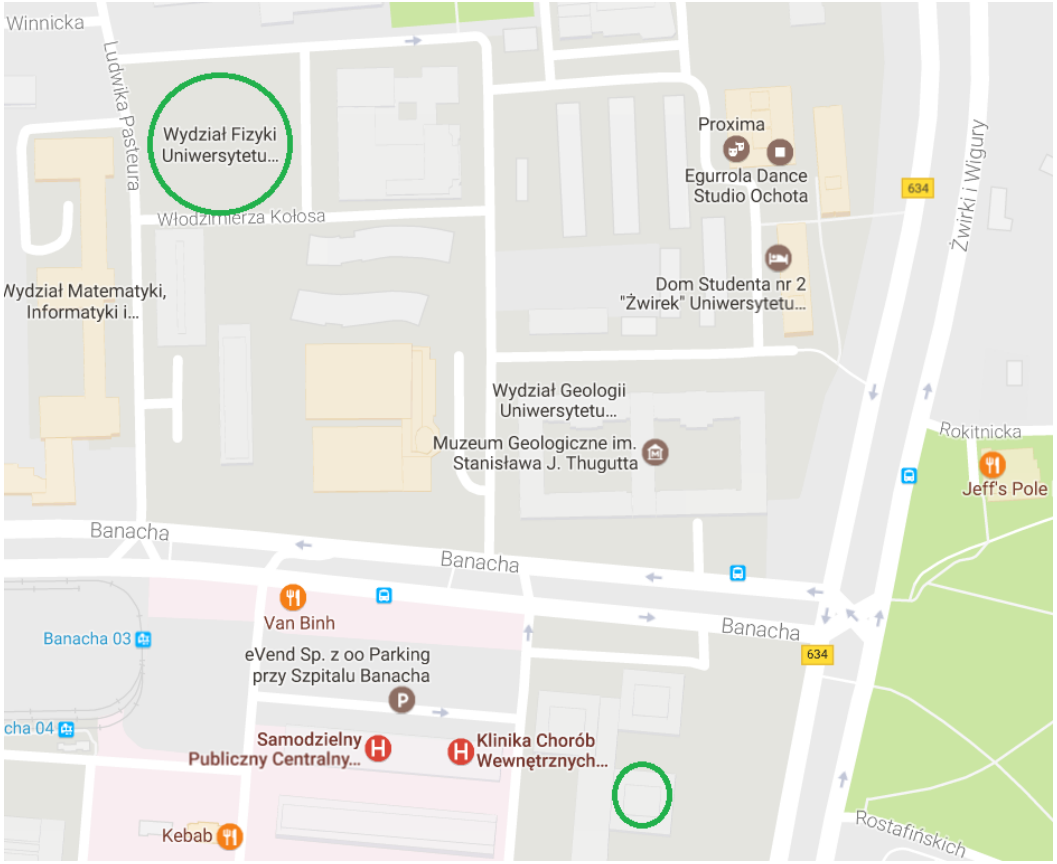
Zastosowanie magnetycznego rezonansu jądrowego w fizyce medycznej i farmacji

dr n. farm. Łukasz Szeleszczuk
dr n. farm. Dariusz Maciej Pisklak

Wydział Farmaceutyczny
z Oddziałem Medycyny Laboratoryjnej
UNIVERSITAS MEDICA VARSOVIENSIS
FACULTAS PHARMACEUTICA
19 26

zakład chemii fizycznej


Winnicka
Ludwika Pasteura
Wydział Fizyki Uniwersytetu...
Włodzimierza Kołosa
Wydział Matematyki, Informatyki i...
Proxima
Egurrola Dance Studio Ochota
634
Żwirki i Wigury
Dom Studenta nr 2 "Żwirek" Uniwersytetu...
Wydział Geologii Uniwersytetu...
Muzeum Geologiczne im. Stanisława J. Thugutta
Rokitnicka
Jeff's Pole
Banacha
Banacha
Banacha
Van Binh
Banacha 03
eVend Sp. z oo Parking przy Szpitalu Banacha
634
Samodzielny Publiczny Centralny...
Klinika Chorób Wewnętrznych...
Kebab
Rostafińskich

NMR-owskie nagrody Nobla

• 1944 I. I. Rabi – Fizyka: za prace na temat wiązek molekularnych, szczególnie metodę rezonansową.

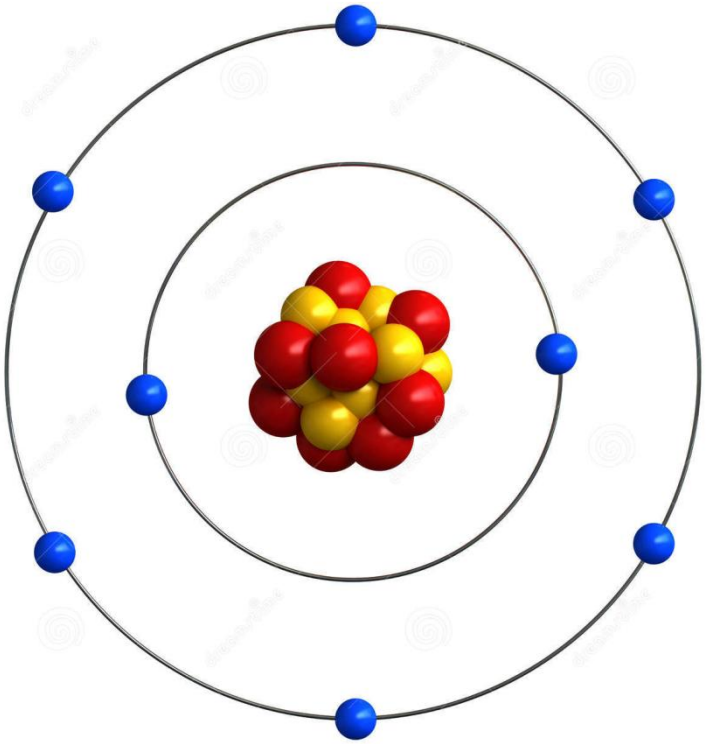
• 1952 F. Bloch i E. M. Purcell – Fizyka: za odkrycia w dziedzinie NMR.

• 1991 R. R. Ernst - Chemia: za wprowadzenie FT do NMR i za 2D NMR.

• 2002 K. Wüthrich – Chemia: za wykorzystanie NMR do badania struktury białek.

• 2003 P. Lauterbur i P. Mansfield – Medycyna: za pionierskie prace w dziedzinie obrazowania NMR (MRI).

Spin

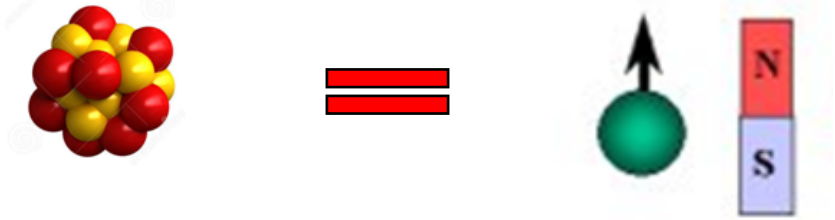


NMR

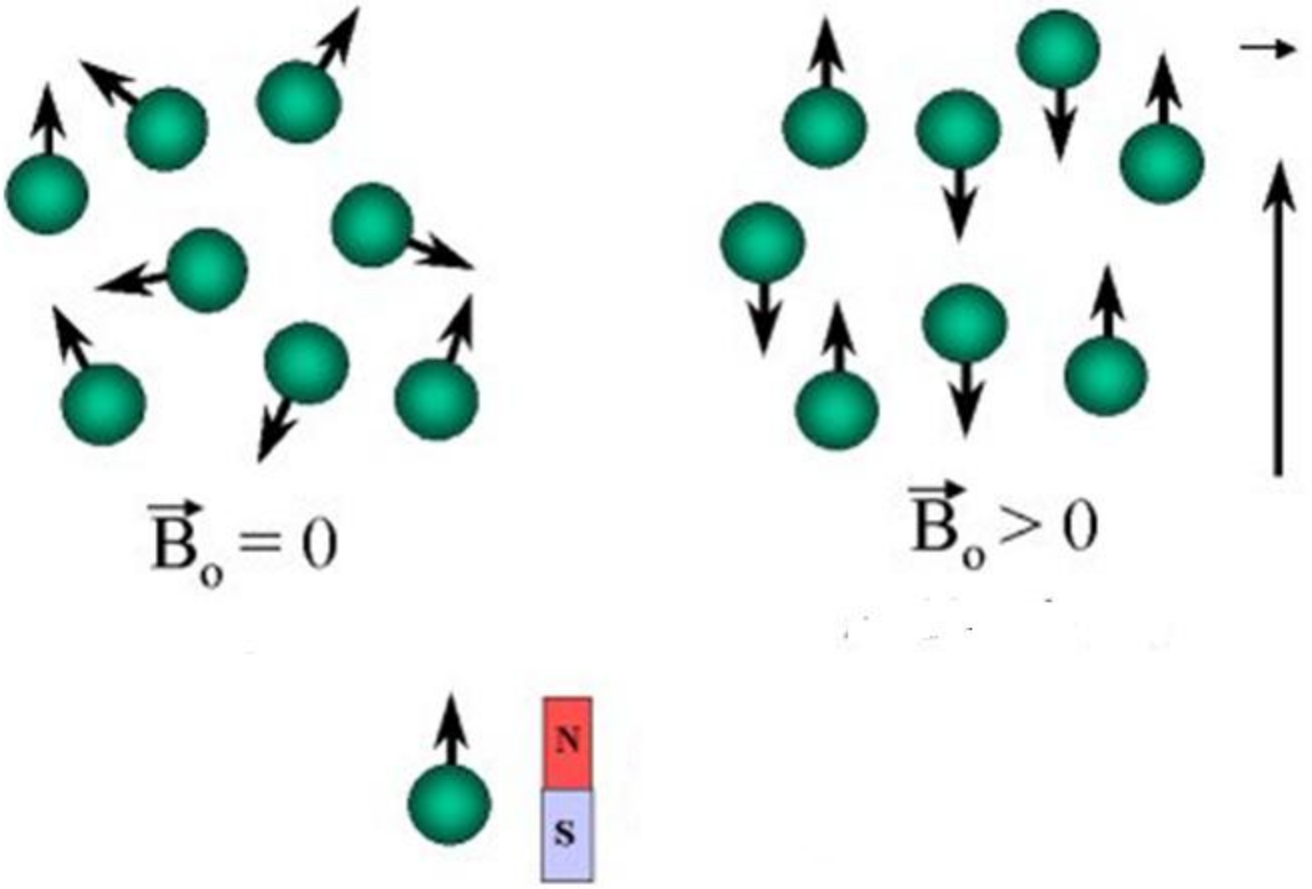
MRJ

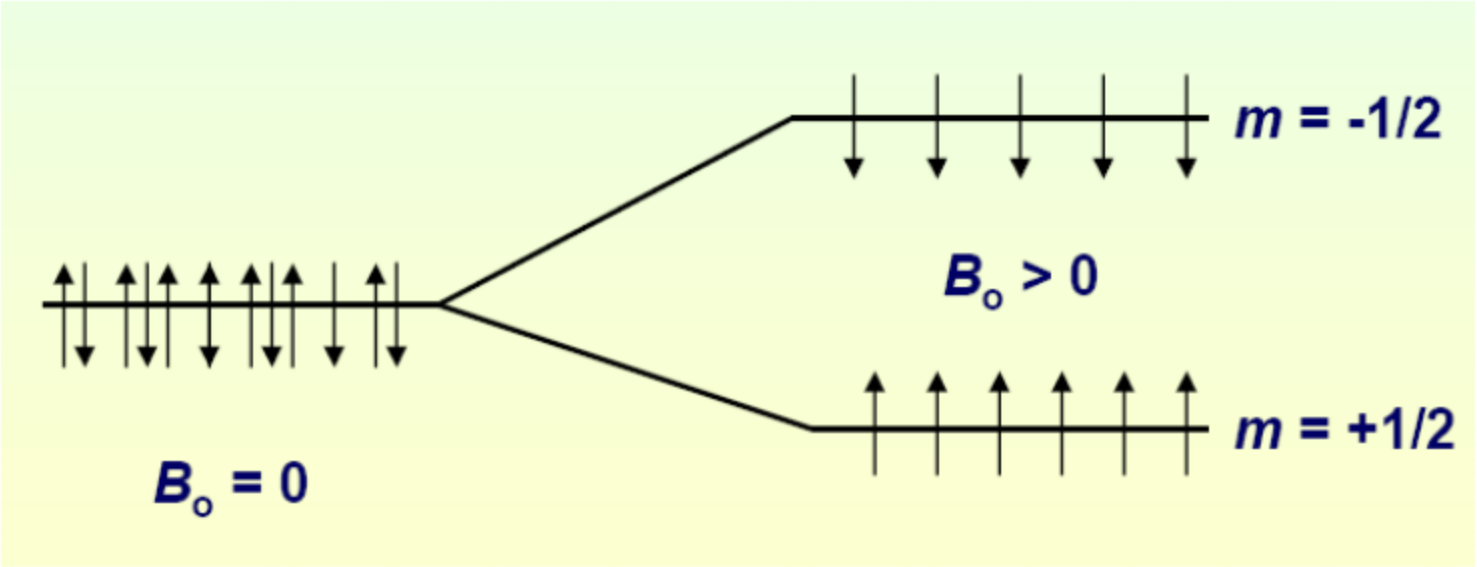
MRI

MRS



Spin w polu magnetycznym





Jądrowy efekt Zeemana

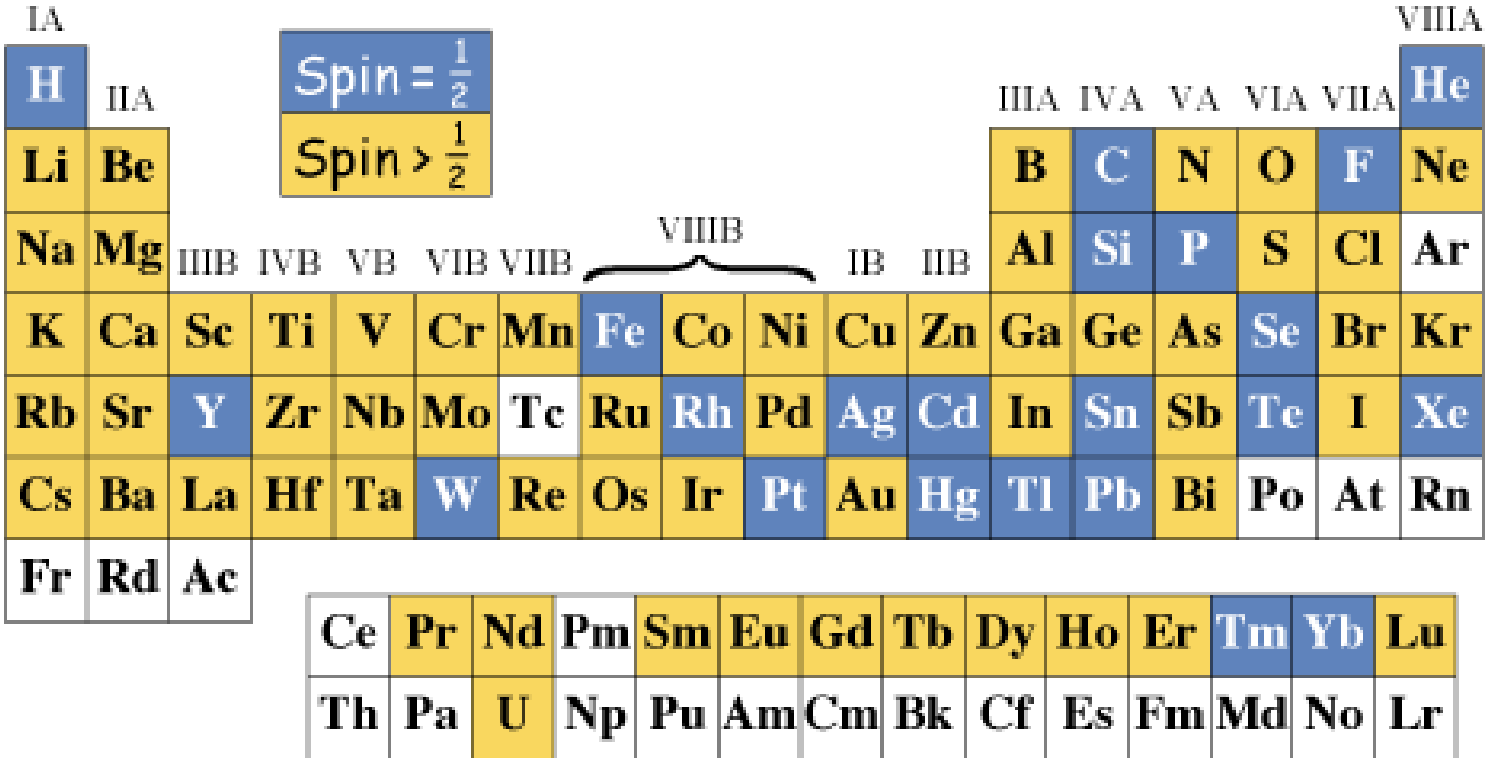
Rodzaje widm cząsteczkowych

Rodzaj widma	Obszar widmowy (λ)	Energia przejść widmowych (J/mol)	Energia przejść widmowych (cm^{-1})	Energia przejść widmowych (s^{-1})
NMR	Fale radiowe 10-100m	$10^{-2} – 10^{-3}$	$10^{-3} – 10^{-4}$	$10^{7} – 10^{6}$
EPR	Mikrofale (1cm)	10	10^{0}	10^{10}
Rotacyjne	Mikrofale (100 μm – 1 cm)	$10^{3} – 10^{0}$	$10^{2} – 10^{1}$	$10^{12} – 10^{9}$
Oscylacyjne	Bliska i średnia podczerwień (1 -50 μm)	$10^{5} – 10^{3}$	$10^{4} – 10^{2}$	$10^{14} – 10^{12}$
Elektronowe	UV-VIS (100-1000nm)	$10^{6} – 10^{5}$	$10^{5} – 10^{4}$	$10^{15} – 10^{14}$

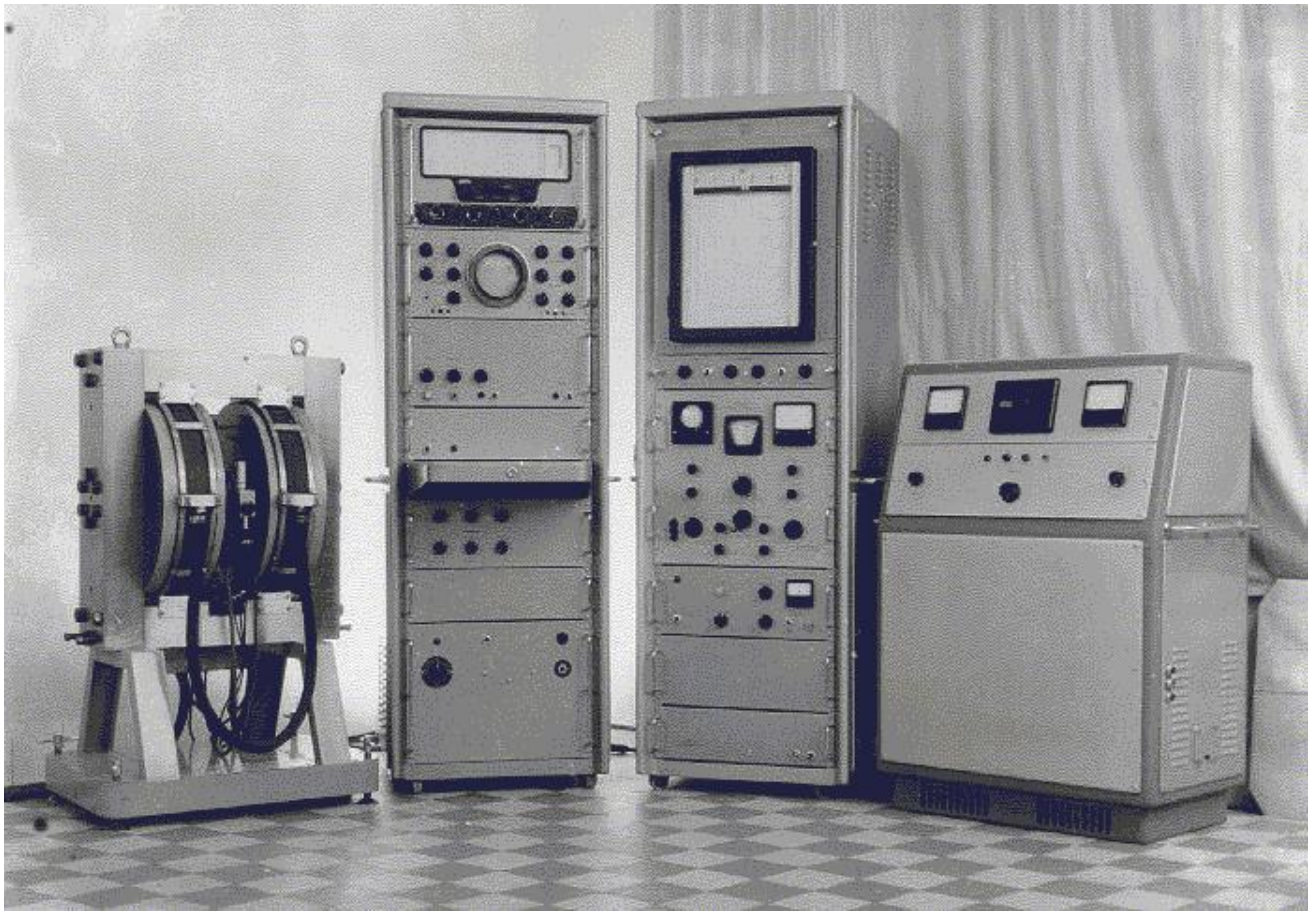
NMR

Pole magnetyczne + Impulsy elektromagnetyczne

Jakie izotopy można badać



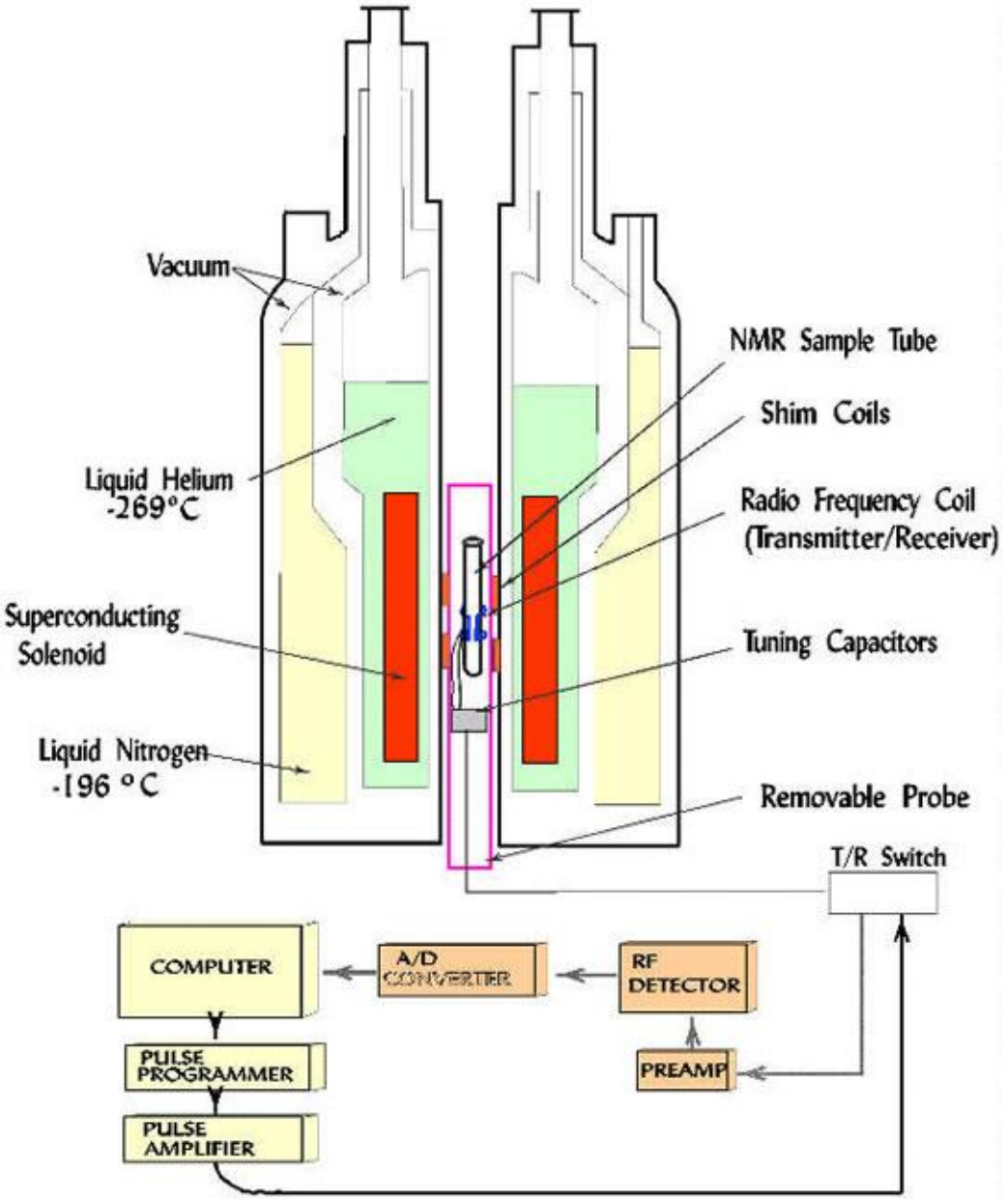
PIERWSZE SPEKTROMETRY NMR



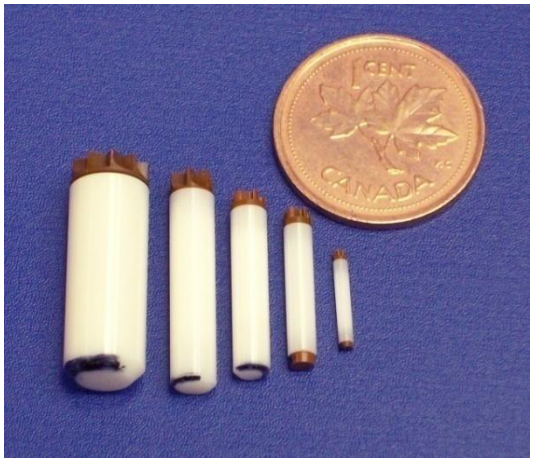
NMR na farmacji

Najnowsze spektrometry NMR

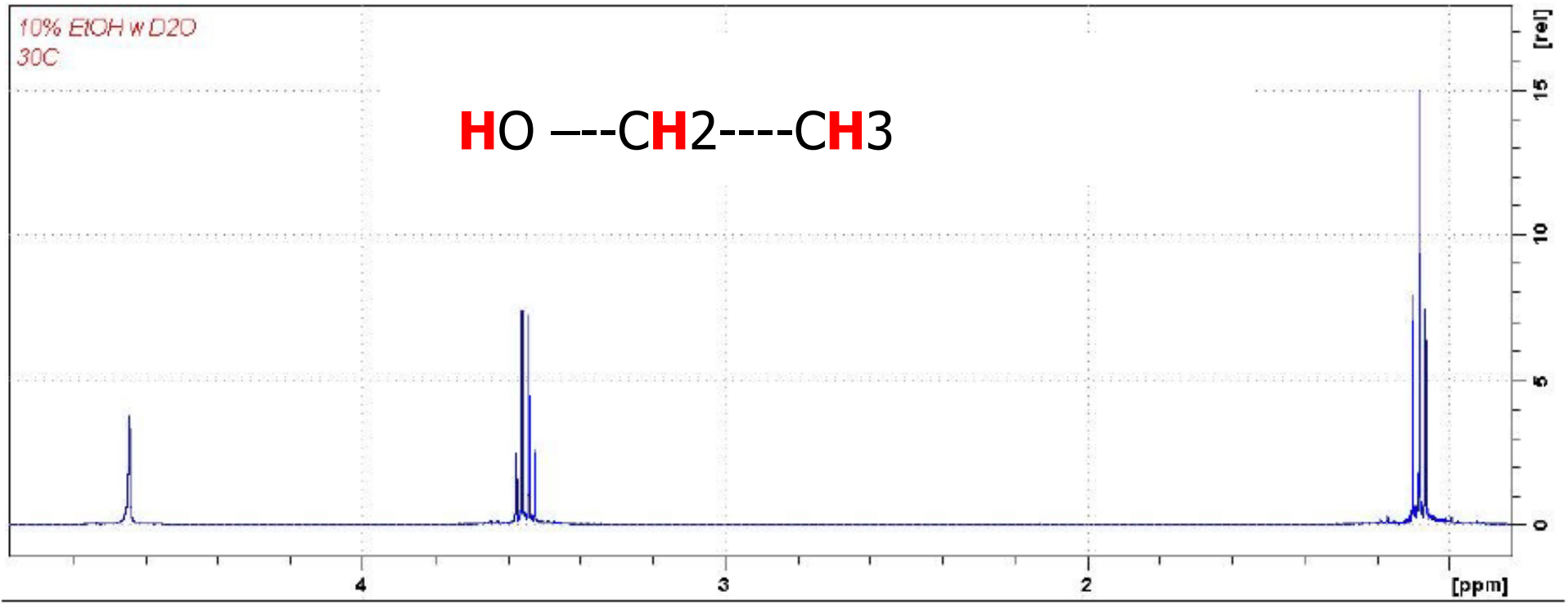
BRUKER
600
UltraShield™


Vacuum
NMR Sample Tube
Shim Coils
Liquid Helium
-269°C
Radio Frequency Coil
(Transmitter/Receiver)
Superconducting
Solenoid
Tuning Capacitors
Liquid Nitrogen
-196 °C
Removable Probe
T/R Switch
COMPUTER
A/D
CONVERTER
RF
DETECTOR
PULSE
PROGRAMMER
PREAMP
PULSE
AMPLIFIER

BRUKER
Ascend™ 850

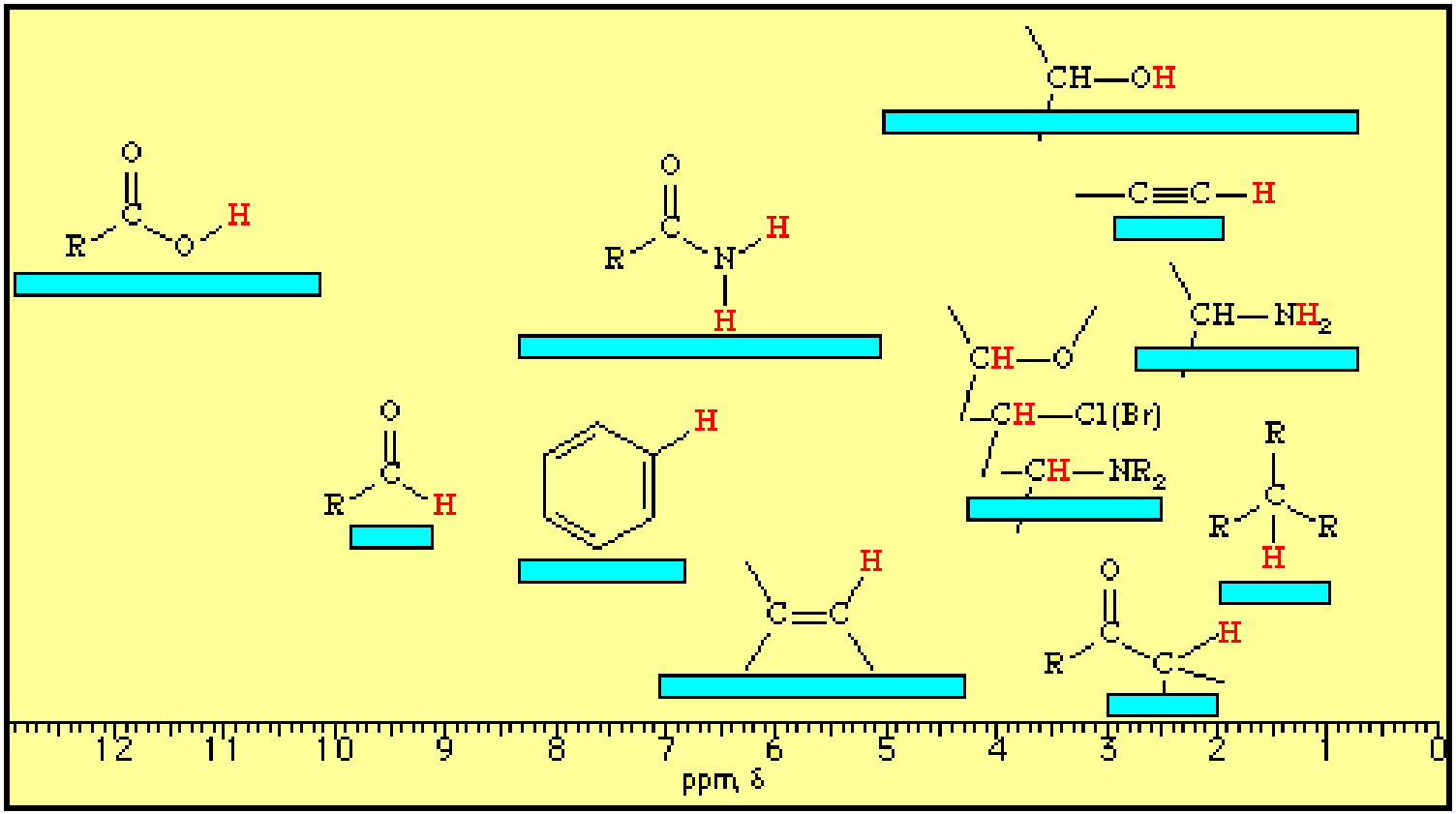

1 CENT
CANADA

Widmo 1H NMR



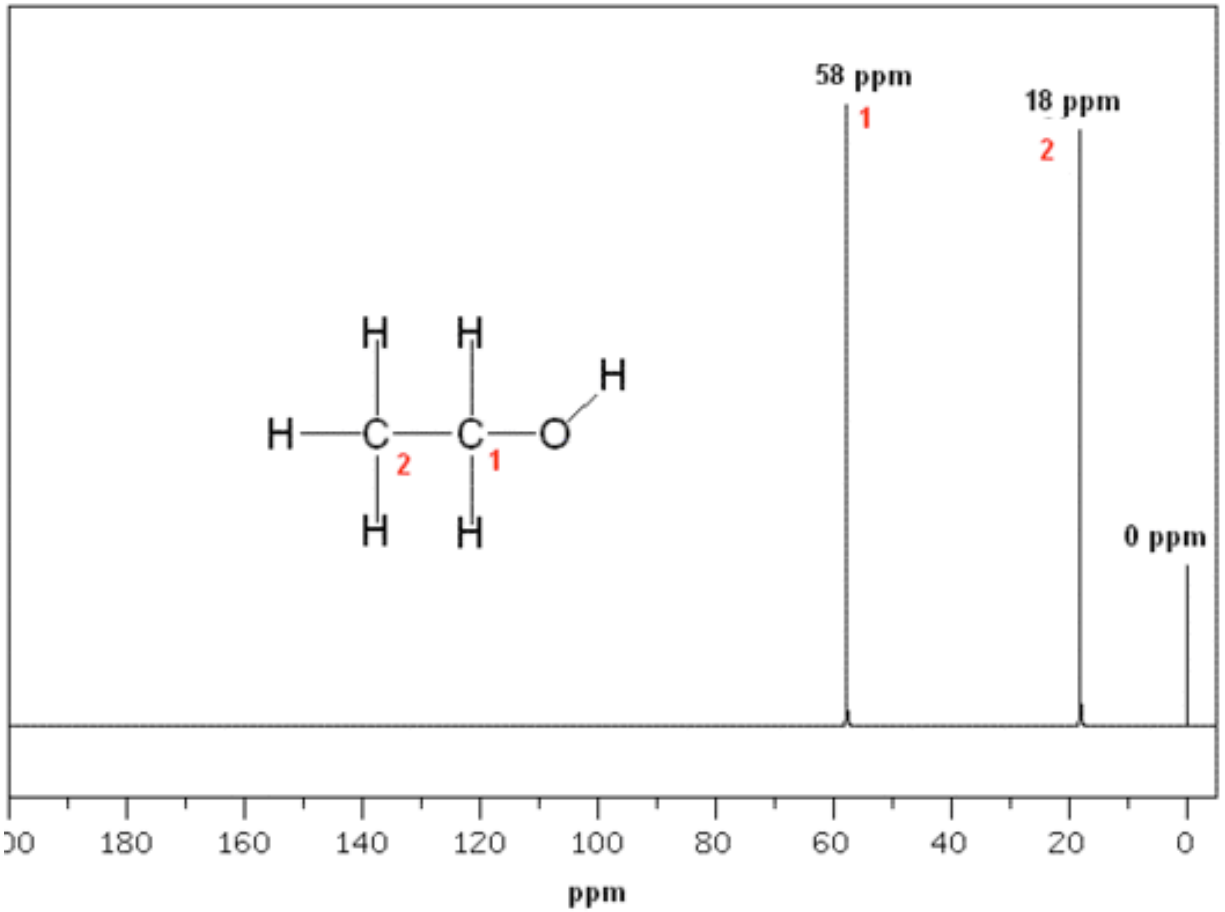
$$\Delta E = h\nu = \gamma \hbar B_0 (1 - \sigma)$$

Przesunięcie chemiczne
informacja o strukturze molekuły

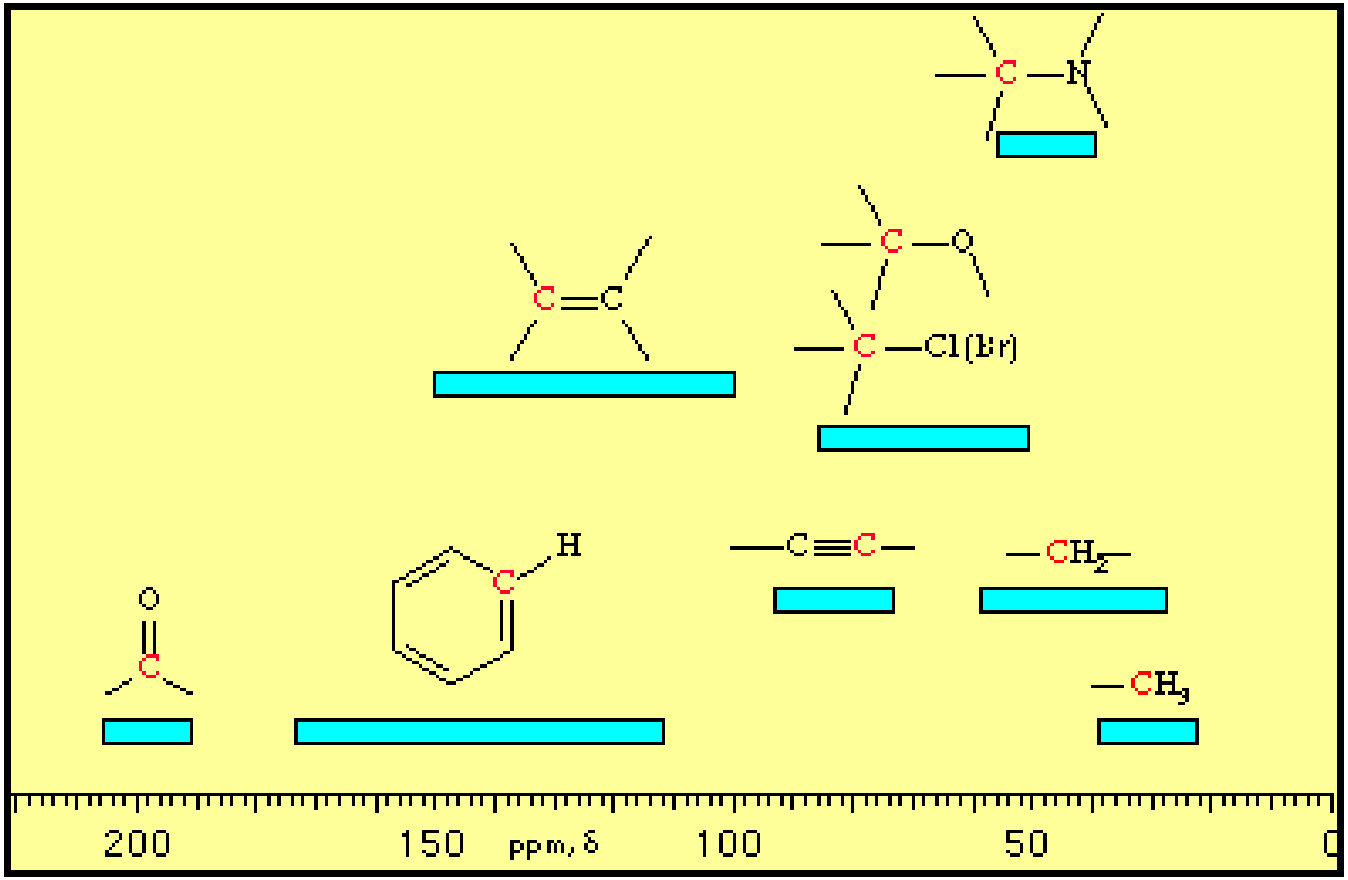


$$\Delta E = h\nu = \gamma \hbar B_0 (1 - \sigma)$$

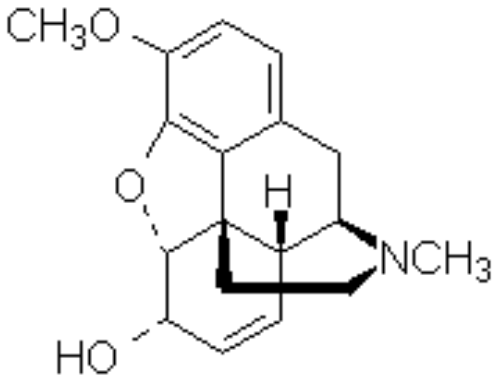
Widma 13C NMR



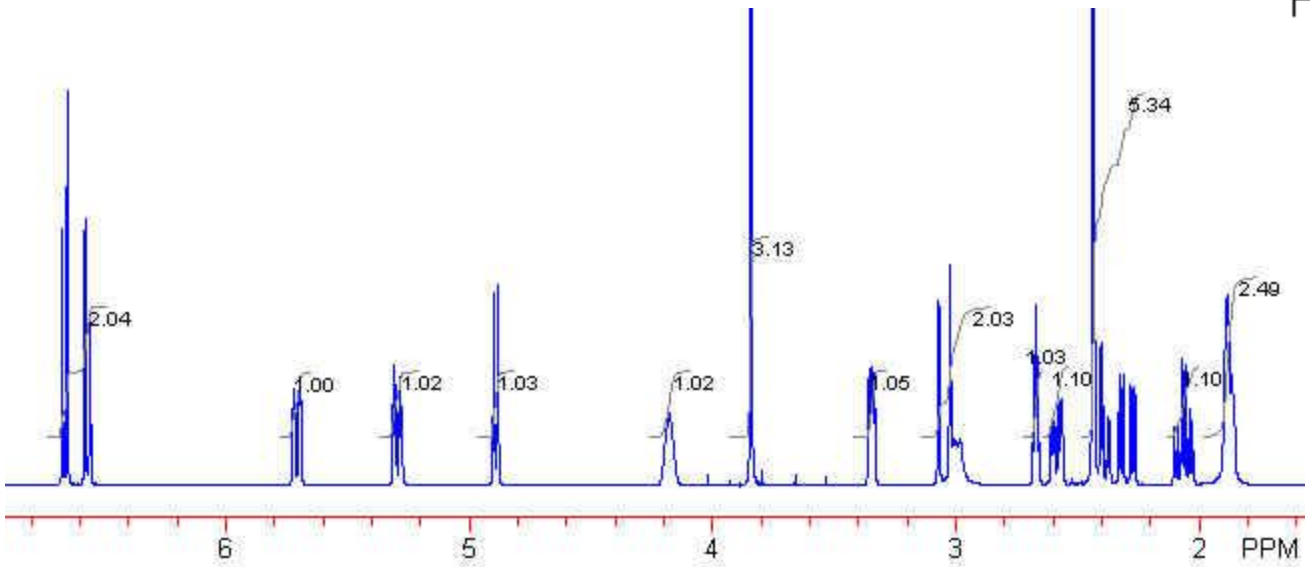
13C NMR
Przesunięcia chemiczne



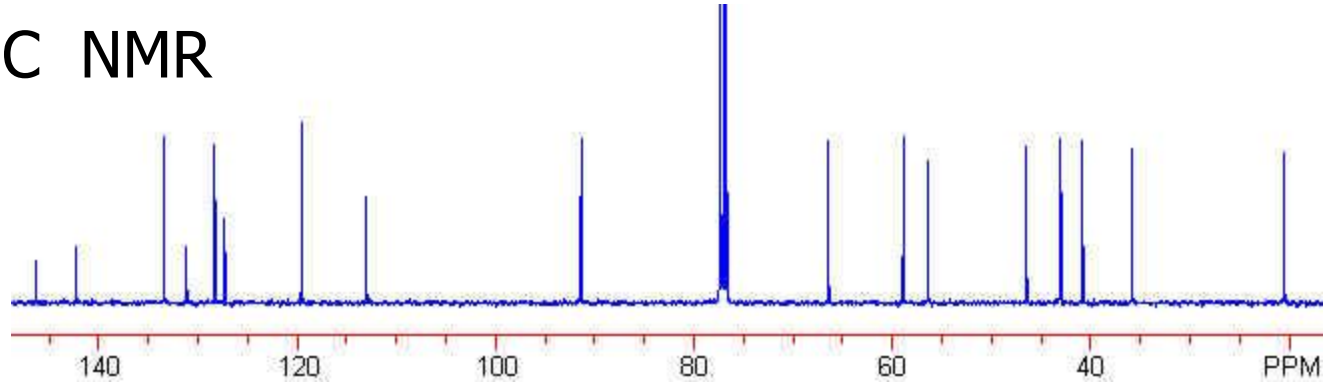
Kodeina widma NMR



^{1}H NMR



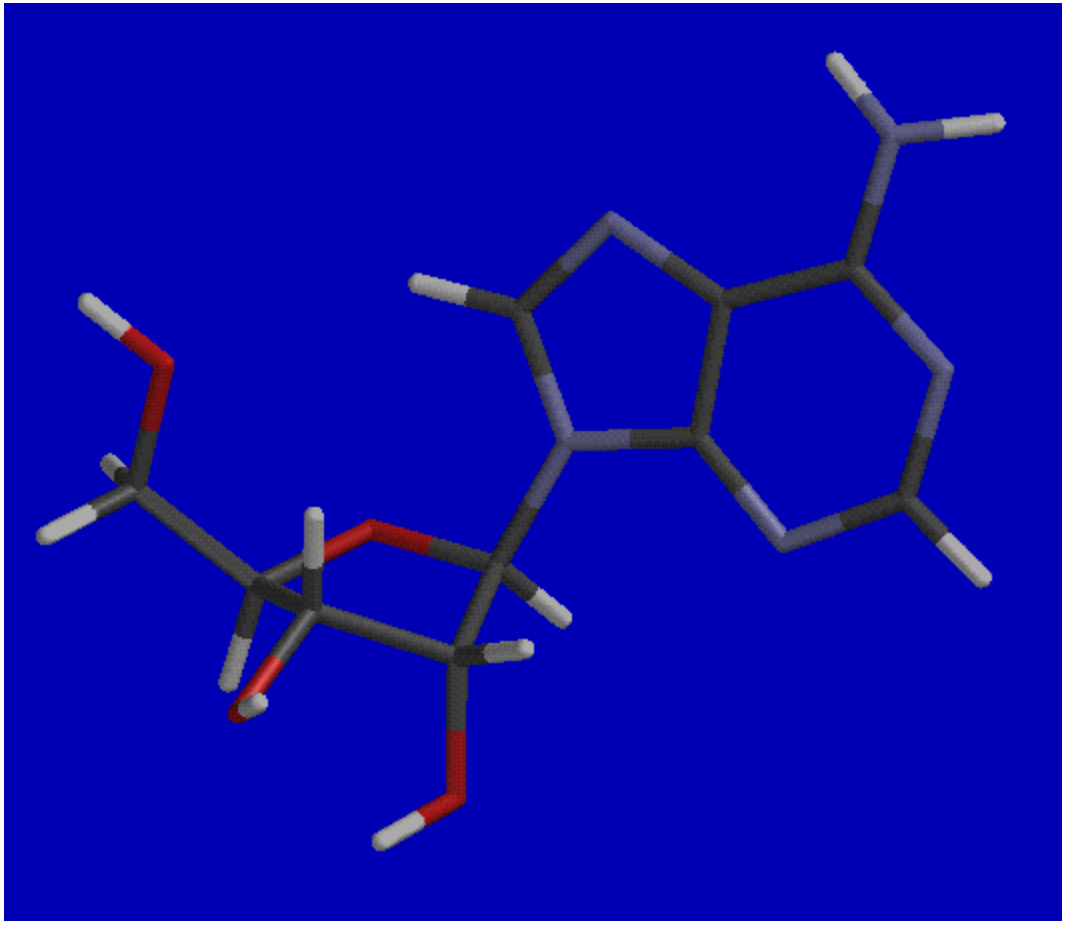
^{13}C NMR



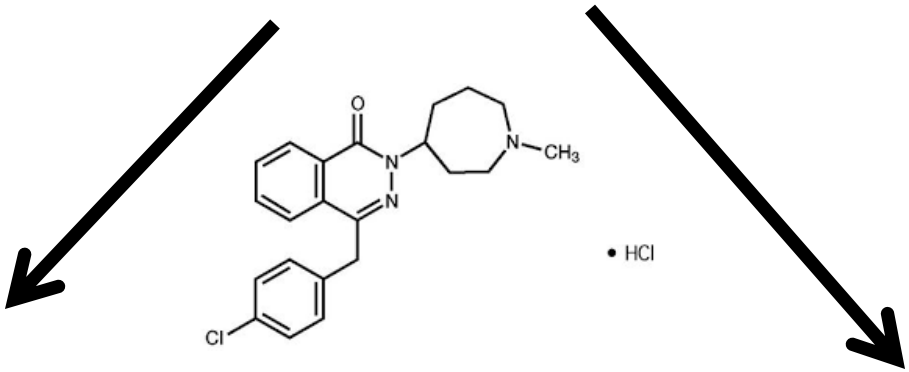
NMR - struktura i konformacja

NMR

$C_xH_yO_z$



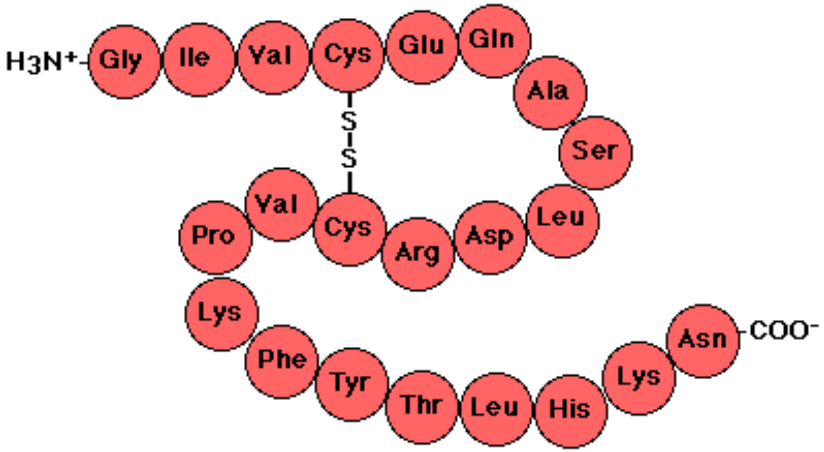
NMR

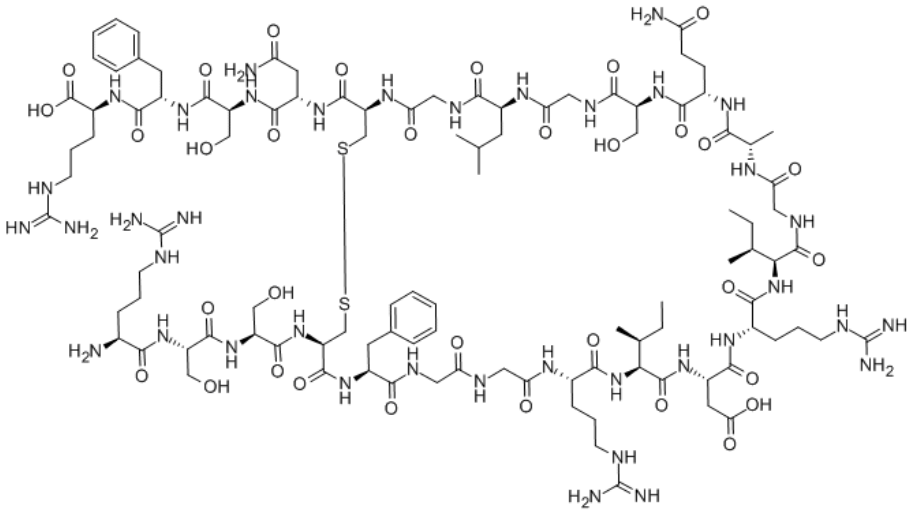


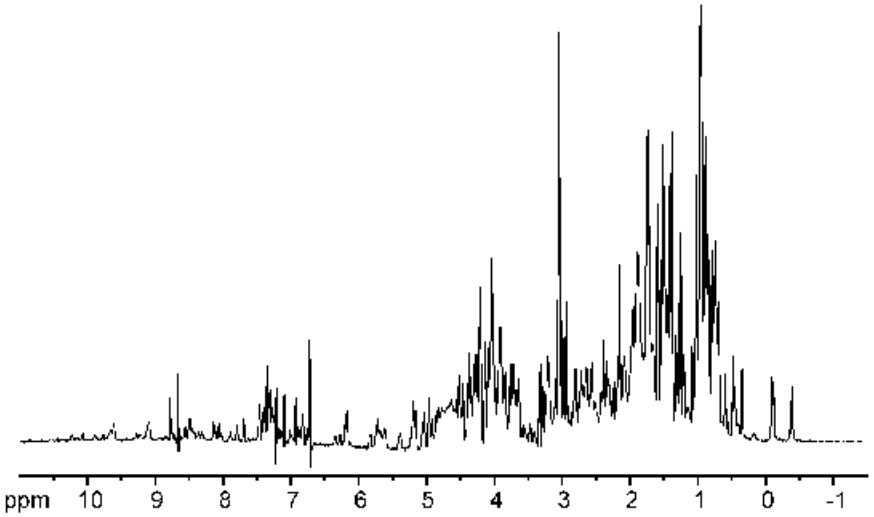
Związki syntetyczne

Związki naturalne

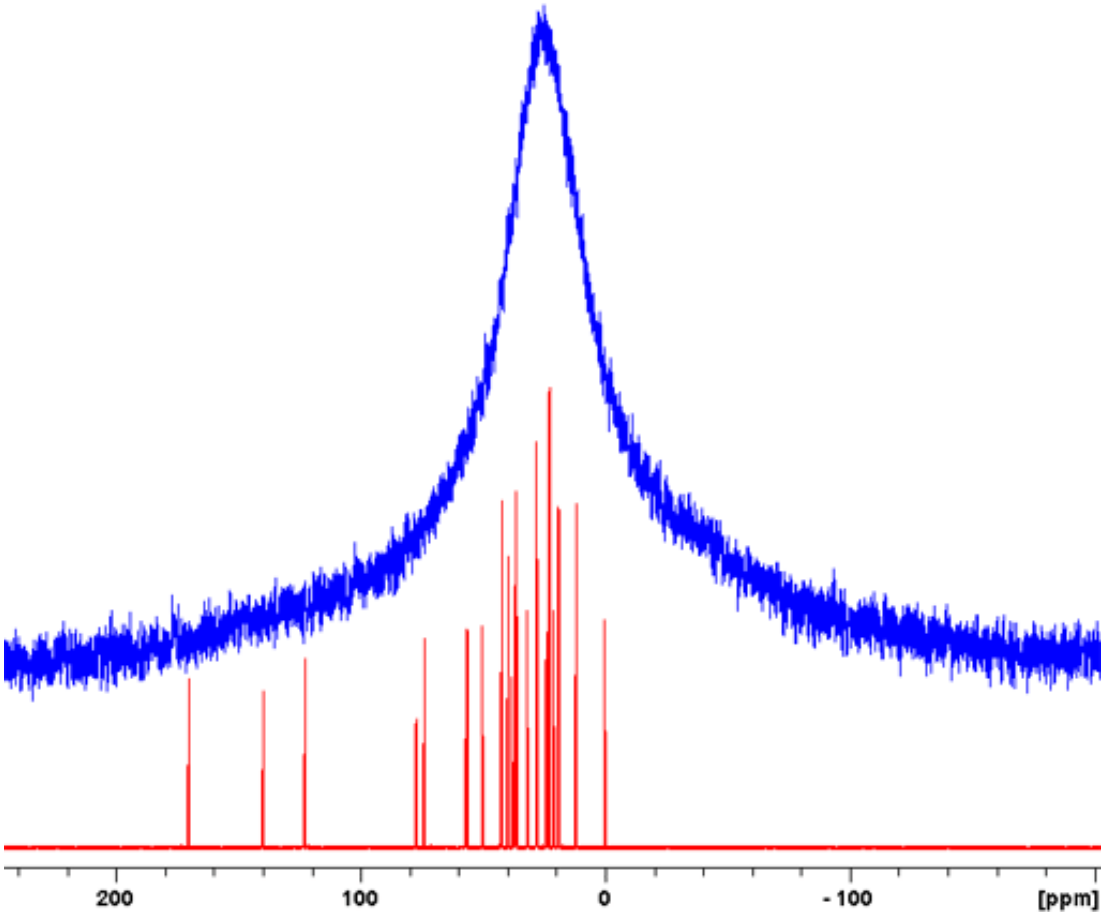
NMR białek


H3N+
Gly
Ile
Val
Cys
Glu
Gln
Ala
Ser
Val
Cys
Pro
Arg
Asp
Leu
Lys
Phe
Tyr
Thr
Leu
His
Lys
Asn
COO-

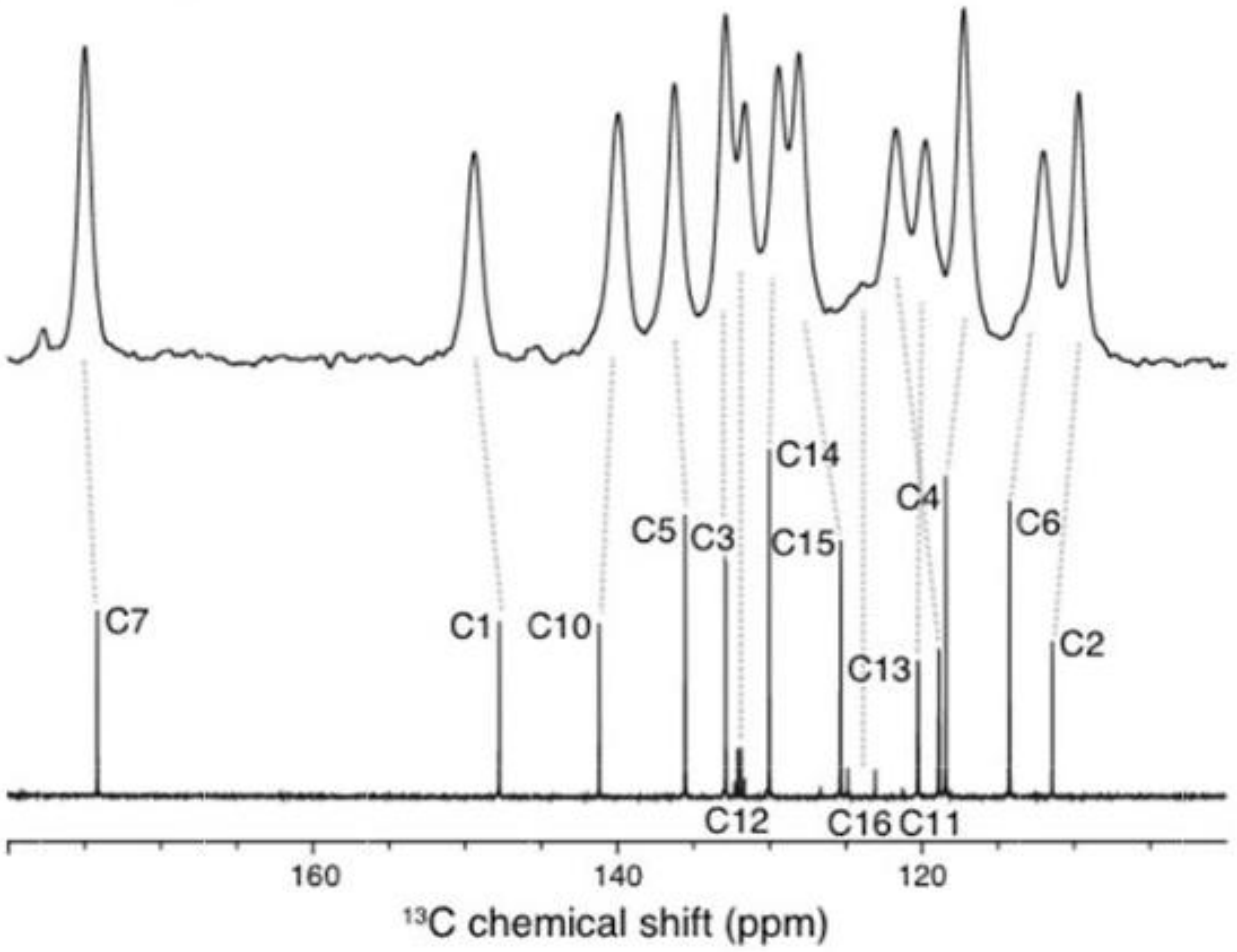



ppm
10
9
8
7
6
5
4
3
2
1
0
-1

NMR w ciele stałym



Widma MAS NMR



Spektroskopia ^{13}C NMR wysokiej zdolności rozdzielczej

w ciele stałym ≡ **^{13}C CP/MAS NMR**

⇓

Wirowanie próbki pd kątem magicznym – akronim **MAS**

od ang. **M**agic-**A**ngle **S**pinning

+

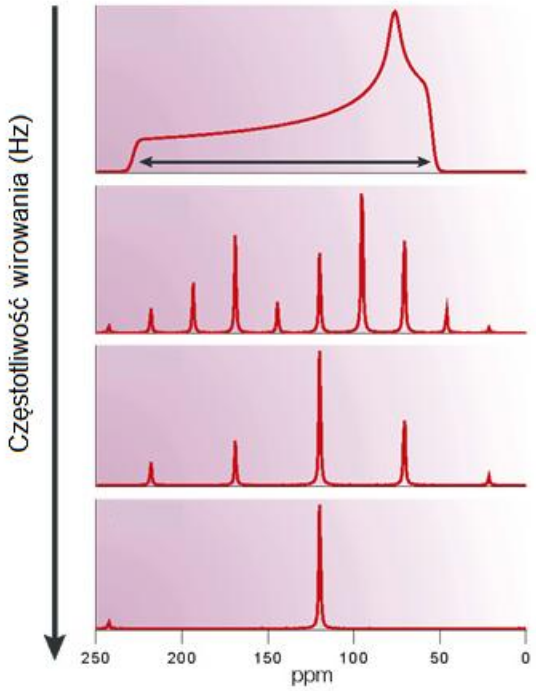
Rozprzęganie protonów rezonansowym promieniowaniem

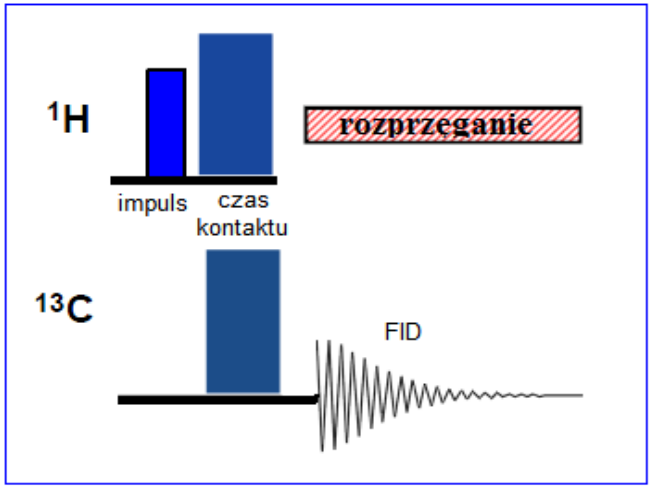
radiowym o wysokiej mocy

+

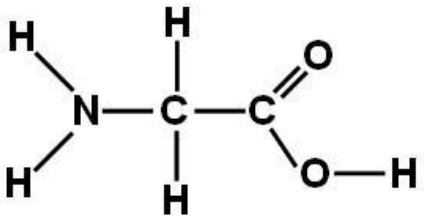
Polaryzacja skrośna – akronim **CP**

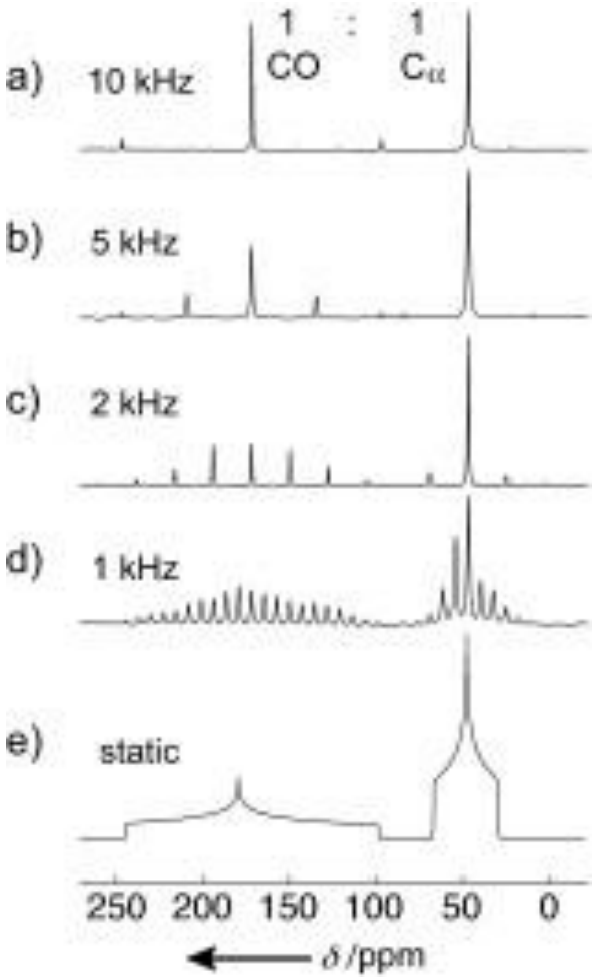
od ang. **C**ross - **P**olarization

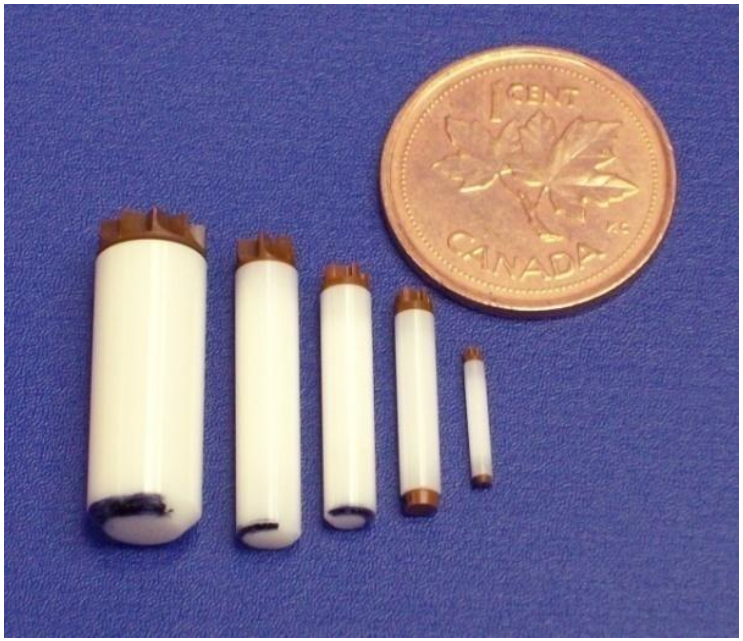


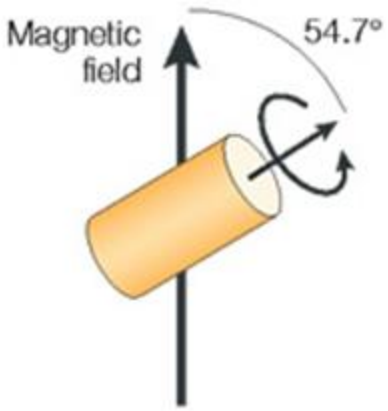


Wirowanie próbki pod kątem magicznym



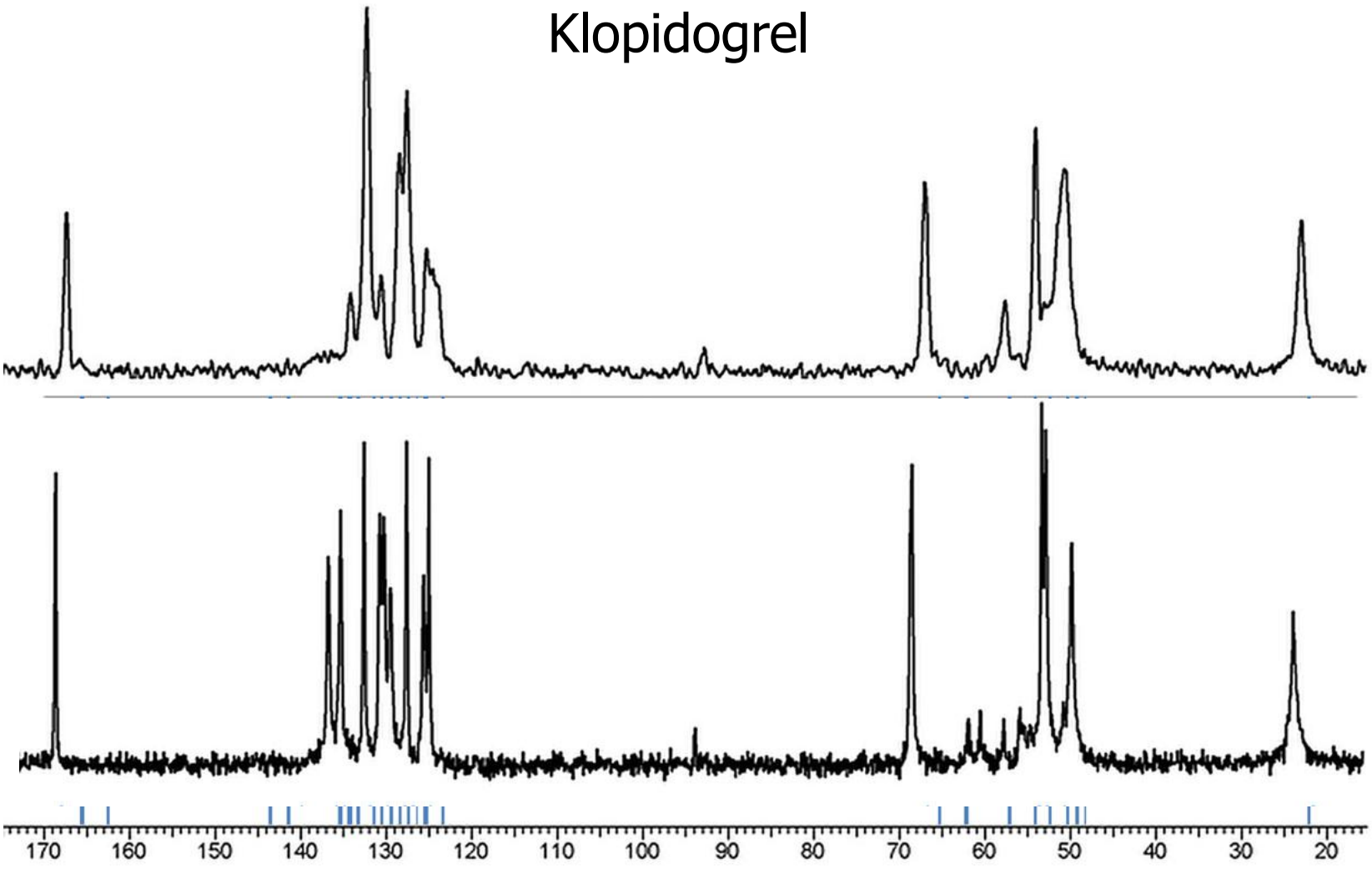






Badania polimorfizmu substancji leczniczych

Klopidogrel



GIPAW-CASTEP

Calculating NMR shielding tensors using pseudopotentials

A uniform external magnetic field, **B**, applied to a sample induces an electric current. In an insulating non-magnetic material, only the orbital motion of the electrons contributes to the this current. In addition, for the field strengths typically used in NMR experiments, the induced electric current is proportional to the external field, **B**. This first-order induced current, $\mathbf{j}^{(1)}(\mathbf{r})$, produces a non-uniform magnetic field:

Eq. CASTEP 42

$$\mathbf{B}_{in}^{(1)}(\mathbf{r}) = \frac{1}{c}\int d^3r' \mathbf{j}^{(1)}(\mathbf{r}') \times \frac{\mathbf{r}-\mathbf{r}'}{|\mathbf{r}-\mathbf{r}'|^3}$$

The shielding tensor, σ(**r**), connects the induced magnetic field to the applied magnetic field:

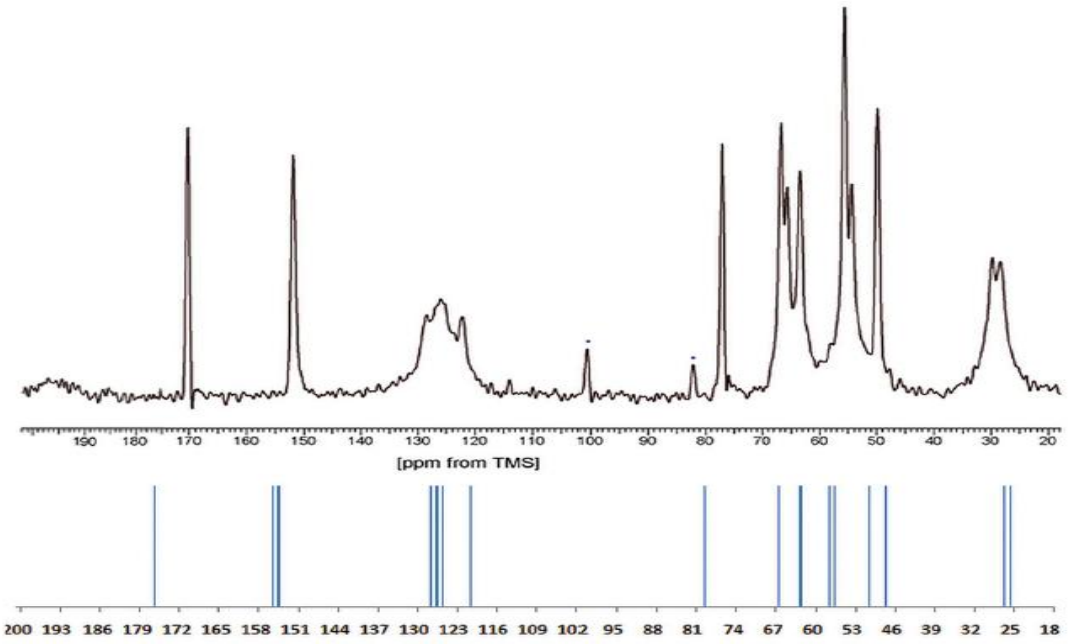
Eq. CASTEP 43

$$\mathbf{B}_{in}^{(1)}(\mathbf{r}) = -\overleftrightarrow{\sigma}(\mathbf{r})\mathbf{B}$$

and the isotropic shielding is given by:

Eq. CASTEP 44

$$\sigma(\mathbf{r}) = \frac{Tr[\overleftrightarrow{\sigma}(\mathbf{r})]}{3}$$



Klopidogrel

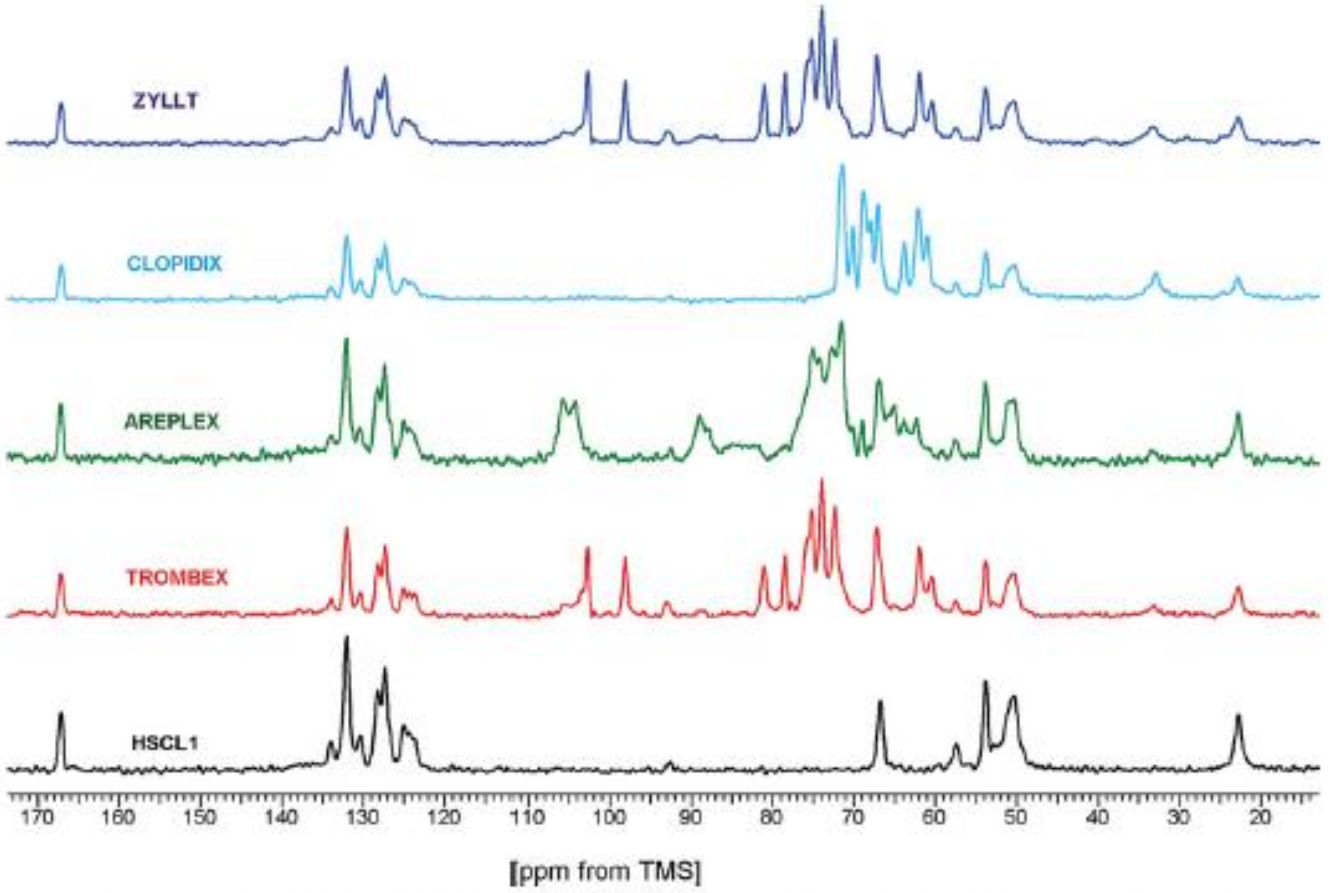
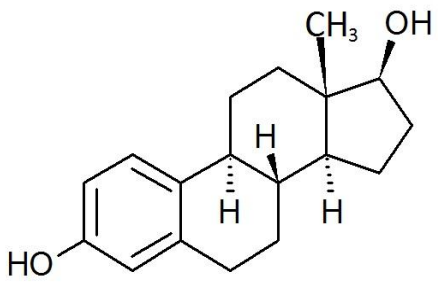
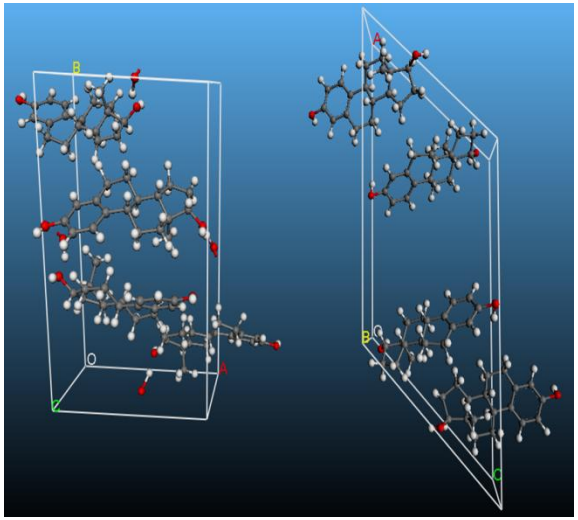


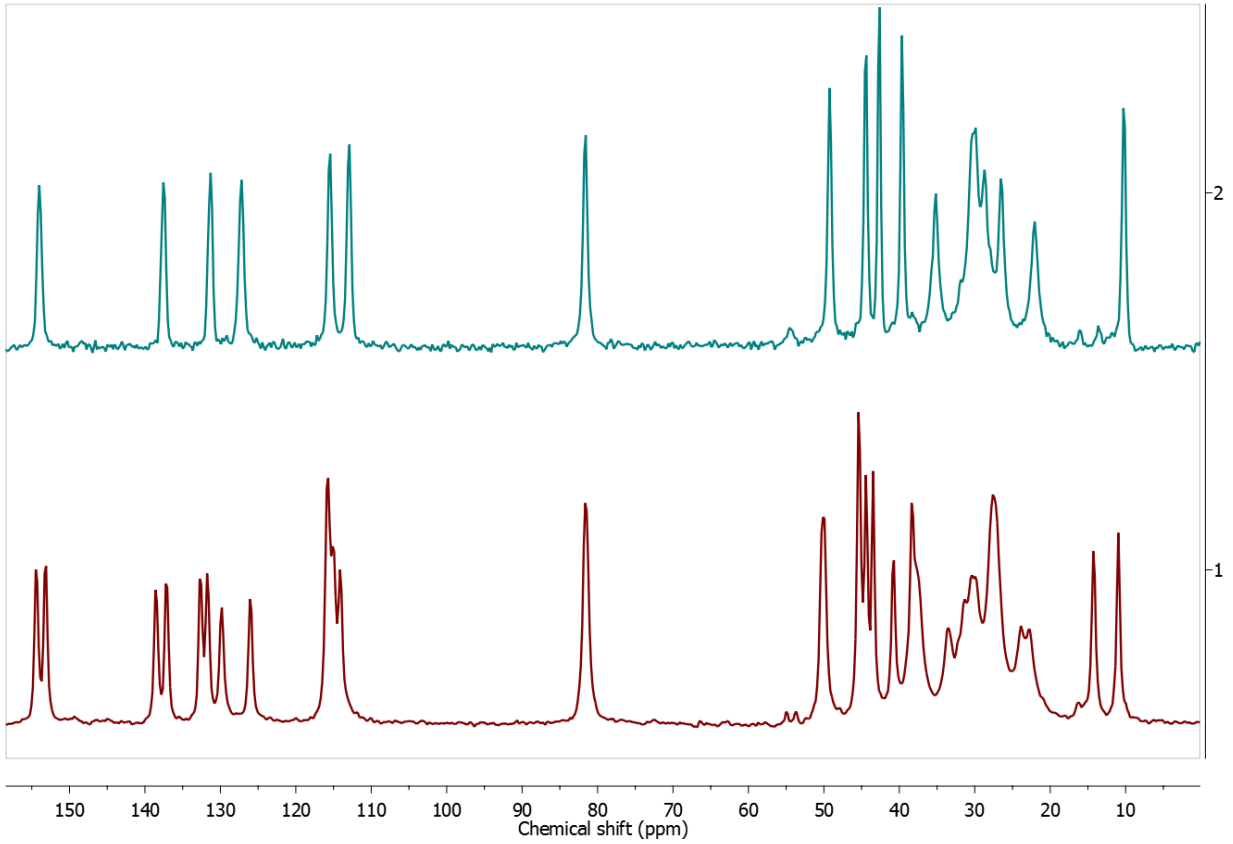
Figure 4. ^{13}C CP/MAS NMR spectra of **HSCL 1** containing tablets (ZYLLT®, CLOPIDIX®, AREPLEX, and TROMBEX®).

Badania polimorfizmu substancji leczniczych

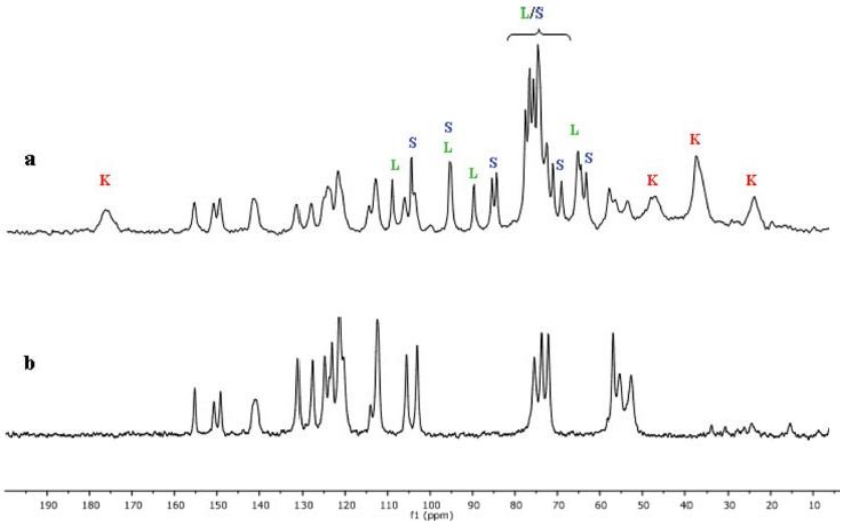


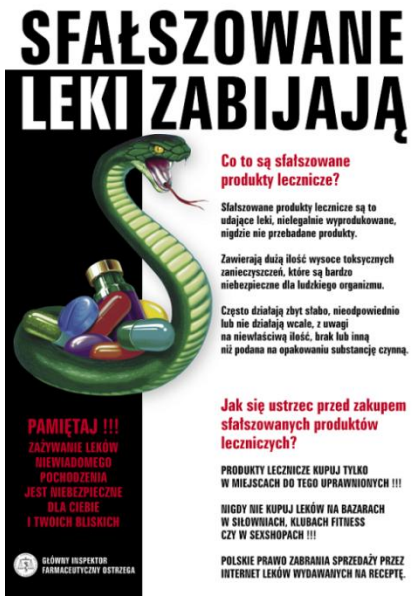
Estradiol

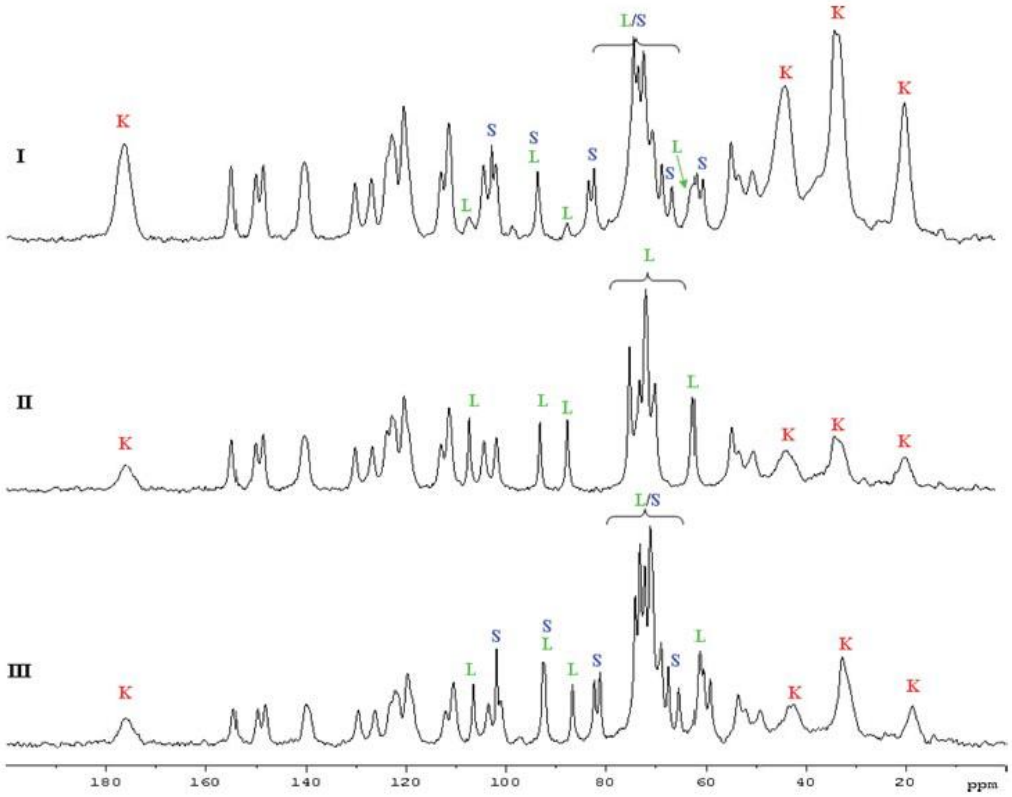




Formulacje farmaceutyczne







„Chromatografia” NMR

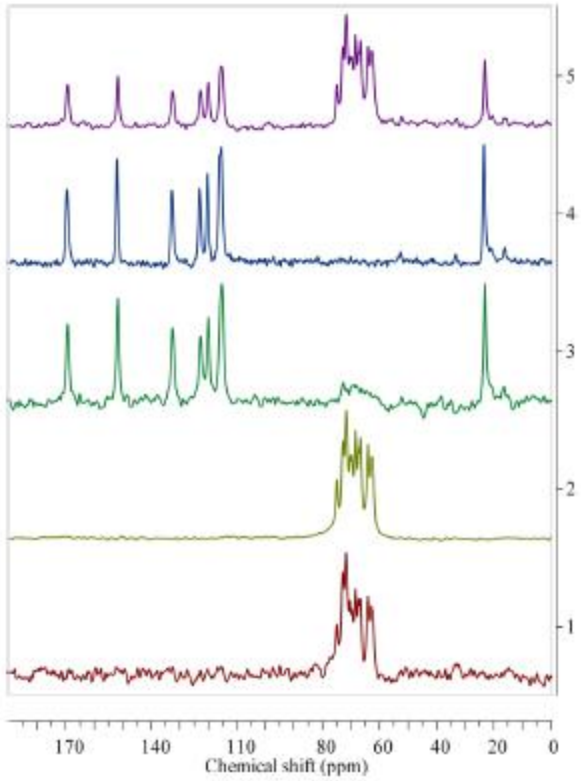


Fig. 4. 13C ssNMR analysis of APAP Junior granules: (5) ns = 16; standard 13C CP/MAS NMR spectrum of APAP Junior, (4) ns = 256; standard 13C CP/MAS NMR spectrum of pure acetaminophen, (3) ns = 160; 13C pre-CP inversion recovery spectrum of APAP Junior; τ = 6 s, (2) ns = 24; standard 13C CP/MAS NMR spectrum of pure sorbitol, (1) ns = 160; 13C pre-CP inversion recovery spectrum of APAP Junior; τ = 12 s.

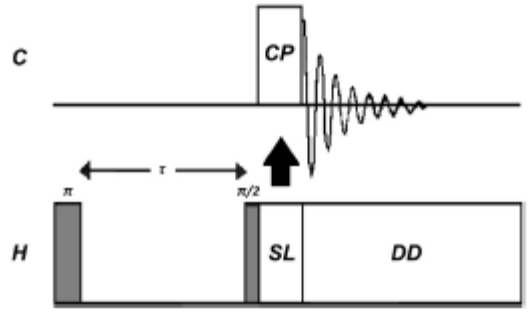
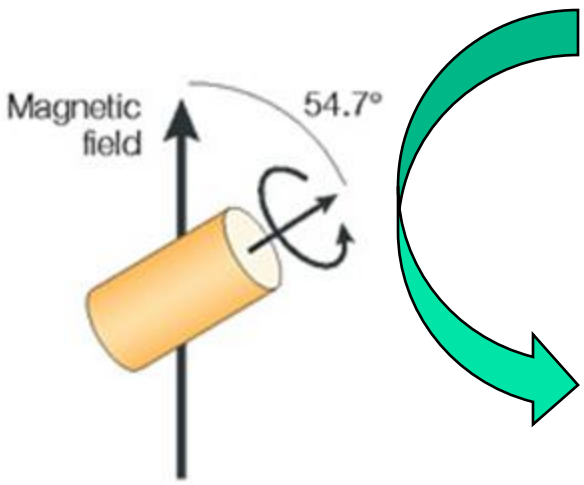
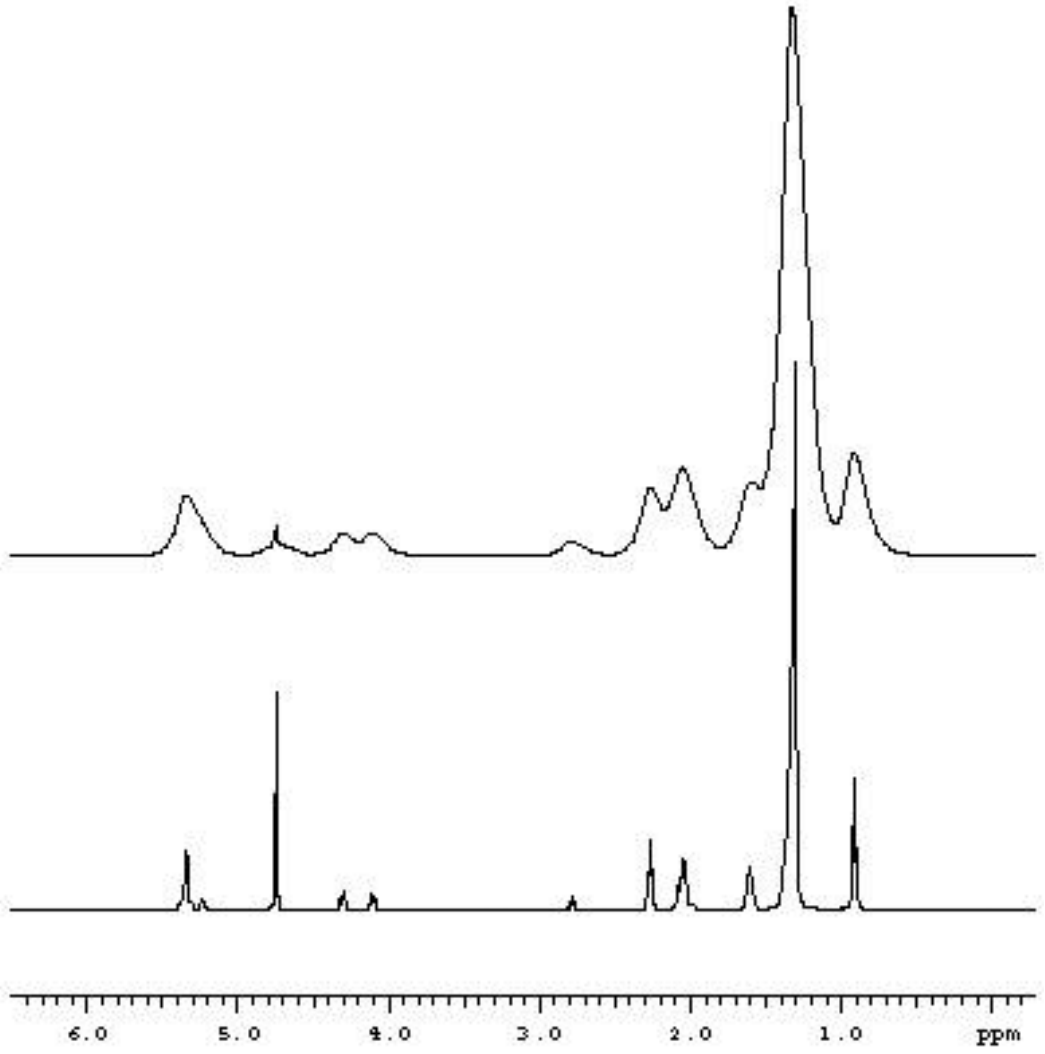


Fig. 1. Pre-CP inversion recovery sequence (SL—Spin Lock, CP—Cross Polarization, DD—Dipolar Decoupling).

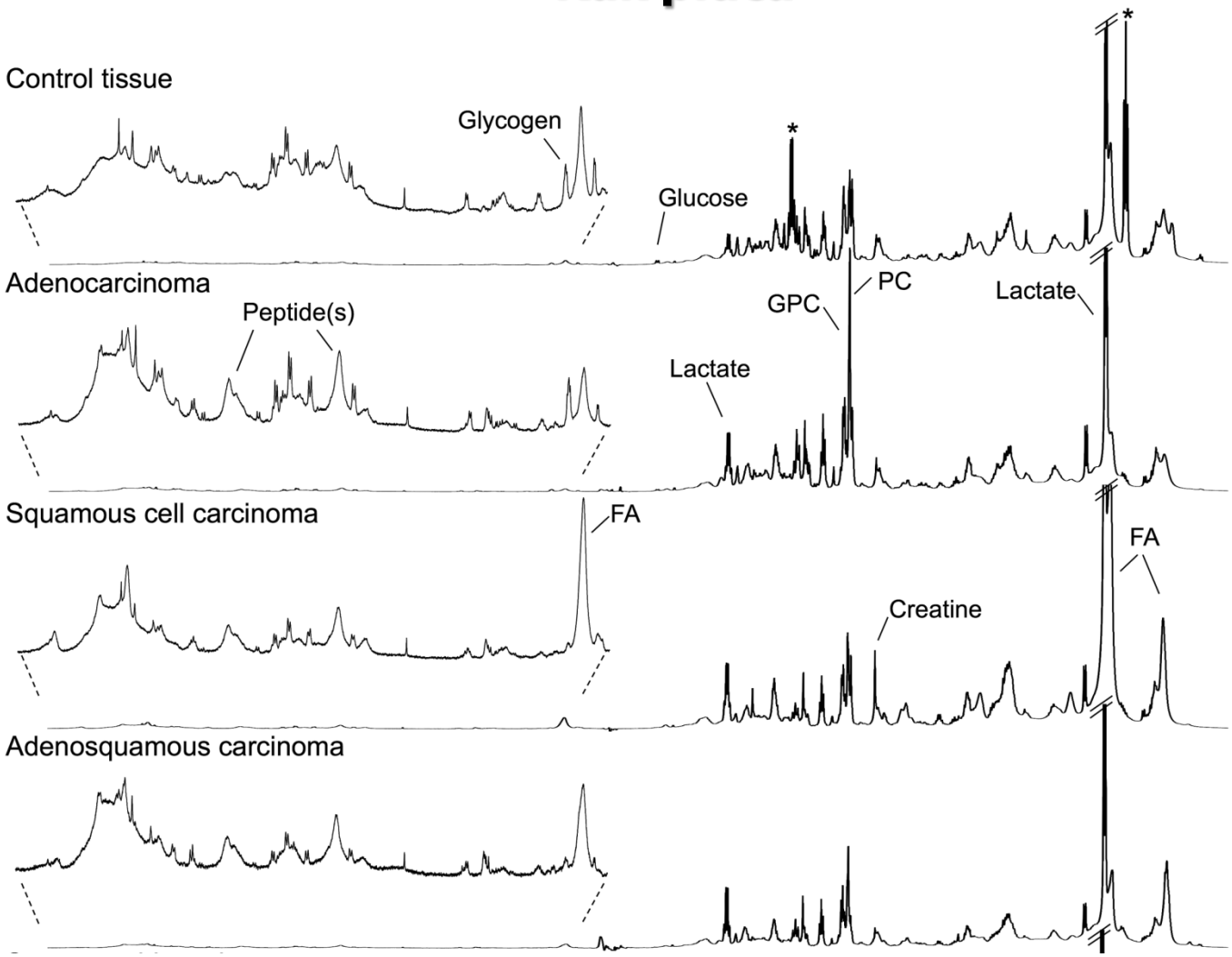
HRMAS NMR - metabolomika NMR





Diagnostyka NMR

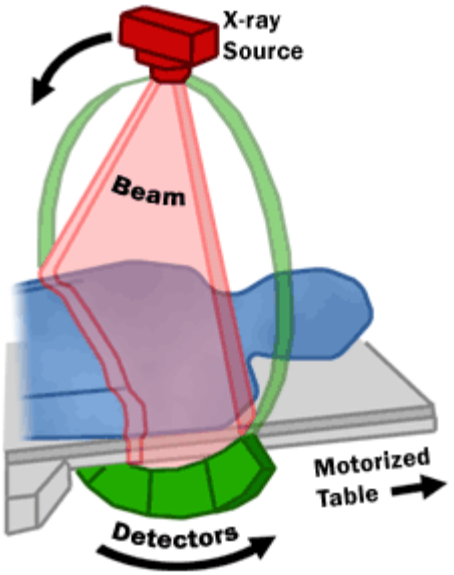
Rak płuca



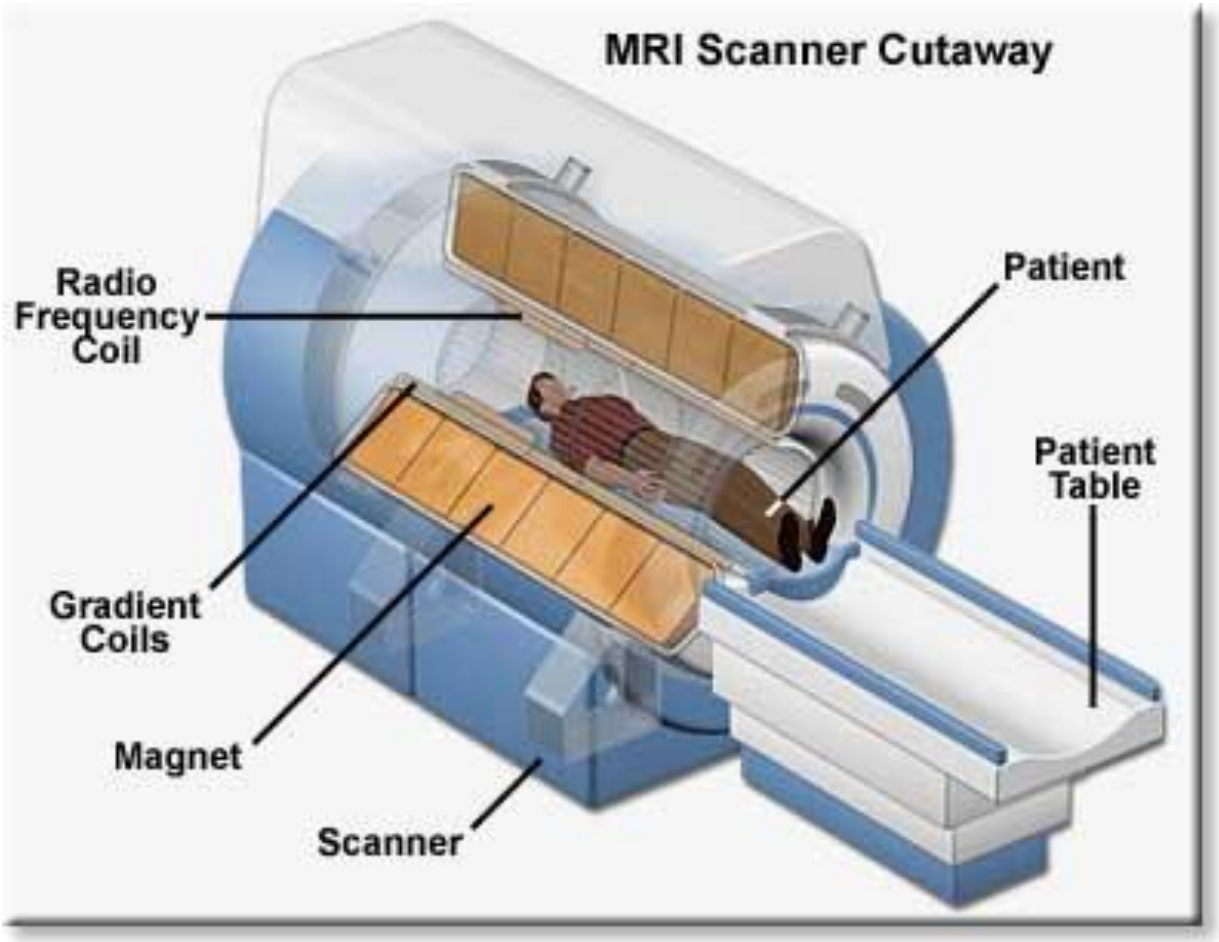
Tomografia MRI

Tomografia komputerowa

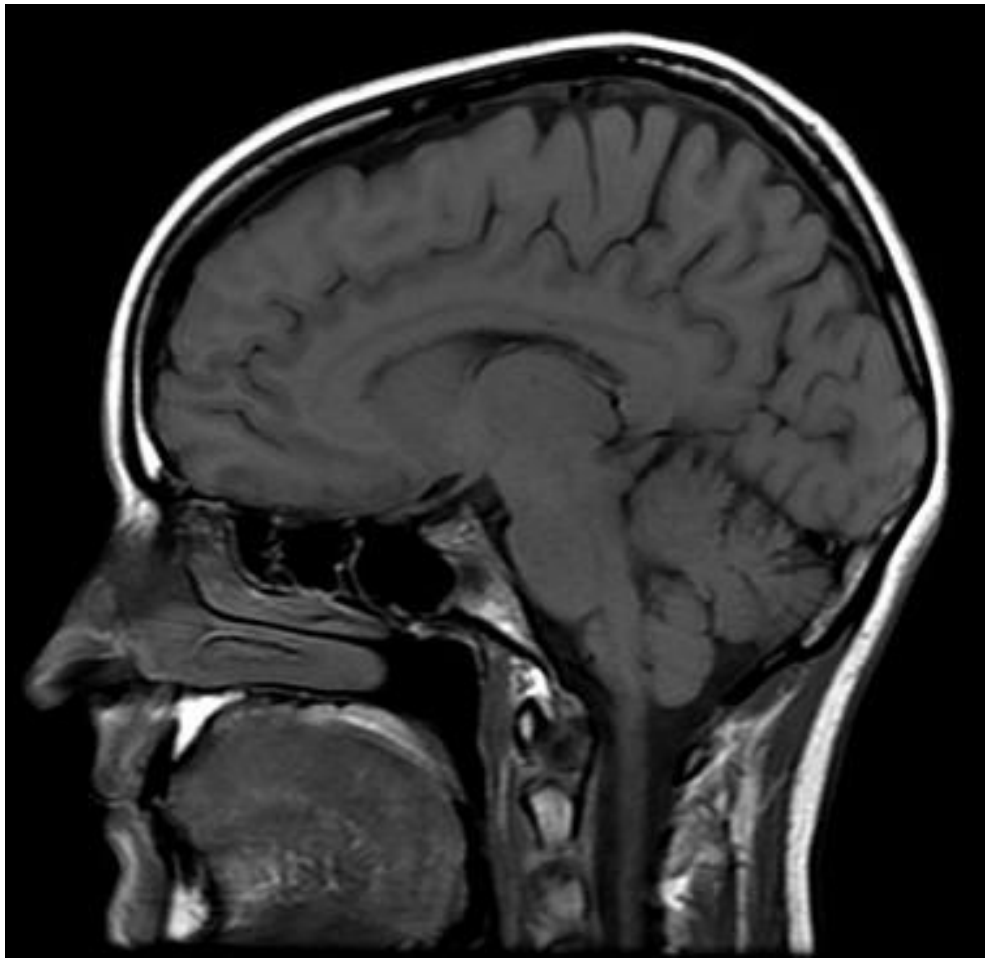
CT≠NMR



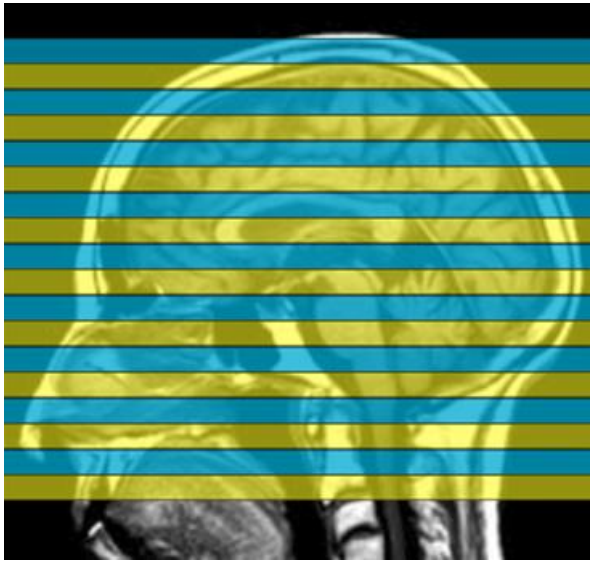
Tomografia NMR MRI

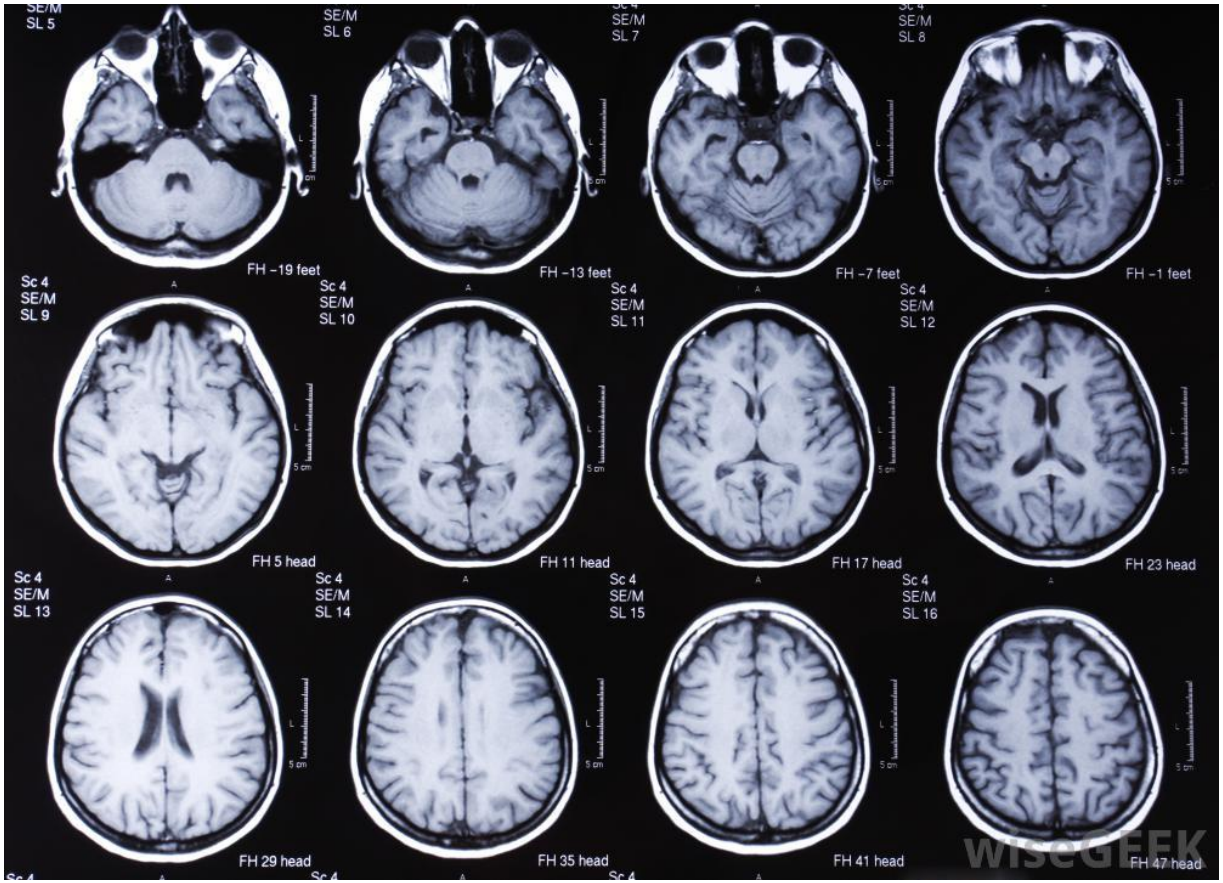


Obraz MRI

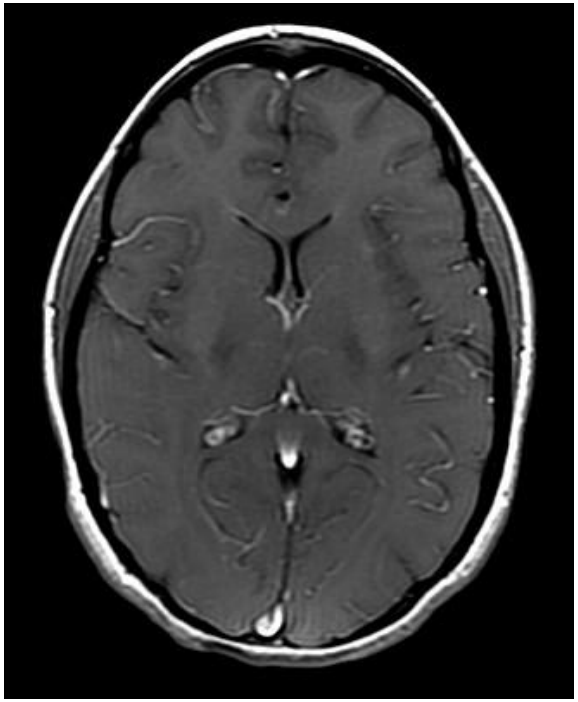


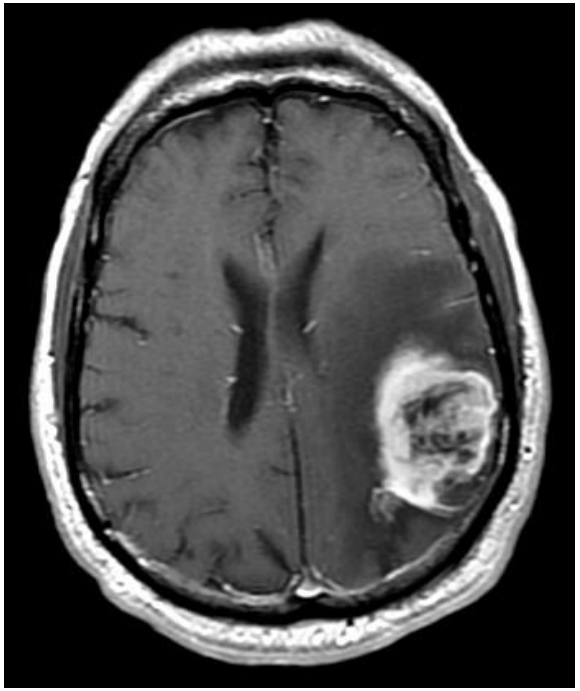
MRI



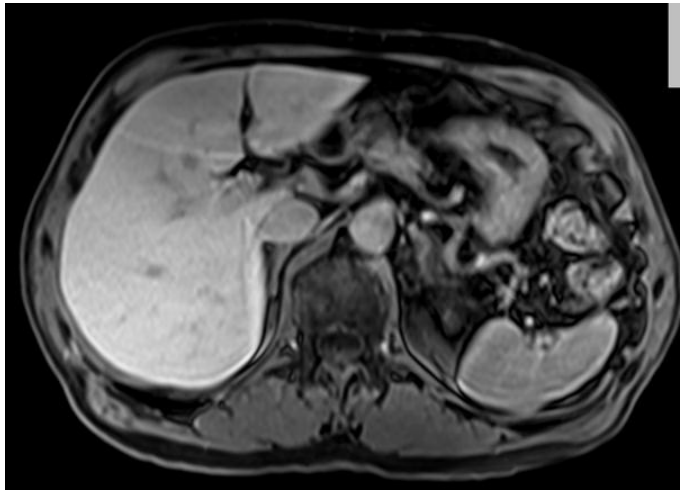

SE/M
SL 5
SE/M
SL 6
SE/M
SL 7
SE/M
SL 8
FH –19 feet
FH –13 feet
FH –7 feet
FH –1 feet
Sc 4
SE/M
SL 9
Sc 4
SE/M
SL 10
Sc 4
SE/M
SL 11
Sc 4
SE/M
SL 12
FH 5 head
FH 11 head
FH 17 head
FH 23 head
Sc 4
SE/M
SL 13
Sc 4
SE/M
SL 14
Sc 4
SE/M
SL 15
Sc 4
SE/M
SL 16
FH 29 head
FH 35 head
FH 41 head
FH 47 head
wiseGEEK

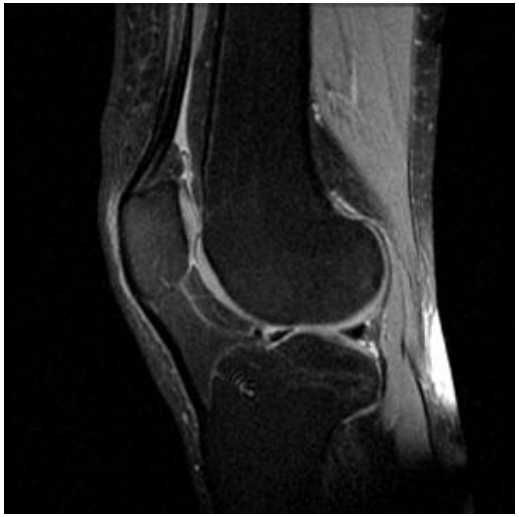
Diagnostyka MRI



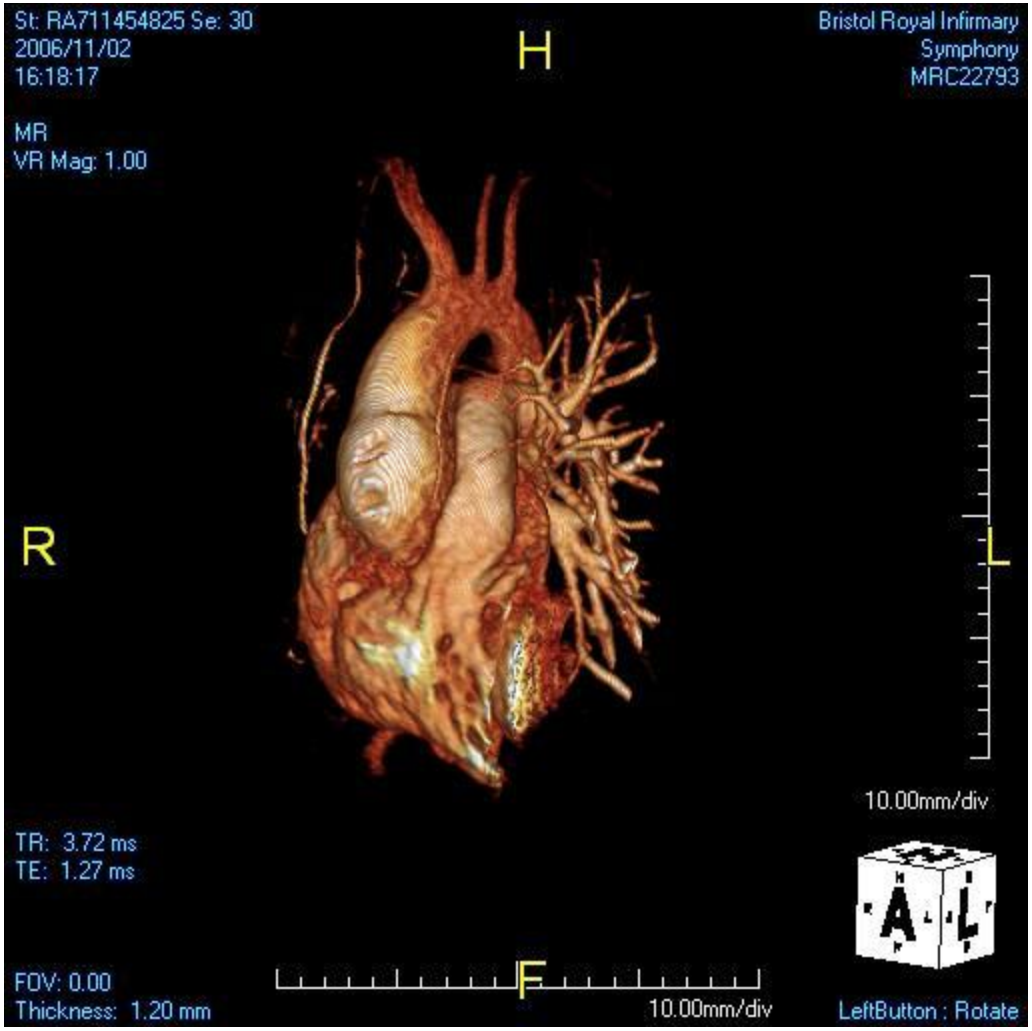


Wszechstronne zastosowanie MRI

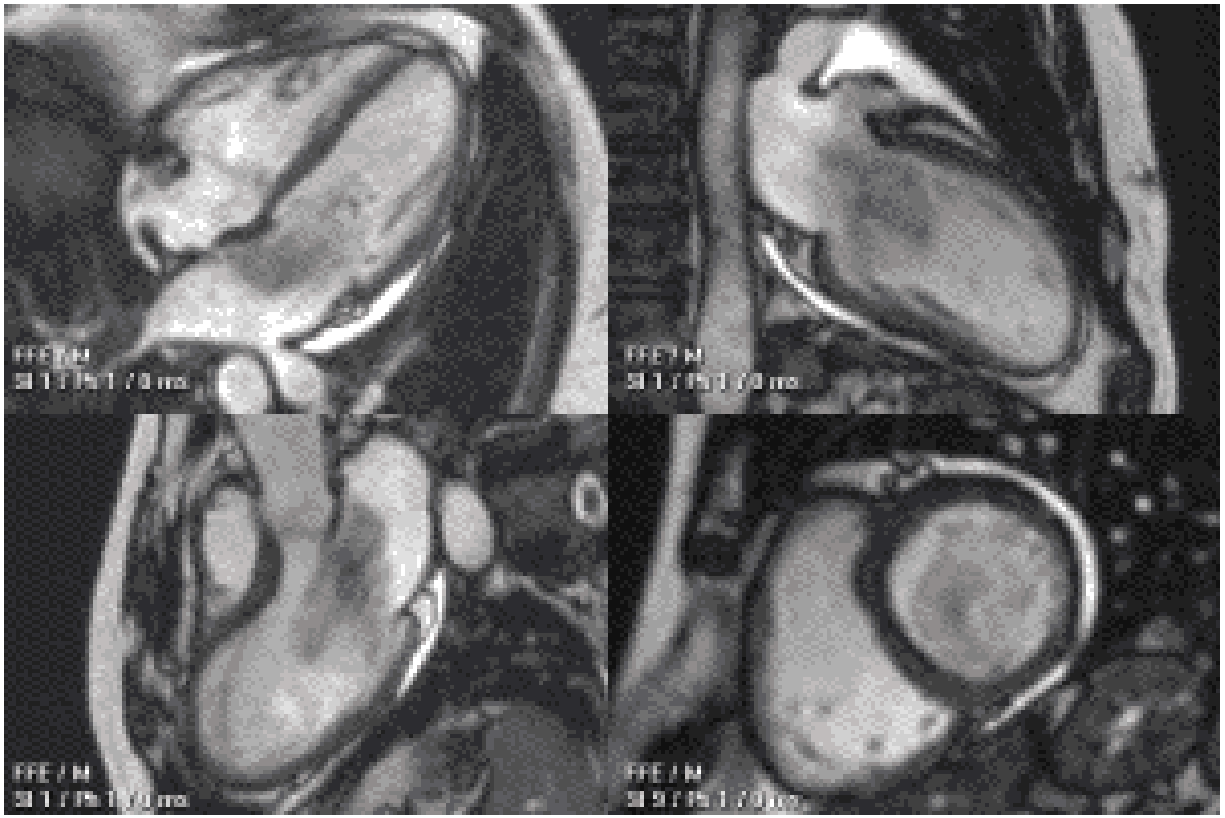




3D MRI


St: RA711454825 Se: 30
2006/11/02
16:18:17
H
Bristol Royal Infirmary
Symphony
MRC22793
MR
VR Mag: 1.00
R
L
10.00mm/div
TR: 3.72 ms
TE: 1.27 ms
A
L
FOV: 0.00
Thickness: 1.20 mm
F
10.00mm/div
LeftButton : Rotate

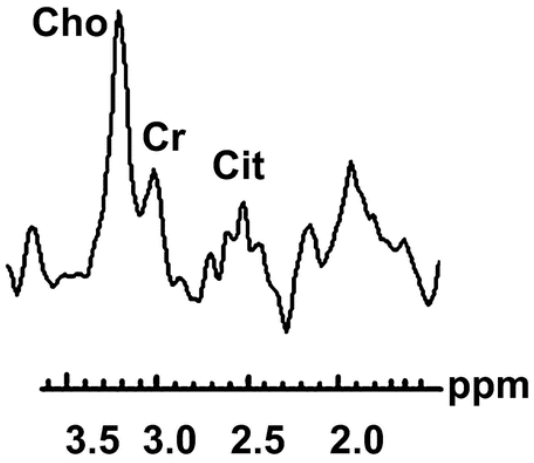
Badania dynamiczne MRI



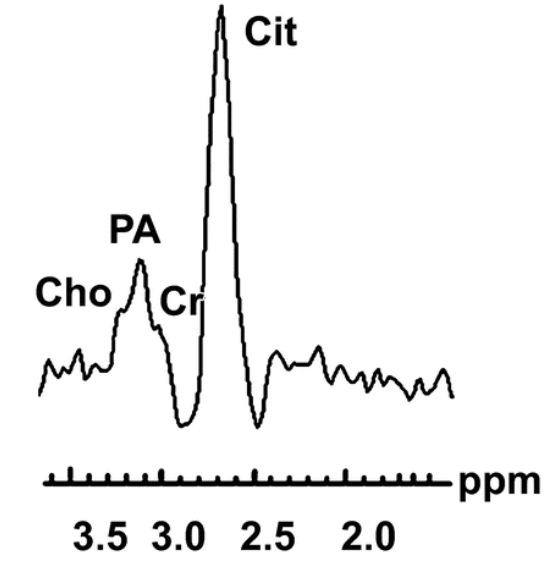
Angiografia MRI

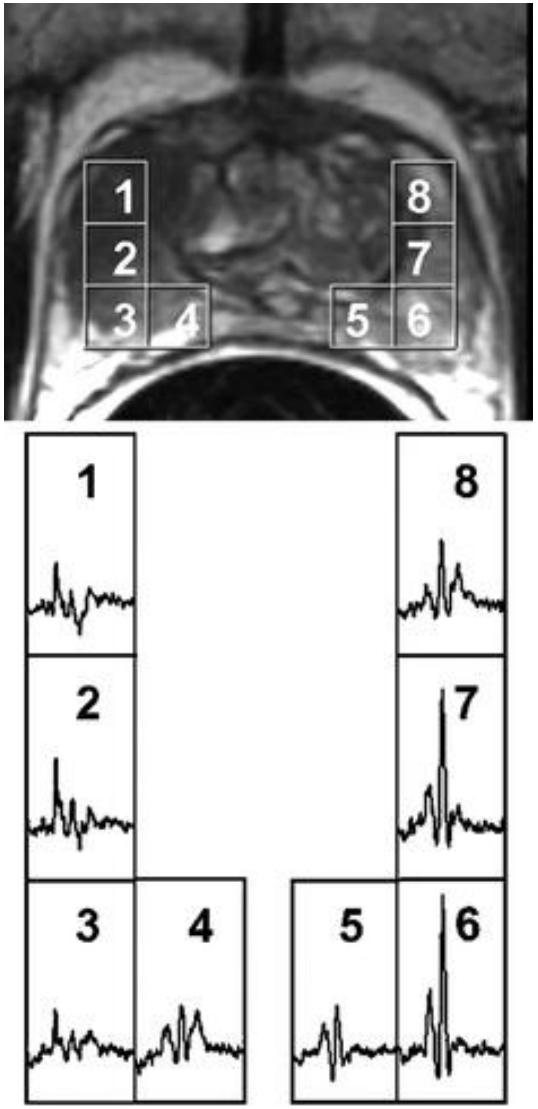
Spektroskopia MRI in vivo

Tkanka zdrowa

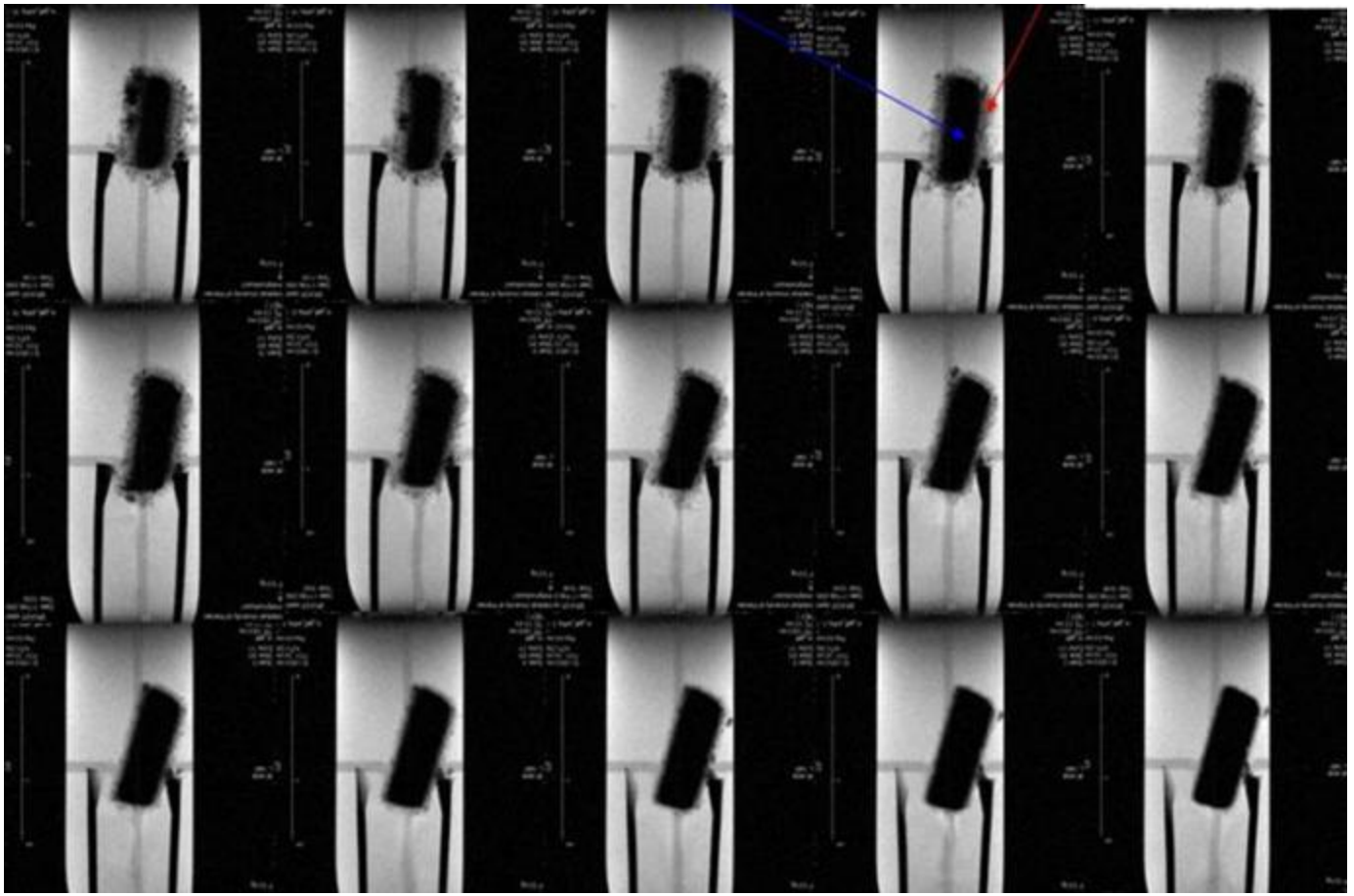


Tkanka nowotworowa

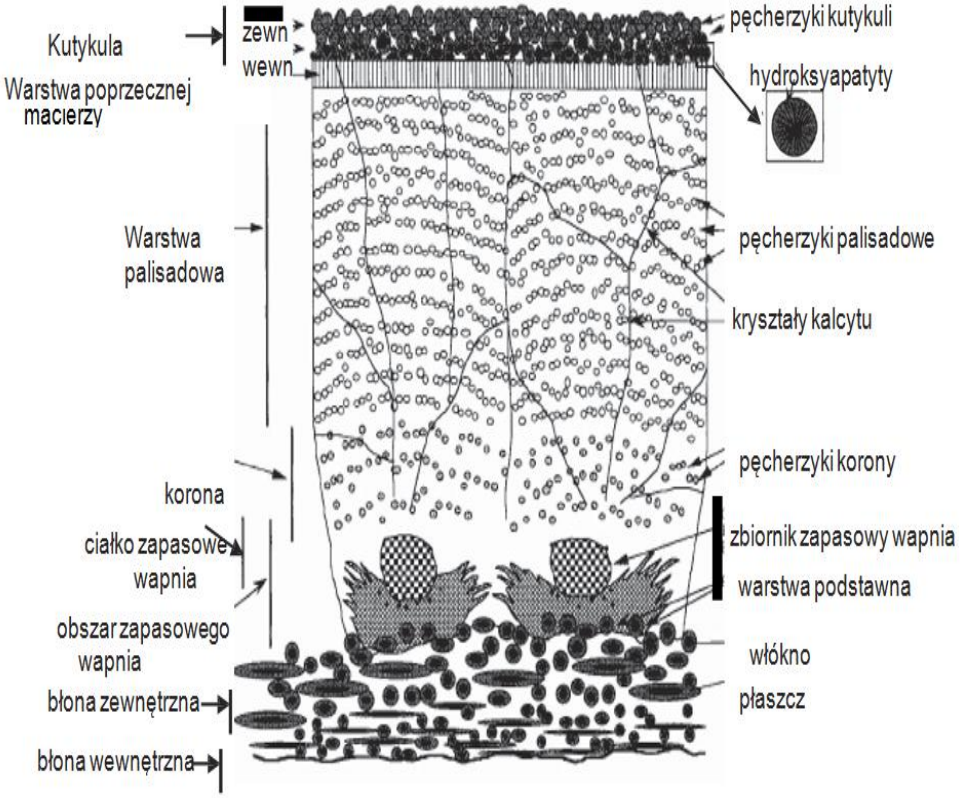


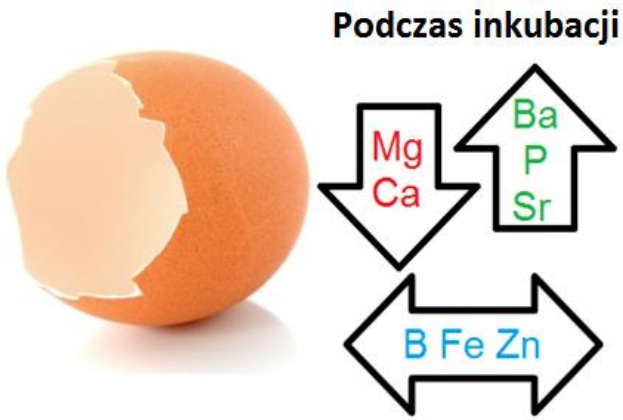


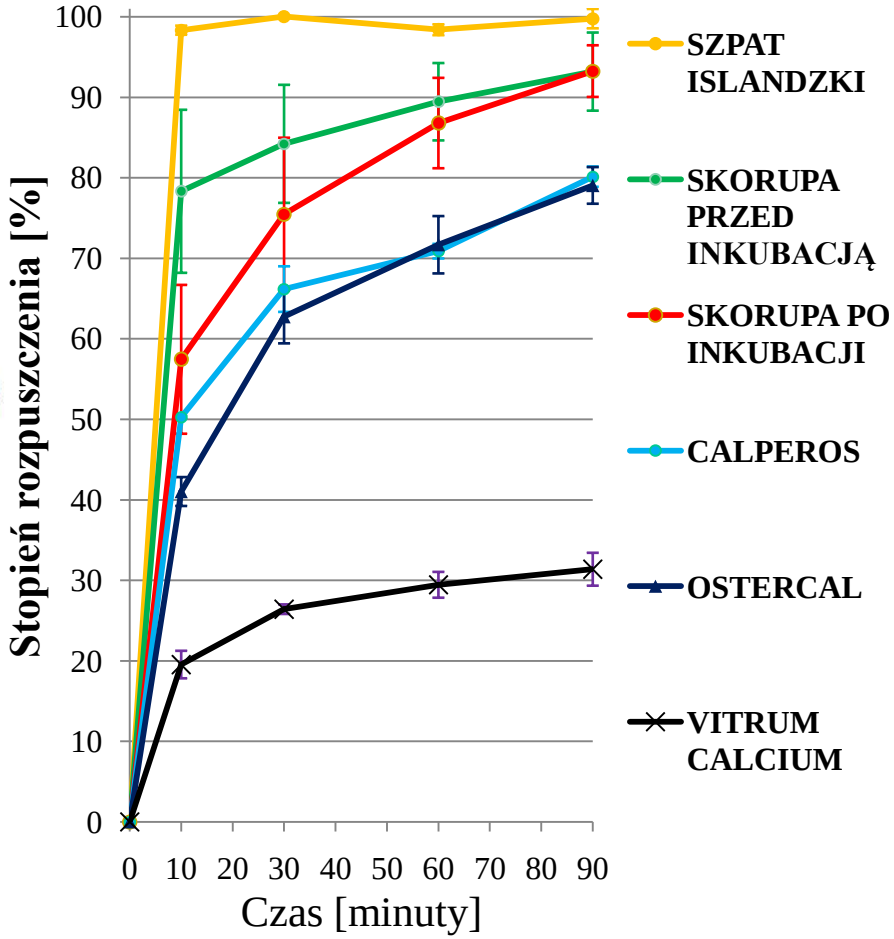
Badania tabletek metodą MRI



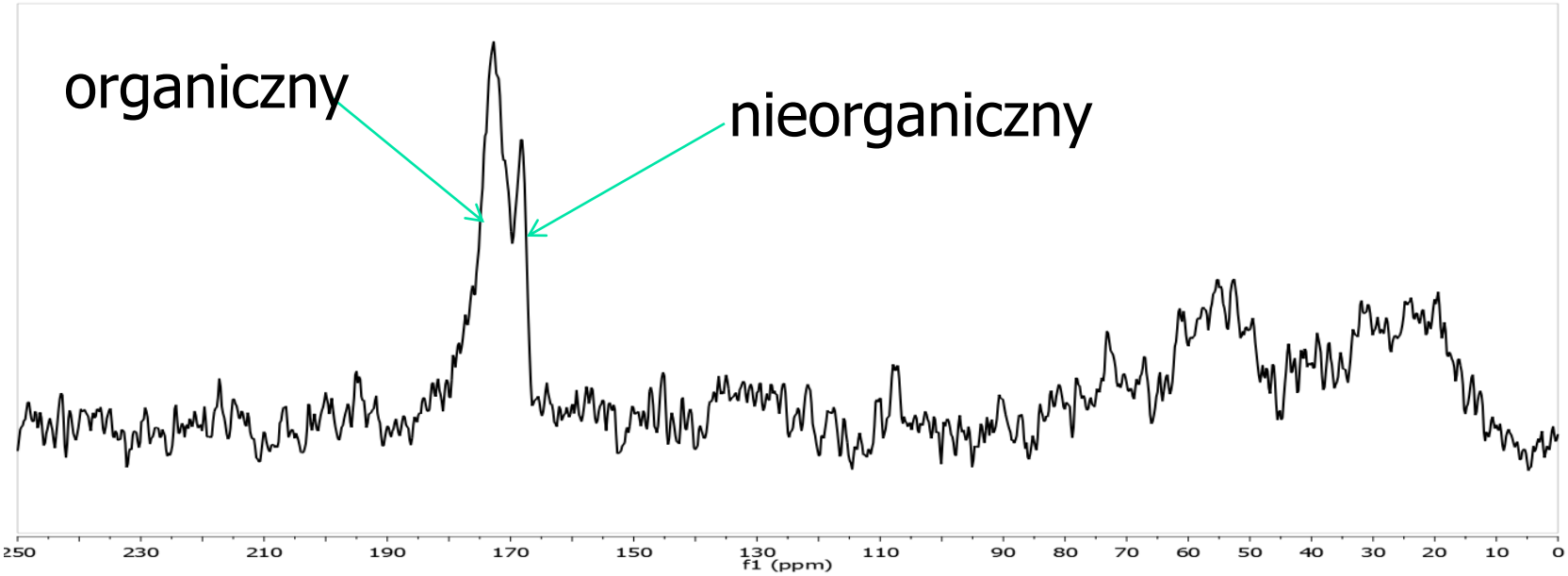
Spektroskopowe badania skorupy jaja kurzego

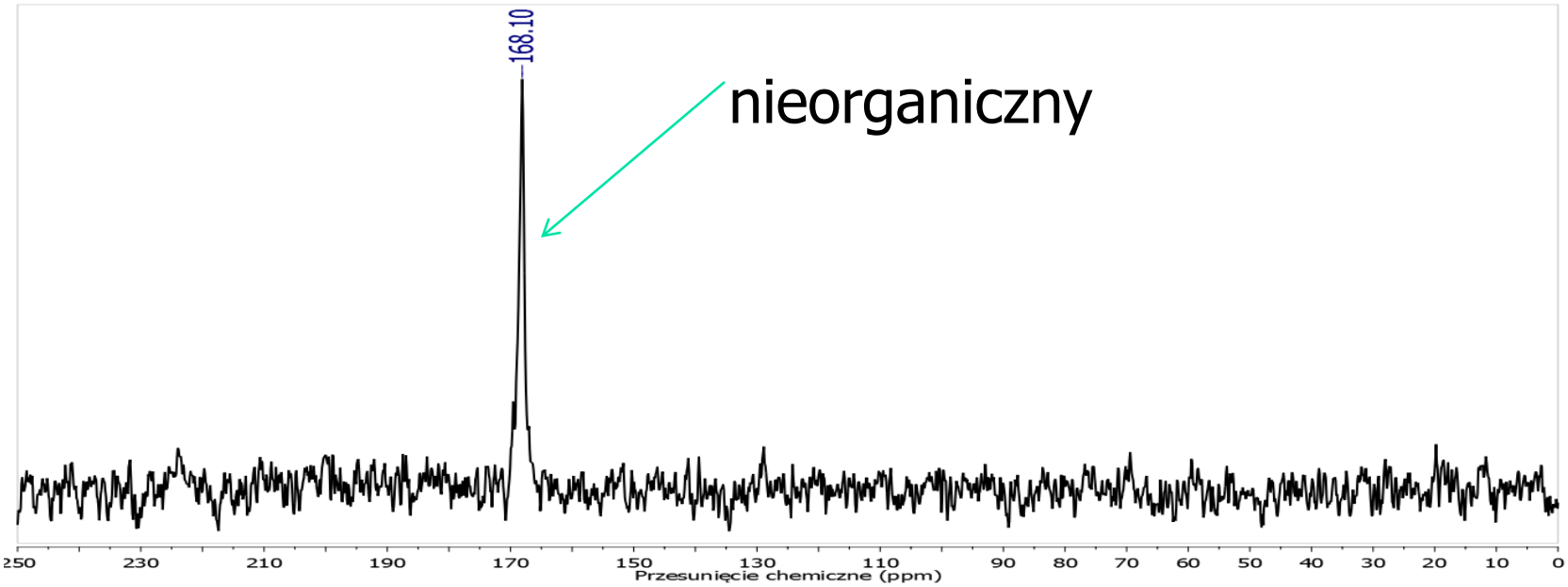




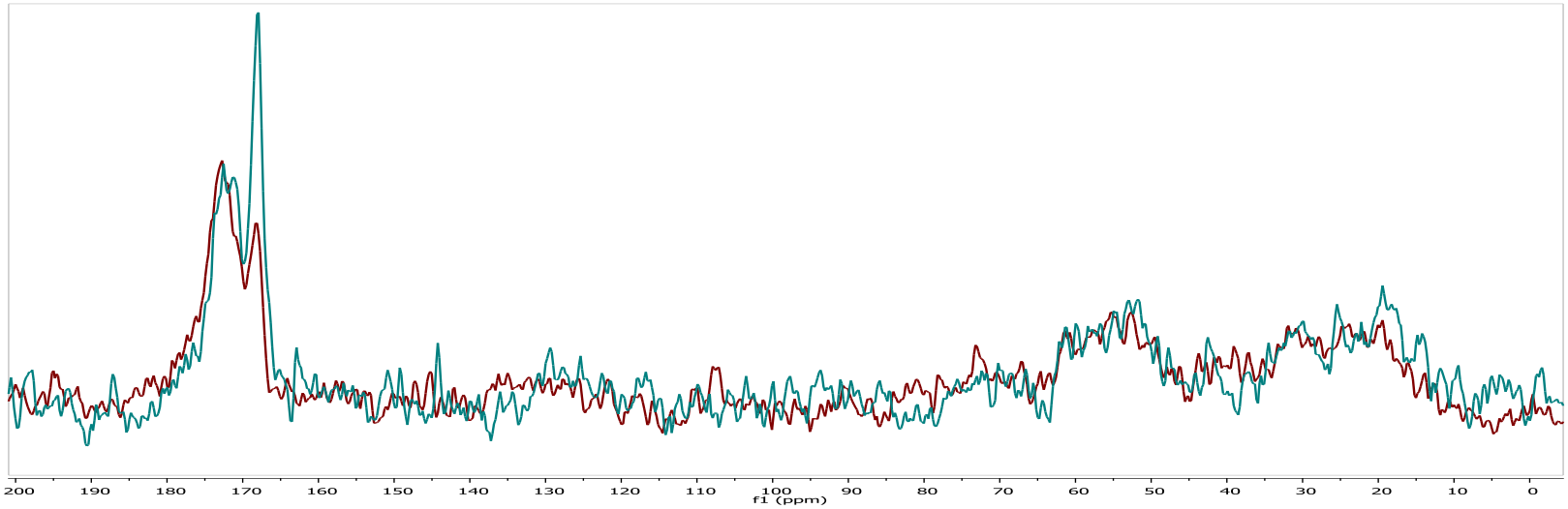


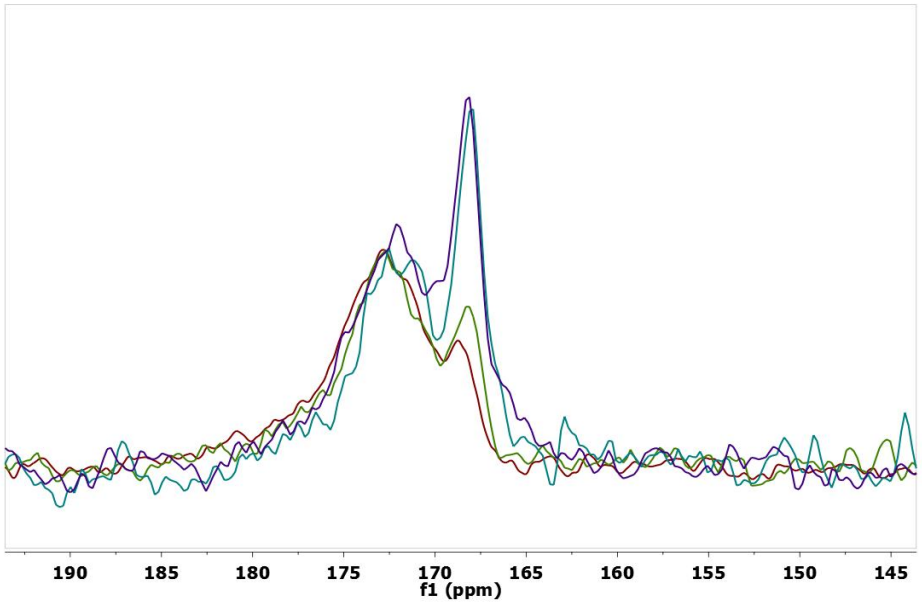
^{13}C MAS NMR


organiczny
nieorganiczny
250
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


168.10
nieorganiczny
250
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
Przesunięcie chemiczne (ppm)

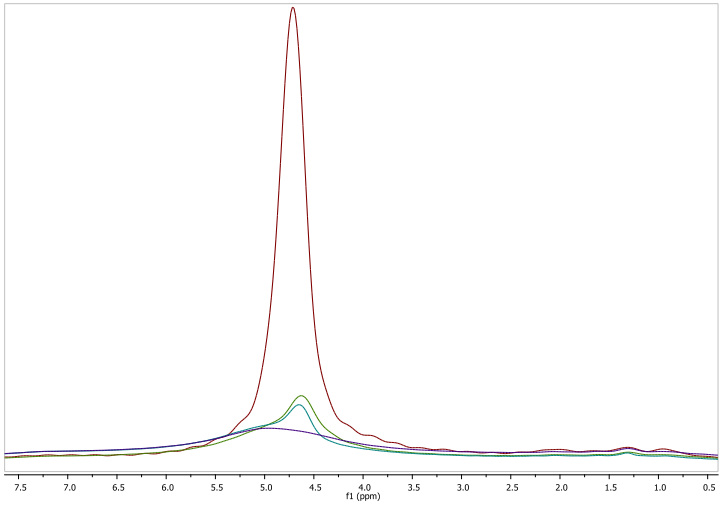
^{13}C CP MAS NMR

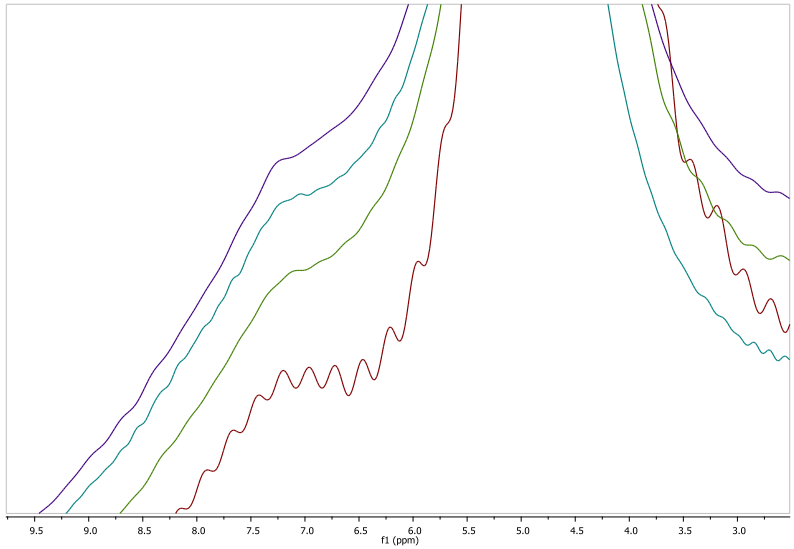




1. Dzień inkubacji
14. Dzień inkubacji
18. Dzień inkubacji
21. Dzień inkubacji

^{1}H MAS NMR





1. Dzień inkubacji
14. Dzień inkubacji
18. Dzień inkubacji
21. Dzień inkubacji

$$2H^{+}+2CaCO_3 \rightarrow Ca(HCO_3)_2 + Ca^{2+}$$

Dziękujemy za uwagę