the non-radioactive reunion of excited electrons. Moreover, electron-releasing functional groups such as the amino groups can also increase the excited energy states' stability by improving the pi electrons' conjugation system in the CNDs skeleton. This can improve the electron transition from the ground state to the excited state so the N atom can contribute to the quantum yield of CNDs.

Nowadays, the S atom is also employed as a dopant to improve the quantum yield of CNDs [39][40]. Zhang et al. [41] investigated the electronic structures of carbon dots (CDs), S-doped CDs, and N, S co-doped CDs to describe the high quantum yield of the red and orange emissions of N, S co-doped CDs. The observed results show that the heteroatoms can create more electronic states and in-gap trap states as recombination points. The heteroatoms (N and S) can quickly bind to carbon owing to their similar atomic radii and the accessibility of the 5 and 6 electrons in their valence band. Thus, N and S doping can alter the band gap of CDs and increase the probability of electronic transition from the singlet ground level to the triplet excited level, concluding in a remarkably high quantum yield of CDs. Similar to the above investigation, Dong et al. [37] analyzed the outcome of N and S co-doped CDs and demonstrated a noteworthy improvement in the quantum yield of S,N co-doped CDs of 73% compared to N-doped CDs with 16.9% and CDs with 5.3%. Moreover, the observed lifetime of N and S co-doped CDs (12.11 ns) was higher than that of non-doped CDs (7.45 ns). The results confirmed that a novel surface energy state formed in CDs through the N-doping method, together with the further co-doping of the S element, can remarkably improve the density of this state. Certainly, the S element can remove the O elements from the surface state and become stable and then improve the surface state of the N element.

In recent years, many metal ions have been doped to enhance the luminescence properties of CNDs. The metal doping agents can enhance the quantum yield due to the presence of the valence electron and its electron-transferring processes, which aid the radioactive recombination of holes and electrons on the externally modified surface of the CNDs [42][43][44]. Generally, metal-doped CNDs exhibit a solid and broad absorption band between 200 nm and 600 nm. Compared with CNDs, the emission color of metal-doped CNDs is greatly improved in the visible space at a similar level of concentration owing to the possibility of a charge transfer between the metal dopants and graphite [45][46]. Moreover, most of the metal-doped CNDs show emissions with various colors of fluorescence in a 360 nm UV-vis region, such as yellow [47], green [26], blue [48], blue-green [49], and so on. When compared with CNDs, metal-doped CNDs exhibit a red shift in the fluorescence emission owing to their excitation-based luminescence properties and the emission peaks also demonstrate a higher wavelength with the intensity slowdown as the excitation wavelength exhibits a red shift [19][24][50][51][52][53]. Moreover, almost all oxygen-holding functional ligands on the metal-doped CNDs decrease owing to their chemical treatment with the doping metal ions but still show high solubility in aqueous and organic solvents. For instance, Wang et al. [54] showed that the emission fluorescence color of Mn-doped carbon dots changed from blue to yellow as the solvent polarity increased, whereas the emission color of the non-doped CDs was blue with similar solvents and denotes the vital role of Mn doping on CNDs. Heteroatom/metal-doped CNDs can synergistically deliver disease imaging and targeting via PDT, which can be utilized as a new approach for forthcoming cancer theranostics.

2.2. Biological Properties of Doped CNDs

Even though the possibilities of using CNDs in nanomedicine are vast, it is essential to study the vital biohazards of CNDs due to the interactions between the CNDs' biomaterials and the body's organs [55][56][57]. Basically, once CNDs are offered for a particular biomedical use, they must elevate their adequate bio-functions, which can lead to clean renal clearance without side effects [58][59][60]. Therefore, it is vital to systematically evaluate the toxic nature of heteroatom/metal-doped CNDs from the perspective of toxicology studies. To determine the cytotoxicity in vitro, a few biological chemical pointers, namely apoptosis, DNA damage, and reduced oxidative stress, are commonly utilized to fully demonstrate the biocompatibility of heteroatom/metal-doped CNDs with a cell-line medium. Various intravenous processes to introduce CNDs can effectively alter the physiological system and disturb the pharmacokinetics, which depends on the timeline and

outcome of the intake, circulation in the bloodstream, metabolic activity, bio-distribution, renal excretion, and bio-interface interaction of superficially introduced CNDs in an organism [61][62][63].

The quantum yield improvement of doped CNDs is noticeable and important due to the heteroatom/metal doping, which sorts doped CNDs into more convenient biomedical applications. Moreover, the related issue of cytotoxicity caused by the doping of heteroatoms/metals should be observed particularly for their vital role in cancer theranostics applications. Evaluating the cytotoxicity of CNDs through in vitro and in vivo assays to allow for their biomedical applications is necessary for their supplementary advancement. To date, many scientists have assessed the in vitro biocompatibility of different heteroatom/metal-doped CNDs. Commonly, in vitro cytotoxicity models expose cell viability measurements via specific assays namely CCK-8, MTT, and WST-1. Due to their nanosize, which is a major factor affecting their toxicities, CNDs indicate fairly small cytotoxicity in many in vitro models.

Surface-modified CNDs with functional groups, namely $–NH_2$, –OH, –COOH, and heteroatom/metal-doped CNDs, also show low cytotoxicity. **Table 2** shows a summary of the biocompatibility experiments of heteroatom/metal-doped CNDs. Many reports have demonstrated the outstanding cell viability of heteroatom-doped CNDs [64][65][66][67]. For instance, Edison et al. [68] showed that the nitrogen-doped carbon dots have low cytotoxicity on HeLa cells. Xu et al. [69] achieved a 100% cell viability assay with HeLa and HepG2 cells on doped carbon dots after 24 and 48 h. The biocompatibility reports showed that metal-doped CNDs had low toxicity [48][49][70][71][72][73][74][75][76]. For instance, Xu et al. [77] placed an in vivo investigation of Gd-doped carbon dots in liquid form (20 mmol/kg) into mice via a tail vein. After a week of observation, the histological differences in the heart, liver, spleen, kidney, and intestine were analyzed through hematoxylin and eosin staining. The results showed that there were no significant variations between the control and experiment groups and there were no tissue pathological impairments resulting from the intravenous injection of Gd-doped carbon dots.

Table 2. Biocompatibility of doped CNDs.

S. No.	Doped-CND	Cell Model	Assay	Incubation	Viability/ Concentration	Ref.
1.	Mg–EDA–CDs	L929	MTT	24 h	90% (250 mg mL^{-1})	[21]
2.	Mn-CDs@Anti-HE4	HO8910	MTS	24 h	85% (3 mg mL^{-1})	[24]
3.	Gd-CDs	C6	MTT	24 h	83% (1 mg mL^{-1})	[26]
4.	Gd-QCDs	NIH3T3	MTT	24 h	121.4 mg mL^{-1}	[78]
5.	NPCDs	HepG2	MTT	24 h	88% (100 mg mL^{-1})	[79]
6.	Te-CDs	HeLa	MTT	24 h	80% (200 mg mL^{-1})	[61]
7.	N-O-CDs	HeLa	MTT	24 h	80%	[80]
8.	S, Se-codoped CDs	HeLa	MTT	24 h	>80% (40 mg mL^{-1})	[81]
9.	PMn@Cdots/HA	HEL	WST-1	24 h	100% (20 mg mL^{-1})	[82]
10.	MnNS:CDs@HA	B16F1	WST-1	24 h	90% (500 mg mL^{-1})	[83]

References

1. Lin, H.; Huang, J.; Ding, L. Preparation of carbon dots with high-fluorescence quantum yield and their application in dopamine fluorescence probe and cellular imaging. J. Nanomater. 2019, 2019, 5037243.
2. Anwar, S.; Ding, H.; Xu, M.; Hu, X.; Li, Z.; Wang, J.; Liu, L.; Jiang, L.; Wang, D.; Dong, C. Recent advances in synthesis, optical properties, and biomedical applications of carbon dots. ACS Appl. Bio Mater. 2019, 2, 2317–2338.
3. Hassan, M.; Gomes, V.G.; Dehghani, A.; Ardekani, S.M. Engineering carbon quantum dots for photomediated theranostics. Nano Res. 2018, 11, 1–41.
4. Jiang, B.; Zhou, B.; Lin, Z.; Liang, H.; Shen, X. Recent advances in carbon nanomaterials for cancer phototherapy. Chem. Eur. J. 2019, 25, 3993–4004.
5. Du, J.; Xu, N.; Fan, J.; Sun, W.; Peng, X. Carbon dots for in vivo bioimaging and theranostics. Small 2019, 15, 1805087.

6. Miao, S.; Liang, K.; Zhu, J.; Yang, B.; Zhao, D.; Kong, B. Hetero-Atom-Doped carbon dots: Doping strategies, properties and applications. Nano Today 2020, 33, 100879.
7. Siddique, S.; Chow, J.C.L. Application of nanomaterials in biomedical imaging and cancer therapy. Nanomaterials 2020, 10, 1700.
8. Wang, L.; Yin, Y.; Jain, A.; Zhou, H.S. Aqueous phase synthesis of highly luminescent, nitrogen-doped carbon dots and their application as bioimaging agents. Langmuir 2014, 30, 14270–14275.
9. Luo, T.-Y.; He, X.; Zhang, J.; Chen, P.; Liu, Y.-H.; Wang, H.-J.; Yu, X.-Q. Photoluminescent F-doped carbon dots prepared by ring-opening reaction for gene delivery and cell imaging. RSC Adv. 2018, 8, 6053–6062.
10. Yang, F.; He, X.; Wang, C.; Cao, Y.; Li, Y.; Yan, L.; Liu, M.; Lv, M.; Yang, Y.; Zhao, X. Controllable and eco-friendly synthesis of P-riched carbon quantum dots and its application for copper (II) ion sensing. Appl. Surf. Sci. 2018, 448, 589–598.
11. Jia, Y.; Hu, Y.; Li, Y.; Zeng, Q.; Jiang, X.; Cheng, Z. Boron doped carbon dots as a multifunctional fluorescent probe for sorbate and vitamin B12. Microchim. Acta 2019, 186, 84.
12. Qian, Z.; Ma, J.; Shan, X.; Feng, H.; Shao, L.; Chen, J. Highly luminescent N-doped carbon quantum dots as an effective multifunctional fluorescence sensing platform. Chem. Eur. J. 2014, 20, 2254–2263.
13. Zuo, G.; Xie, A.; Pan, X.; Su, T.; Li, J.; Dong, W. Fluorine-Doped cationic carbon dots for efficient gene delivery. ACS Appl. Nano Mater. 2018, 1, 2376–2385.
14. Zhou, J.; Shan, X.; Ma, J.; Gu, Y.; Qian, Z.; Chen, J.; Feng, H. Facile synthesis of P-doped carbon quantum dots with highly efficient photoluminescence. RSC Adv. 2014, 4, 5465–5468.
15. Shan, X.; Chai, L.; Ma, J.; Qian, Z.; Chen, J.; Feng, H. B-Doped carbon quantum dots as a sensitive fluorescence probe for hydrogen peroxide and glucose detection. Analyst 2014, 139, 2322–2325.
16. Meiling, T.T.; Schürmann, R.; Vogel, S.; Ebel, K.; Nicolas, C.; Milosavljević, A.R.; Bald, I. Photophysics and chemistry of nitrogen-doped carbon nanodots with high photoluminescence quantum yield. J. Phys. Chem. C 2018, 122, 10217–10230.
17. Wang, W.; Li, Y.; Cheng, L.; Cao, Z.; Liu, W. Water-Soluble and phosphorus-containing carbon dots with strong green fluorescence for cell labeling. J. Mater. Chem. B 2014, 2, 46–48.
18. Bourlinos, A.B.; Trivizas, G.; Karakassides, M.A.; Baikousi, M.; Kouloumpis, A.; Gournis, D.; Bakandritsos, A.; Hola, K.; Kozak, O.; Zboril, R. Green and simple route toward boron doped carbon dots with significantly enhanced non-linear optical properties. Carbon N. Y. 2015, 83, 173–179.
19. Ren, X.; Liu, J.; Ren, J.; Tang, F.; Meng, X. One-Pot synthesis of active copper-containing carbon dots with laccase-like activities. Nanoscale 2015, 7, 19641–19646.
20. Xu, Q.; Liu, Y.; Su, R.; Cai, L.; Li, B.; Zhang, Y.; Zhang, L.; Wang, Y.; Wang, Y.; Li, N. Highly fluorescent Zn-doped carbon dots as Fenton reaction-based bio-sensors: An integrative experimental–theoretical consideration. Nanoscale 2016, 8, 17919–17927.
21. Li, F.; Liu, C.; Yang, J.; Wang, Z.; Liu, W.; Tian, F. Mg/N double doping strategy to fabricate extremely high luminescent carbon dots for bioimaging. RSC Adv. 2014, 4, 3201–3205.
22. Ma, Y.; Cen, Y.; Sohail, M.; Xu, G.; Wei, F.; Shi, M.; Xu, X.; Song, Y.; Ma, Y.; Hu, Q. A ratiometric fluorescence universal platform based on N, Cu codoped carbon dots to detect metabolites participating in H2O2-generation reactions. ACS Appl. Mater. Interfaces 2017, 9, 33011–33019.
23. Cheng, J.; Wang, C.-F.; Zhang, Y.; Yang, S.; Chen, S. Zinc ion-doped carbon dots with strong yellow photoluminescence. RSC Adv. 2016, 6, 37189–37194.
24. Han, C.; Xu, H.; Wang, R.; Wang, K.; Dai, Y.; Liu, Q.; Guo, M.; Li, J.; Xu, K. Synthesis of a multifunctional manganese (II)–carbon dots hybrid and its application as an efficient magnetic-fluorescent imaging probe for ovarian cancer cell imaging. J. Mater. Chem. B 2016, 4, 5798–5802.
25. Yang, W.; Huang, T.; Zhao, M.; Luo, F.; Weng, W.; Wei, Q.; Lin, Z.; Chen, G. High peroxidase-like activity of iron and nitrogen co-doped carbon dots and its application in immunosorbent assay. Talanta 2017, 164, 1–6.
26. Gong, N.; Wang, H.; Li, S.; Deng, Y.; Chen, X.; Ye, L.; Gu, W. Microwave-assisted polyol synthesis of gadolinium-doped green luminescent carbon dots as a bimodal nanoprobe. Langmuir 2014, 30, 10933–10939.
27. Yan, Y.; Gong, J.; Chen, J.; Zeng, Z.; Huang, W.; Pu, K.; Liu, J.; Chen, P. Recent advances on graphene quantum dots: From chemistry and physics to applications. Adv. Mater. 2019, 31, 1808283.
28. Lu, H.; Li, W.; Dong, H.; Wei, M. Graphene quantum dots for optical bioimaging. Small 2019, 15, 1902136.

29. De Menezes, F.D.; Dos Reis, S.R.R.; Pinto, S.R.; Portilho, F.L.; e Mello, F.D.V.C.; Helal-Neto, E.; De Barros, A.O.D.S.; Alencar, L.M.R.; De Menezes, A.S.; Dos Santos, C.C.; et al. Graphene quantum dots unraveling: Green synthesis, characterization, radiolabeling with 99mTc, in vivo behavior and mutagenicity. Mater. Sci. Eng. C 2019, 102, 405–414.
30. Li, H.; He, X.; Kang, Z.; Huang, H.; Liu, Y.; Liu, J.; Lian, S.; Tsang, C.H.A.; Yang, X.; Lee, S. Water-Soluble fluorescent carbon quantum dots and photocatalyst design. Angew. Chem. Int. Ed. 2010, 49, 4430–4434.
31. Kim, S.; Hwang, S.W.; Kim, M.-K.; Shin, D.Y.; Shin, D.H.; Kim, C.O.; Yang, S.B.; Park, J.H.; Hwang, E.; Choi, S.-H. Anomalous behaviors of visible luminescence from graphene quantum dots: Interplay between size and shape. ACS Nano 2012, 6, 8203–8208.
32. Zhu, S.; Song, Y.; Zhao, X.; Shao, J.; Zhang, J.; Yang, B. The photoluminescence mechanism in carbon dots (graphene quantum dots, carbon nanodots, and polymer dots): Current state and future perspective. Nano Res. 2015, 8, 355–381.
33. Yan, F.; Sun, Z.; Zhang, H.; Sun, X.; Jiang, Y.; Bai, Z. The fluorescence mechanism of carbon dots, and methods for tuning their emission color: A review. Microchim. Acta 2019, 186, 583.
34. Zhou, W.; Mo, F.; Sun, Z.; Luo, J.; Fan, J.; Zhu, H.; Zhu, Z.; Huang, J.; Zhang, X. Bright red-emitting P, Br co-doped carbon dots as “OFF-ON” fluorescent probe for Cu2+ and L-cysteine detection. J. Alloys Compd. 2022, 897, 162731.
35. Sonsin, A.F.; Silva, E.C.O.; Marques, A.L.X.; Silva, L.V.A.T.; Nascimento, S.M.S.; Souza, S.T.; Borbely, A.U.; Barbosa, C.D.E.S.; Fonseca, E.J.S. Tuning the photoluminescence by engineering surface states/size of S, N co-doped carbon dots for cellular imaging applications. Nanotechnology 2022, 33, 235708.
36. Durrani, S.; Zhang, J.; Yang, Z.; Pang, A.-P.; Zeng, J.; Sayed, S.M.; Khan, A.; Zhang, Y.; Wu, F.-G.; Lin, F. Plant-derived Ca, N, S-Doped carbon dots for fast universal cell imaging and intracellular Congo red detection. Anal. Chim. Acta 2022, 1202, 339672.
37. Dong, Y.; Pang, H.; Yang, H.B.; Guo, C.; Shao, J.; Chi, Y.; Li, C.M.; Yu, T. Carbon-Based dots co-doped with nitrogen and sulfur for high quantum yield and excitation-independent emission. Angew. Chem. Int. Ed. 2013, 52, 7800–7804.
38. Xu, Q.; Pu, P.; Zhao, J.; Dong, C.; Gao, C.; Chen, Y.; Chen, J.; Liu, Y.; Zhou, H. Preparation of highly photoluminescent sulfur-doped carbon dots for Fe (III) detection. J. Mater. Chem. A 2015, 3, 542–546.
39. Wu, F.; Yang, M.; Zhang, H.; Zhu, S.; Zhu, X.; Wang, K. Facile synthesis of sulfur-doped carbon quantum dots from vitamin B1 for highly selective detection of Fe3+ ion. Opt. Mater. 2018, 77, 258–263.
40. Liu, Y.; Duan, W.; Song, W.; Liu, J.; Ren, C.; Wu, J.; Liu, D.; Chen, H. Red emission B, N, S-co-doped carbon dots for colorimetric and fluorescent dual mode detection of Fe3+ ions in complex biological fluids and living cells. ACS Appl. Mater. Interfaces 2017, 9, 12663–12672.
41. Zhang, M.; Su, R.; Zhong, J.; Fei, L.; Cai, W.; Guan, Q.; Li, W.; Li, N.; Chen, Y.; Cai, L. Red/orange dual-emissive carbon dots for pH sensing and cell imaging. Nano Res. 2019, 12, 815–821.
42. Lin, L.; Luo, Y.; Tsai, P.; Wang, J.; Chen, X. Metal ions doped carbon quantum dots: Synthesis, physicochemical properties, and their applications. TrAC Trends Anal. Chem. 2018, 103, 87–101.
43. Xu, Q.; Su, R.; Chen, Y.; Theruvakkattil Sreenivasan, S.; Li, N.; Zheng, X.; Zhu, J.; Pan, H.; Li, W.; Xu, C. Metal charge transfer doped carbon dots with reversibly switchable, ultra-high quantum yield photoluminescence. ACS Appl. Nano Mater. 2018, 1, 1886–1893.
44. Tejwan, N.; Saini, A.K.; Sharma, A.; Singh, T.A.; Kumar, N.; Das, J. Metal-Doped and hybrid carbon dots: A comprehensive review on their synthesis and biomedical applications. J. Control. Release 2021, 330, 132–150.
45. Wu, W.; Zhan, L.; Fan, W.; Song, J.; Li, X.; Li, Z.; Wang, R.; Zhang, J.; Zheng, J.; Wu, M. Cu–N dopants boost electron transfer and photooxidation reactions of carbon dots. Angew. Chem. Int. Ed. 2015, 54, 6540–6544.
46. Zhang, Q.; Xu, W.; Han, C.; Wang, X.; Wang, Y.; Li, Z.; Wu, W.; Wu, M. Graphene structure boosts electron transfer of dual-metal doped carbon dots in photooxidation. Carbon N. Y. 2018, 126, 128–134.
47. Bourlinos, A.B.; Rathi, A.K.; Gawande, M.B.; Hola, K.; Goswami, A.; Kalytchuk, S.; Karakassides, M.A.; Kouloumpis, A.; Gournis, D.; Deligiannakis, Y. Fe (III)-functionalized carbon dots—Highly efficient photoluminescence redox catalyst for hydrogenations of olefins and decomposition of hydrogen peroxide. Appl. Mater. Today 2017, 7, 179–184.
48. Liao, H.; Wang, Z.; Chen, S.; Wu, H.; Ma, X.; Tan, M. One-pot synthesis of gadolinium (III) doped carbon dots for fluorescence/magnetic resonance bimodal imaging. RSC Adv. 2015, 5, 66575–66581.
49. Yuan, Y.H.; Li, R.S.; Wang, Q.; Wu, Z.L.; Wang, J.; Liu, H.; Huang, C.Z. Germanium-Doped carbon dots as a new type of fluorescent probe for visualizing the dynamic invasions of mercury (II) ions into cancer cells. Nanoscale 2015, 7, 16841–16847.

50. Wang, Y.; Zhang, Y.; Jia, M.; Meng, H.; Li, H.; Guan, Y.; Feng, L. Functionalization of carbonaceous nanodots from MnII-coordinating functional knots. Chem. Eur. J. 2015, 21, 14843–14850.

51. Zhu, C.; Yang, S.; Sun, J.; He, P.; Yuan, N.; Ding, J.; Mo, R.; Wang, G.; Ding, G.; Xie, X. Deep ultraviolet emission photoluminescence and high luminescece efficiency of ferric passivated graphene quantum dots: Strong negative inductive effect of Fe. Synth. Met. 2015, 209, 468–472.

52. Lin, L.; Song, X.; Chen, Y.; Rong, M.; Wang, Y.; Zhao, L.; Zhao, T.; Chen, X. Europium-decorated graphene quantum dots as a fluorescent probe for label-free, rapid and sensitive detection of Cu2+ and L-cysteine. Anal. Chim. Acta 2015, 891, 261–268.

53. Liu, T.; Li, N.; Dong, J.X.; Luo, H.Q.; Li, N.B. Fluorescence detection of mercury ions and cysteine based on magnesium and nitrogen co-doped carbon quantum dots and IMPLICATION logic gate operation. Sens. Actuators B Chem. 2016, 231, 147–153.

54. Wang, Y.; Meng, H.; Jia, M.; Zhang, Y.; Li, H.; Feng, L. Intraparticle FRET of Mn (ii)-doped carbon dots and its application in discrimination of volatile organic compounds. Nanoscale 2016, 8, 17190–17195.

55. Peng, Z.; Han, X.; Li, S.; Al-Youbi, A.O.; Bashammakh, A.S.; El-Shahawi, M.S.; Leblanc, R.M. Carbon dots: Biomacromolecule interaction, bioimaging and nanomedicine. Coord. Chem. Rev. 2017, 343, 256–277.

56. Liu, Y.-Y.; Yu, N.-Y.; Fang, W.-D.; Tan, Q.-G.; Ji, R.; Yang, L.-Y.; Wei, S.; Zhang, X.-W.; Miao, A.-J. Photodegradation of carbon dots cause cytotoxicity. Nat. Commun. 2021, 12, 812.

57. Liang, X.; Li, N.; Zhang, R.; Yin, P.; Zhang, C.; Yang, N.; Liang, K.; Kong, B. Carbon-Based SERS biosensor: From substrate design to sensing and bioapplication. NPG Asia Mater. 2021, 13, 8.

58. Li, N.; Than, A.; Sun, C.; Tian, J.; Chen, J.; Pu, K.; Dong, X.; Chen, P. Monitoring dynamic cellular redox homeostasis using fluorescence-switchable graphene quantum dots. ACS Nano 2016, 10, 11475–11482.

59. Li, F.; Li, Y.; Yang, X.; Han, X.; Jiao, Y.; Wei, T.; Yang, D.; Xu, H.; Nie, G. Highly fluorescent chiral N-S-doped carbon dots from cysteine: Affecting cellular energy metabolism. Angew. Chem. 2018, 130, 2401–2406.

60. Song, Y.; Wu, Y.; Wang, H.; Liu, S.; Song, L.; Li, S.; Tan, M. Carbon quantum dots from roasted Atlantic salmon (Salmo salar L.): Formation, biodistribution and cytotoxicity. Food Chem. 2019, 293, 387–395.

61. Chen, H.; Wen, K.; Chen, J.; Xing, W.; Wu, X.; Shi, Q.; Peng, A.; Huang, H. Ultra-Stable tellurium-doped carbon quantum dots for cell protection and near-infrared photodynamic application. Sci. Bull. 2020, 65, 1580–1586.

62. Wang, S.; Cole, I.S.; Li, Q. The toxicity of graphene quantum dots. RSC Adv. 2016, 6, 89867–89878.

63. Mishra, V.; Patil, A.; Thakur, S.; Kesharwani, P. Carbon dots: Emerging theranostic nanoarchitectures. Drug Discov. Today 2018, 23, 1219–1232.

64. Li, J.; Zuo, G.; Pan, X.; Wei, W.; Qi, X.; Su, T.; Dong, W. Nitrogen-Doped carbon dots as a fluorescent probe for the highly sensitive detection of Ag+ and cell imaging. Luminescence 2018, 33, 243–248.

65. Zhang, Q.; Xie, S.; Yang, Y.; Wu, Y.; Wang, X.; Wu, J.; Zhang, L.; Chen, J.; Wang, Y. A facile synthesis of highly nitrogen-doped carbon dots for imaging and detection in biological samples. J. Anal. Methods Chem. 2018, 2018, 7890937.

66. Arul, V.; Edison, T.N.J.I.; Lee, Y.R.; Sethuraman, M.G. Biological and catalytic applications of green synthesized fluorescent N-doped carbon dots using Hylocereus undatus. J. Photochem. Photobiol. B Biol. 2017, 168, 142–148.

67. Edison, T.N.J.I.; Atchudan, R.; Shim, J.-J.; Kalimuthu, S.; Ahn, B.-C.; Lee, Y.R. Turn-Off fluorescence sensor for the detection of ferric ion in water using green synthesized N-doped carbon dots and its bio-imaging. J. Photochem. Photobiol. B Biol. 2016, 158, 235–242.

68. Edison, T.N.J.I.; Atchudan, R.; Sethuraman, M.G.; Shim, J.-J.; Lee, Y.R. Microwave assisted green synthesis of fluorescent N-doped carbon dots: Cytotoxicity and bio-imaging applications. J. Photochem. Photobiol. B Biol. 2016, 161, 154–161.

69. Xu, Y.; Wu, M.; Liu, Y.; Feng, X.; Yin, X.; He, X.; Zhang, Y. Nitrogen-Doped carbon dots: A facile and general preparation method, photoluminescence investigation, and imaging applications. Chem. Eur. J. 2013, 19, 2276–2283.

70. Chen, H.; Wang, G.D.; Tang, W.; Todd, T.; Zhen, Z.; Tsang, C.; Hekmatyar, K.; Cowger, T.; Hubbard, R.B.; Zhang, W. Gd-Encapsulated carbonaceous dots with efficient renal clearance for magnetic resonance imaging. Adv. Mater. 2014, 26, 6761–6766.

71. Ren, X.; Liu, L.; Li, Y.; Dai, Q.; Zhang, M.; Jing, X. Facile preparation of gadolinium (iii) chelates functionalized carbon quantum dot-based contrast agent for magnetic resonance/fluorescence multimodal imaging. J. Mater. Chem. B 2014, 2, 5541–5549.

72. Chen, H.; Wang, G.D.; Sun, X.; Todd, T.; Zhang, F.; Xie, J.; Shen, B. Mesoporous silica as nanoreactors to prepare Gd-encapsulated carbon dots of controllable sizes and magnetic properties. Adv. Funct. Mater. 2016, 26, 3973–3982.
73. Pan, Y.; Yang, J.; Fang, Y.; Zheng, J.; Song, R.; Yi, C. One-Pot synthesis of gadolinium-doped carbon quantum dots for high-performance multimodal bioimaging. J. Mater. Chem. B 2017, 5, 92–101.
74. Shi, Y.; Pan, Y.; Zhong, J.; Yang, J.; Zheng, J.; Cheng, J.; Song, R.; Yi, C. Facile synthesis of gadolinium (III) chelates functionalized carbon quantum dots for fluorescence and magnetic resonance dual-modal bioimaging. Carbon N. Y. 2015, 93, 742–750.
75. Ren, X.Y.; Yuan, X.X.; Wang, Y.P.; Liu, C.L.; Qin, Y.; Guo, L.P.; Liu, L.H. Facile preparation of Gd3+ doped carbon quantum dots: Photoluminescence materials with magnetic resonance response as magnetic resonance/fluorescence bimodal probes. Opt. Mater. 2016, 57, 56–62.
76. Yu, C.; Xuan, T.; Chen, Y.; Zhao, Z.; Liu, X.; Lian, G.; Li, H. Gadolinium-Doped carbon dots with high quantum yield as an effective fluorescence and magnetic resonance bimodal imaging probe. J. Alloys Compd. 2016, 688, 611–619.
77. Xu, Y.; Jia, X.-H.; Yin, X.-B.; He, X.-W.; Zhang, Y.-K. Carbon quantum dot stabilized gadolinium nanoprobe prepared via a one-pot hydrothermal approach for magnetic resonance and fluorescence dual-modality bioimaging. Anal. Chem. 2014, 86, 12122–12129.
78. Bourlinos, A.B.; Bakandritsos, A.; Kouloumpis, A.; Gournis, D.; Krysmann, M.; Giannelis, E.P.; Polakova, K.; Safarova, K.; Hola, K.; Zboril, R. Gd (III)-doped carbon dots as a dual fluorescent-MRI probe. J. Mater. Chem. 2012, 22, 23327–23330.
79. Yang, X.; Zhang, M.; Zhang, Y.; Wang, N.; Bian, W.; Choi, M.M.F. Nitrogen and phosphorus co-doped carbon dots as a “turn-off-on” fluorescence probe for the detection of Hg2+ and GSH and cell imaging. Anal. Methods 2019, 11, 5803–5809.
80. Geng, B.; Yang, D.; Pan, D.; Wang, L.; Zheng, F.; Shen, W.; Zhang, C.; Li, X. NIR-Responsive carbon dots for efficient photothermal cancer therapy at low power densities. Carbon N. Y. 2018, 134, 153–162.
81. Lan, M.; Zhao, S.; Zhang, Z.; Yan, L.; Guo, L.; Niu, G.; Zhang, J.; Zhao, J.; Zhang, H.; Wang, P. Two-Photon-Excited near-infrared emissive carbon dots as multifunctional agents for fluorescence imaging and photothermal therapy. Nano Res. 2017, 10, 3113–3123.
82. Lin, J.-S.; Tsai, Y.-W.; Dehvari, K.; Huang, C.-C.; Chang, J.-Y. A carbon dot based theranostic platform for dual-modal imaging and free radical scavenging. Nanoscale 2019, 11, 20917–20931.
83. Dehvari, K.; Chiu, S.-H.; Lin, J.-S.; Girma, W.M.; Ling, Y.-C.; Chang, J.-Y. Heteroatom doped carbon dots with nanoenzyme like properties as theranostic platforms for free radical scavenging, imaging, and chemotherapy. Acta Biomater. 2020, 114, 343–357.