Інститут хімії поверхні ім. О.О. Чуйка
НАЦІОНАЛЬНА АКАДЕМІЯ НАУК УКРАЇНИ

Gd-containing magnetic nanoparticles for neutron capture therapy and magnetic resonance imaging

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Bukovel

Neutron capture therapy – basic principles (1)

$$^{157}Gd + n \rightarrow {}^{158*}Gd \rightarrow {}^{158}Gd + \gamma\ (2{,}2\ MeV) \qquad (7{,}9\ MeV)$$

→ Internal conversion electrons

→ Auger electrons

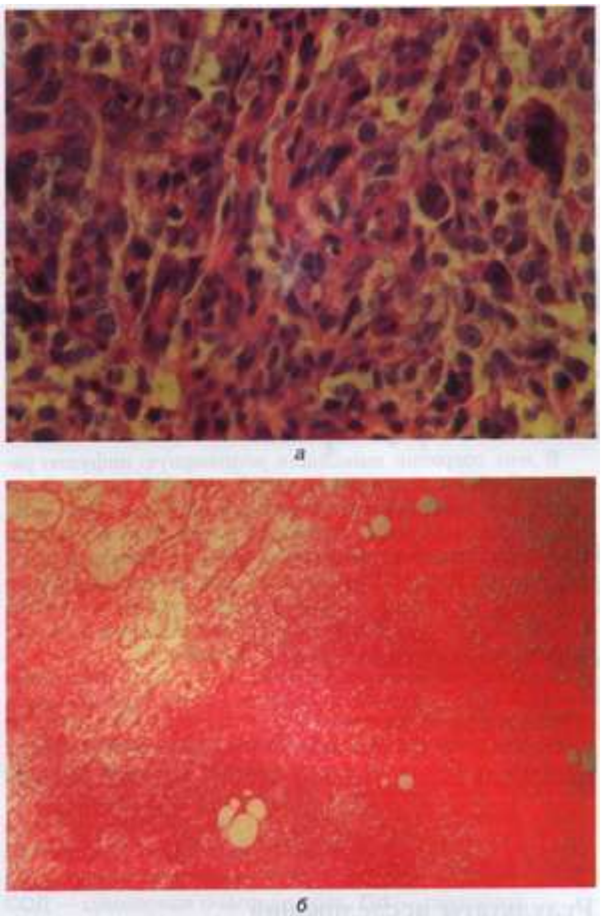
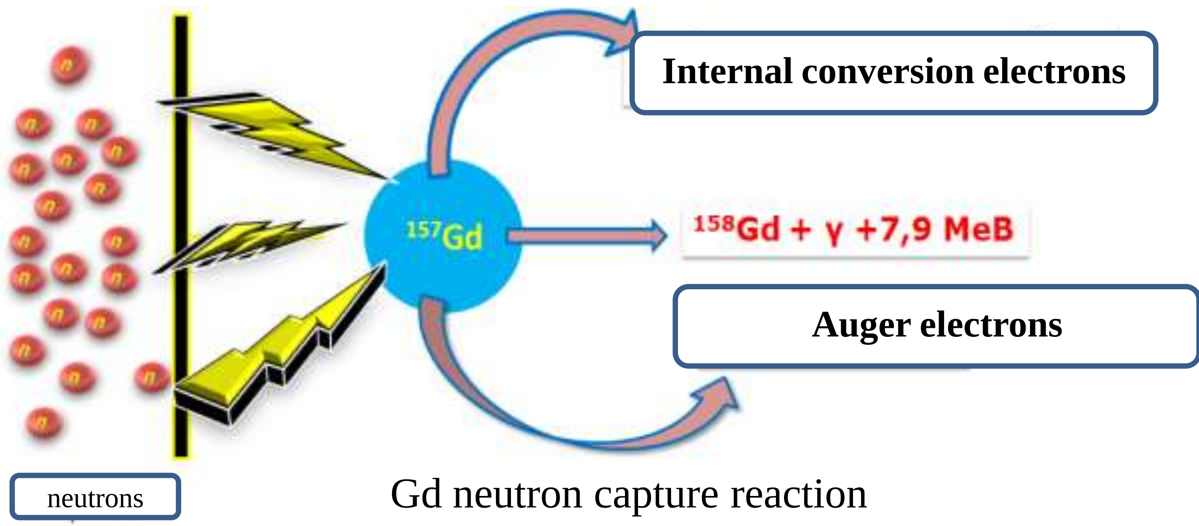


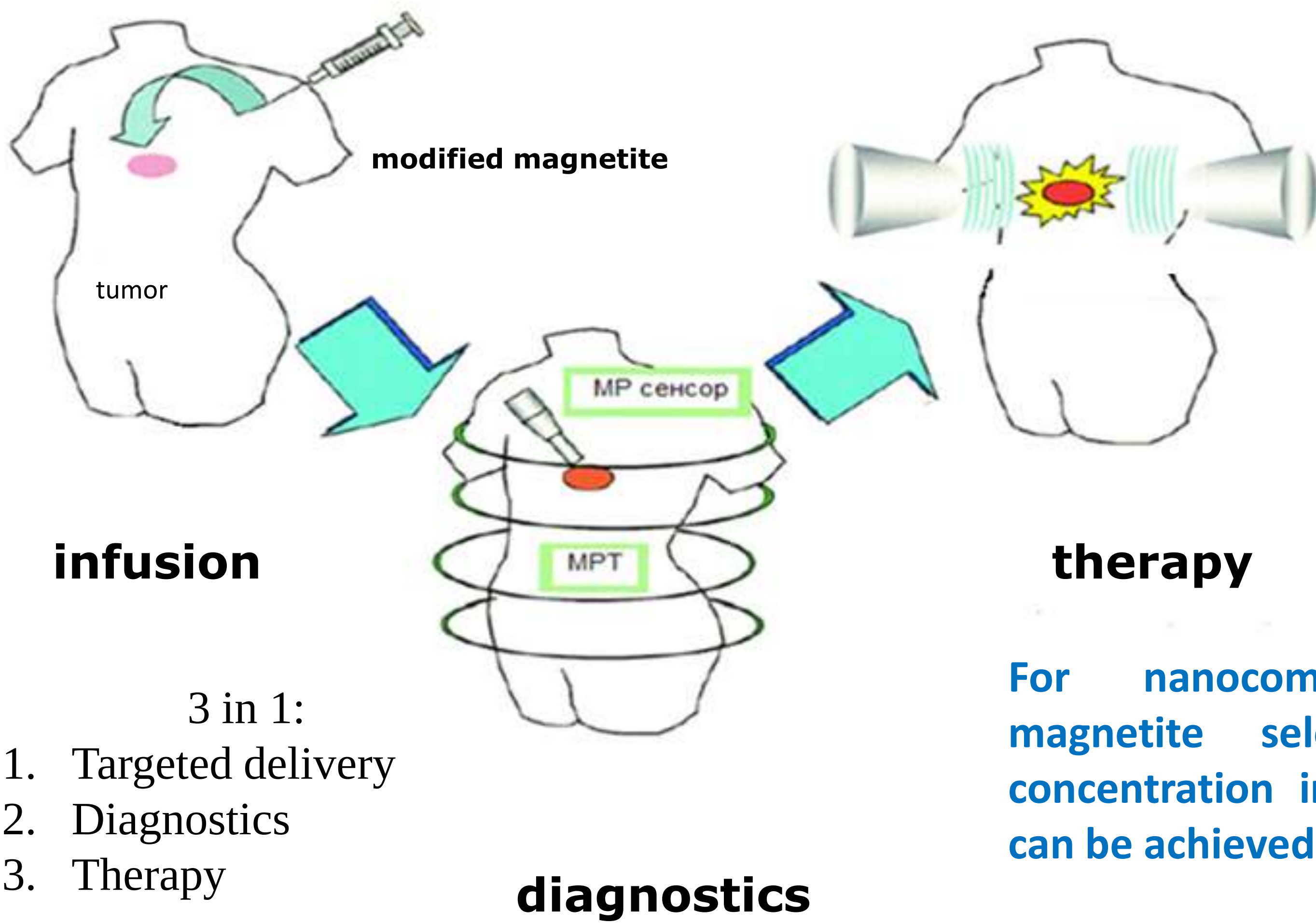
Рис. 3. Результаты ГНЗТ остеосаркомы:
а — до облучения. Мелкоклеточная остеосаркома. Окраска гематоксилином и эозином, ×400; *б* — после облучения. Тотальный некроз опухолевой ткани. Патоморфоз IV степени. Окраска гематоксилином и эозином, ×400



Gd neutron capture reaction

http://www.irsovet.ru/publish/numer3-2007.html

Neutron capture therapy – basic principles (2)



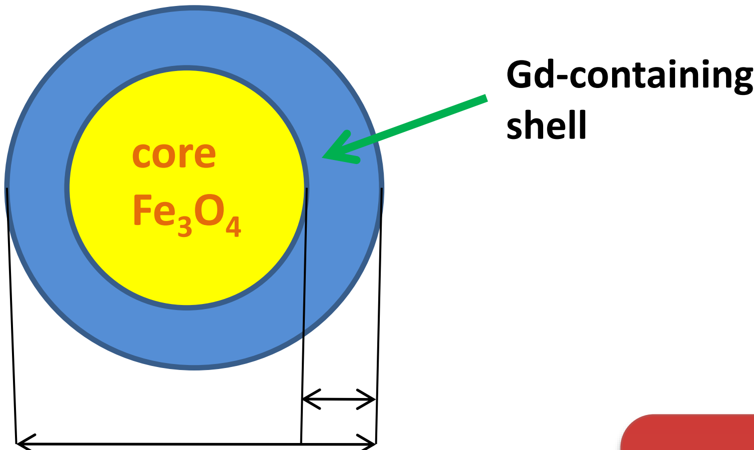
3 in 1:

1. Targeted delivery
2. Diagnostics
3. Therapy

For nanocomposites based on magnetite selective delivery and concentration in the tumor or organ can be achieved by a magnetic field.

Purpose - synthesis of nanocomposites are promising for use in neutron capture therapy, magnetic resonance imaging.

Core-shell magnetic nanostructures



Gd-containing shell obtained by:

Doping :
Gd_2O_3
$GdFeO_3$
$GdBO_3$

Chemical modification:
γ-APS/DTPA/Gd
DMSA/Gd

Fe_3O_4/ Gd_2O_3 Fe_3O_4/ $GdFeO_3$ nanostructures- Synthesis and properies

To a solution of bivalent and trivalent iron salts (1M 2M) was added a solution of 1 mol salt Gd. Solution slowly precipitated with ammonia with vigorous stirring at 80-90 ° C. The precipitate was filtered, washed with distilled water to pH = 7.

Synthesis scheme

$$Gd^{3+} + Fe^{2+} + Fe^{3+} + OH^{-} \longrightarrow Fe_3O_4/\ Gd_2O_3$$

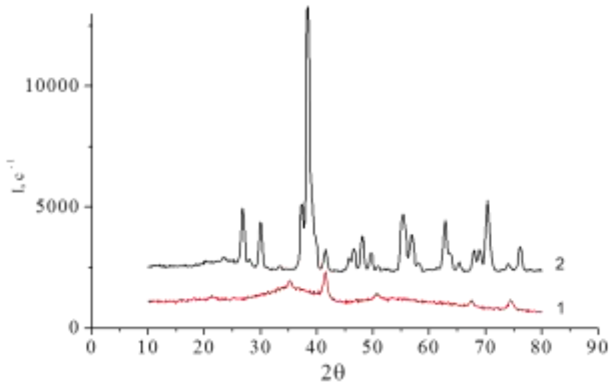
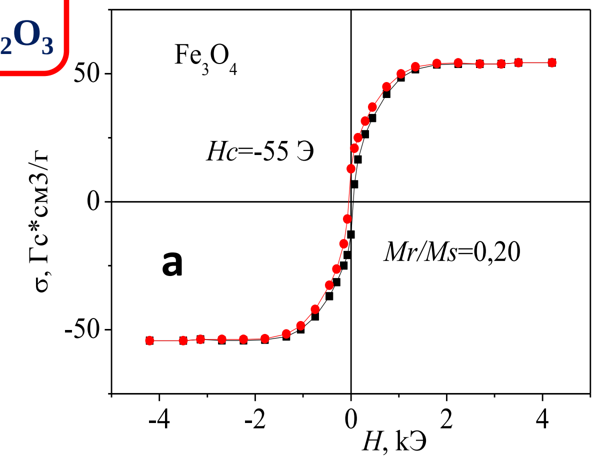
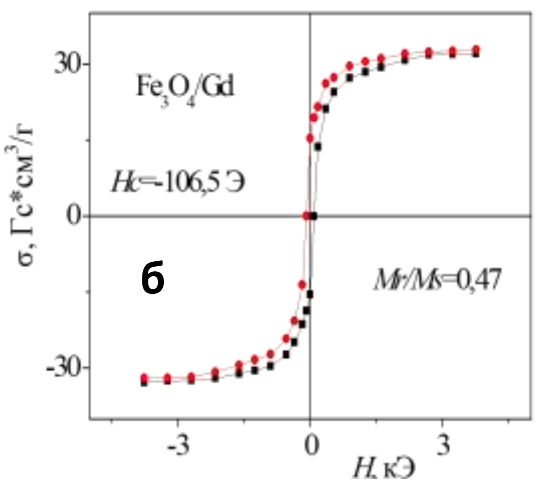
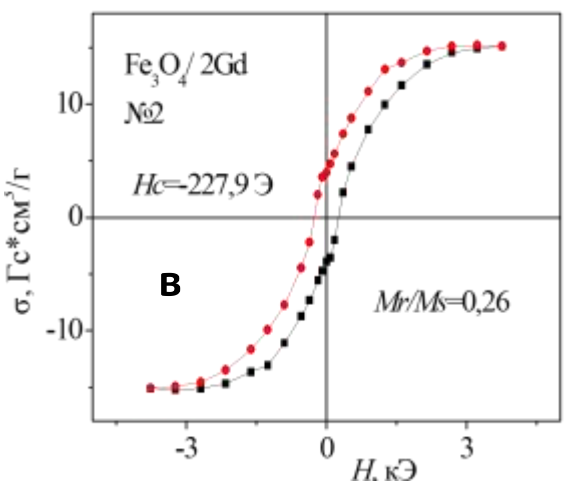


Fig. 1. XRD patterns of magnetite, doped by Gd^{3+}: 1 – sample synthesied at T = 20 ° C; 2 – sample annealed at 1000 ° C

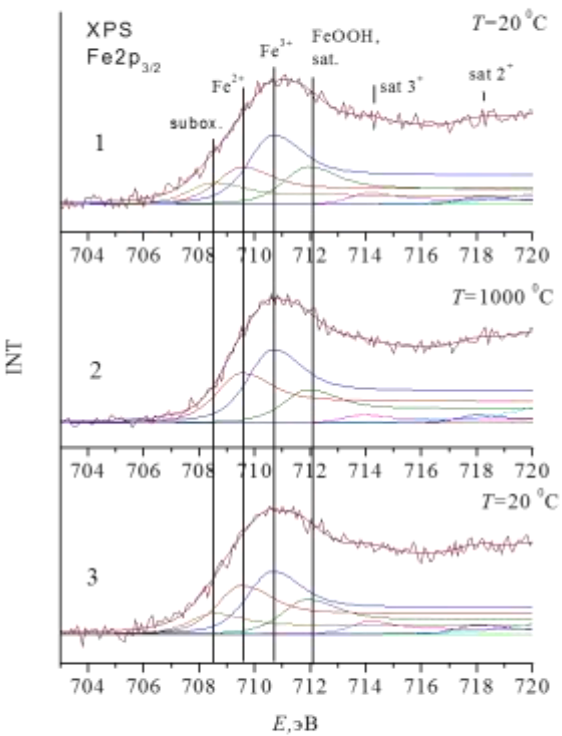




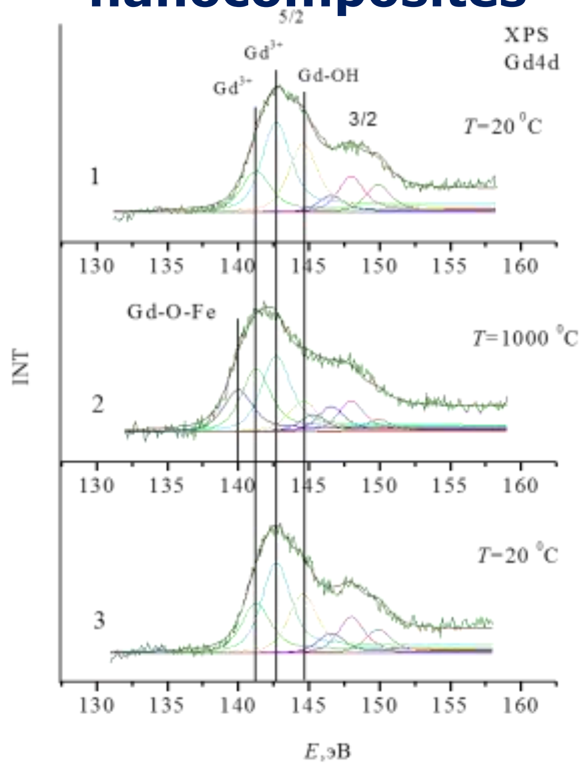


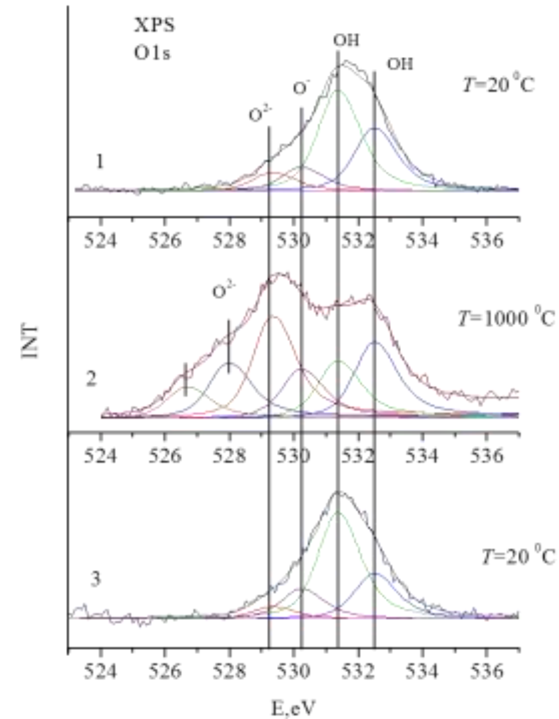
Hysteresis curve of
: a – magnetite, б – magnetite doped with Gd^{3+}, в - magnetite doped with double quantity of Gd^{3+}

XPS study of Fe_3O_4/ Gd_2O_3 nanocomposites



Fe2p XPS from samples Fe_3O_4/Gd, obtained at different temperatures (1, 2), 3 – double contain of Gd^{3+}





a – Gd4d, b – O1s XPS from samples Fe_3O_4/Gd, obtained at different temperatures

In the Eb = 708.5 eV signal is present on the suboxide of iron, which disappears in the spectrum of 2 (Fig. 3) during annealing. In the Eb = 712.1 eV recorded signal, which also can be associated with both phase FeOOH, and with the contribution of the satellite structure and is proportional to the magnetic characteristics.

On the surface of magnetite nanoparticles gadolinium is present in the trivalent state Gd^{3+}. E_b Gd4d5/2 = 141.3 and 142.7 eV, corresponding to Gd_2O_3, and E_b Gd4d5/2 = 144.7 eV - $Gd(OH)_3$. At the E_b Gd4d5/2 = 139.9 eV signal is present, which can be linked to a bond Gd-O-Fe.

Fe_3O_4 / $GdFeO_3$ nanostructures- Synthesis and properies

Proceeding from molar ratio Fe^{2+}: Fe^{3+} = 1:2 for magnetite, Fe^{3+} was partly or totally replaced by Gd^{3+}

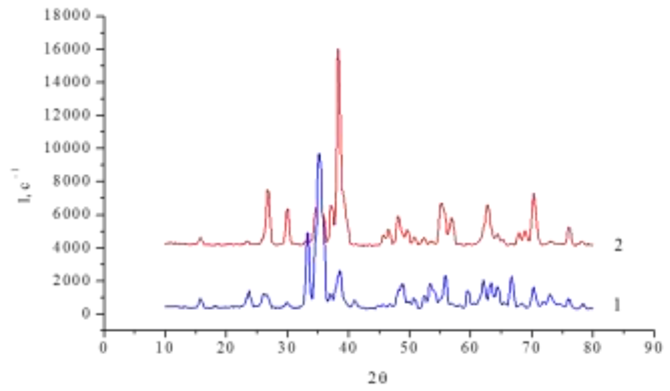
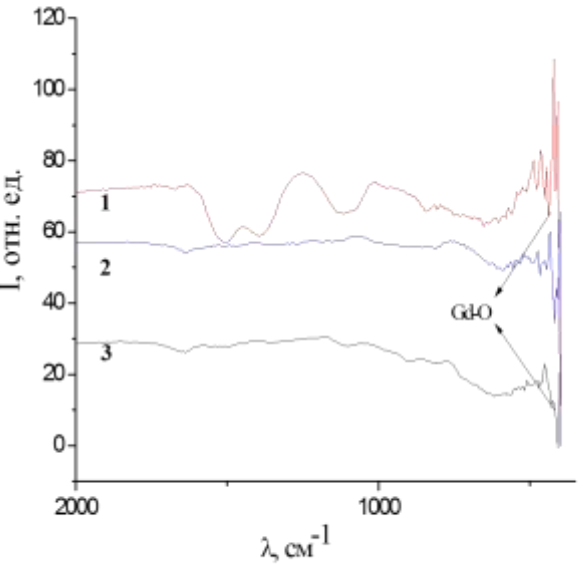
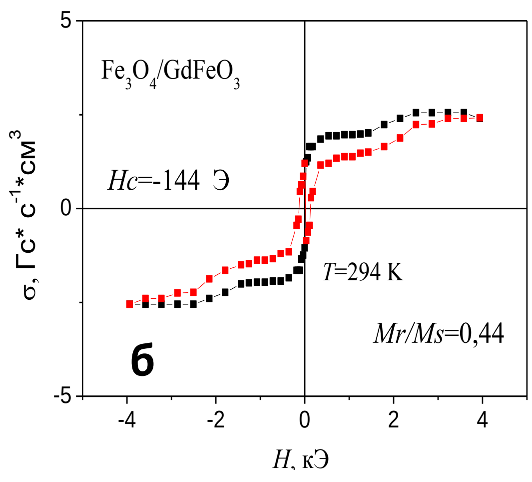
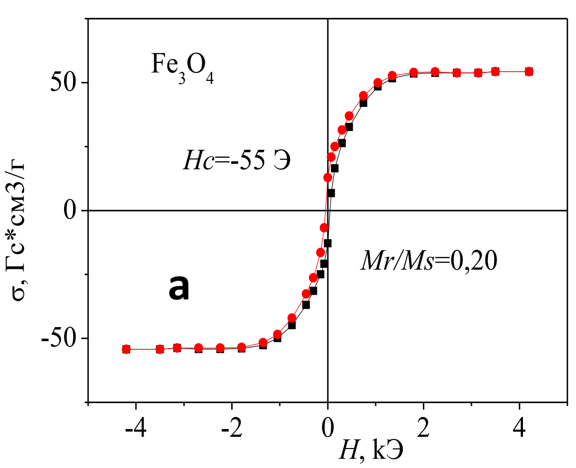


Рис. 5 FT-IR spectra for : 1 - magnetite, doped by Gd^{3+}, 2 - magnetite,, 3 – sample annealed at 1000 ° C ($GdFeO_3$)

Рис. 1. XRD patterns of: obtained by substitution, Fe^{3+} in magnetite to Gd^{3+} in 2:1 molar ratio (Gd^{3+}:Fe^{2+}) (sample 1); by substitution в in molar ratio 1 mole Fe^{3+}: 1 mole Gd^{3+}: 1 mole Fe^{2+} (sample 2), annealed at T = 1000 ° C

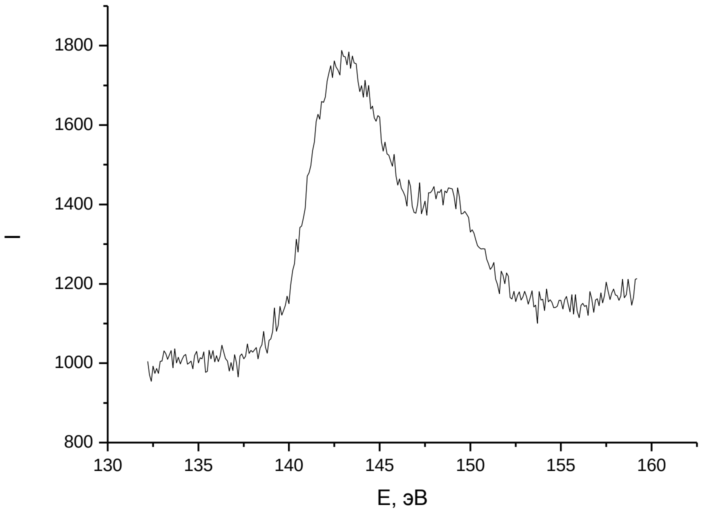






Hysteresis curve of : a – magnetite, б- $GdFeO_3$

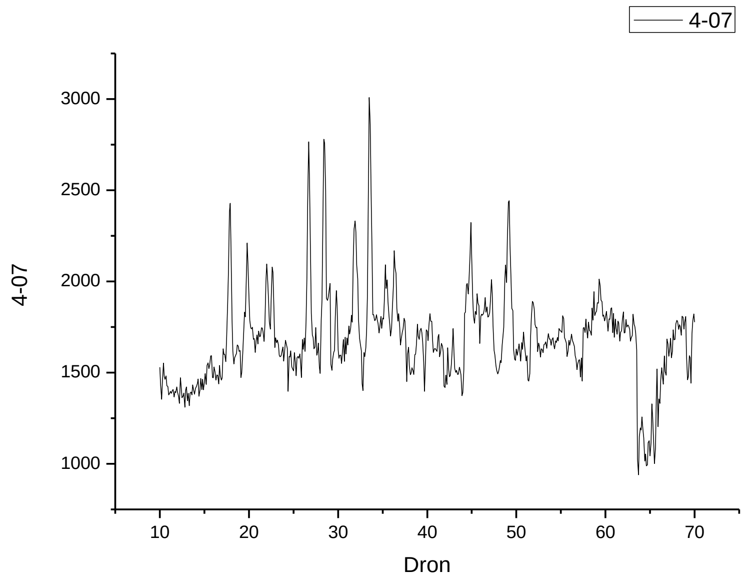
Fe_3O_4 / $GdBO_3$ nanostructures- Synthesis and properties



Gd4d XPS from Gd borate, immobilized on to surface of magnetite

A **scintillator** is a material, which exhibits scintillation—the property of luminescence[1] when excited by ionizing radiation. These materials can convert high energy radiation (X-rays,c-rays, neutrons) into UV-visible light, easily detectable with conventional detectors, is in constant development.

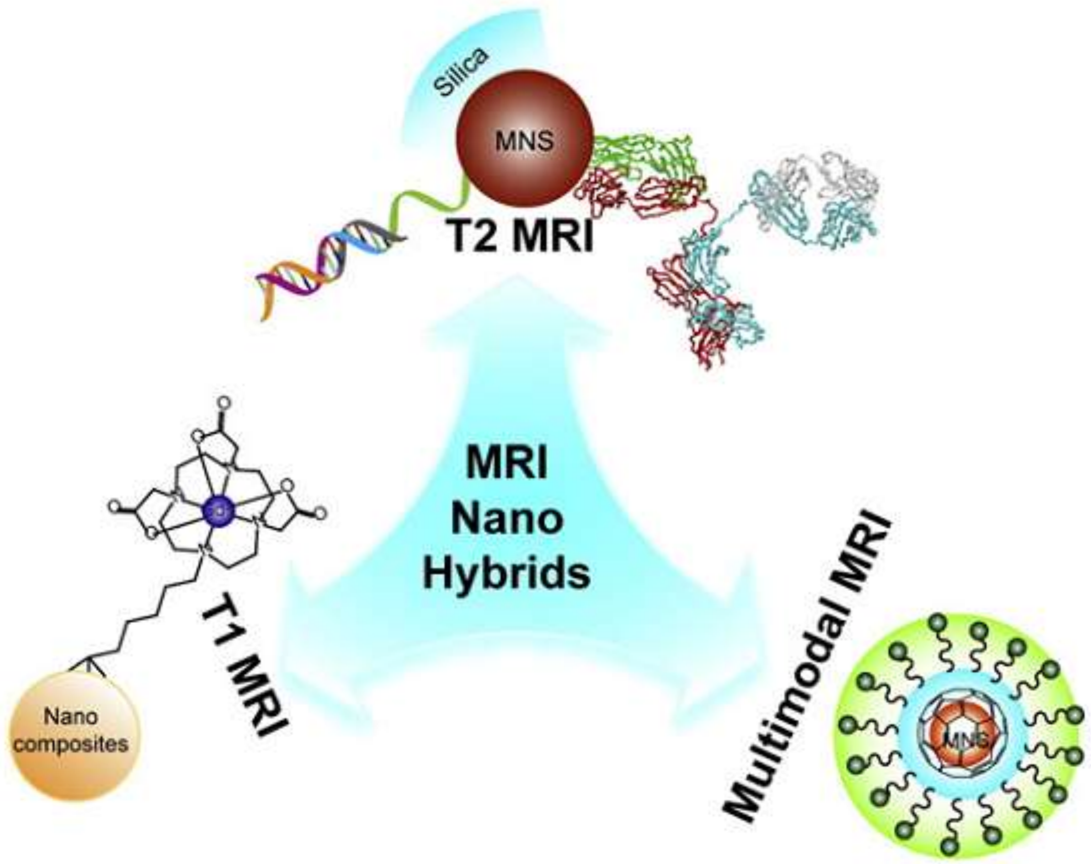
$$Gd^{3+} + BO^{3-} \rightarrow GdBO_3$$



XRD patterns of Gd borate after annealing at 1000° C

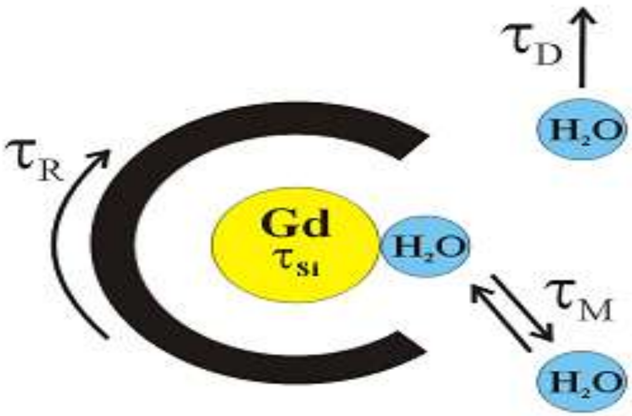
For instance, lithium and boron glass detectors, with high neutron cross-sections are particularly well suited to the detection of thermal (slow) neutrons

Dual modality MRI nanohybrids



Like other nanoparticle agents, iron based MNSs are popular multimodal imaging vehicles. Here, surface conjugation with alternative imaging probes is the most studied methodology for creating **multimodal** agents. **Multimodal** agents may facilitate improved diagnosis.

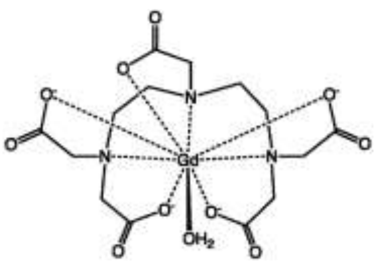
MRI applications.
Gd^{3+} contrast agents



Schematic view of the paramagnetic relaxation mechanism s and
the ma in relaxation parameters for an aqueous solution of a Gd3+ chelate.

The residence time of the water molecules , τM may affect relaxivity by limiting the efficiency of the water exchange process. For systems with one available water coordination site, exchange rates decrease with the presence of bulky substituent groups in the ligand.

The main parameters that affect the solvent relaxation rate are (1) the rotational correlation time, τR, (interval between two successive reorientations or positional changes of the molecule) (2) the coordination number and (3) the mean water residence time τ M.



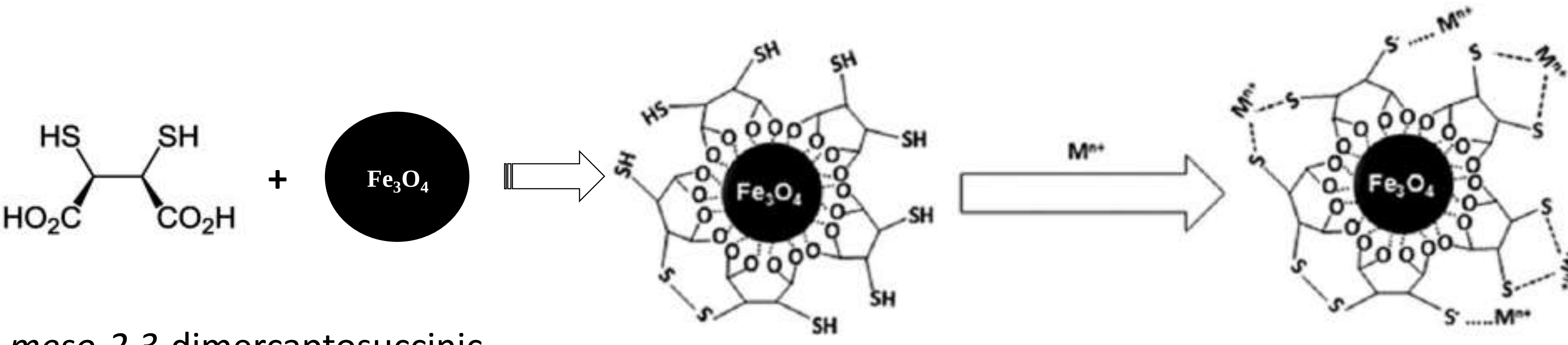
1

2

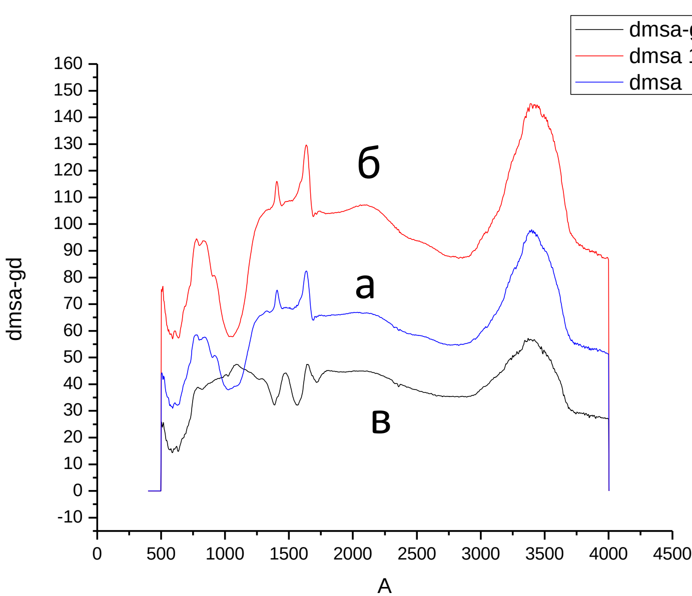
Structures of Gd (DTPA) (left) and Gd (DOTA) (right)

Gd^{3+} affect on T_1 proton relaxivity,
magnetite (Fe_3O_4) –on T_2 proton relaxivity.

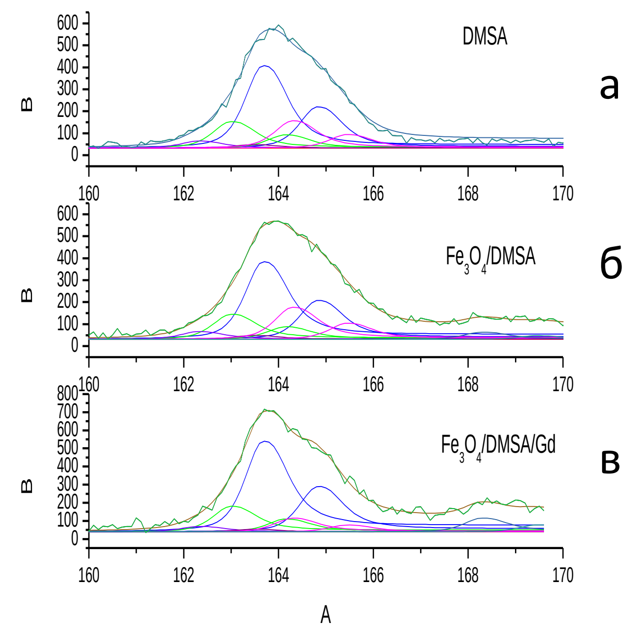
Fe_3O_4 / DMSA /Gd nanocomposite



meso-2,3-dimercaptosuccinic acid(DMSA)

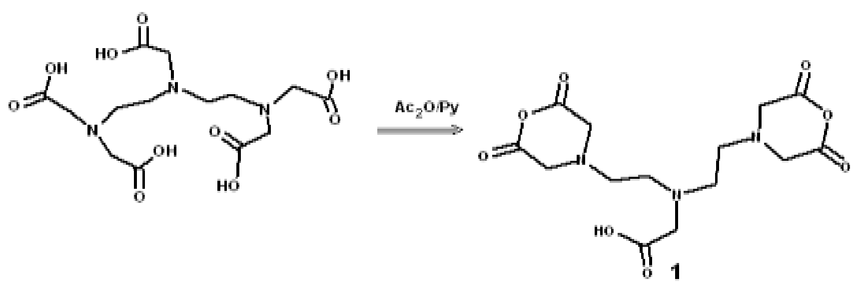


FT-IR spectra for : a – magnetite,coated with DMSA, б – dried at 115C, в – a, coordinated with Gd^{3+}



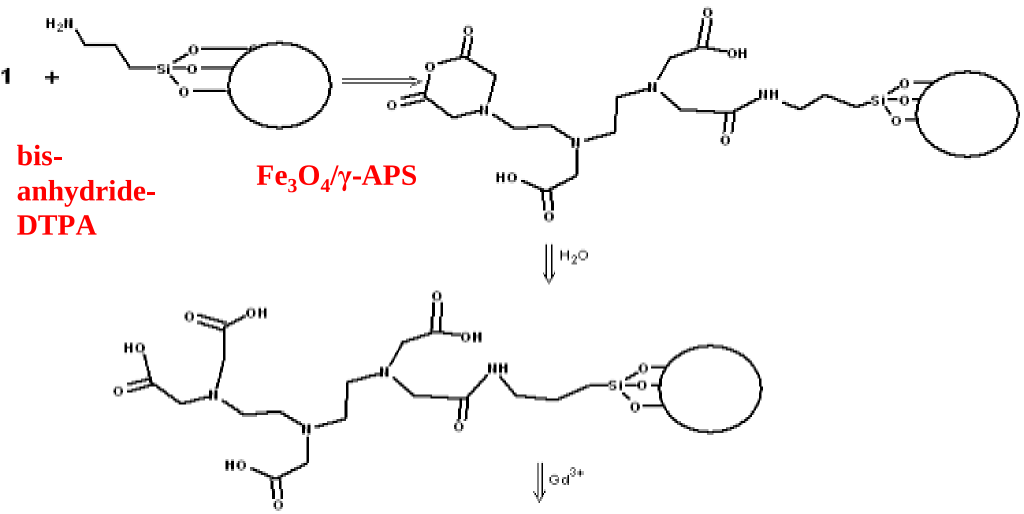
S2p XPS from samples : a- DMSA, б - magnetite,coated with DMSA, в – b, coordinated with Gd^{3+}

Surface functionalization of Fe_3O_4/γ-APS by Gd-DTPA complex



DTPA

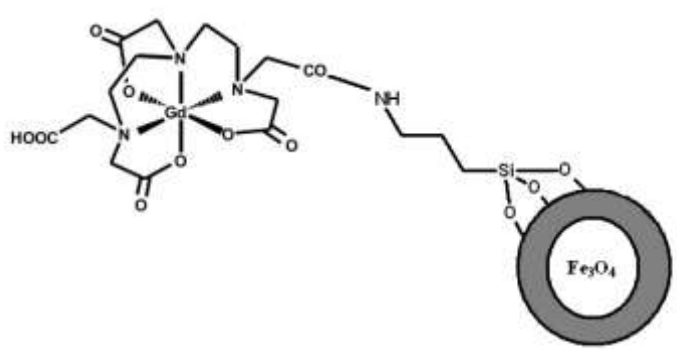
bis-anhydride - DTPA



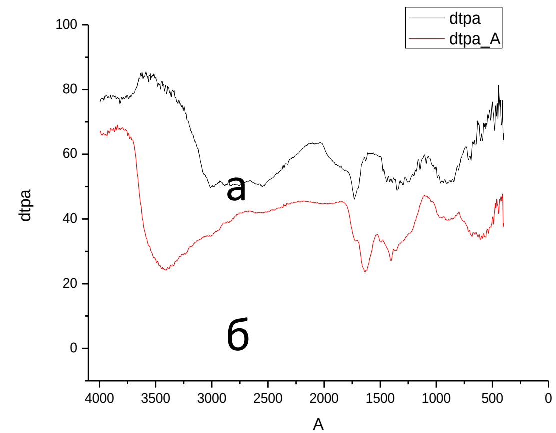
bis-anhydride-DTPA

Fe_3O_4/γ-APS

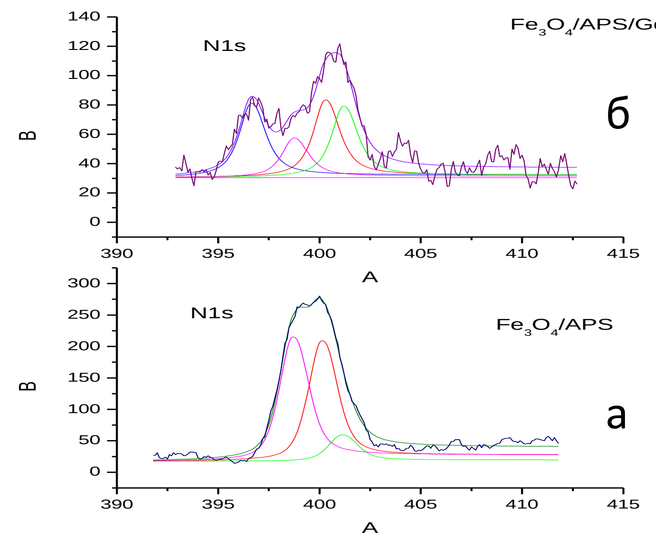
Fe_3O_4/γ-APS/ DTPA



Fe_3O_4/γ-APS/ DTPA-Gd

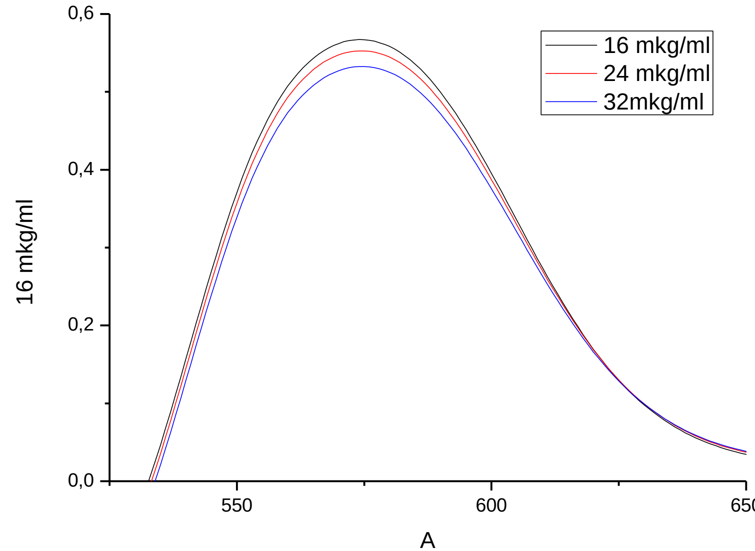


FT-IR spectra for : a-DTPA, б- DTPA-bis-anhydride

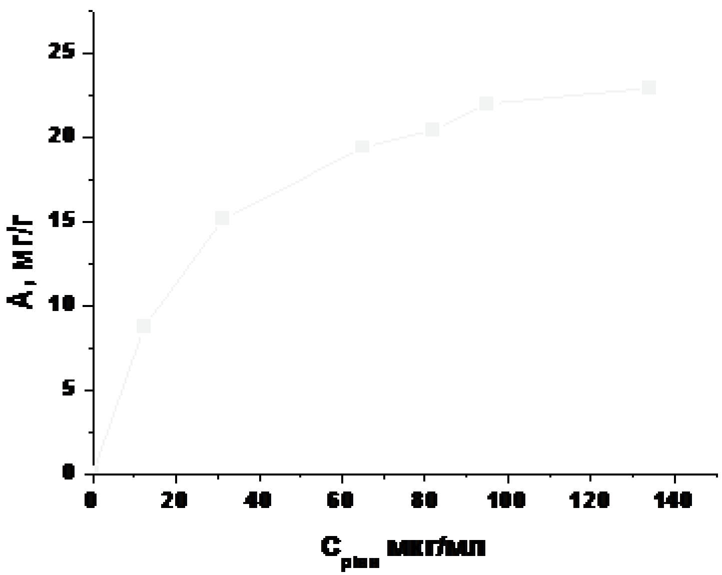


N1s XPS from samples : a-magnetite- γ- APS, б-Fe_3O_4/γ-APS/DTPA-Gd

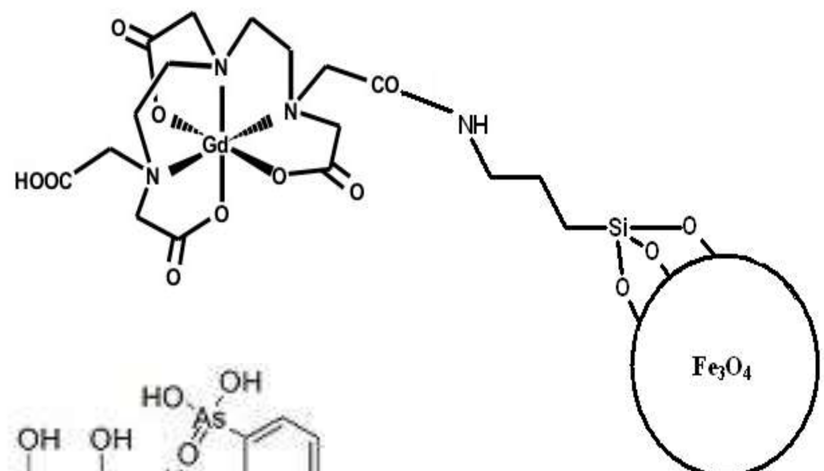
Complexation of Gd ions with Fe_3O_4/γ-APS/DTPA-Gd nanocomposite

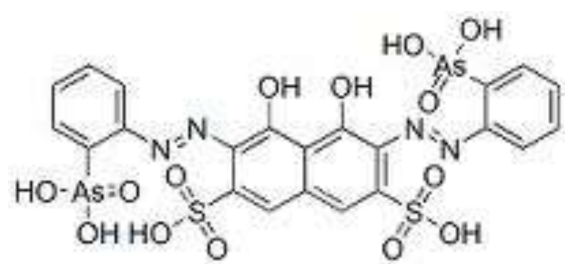


The absorption spectra of the complex arsenazo-3 with different Gd concentrarions.

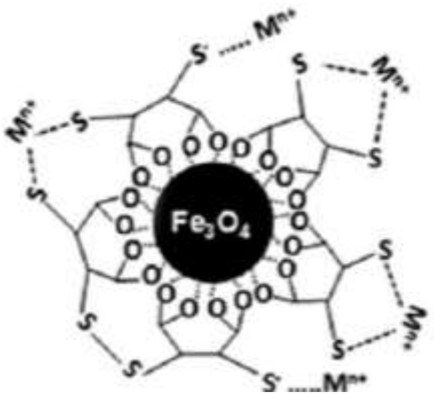


Adsorption of Gd^{3+} ions by Fe_3O_4/γ-APS/ DTPA nanocomposite

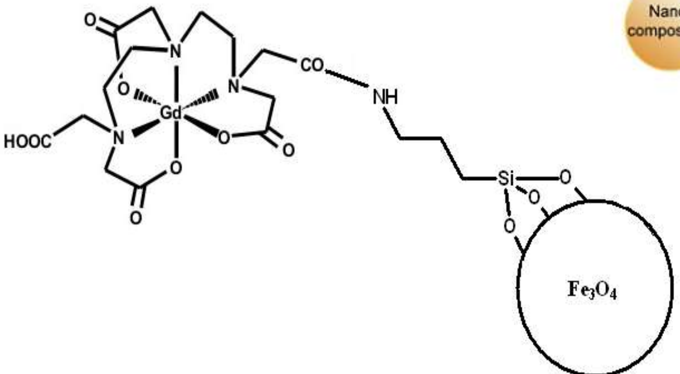




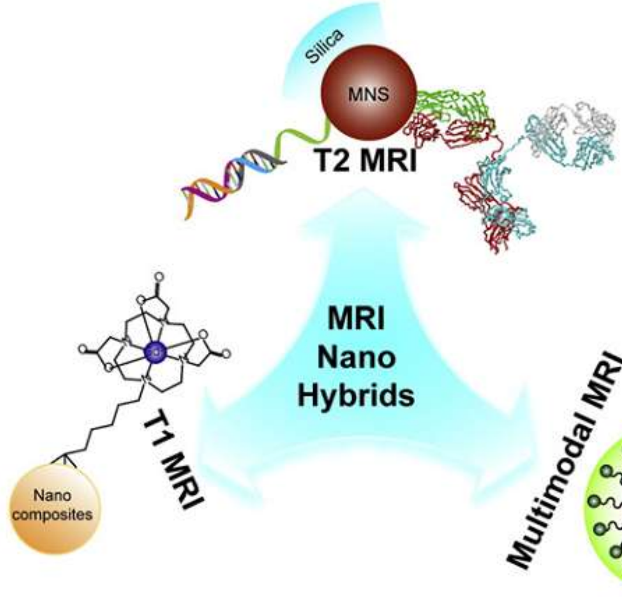
Arsenazo-3



Fe_3O_4 / DMSA /Gd



Fe_3O_4/γ-APS/ DTPA-Gd



	T1	*T2*	Neutron capture agent	Targeting via magnetic field	Hyperthermia
Fe_3O_4	–	+	–	+	+
Surface-modified magnetite	±	+	–	+	+
Modifier	+	–	+	–	–
Resulting nanocomposite	**+**	**+**	**+**	**+**	**+**

Conclusions

1. Synthesized Gd-containing nanocomposites perspective for medicine and biology for the comprehensive use of NC T and T_1/T_2 MRI diagnostics in real time, and were studied some of their physical and chemical properties.

2. The synthesized nanocomposites studied in INR NAS to assess the effectiveness of their interactions with microbiological object in thermal neutron irradiation conditions.