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New Synthetic Strategy of MRI/BNCT Agents Based on Hydroboration Reaction

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Boron Neutron Capture Therapy

Properties for BNCT agents

- Low toxicity
- Good stability in biological environment
- Persistence inside target cells
- High boron introduction in tumor tissue: 20 – 35 µg $^{10}$B /1 gr cancer cells
- Concentration ratio cancer tissue/healthy tissue : 3 – 5 / 1
- Concentration ratio cancer tissue/blood : 5 / 1
- Efficient body scanning

MRI/BNCT dual agent: general structure

MOLECULAR PROBE \( \text{[Gd-DOTA]}^- \) → CARBORANE \( \text{Dicarba-closo-dodecaborane} \) → BIOLOGICAL VECTOR \( \text{Lipoprotein} \)
Examples of MRI/BNCT agents

AT101

MEA01

AC01

New decaborane functionalization strategy: Hydroboration reaction

Efficient strategy for lipophilic moiety introduction on boron cage:
Yield product: 55 – 92 %

New dual agent synthesis: PB01

Synthesis of C-(2-hydroxy)-ethyl-C-H-6-(hexadecil)-o-carborane (3)
a) 1-hexadecene (3.5 eq), bmimCl (0.3 eq), toluene, 125°C, yield 43%; b) 3-butyn-1-ol (4 eq), bmimCl (0.3 eq), toluene, 100°C, yield 40%

Structure 3: Isomer 1
Chemical shift for C-H

$^1$H: 4.1 ppm
$^{13}$C: 60.35 ppm

Structure 3’: Isomer 2
Chemical shift for C-H

$^1$H: 3.8 ppm
$^{13}$C: 61.47 ppm

\(^a\) Molecular structure defined by X-ray diffrattometric study
Structure acquired by Dott.ssa Domenica Marabello
New dual agent synthesis: PB01

General procedure:
Synthesis of $C\{R_3\text{-DOTAMA-C}_6\}$-acetamide-$C^2\text{H}-6$(hexadecil)$\alpha$-carborane (6)

a) 1-hexadecene (3.5 eq), bmimCl (0.3 eq), toluene, 125°C, yield 43%;
b) 3-butyn-1-ol (4 eq), bmimCl (0.3 eq), toluene, 100°C, yield 40%;
c) CrO$_3$ (4 eq), H$_2$SO$_4$ (3M), acetone, room temperature, yield 77%;
d) $\alpha$-hydroxysuccinimide [NHS] (1.15 eq), dicyclohexilcarbodiimide [DCC] (1.2 eq), CH$_2$Cl$_2$, room temperature;
e) $R_3$-DOTAMA-C$_6$ (0.95 eq), diisopropylethylamine [DIEA] (0.95 eq), CH$_2$Cl$_2$, room temperature, yield: 13 – 42%

Protecting groups

$R' = \text{ter-Butyl}$

$R'' = \text{Benzyl}$
New dual agent synthesis: PB01

Synthesis of PB01:

a) i R = ter-(Butyl) CF₃COOH (2 ml), CH₂Cl₂, room temperature, yield: > 99%
   ii R = Benzyl H₂, Pd on carbon (20% w/w), CH₂Cl₂/CH₃OH (1/1), room temperature, yield: > 99%

b) GdCl₃, H₂O, t. amb., pH 7
Comparison PB01-AT101

NMRD PROFILE

Synthetic steps required: 6

Synthetic steps required: 14

Dott.ssa Simonetta Geninatti Crich
Dott. Diego Alberti
Conclusions

Synthesis of MRI/BNCT dual agent based on hydroboration reaction:
- efficient strategy for lipophilic moiety introduction on boron cage
- reduction of synthetic steps required

Experimental evidence for molecular structure of precursor (3):
X-ray diffractometric study

Preliminary relaxometric tests on PB01 interaction with LDLs show a Nuclear Magnetic Relaxation Dispersion (NMRP) profile superior in comparison with AT101
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