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Supplemantary Information for

Modulation of the structural properties of mesoporous silica nanoparticles to enhance the T_1-weighted MR imaging capability

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SUPPORTING INFORMATION

Samples Abbrivation List:

$[MSN]_{cal.}$ = Regular mesoporous silica nanoparticles (MSN) and surfactant (the structure directing agent- SDA) was removed by calcination
$[MSN]_{extr.}$ = Regular MSN and SDA was removed by solvent extraction
$[H\text{-}MSN]_{cal.}$ = Hollow structured mesoporous silica nanoparticles (Hollow MSN) with expanded pore size and SDA was removed by calcination
$[H\text{-}MSN]_{extr.}$ = Hollow MSN with expanded pore size and SDAwas removed by solvent extraction
$[MSN]_{cal..}$: **$(Gd(Cl)_3)_{in\ situ}$**=Regular MSN ,$GdCl_3$ was added into synthesis solution(*in situ synthesis doping*) and SDA was removed by calcination
$[MSN]_{cal.}$: $(Gd(aca)_3)_{in\ situ}$= Regular MSN ,$Gd(aca)_3$ was added into synthesis solution(*in situ synthesis doping*) and SDA was removed by calcination
$[H\text{-}MSN]_{cal.}$: $(Gd(Cl)_3)_{in\ situ}$ = Hollow MSN with expanded pore size ,$GdCl_3$ was added into synthesis solution(*in situ synthesis doping*) and SDA was removed by calcination
$[H\text{-}MSN]_{cal.}$: $(Gd(aca)_3)_{in\ situ}$ =Hollow MSN with expanded pore size ,$Gd(aca)_3$ was added into synthesis solution(*in situ synthesis doping*) and SDAwas removed by calcination
$[MSN]_{extr.}$-$(DOTA)_{in\ situ}$= Regular MSN ,DOTA was added into synthesis solution(after pre-reacting with APTES) and SDA was removed by solvent extraction
$[H\text{-}MSN]_{extr.}$- $(DOTA)_{in\ situ}$= Hollow MSN with expanded pore size ,DOTA was added into synthesis solution(after pre-reacting with APTES) and SDA was removed by solvent extraction
$[MSN]_{cal.}$: $(Gd(Cl)_3)_{post}$ = Regular MSN, SDA was removed by calcination ,$Gd(Cl)_3$ was doped on pristine MSN (*post synthesis doping*)
$[MSN]_{extr.}$: $(Gd(Cl)_3)_{post}$= Regular MSN, SDA was removed by solvent extraction ,$Gd(Cl)_3$ was doped on pristine MSN (*post synthesis doping*)
$[MSN]_{calc.}$: $(Gd(aca)_3)_{post}$ = Regular MSN, SDA was removed by calcination ,$Gd(aca)_3$ was doped on pristine MSNs (*post synthesis doping*)
$[MSN]_{extr.}$: $(Gd(aca)_3)_{post}$ = Regular MSN, SDA was removed by solvent extraction ,$Gd(aca)_3$ was doped on pristine MSN (*post synthesis doping*)
$[H\text{-}MSN]_{cal.}$: $(Gd(Cl)_3)_{post}$ = Hollow MSN with expanded pore size , SDA was removed by calcination ,$Gd(Cl)_3$ was doped on pristine H-MSN (*post synthesis doping*)
$[H\text{-}MSN]_{extr.}$: $(Gd(Cl)_3)_{post}$ = Hollow MSN with expanded pore size , SDA was removed by solvent extraction ,$Gd(Cl)_3$ was doped on pristine H-MSN (*post synthesis doping*)
$[H\text{-}MSN]_{cal}$: $(Gd(aca)_3)_{post}$ =Hollow MSN with expanded pore size , SDA was removed by calcination ,$Gd(aca)_3$ was doped on pristine H-MSN (*post synthesis doping*)
$[H\text{-}MSN]_{extr.}$: $(Gd(aca)_3)_{post}$= Hollow MSN with expanded pore size , SDA was removed by solvent extraction ,$Gd(aca)_3$ was doped on pristine H-MSN (*post synthesis doping*)

$[MSN]_{cal.}$-$(DOTA)_{post}$=Regular MSN and SDA was removed by calcination ,DOTA was post grafted on pristine MSNs (after pre-reacting with APTES)
$[MSN]_{extr.}$- $(DOTA)_{post}$=Regular MSN and SDA was removed by solvent ,DOTA was post conjugated on pristine MSNs
$[H\text{-}MSN]_{cal}$- $(DOTA)_{post}$= Hollow MSN with expanded pores size and SDA was removed by calcination ,DOTA was post grafted on pristine H-MSN (after pre-reacting with APTES)
$[H\text{-}MSN]_{extr.}$-$(DOTA)_{post}$=Hollow MSN with expanded pores size and SDA was removed by solvent extraction ,DOTA was post conjugated on pristine H-MSN

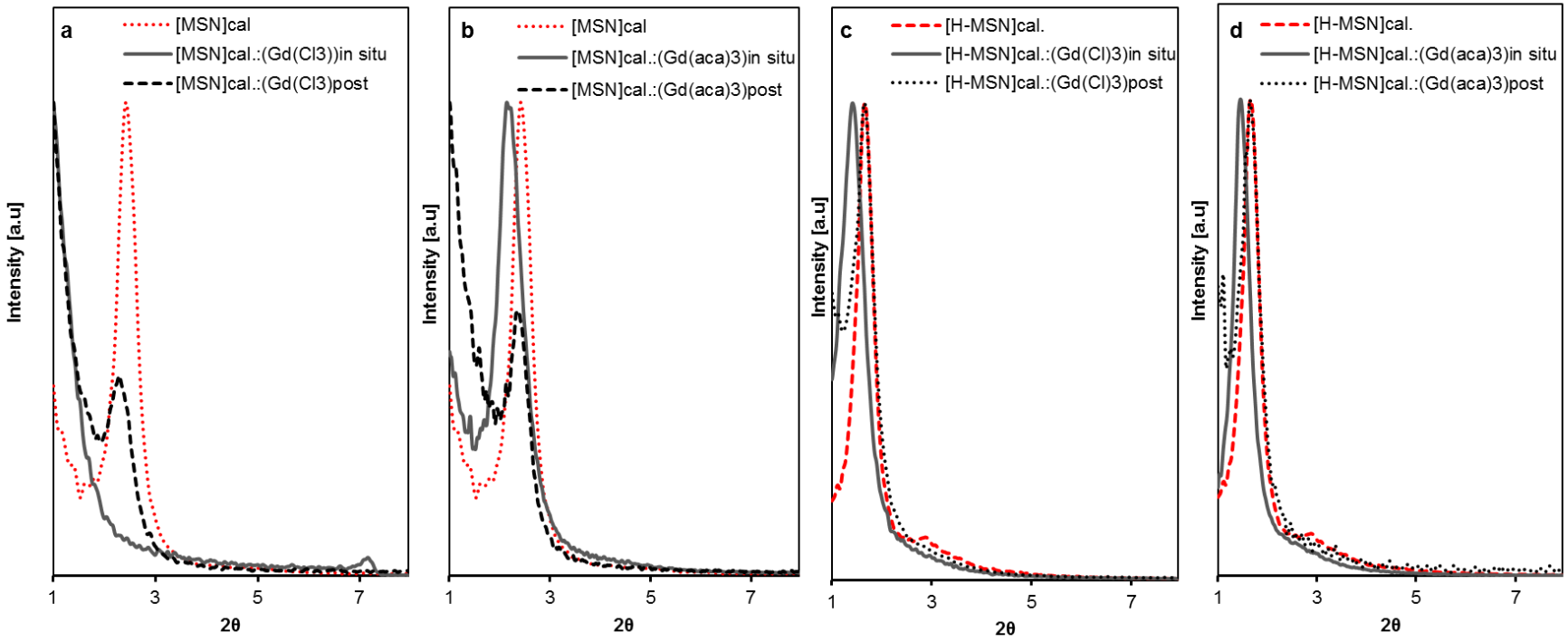

Figure S1. Powder X-ray diffraction (PXRD) pattern of prepared MSN based contrast agents a)different ways of $GdCl_3$ doping in regular MSN matrices b) different ways of $Gd(aca)_3$ doping in regular MSN matrices c)different ways of $GdCl_3$ doping in H-MSN matrices d) c)different ways of $Gd(aca)_3$ doping in H-MSN matrices

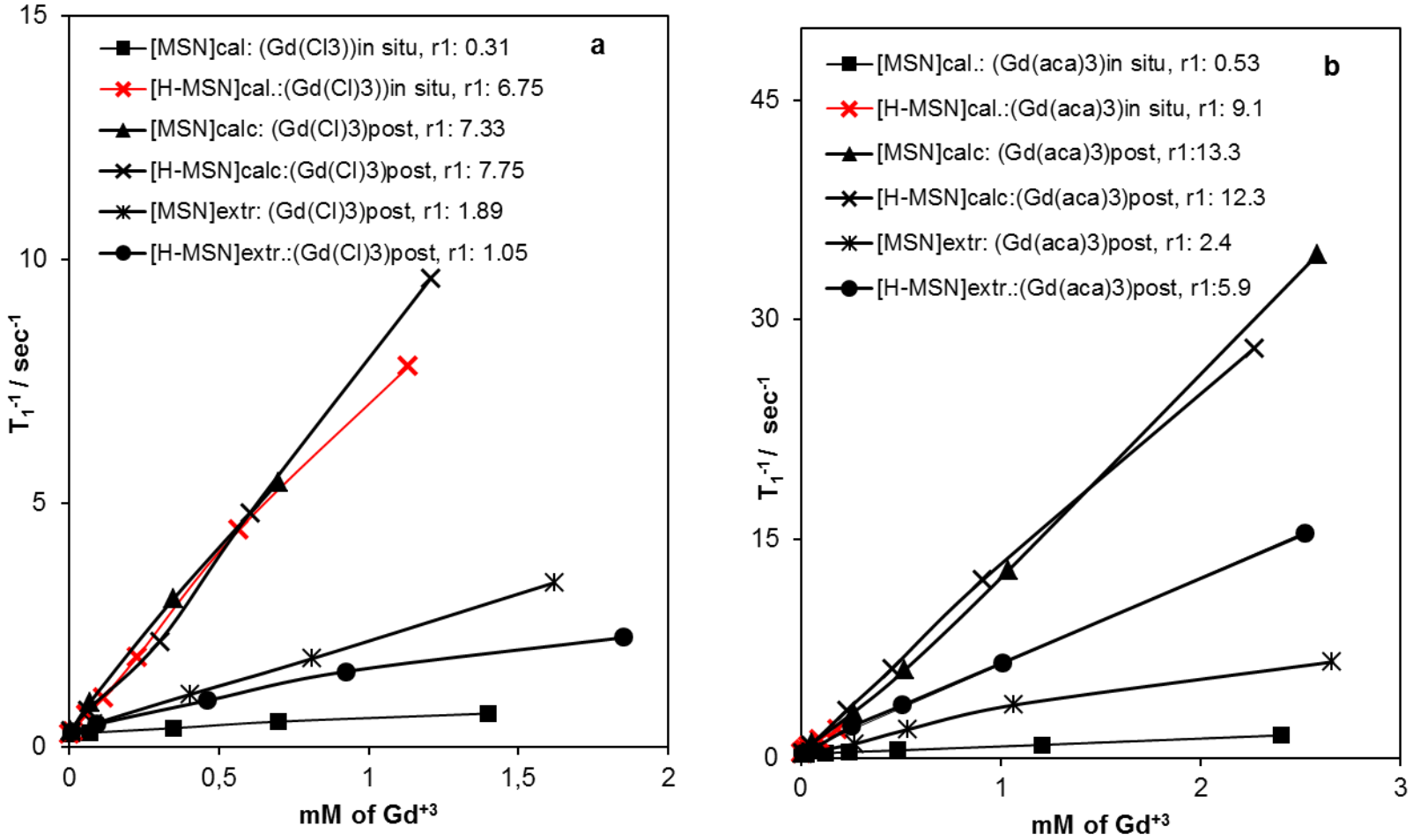

Figure S2.a) r_1 relaxivitiy values of MSN based contrast agents by doping a) $GdCl_3$ and b) $Gd(aca)_3$

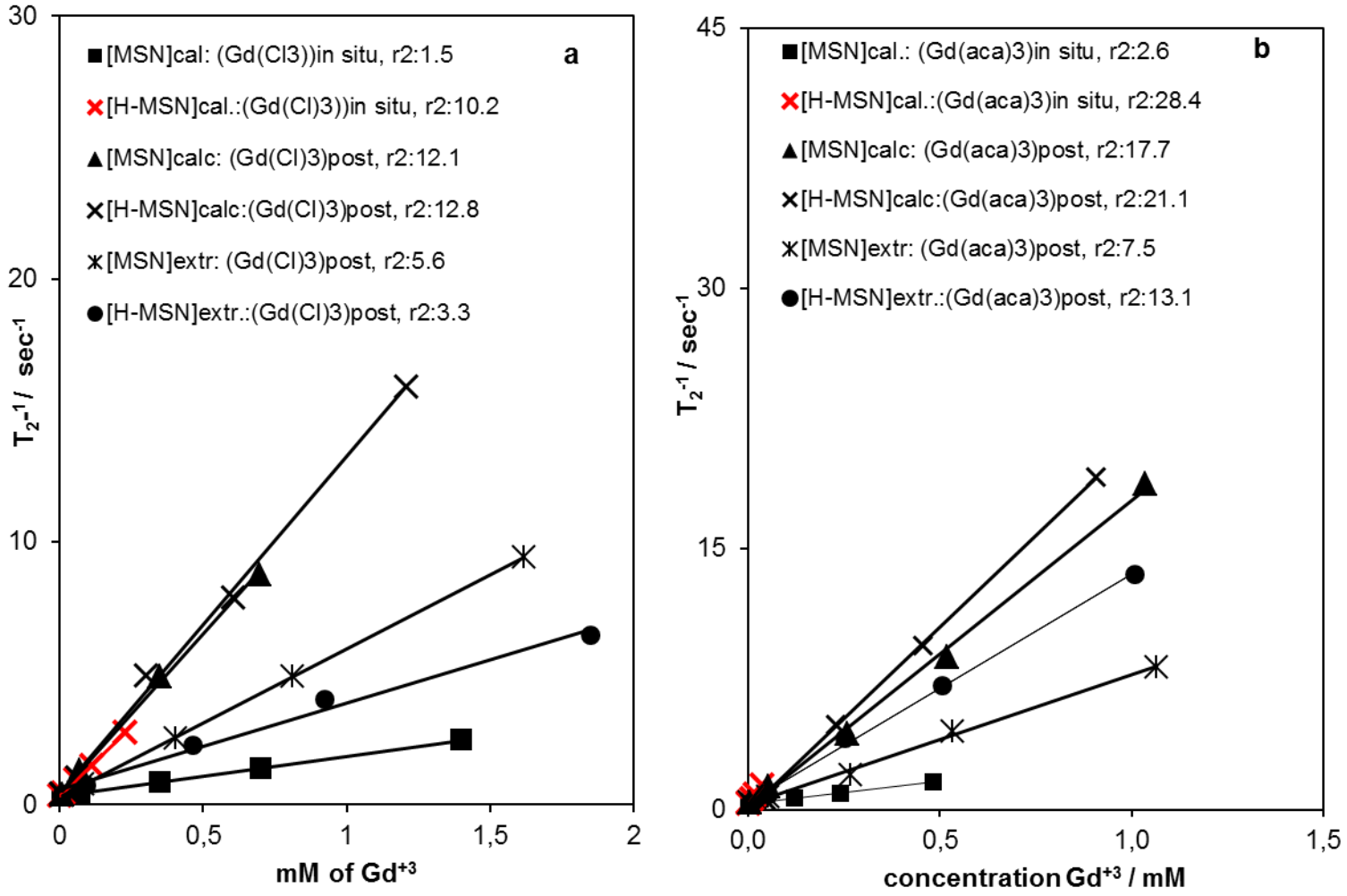

Figure S3.a) r_2 relaxivitiy values of MSN based contrast agents by doping a) $GdCl_3$ and b) $Gd(aca)_3$

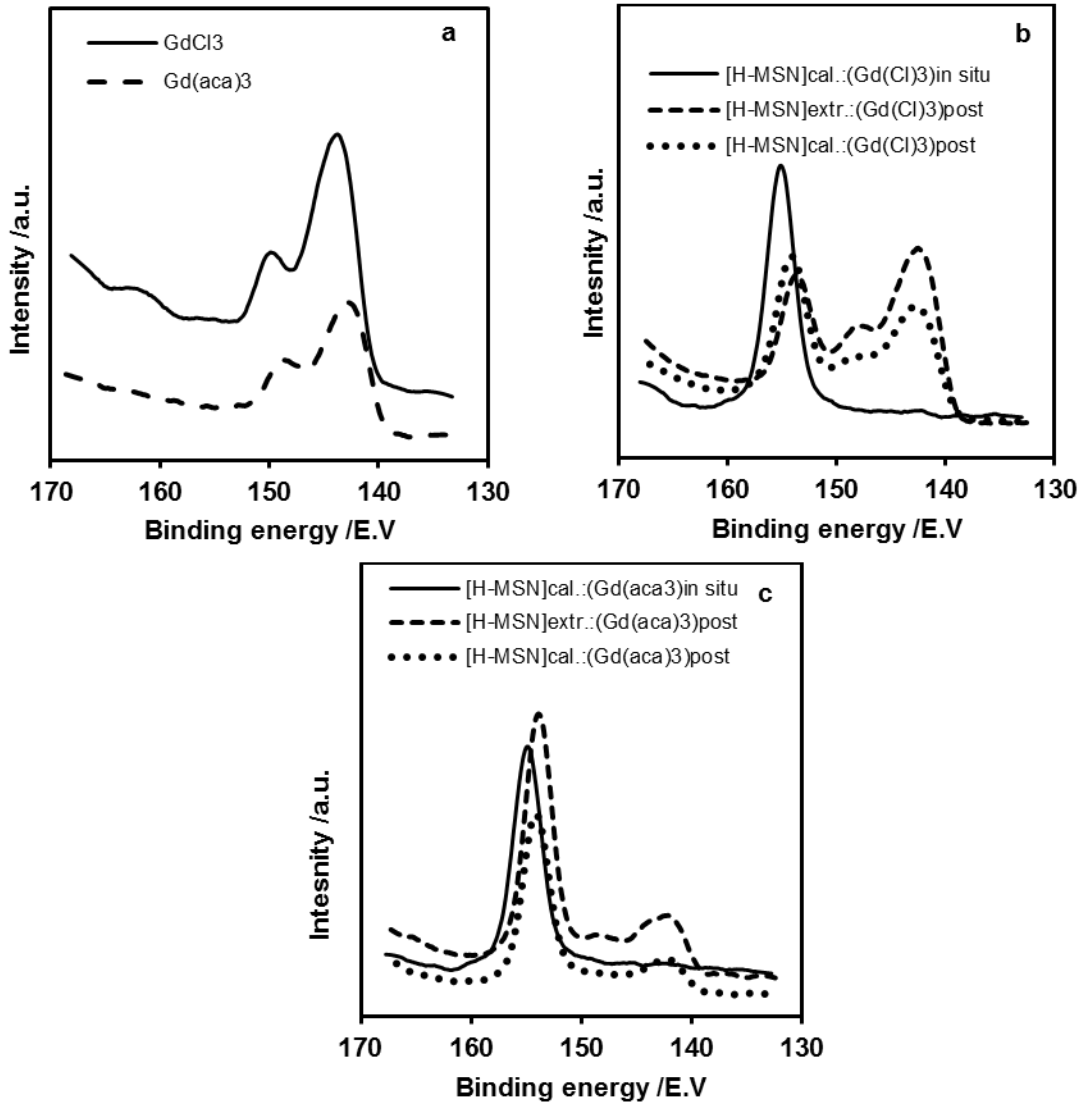

Figure S4. Photoelectron peak shift of Gd $4d_{3/2}$ and $4d_{5/2}$ for a)$GdCl_3$ and $Gd(acac)_3$ b) GdCl3 doped the H-MSN matrices c) $Gd(acac)_3$ doped H-MSN matrices.

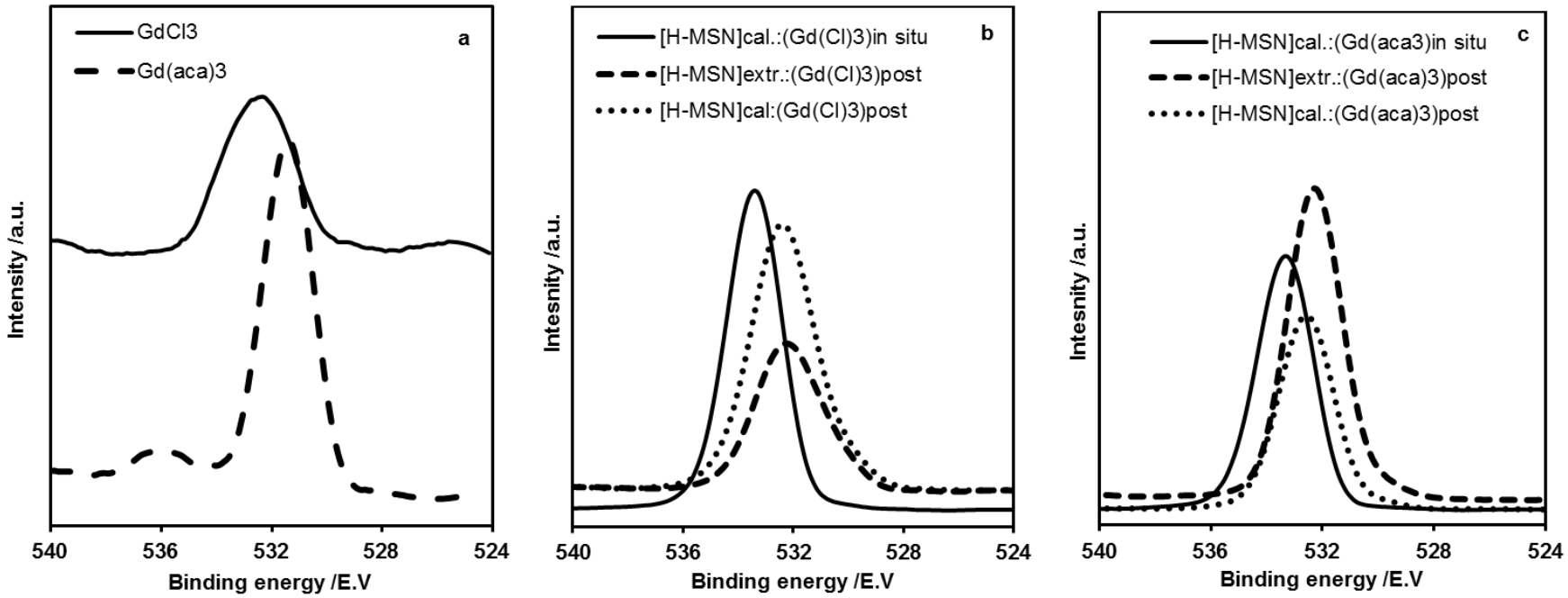

Figure S5. Photoelectron peak of O 1s for a)$GdCl_3$ and $Gd(acac)_3$ b) GdCl3 doped the H-MSN matrices c) $Gd(acac)_3$ doped H-MSN matrices.

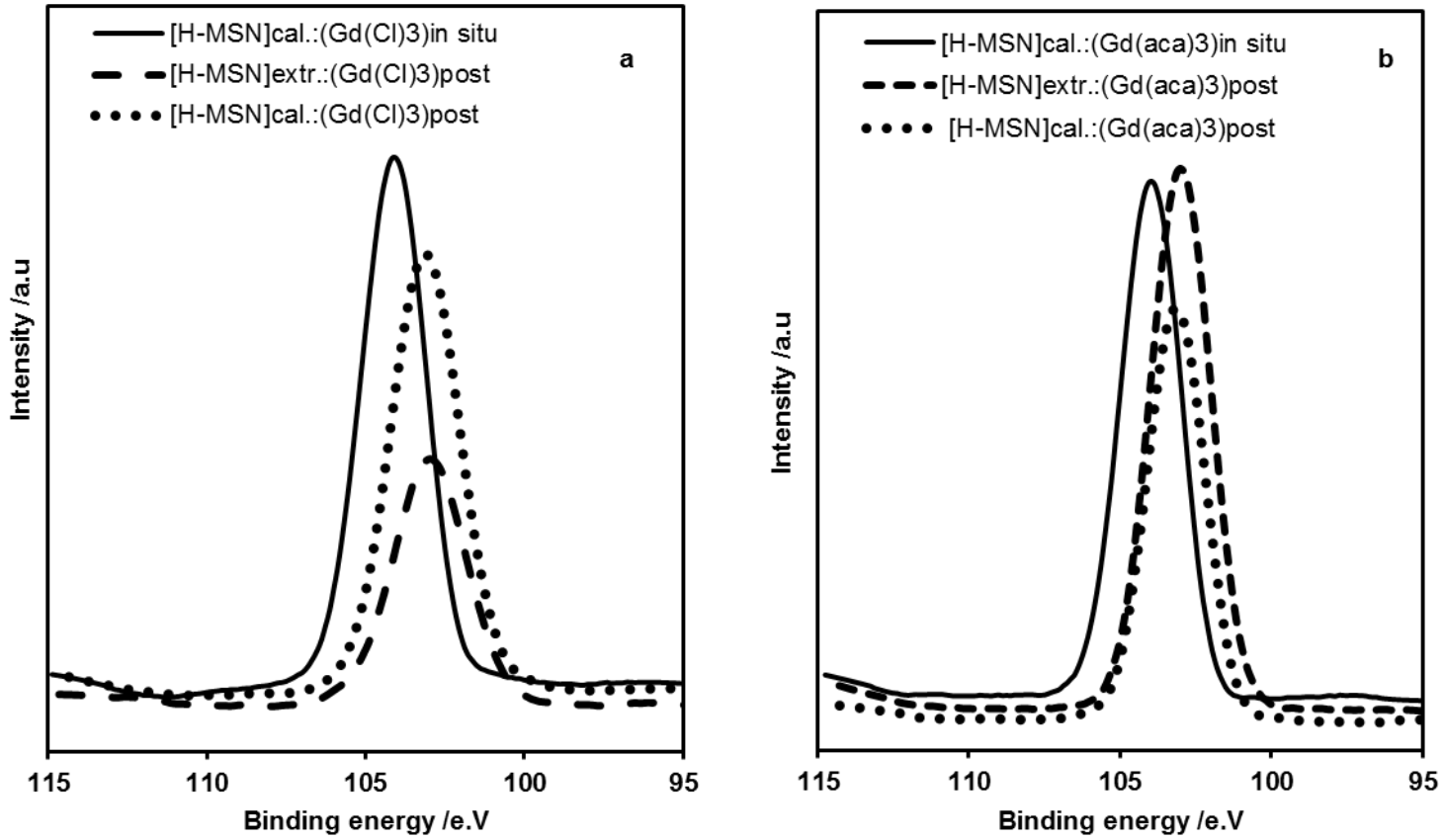

Figure S6. Photoelectron peak of Si 2p for a) GdCl3 doped the H-MSN matrices b) $Gd(acac)_3$ doped H-MSN matrices.

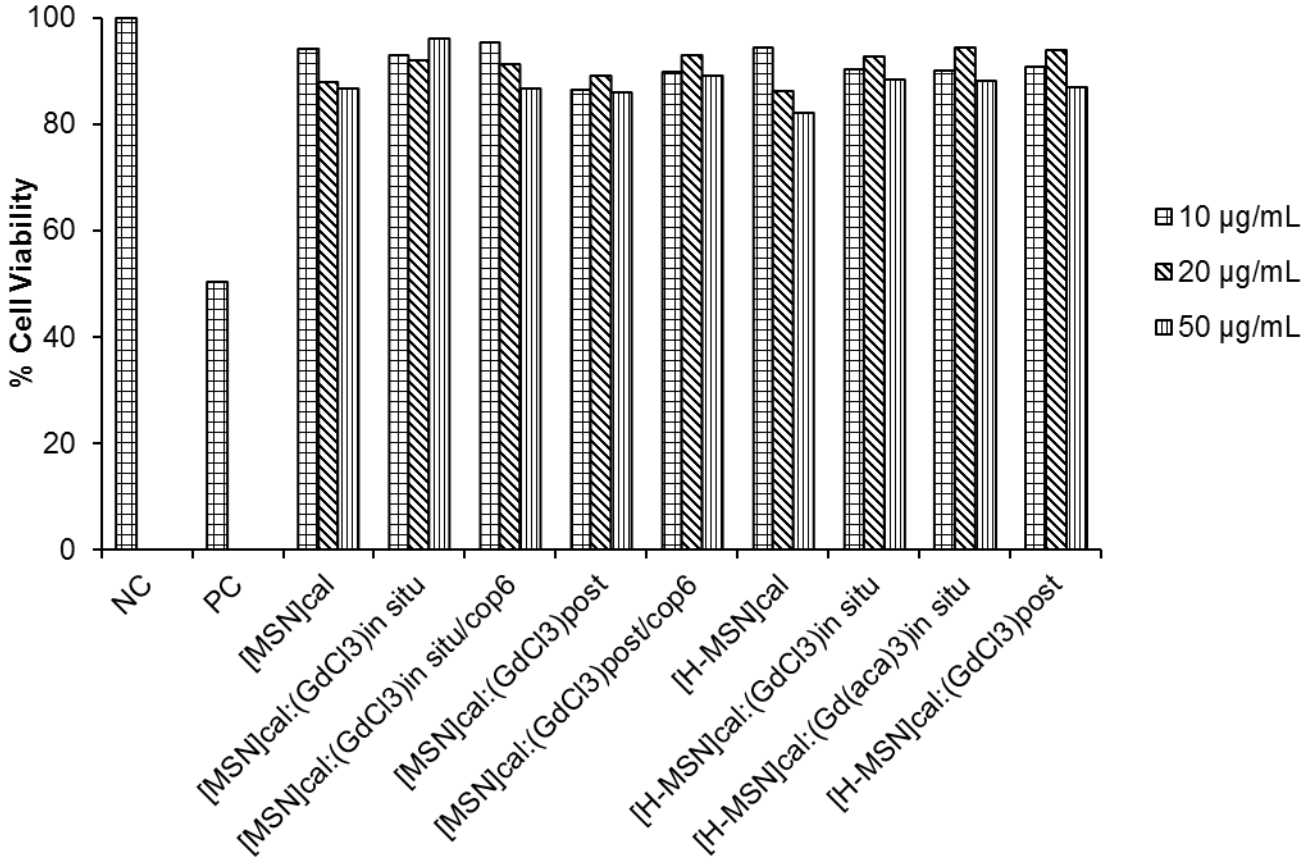

Figure S7. *In vitro* dose dependent cell viability data of some of the prepared CAs after 48 h incubation time on HeLa cell line

Chick Embryo Chorioallantoic Membrane (CAM) as model of *in vivo* imaging

The best potential MSN based contrast agent ($[H\text{-}MSN]_{cal}.:Ga(acac)_3$) was evaluated with T1-weighted imaging using the the CAM of chick embryo as a *in vivo* model. CAM is an extraembryonic membrane, which is formed on the 4^{th} day of incubation. HeLa cells were implanted on the model in order to provide tumor growth. Before the implantation of the HeLa cells the prepared the best potential contrast agent candidate ($[H\text{-}MSN]_{cal}.:Ga(acac)_3$) was incubated with the cells for o/n and implanted on the 8^{th} day of CAM model incubation(called as pre-labelling). Imaging of implanted tumor cells on the model was performed on 14^{th} day of the model incubation.

3 million cells (HeLa cells) were used for the tumor implantation and the concentration of incubated ($[H\text{-}MSN]_{cal}.:Ga(acac)_3$ was 50 μg/ml used for labelling the HeLa cells. the incubation was for overnight. After incubation process the labeled cells were mixed to Matrigel and cell culture Media (without antibiotic) and finally implanted over the CAM. Plastic ring was used in order to prevent the cancer cells from spreading on the CAM during the implanting tumor cells.

MRI instrumental settings for Phantom and CAM of chick embryo Imaging

MRI imaging was performed by using a dedicated small animal coil for preclinical MRI (8 channel Rat Whole-body Coil, Rapid Biomedical GmbH, Germany) . Phantom images were analyzed by using software ImageJ while the CAM model images were analyzed with OsiriX (Pixmeo, Switzerland).

<u>For Phantom imaging settings</u> ;

2D T1-weighted spin echo sequence (SE) TR=400 ms

TE=20 ms

FOV=120 mm X 120 mm

Acquisition matrix = 212 × 219

Slice thickness = 0.8 mm

The images were analyzed by ImageJ software.

<u>For CAM model imaging settings</u>;

3D T1-weighted spoiled gradient echo (SPGR) TR=100 ms

TE=1.831 ms

FA=80

FOV=120 mm x 120 mm

Acquisition matrix = 120 × 120

Slice thickness = 1 mm

The images were extracted and by OsiriX imaging software.