Arilsulfatasi A: progettazione razionale e sintesi di potenziali inibitori

SAPIENZA
UNIVERSITÀ DI ROMA

Facoltà di Farmacia e Medicina
Corso di Laurea in Biotecnologie Farmaceutiche
Tesi Sperimentale in Chimica Farmaceutica
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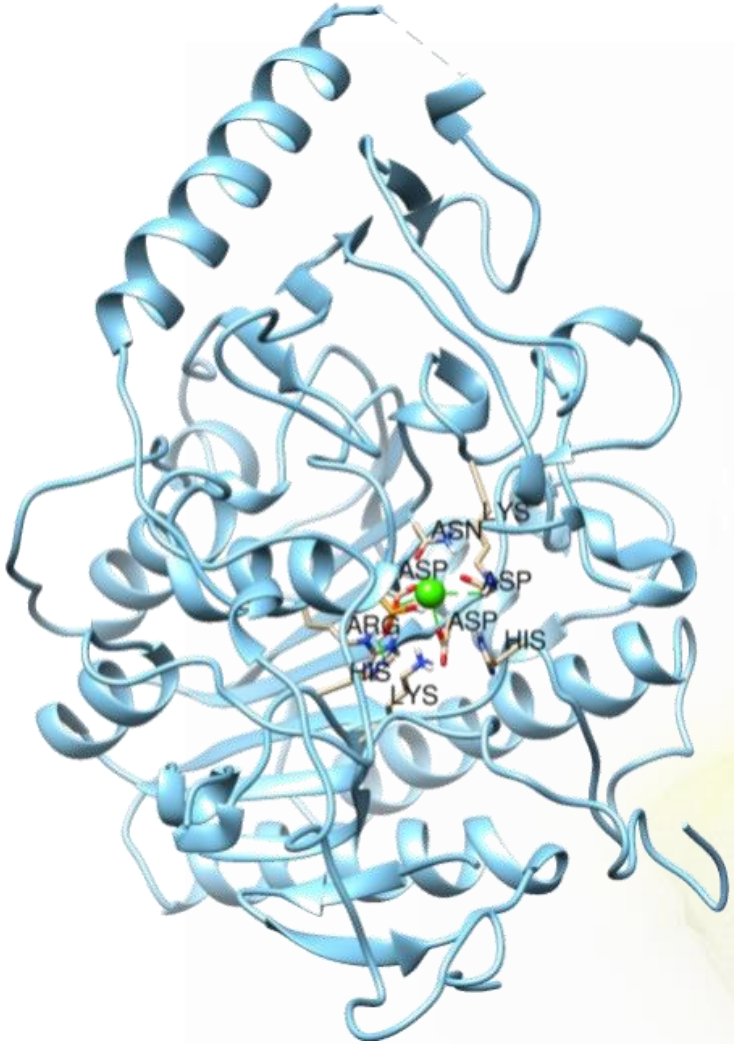
Correlatore: Prof. Gilbert Kirsch

SRSMC
UMR 7565

UNIVERSITÉ DE LORRAINE

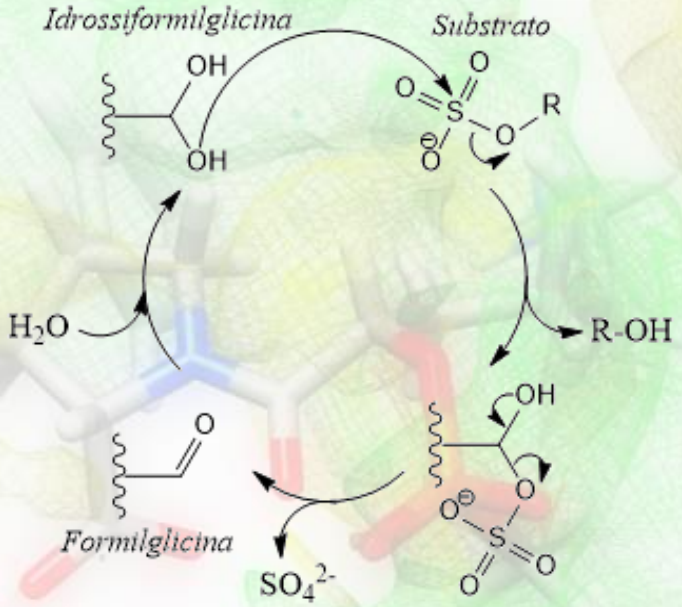
Enzima Arilsulfatasi A



Codice PDB: 1E33

- ✓ *Classificazione*
- ✓ *Meccanismo d'azione*
- ✓ *Patologie associate e risvolti clinici*

Meccanismo d'azione



Potenziali inibitori dell'Arilsulfatasi A

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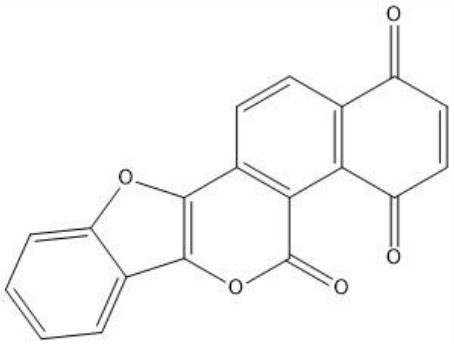
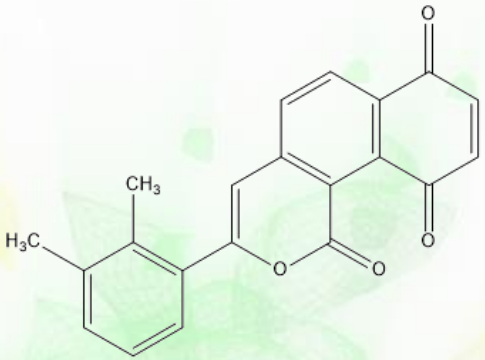
XU39



XU49



Studi di *Docking* Molecolare

- **Autodock**
- **Autodock Vina**

Ricerca di strategie di sintesi

Balloon: risultati analisi conformazionale

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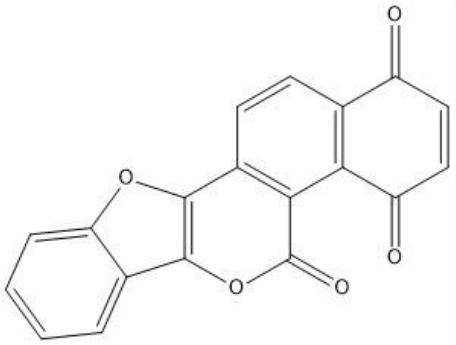
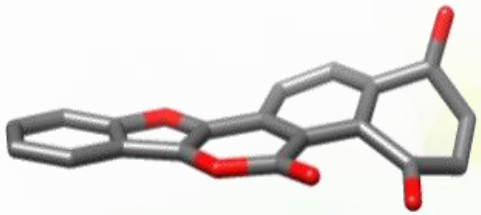
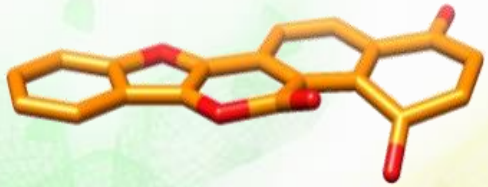
XU39







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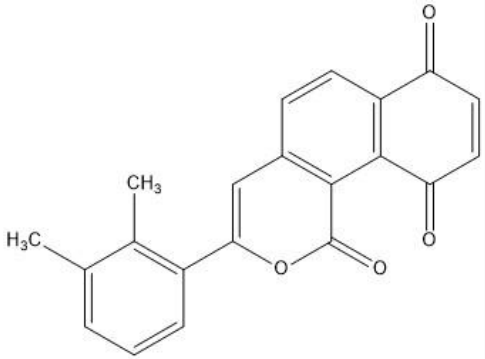
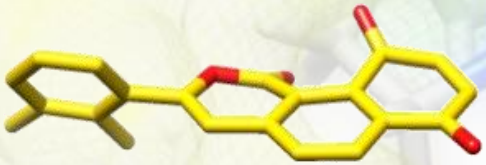
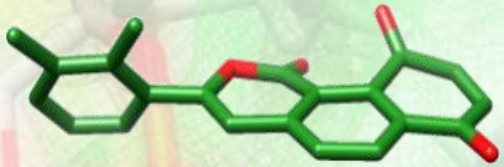
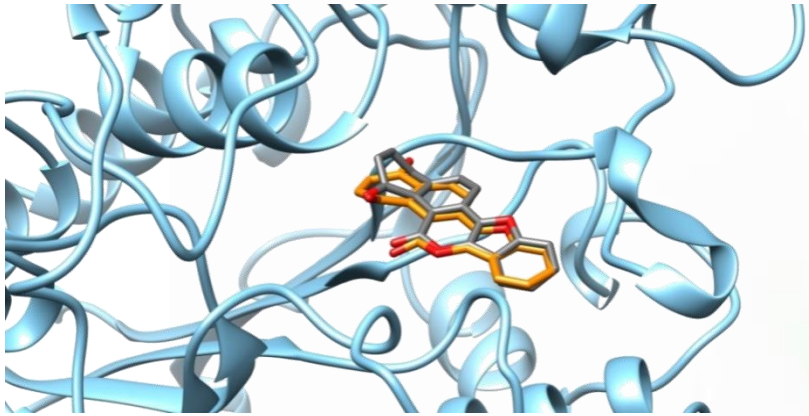




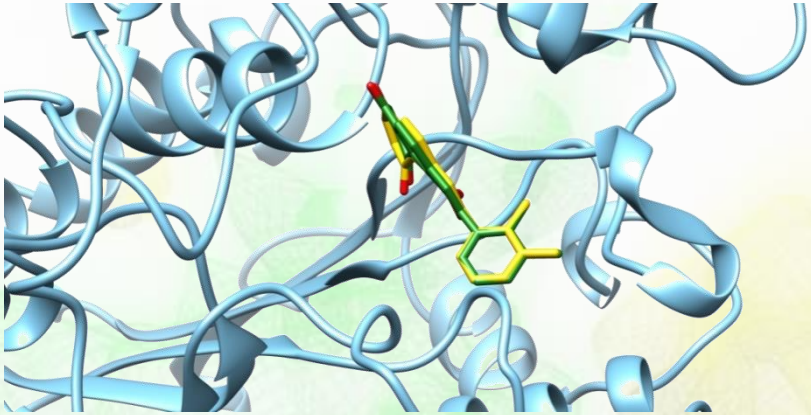


Autodock

XU39

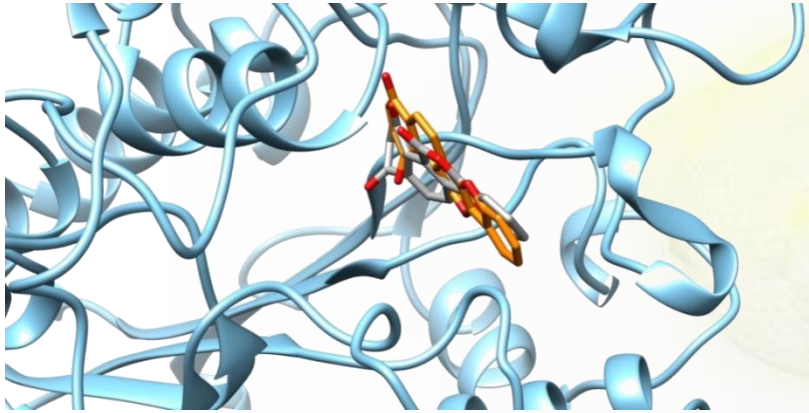


XU49



Autodock Vina

XU39



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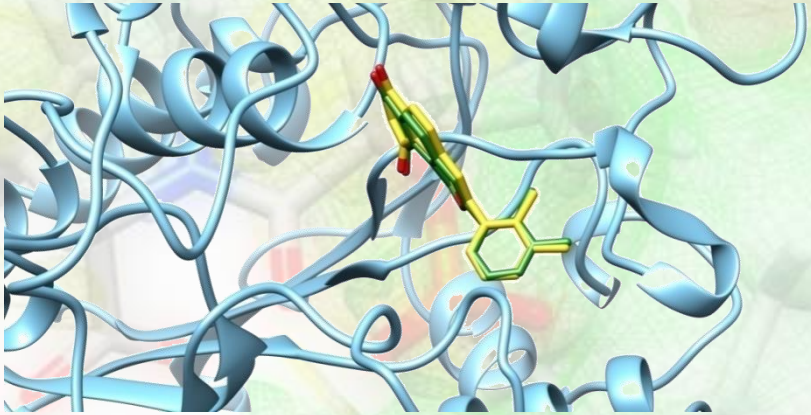
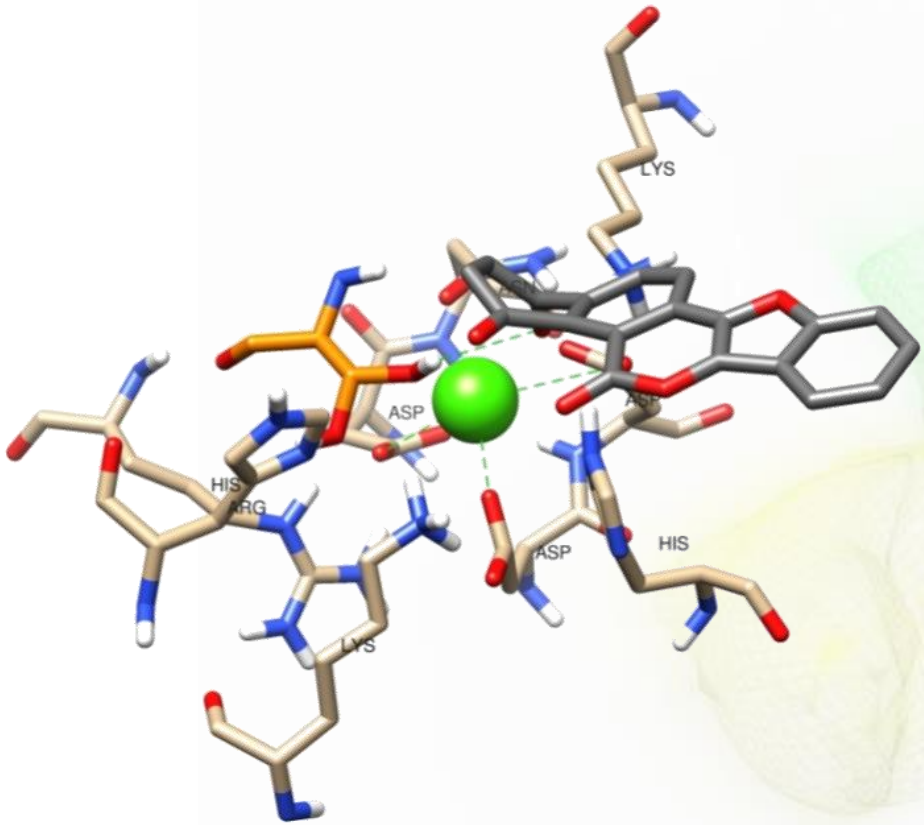


Binding Mode

XU39



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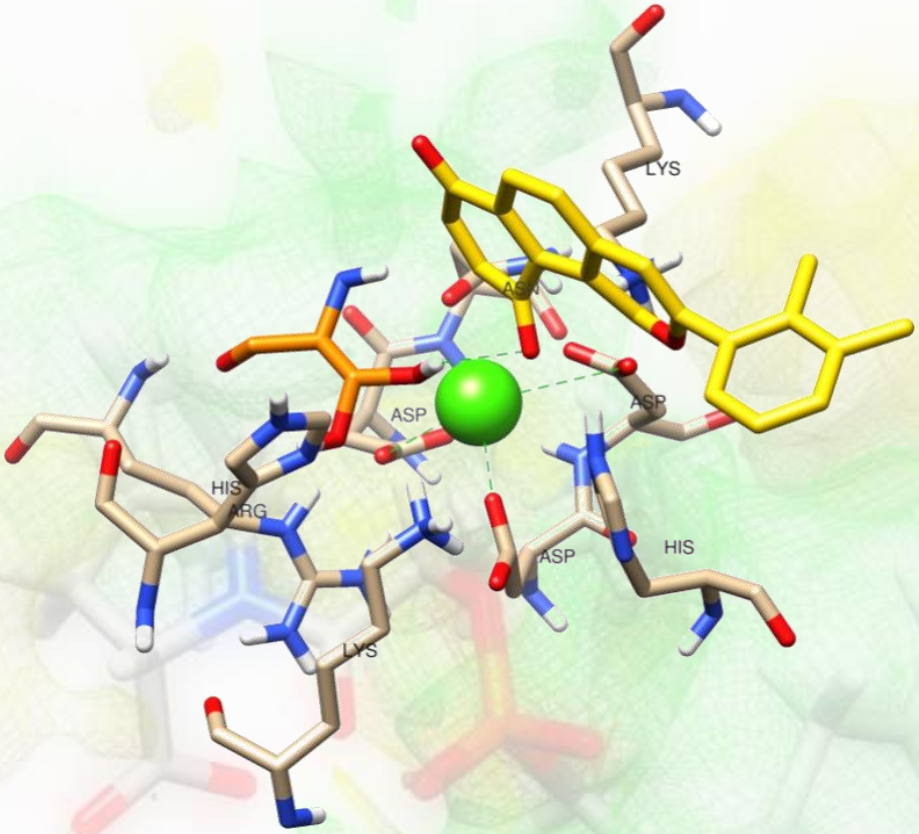
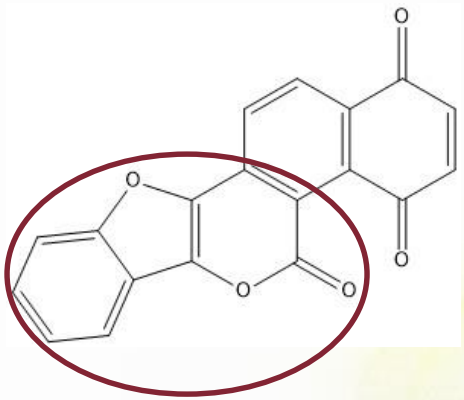
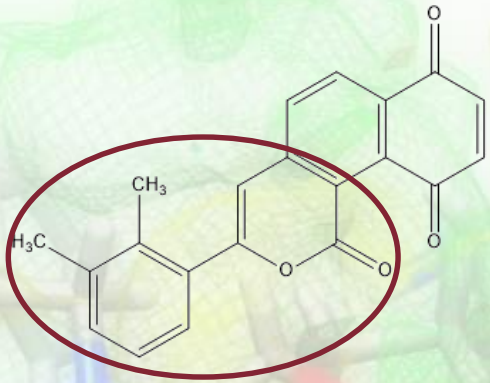


Strategie di sintesi dei ligandi XU39 e XU49

XU39

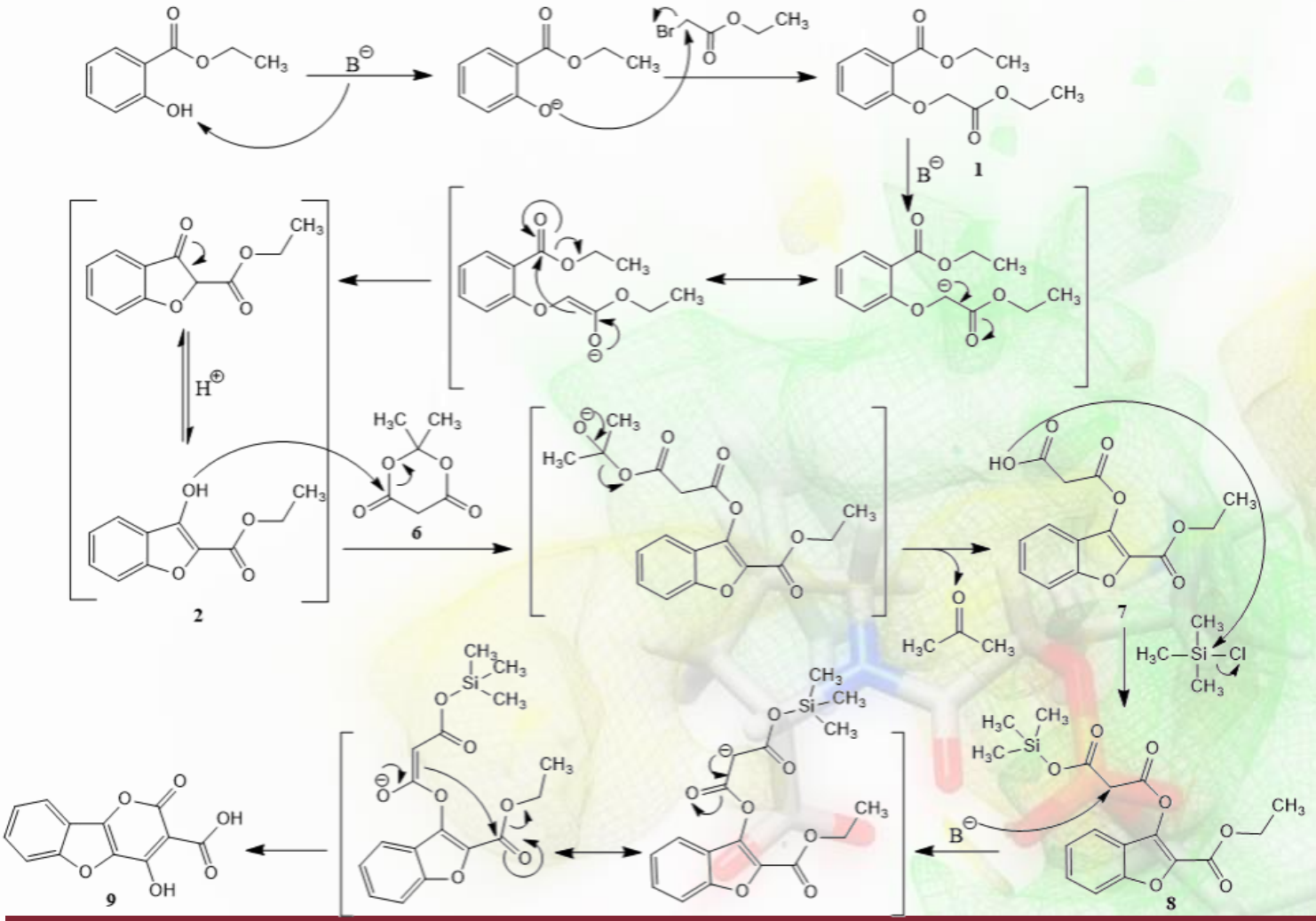


XU49

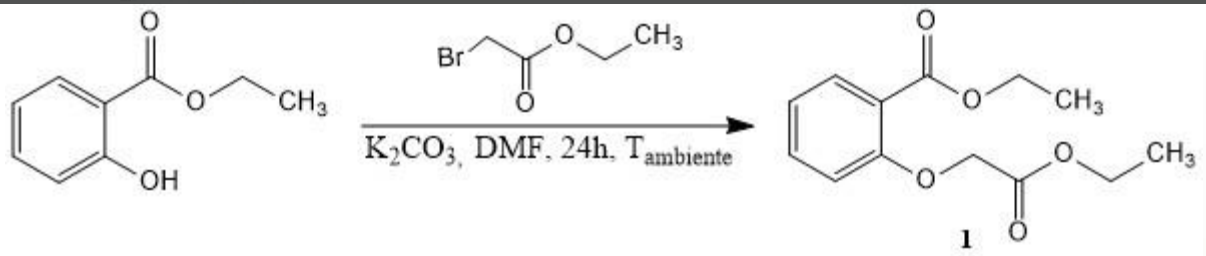


Schema generale per la preparazione di XU39

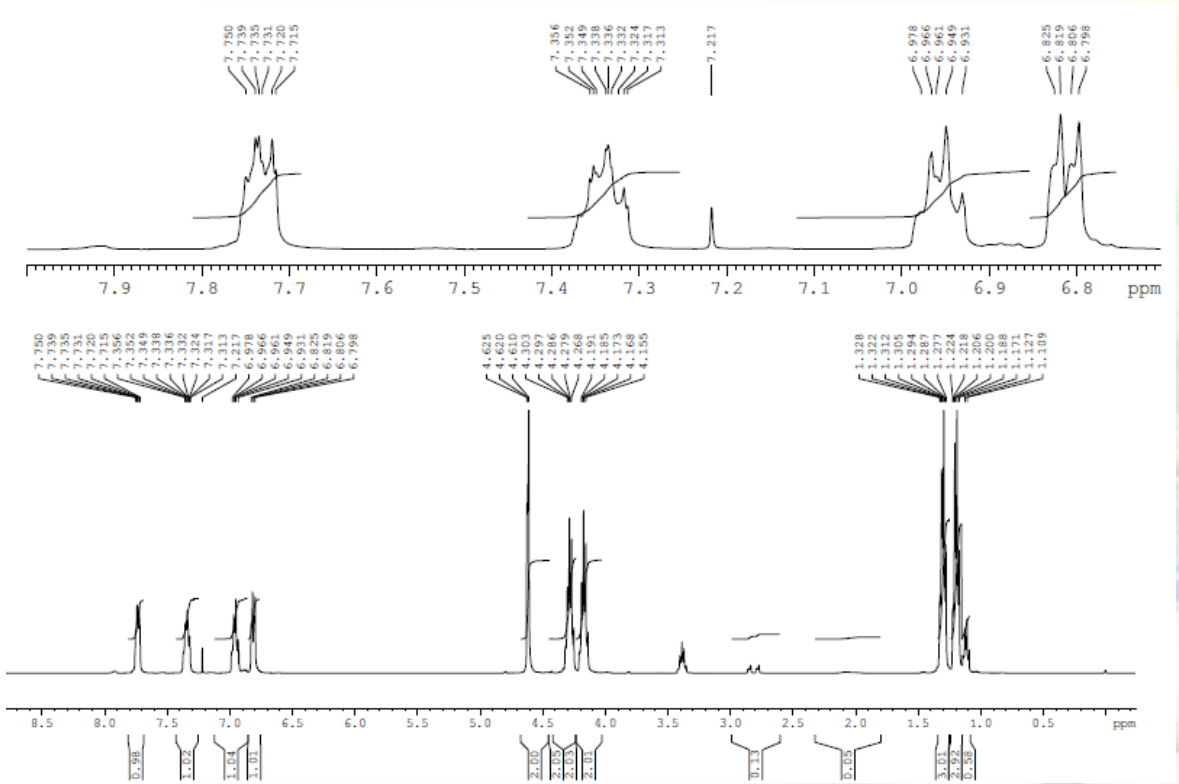
Sintesi del composto ***4-idrossi-2-osso-2H-pirano[3,2-b]benzofuran-3-carbossilico*** (**9**)



Step 1: Sintesi del composto
Etil 2-(2-etossi-2-ossoetossi)benzoato (1)



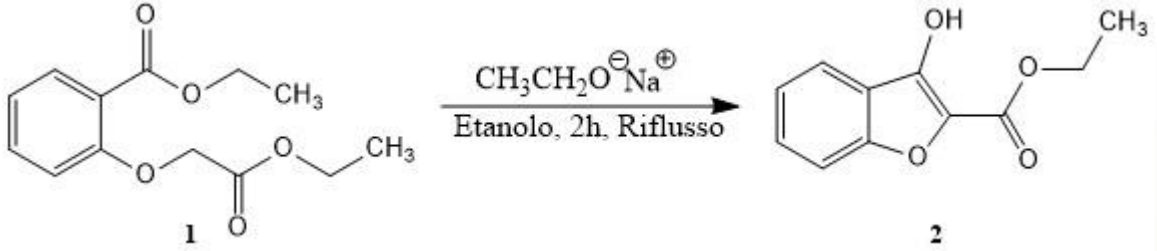
Composto 1
Formula chimica: $C_{13}H_{16}O_5$
PM: 252.27 g/mol
Resa: 85%
Aspetto: olio giallo

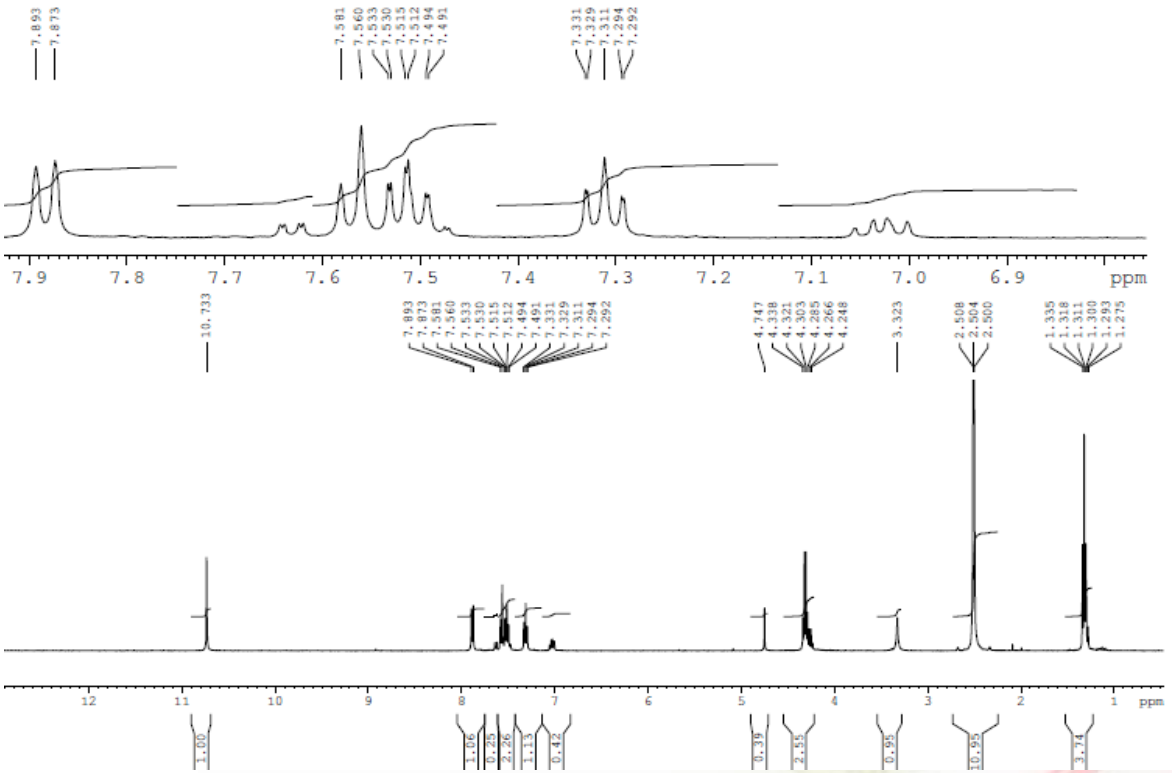


Solvente usato per l'analisi NMR: CDCl3

Referenze 1-3

Step 2: Sintesi del composto
Etil 3-idrossi-1-benzofuran-2-carbossilato (2)



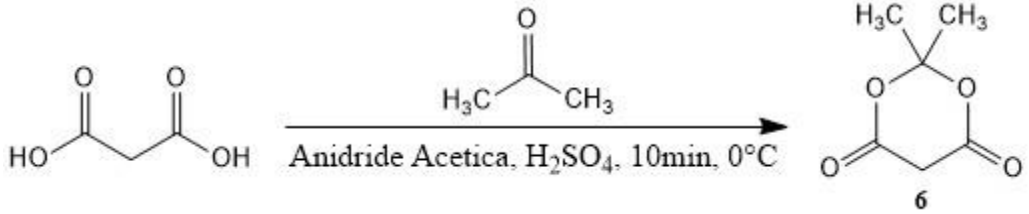


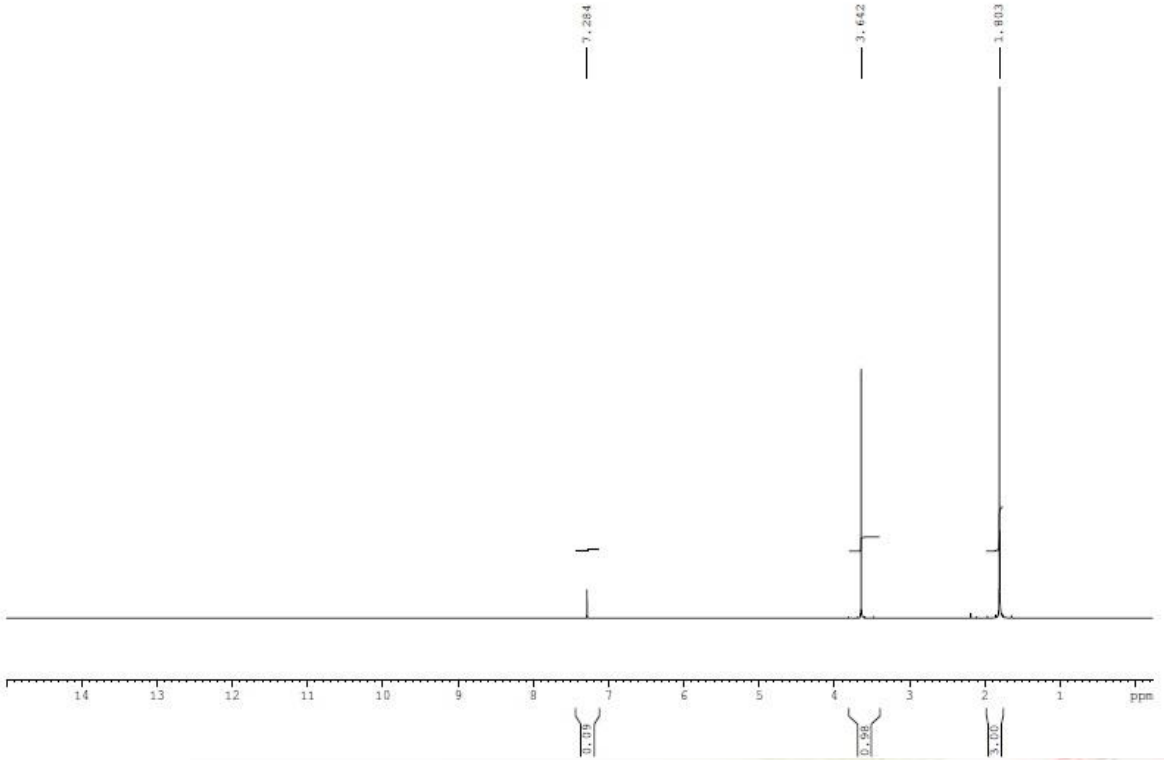
Composto 2
Formula chimica: $C_{11}H_{10}O_4$
PM: 206.06 g/mol
Punto di fusione: 70° C
Resa: 77%
Aspetto: solido giallo

Solvente usato per l'analisi NMR: DMSO

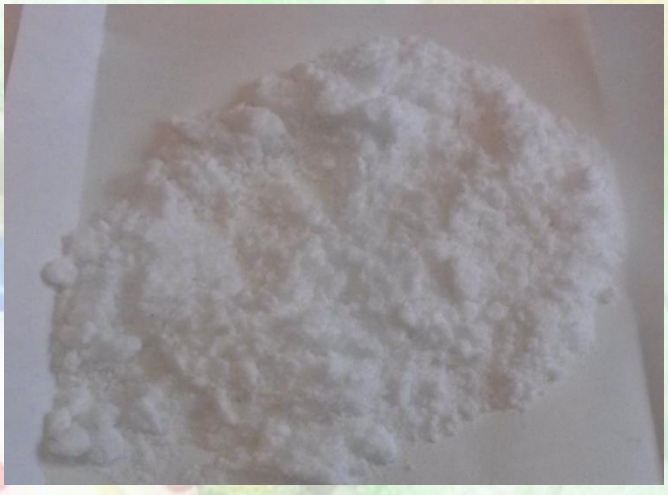
Referenze 1-3

Preparazione dell'acido di *Meldrum* (6)





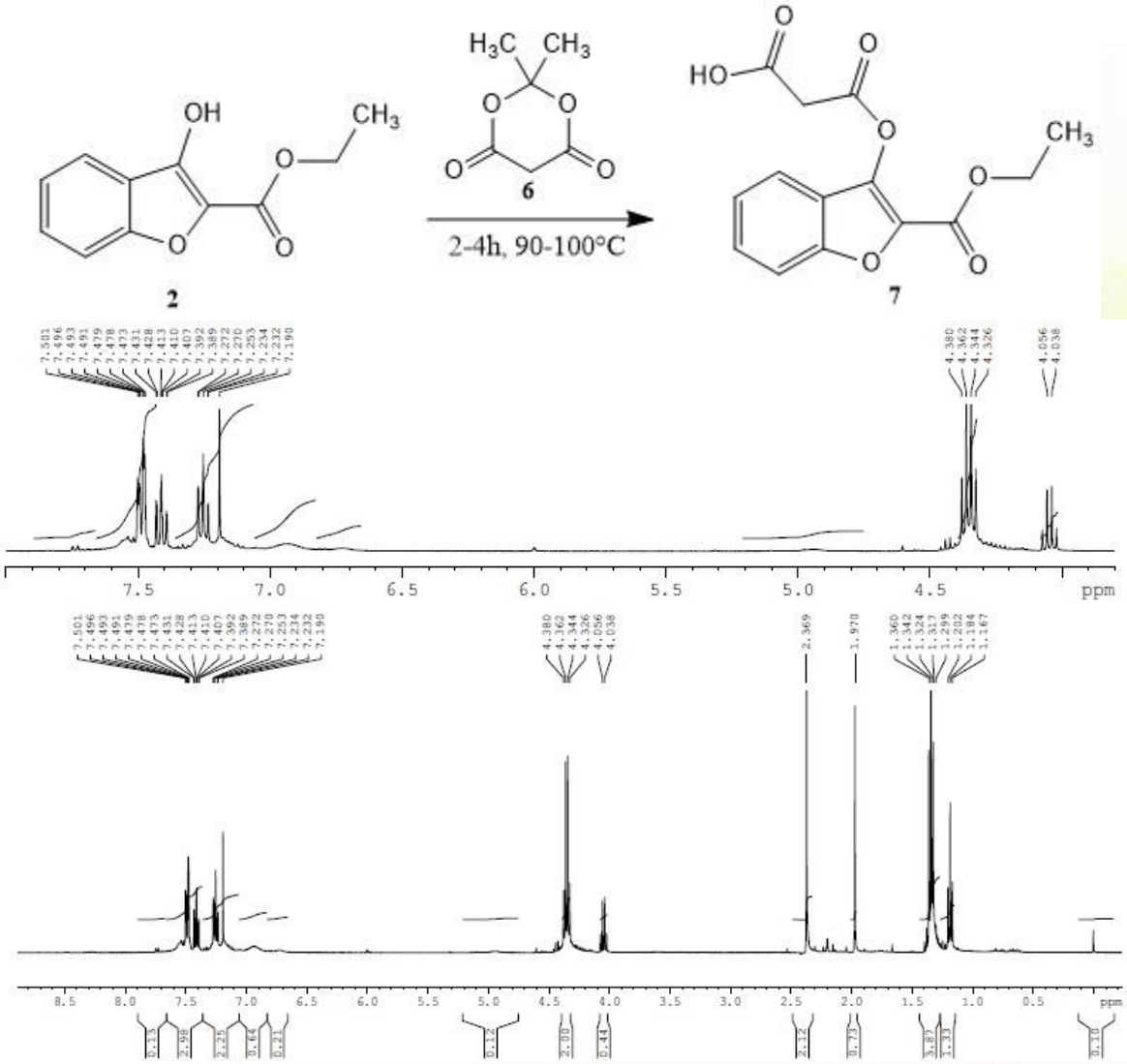
Acido di *Meldrum*
Formula chimica: $C_6H_8O_4$
PM: **144.13 g/mol**
Punto di fusione: **95° C**
Resa: **73%**
Aspetto: **solido bianco**



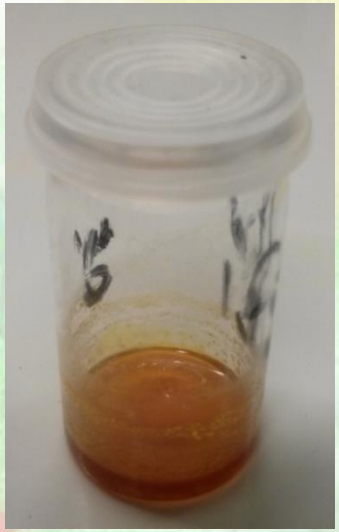
Solvente usato per l'analisi NMR: CDCl3

Referenza 6

Step 3: Sintesi dell'*acido 3-{[2-(etossicarbonil)-1-benzofuran-3-il]ossi}-3-ossopropanoico (7)*



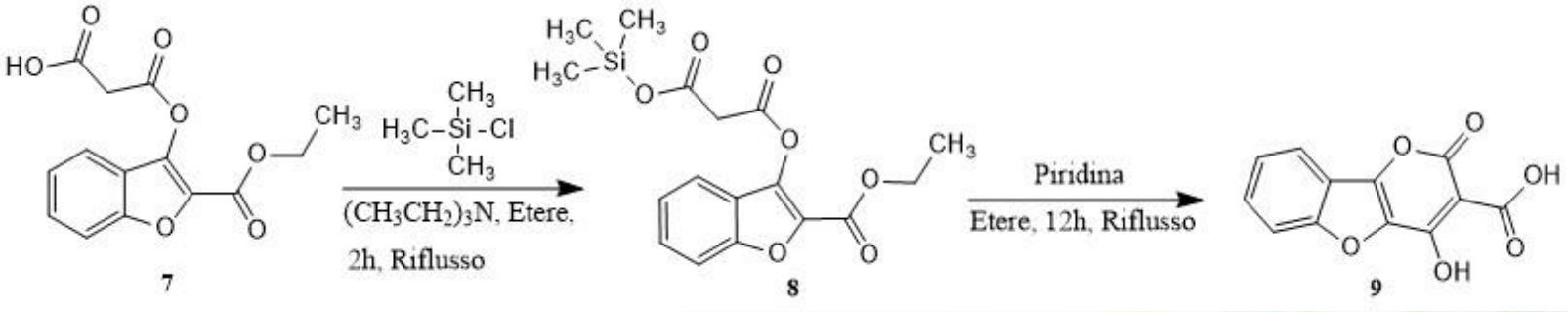
Composto 7
Formula chimica: $C_{14}H_{12}O_7$
PM: **292.24 g/mol**
Resa: **82%**
Aspetto: **olio rossastro**



Solvente usato per l'analisi NMR: CDCl3

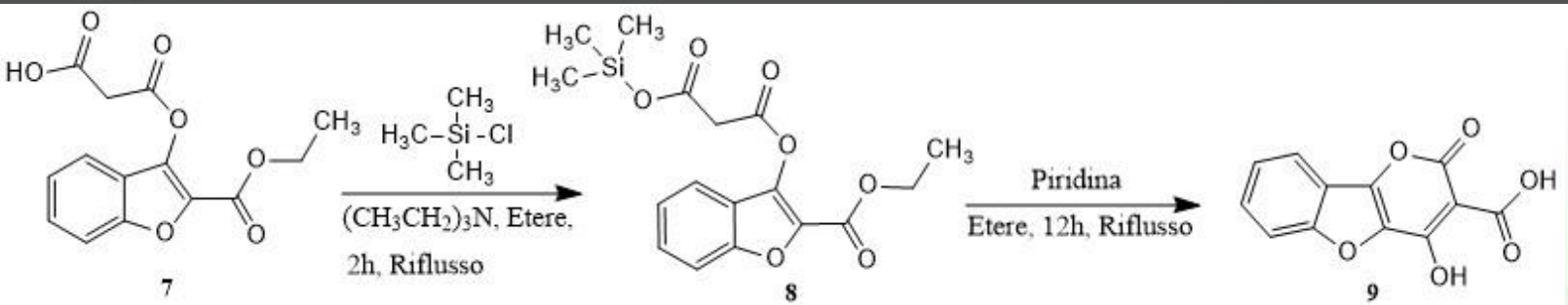
Referenze 4-5

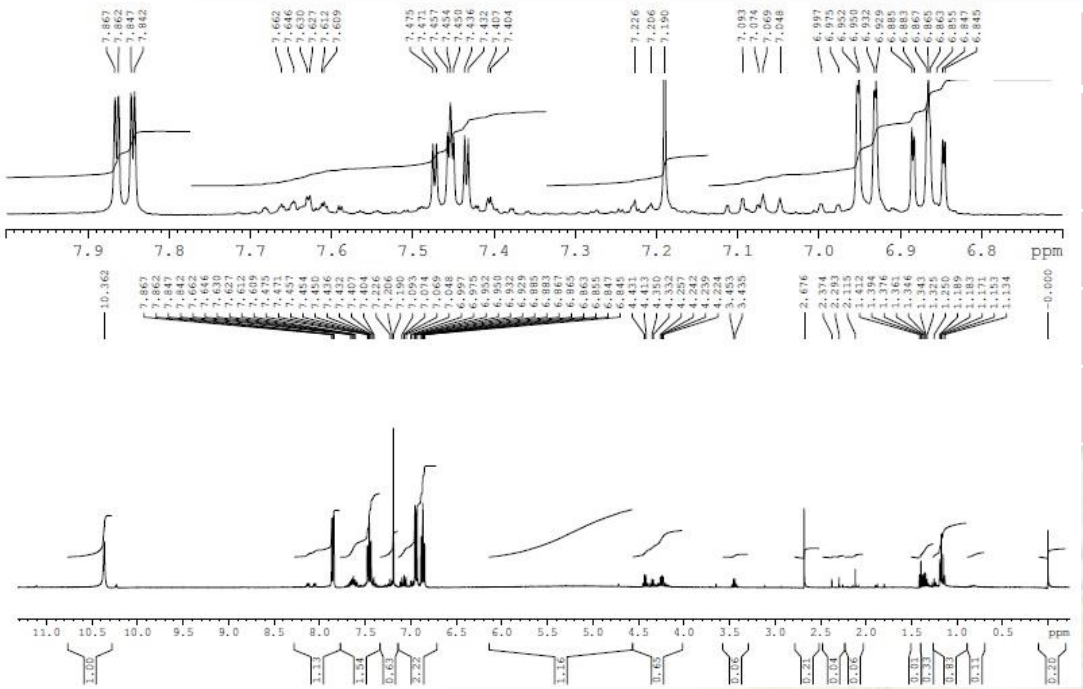
Step 4: Sintesi dell'*acido 4-idrossi-2-osso-2H-pirano[3,2-b]benzofuran-3-carbossilico (9)*



Composto 8
Formula chimica: $C_{17}H_{20}O_7Si$
PM: **364.43 g/mol**
Resa: **88%**
Aspetto: **olio rossastro**

Step 4: Sintesi dell'*acido 4-idrossi-2-osso-2H-pirano[3,2-b]benzofuran-3-carbossilico (9)*

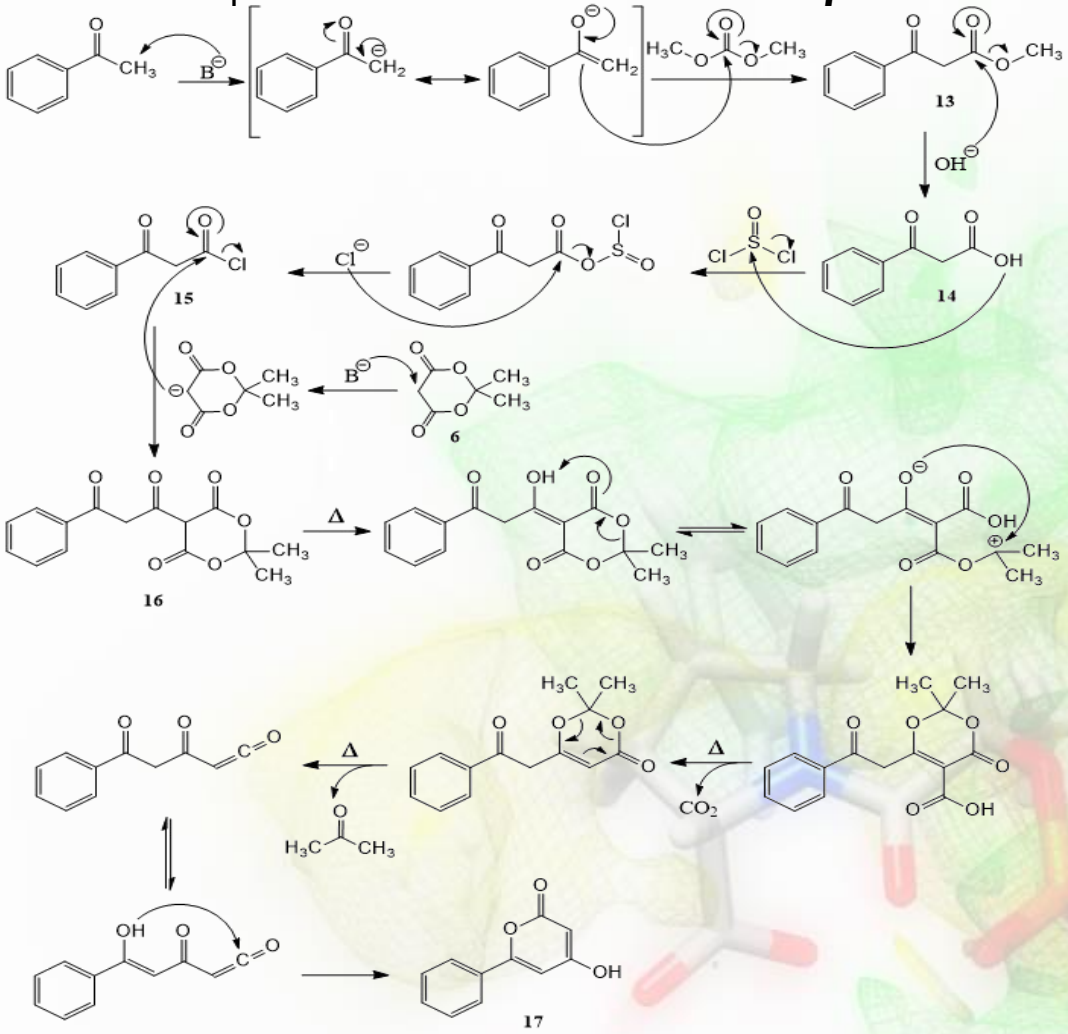




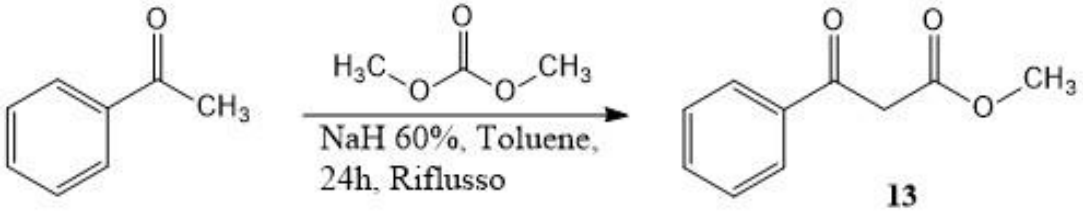
Composto 9
Formula chimica: $C_{12}H_6O_6$
PM: **246.17 g/mol**
Resa: **66%**
Aspetto: **solido giallo**

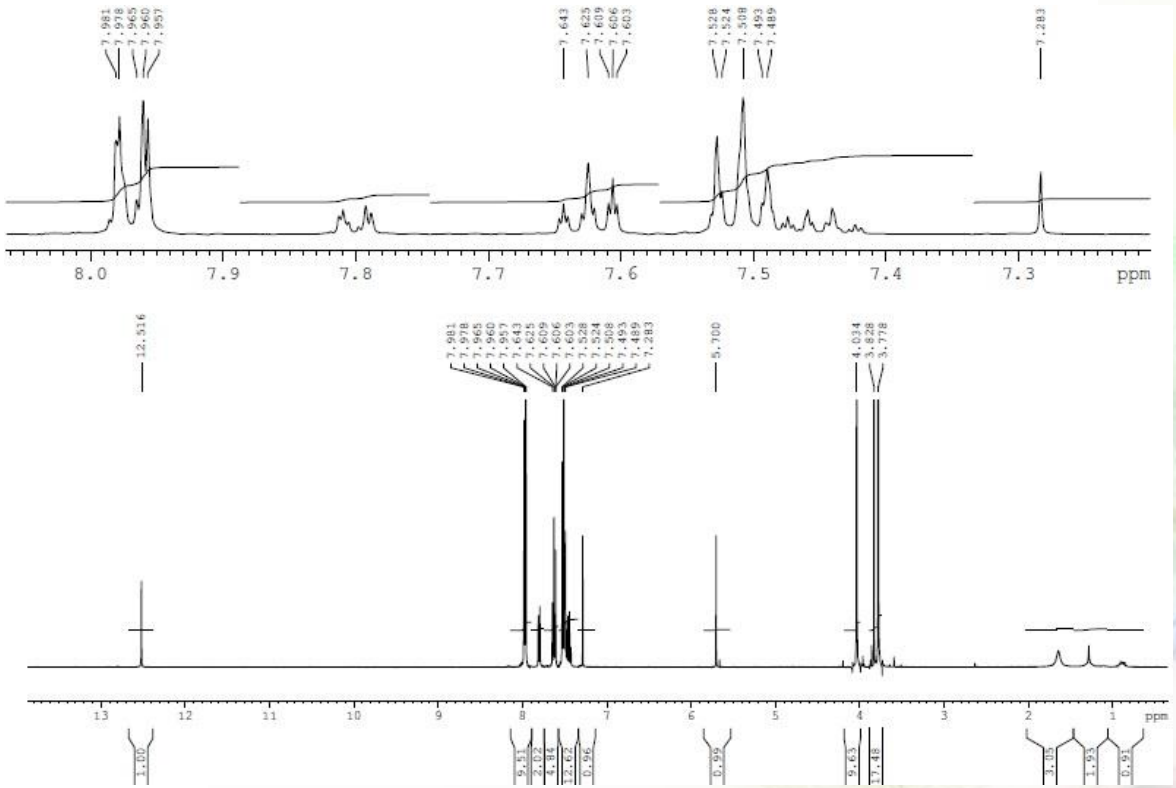
Solvente usato per l'analisi NMR: CDCl3

Sintesi del composto ***4-idrossi-6-fenil-2H-piran-2-one*** (**17**)



Step 1: Sintesi del composto
Metil 3-osso-3-fenilpropanoato (13)



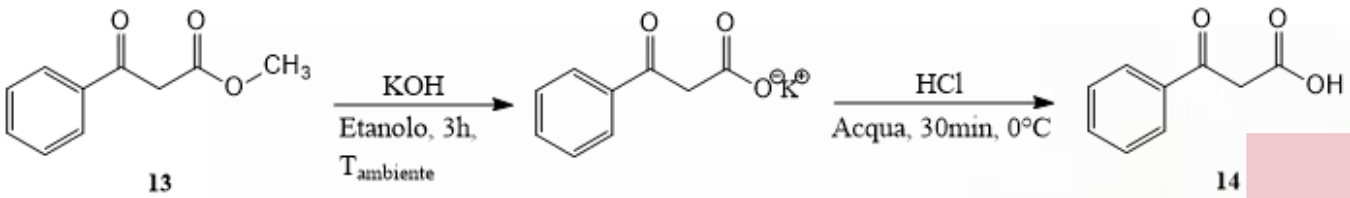


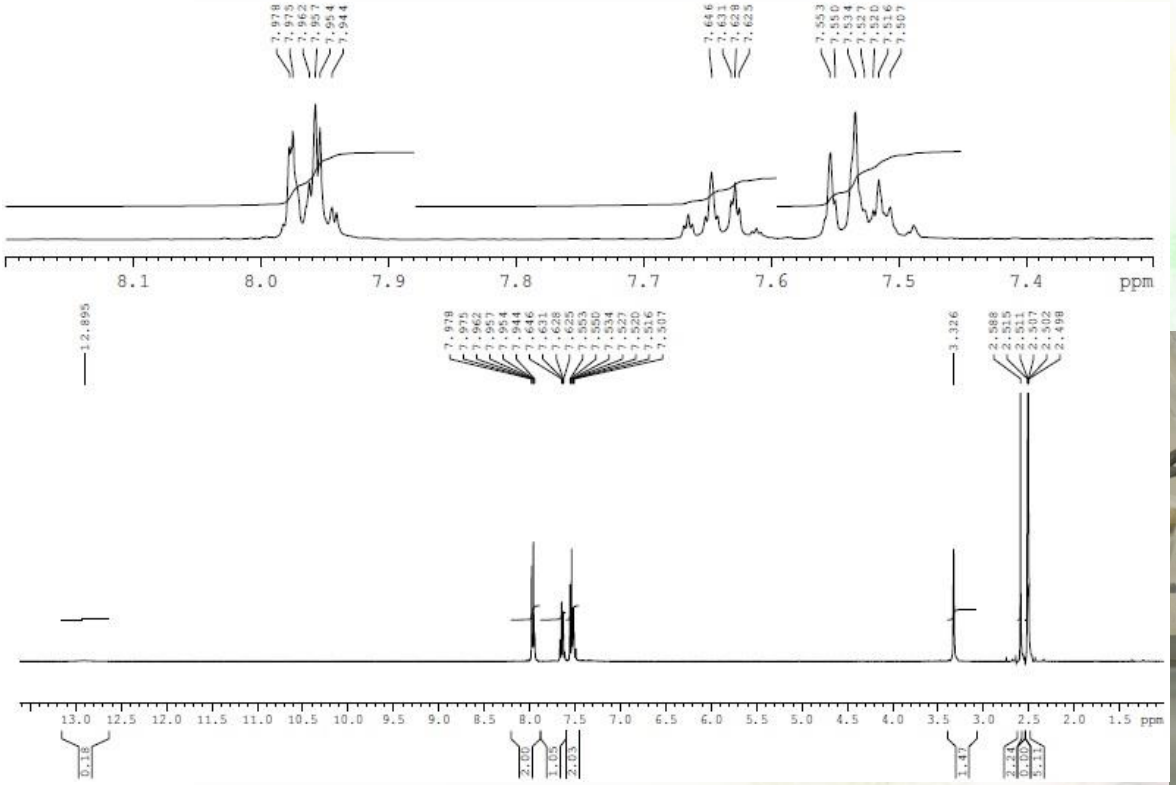
Composto 13
Formula chimica: $C_{10}H_{10}O_3$
PM: 178.19 g/mol
Resa: 66%
Aspetto: olio arancione

Solvente usato per l'analisi NMR: CDCl3

Referenza 7

Step 2: Sintesi dell'*acido 3-osso-3-fenilpropanoato (14)*



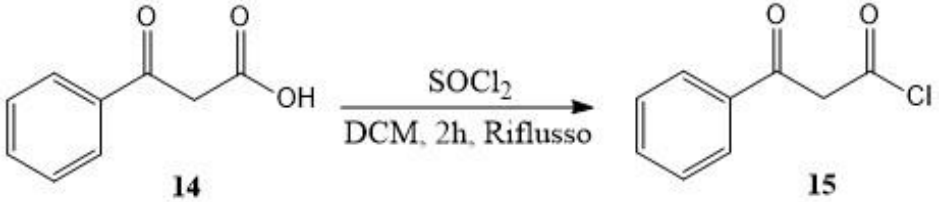


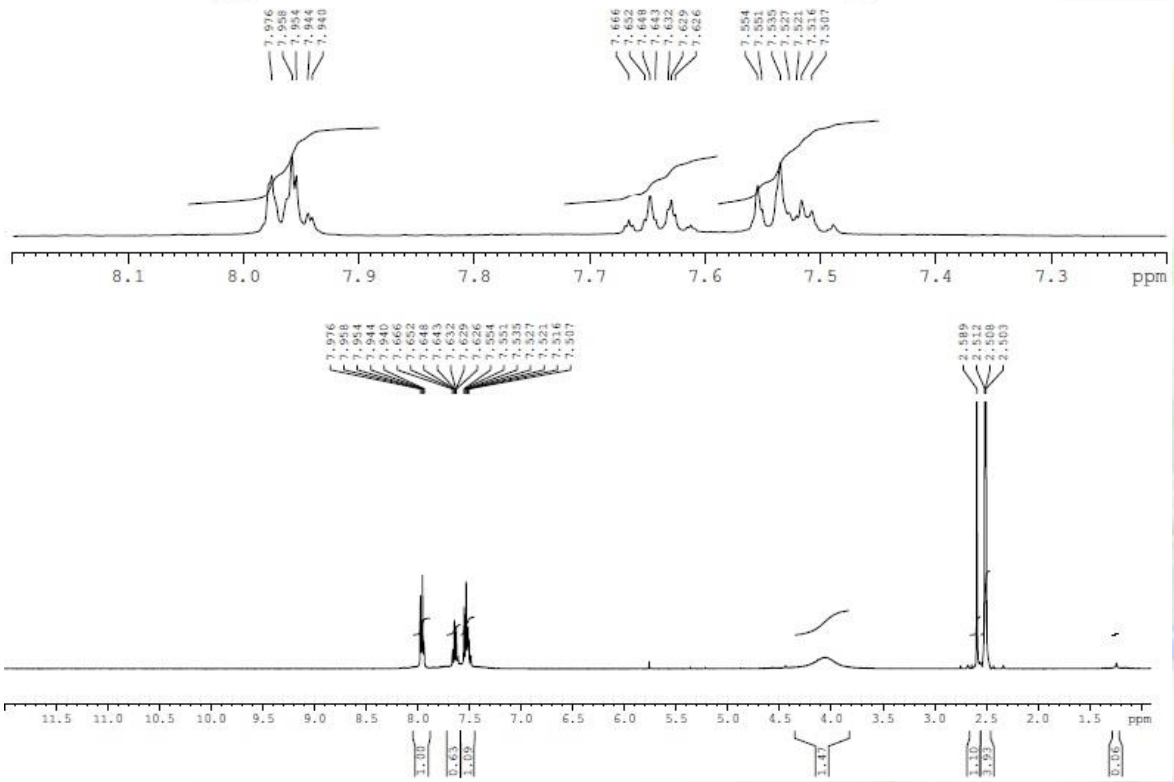
Composto 14
Formula chimica: $C_9H_8O_3$
PM: 164.16 g/mol
Resa: 32%
Aspetto: olio arancione

Solvente usato per l'analisi NMR: DMSO

Referenza 8

Step 3: Sintesi del composto 3-osso-3-fenilpropanoil cloruro (15)



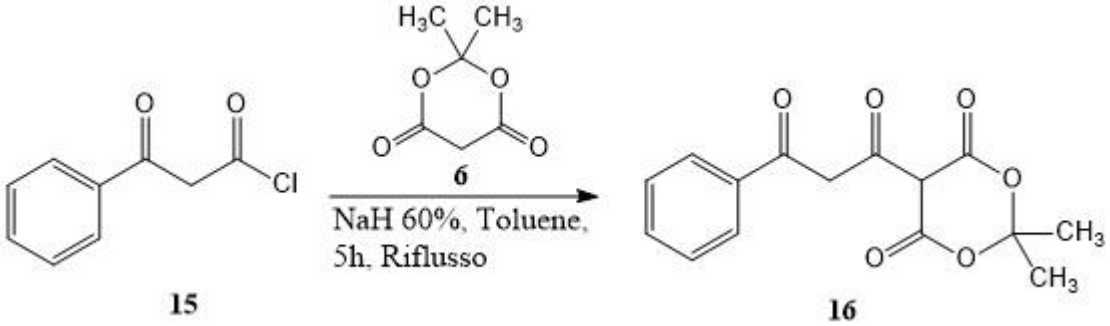


Composto 15
Formula chimica: $C_9H_7ClO_2$
PM: 182.60 g/mol
Resa: 87%
Aspetto: olio marrone scuro

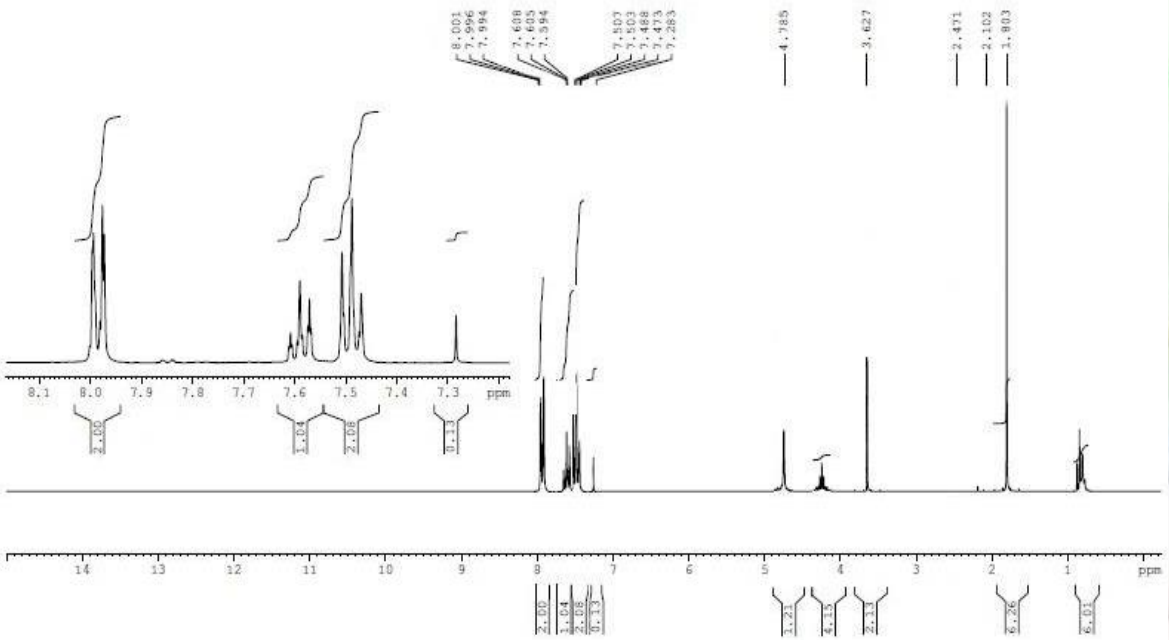
Solvente usato per l'analisi NMR: DMSO

Referenze 9-10

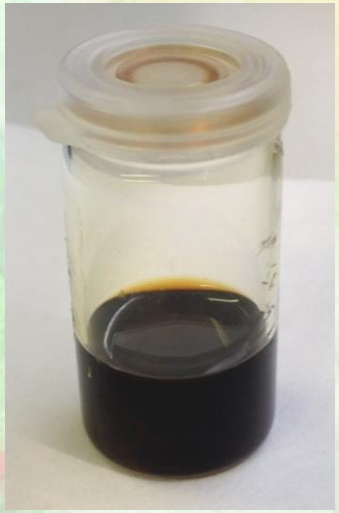
Step 4: Sintesi del composto 2,2-dimetil-5-(3-osso-3-fenilpropanoil)-1,3-diossan-4,6-dione (16)



15 16



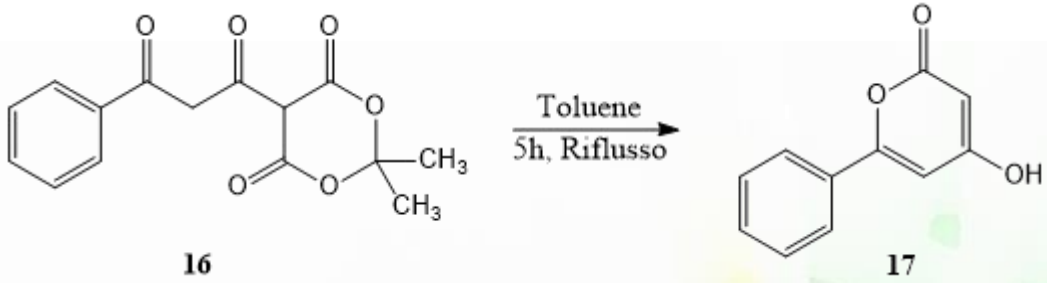
Composto 16
Formula chimica: $C_{15}H_{14}O_6$
PM: 290.27 g/mol
Resa: 61%
Aspetto: olio marrone scuro



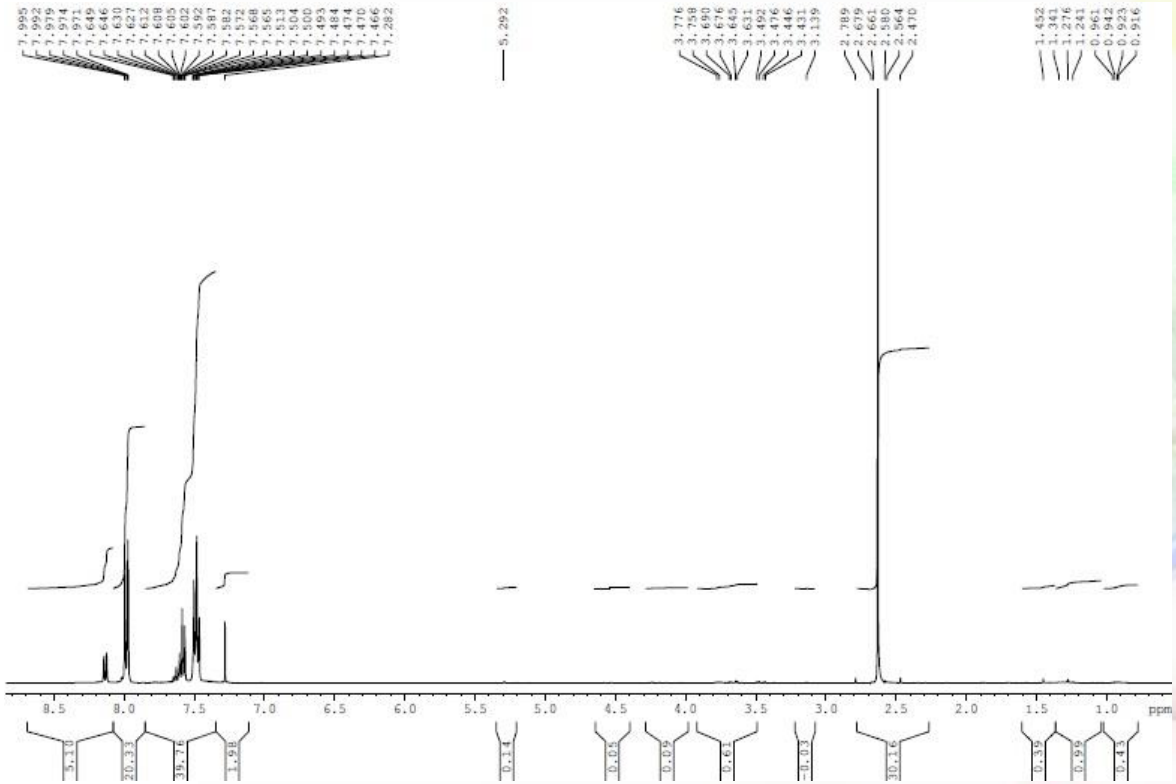
Solvente usato per l'analisi NMR: CDCl3

Referenza 11

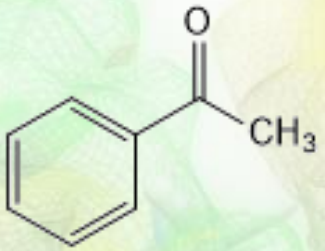
Step 5: Sintesi del composto 4-idrossi-6-fenil-2H-piran-2-one (17)



16 17



Prodotto ottenuto:



Solvente usato per l'analisi NMR: CDCl3

Referenza 11

Conclusioni e prospettive future

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Gli ottimi risultati ottenuti da studi *in silico* ci hanno spinto alla ricerca di strategie per la sintesi dei due composti XU39 e XU49.

Il protocollo di sintesi, adottato per la preparazione del ligando XU39, ha permesso di ottenere, con buone rese di reazione, l'***acido 4-idrossi-2-osso-2H-pirano[3,2-b]benzofuran-3-carbossilico*** (**9**) che rappresenta, però, solo una parte del ligando. Sarà necessario, perciò, ripartire dal composto **9** sintetizzato per ultimare la preparazione del ligando XU39.
Al contrario, il protocollo di sintesi, per la preparazione del ligando XU49, è risultato poco produttivo. E' stato sintetizzato, con buone rese, il composto **2,2-dimetil-5-(3-osso-3-fenilpropanoil)-1,3-diossan-4,6-dione** (**16**) ma la reazione di preparazione del composto finale ***4-idrossi-6-fenil-2H-piran-2-one*** (**17**), non ha avuto esito positivo. Probabilmente occorrerà adottare una nuova strategia di sintesi.

Dopo aver portato a termine la sintesi dei due potenziali inibitori dell'enzima Arilsulfatasi A, sarà necessario effettuare dei saggi biologici che ne accertino la reale attività inibitoria.
Gli studi *in vitro* potranno dimostrare la capacità di questi composti nell'ostacolare le interazioni tra lo spermatozoo e l'uovo, ciò potrebbe tradursi in una riduzione della fecondazione e, quindi, nello sviluppo di potenziali contraccettivi.

Grazie per l'attenzione

Riferimenti bibliografici:

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