

Grip A, alarmisme o perill real? Noves molècules actives contra soques resistents

8ns Debats de Recerca:
Física i Química, investigant la realitat

5 de Novembre 2014
Matías Rey Carrizo

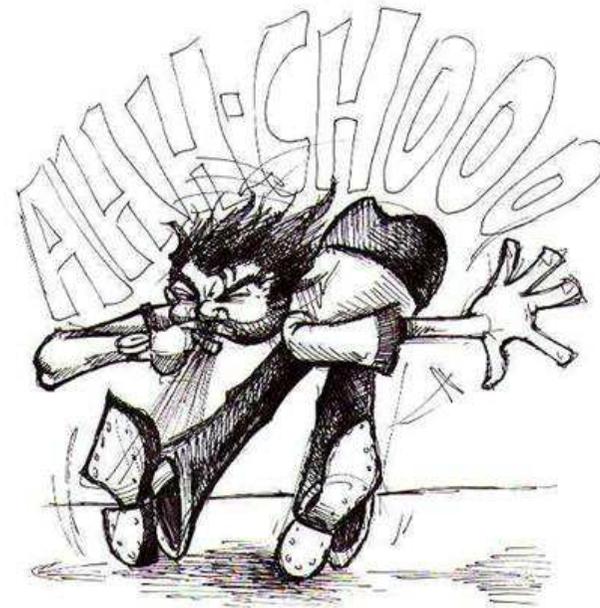


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La grip

Síntomes:

- ❖ Tos i mal de coll
- ❖ Nas tapat o mocós
- ❖ Esternuts
- ❖ Ulls plorosos
- ❖ Fatiga/dolor muscular
- ❖ Febre



La grip

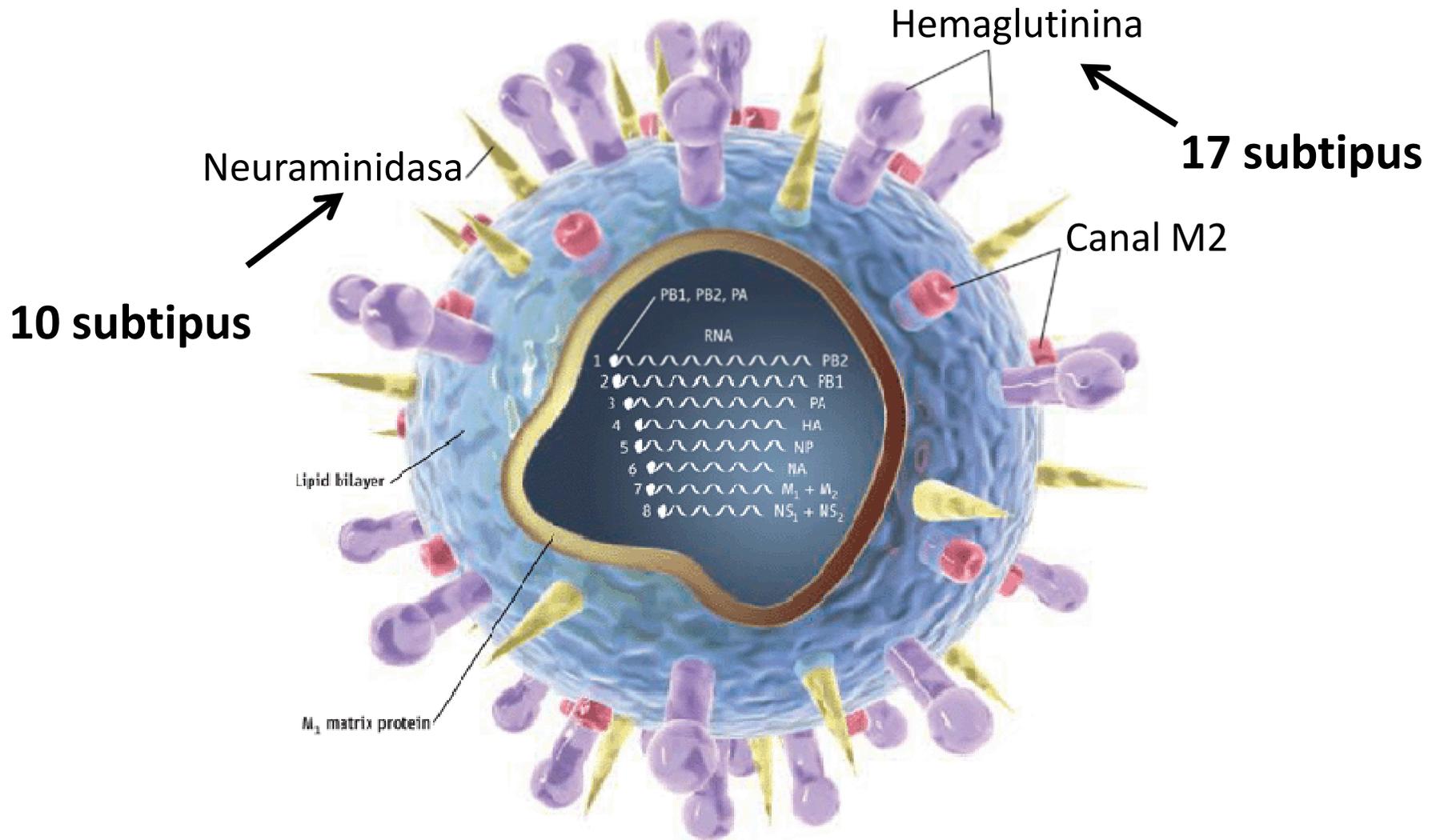
Pandèmia: ràpid contagi d'una malaltia infecciosa a un gran nombre de persones (epidèmia) en varis països, continents o el món sencer.

Grip comú	Grip pandèmica
Composició genètica coneguda	Composició genètica desconeguda
Baix nivell d'infecció	Alt nivell d'infecció
Tractament simptomàtic. Recuperació en 1-2 setmanes	Pot causar pneumònies virals que poden acabar en mort
Mortalitat en persones de la tercera edat	Mortalitat en persones de qualsevol edat

La grip A

Nom de la grip	Subtipus	Mortalitat
Grip espanyola (1918-1920)	H1N1	~ 50 milions [un ⅓ de la població mundial (~500 milions) infectada] Taxa de mortalitat del ~ 2.5%
Grip asiàtica (1957-1958)	H2N2	~ 2-3 milions
Grip de Hong Kong (1968-1970)	H3N2	700 000 (ara circula com a grip comú)
Grip aviar (2003-actualitat)	H5N1	393 (taxa de mortalitat del ~ 60%) no es transmet entre humans
Grip porcina (2009-2010)	H1N1	290 000 en 48 països (80% tenien menys de 65 anys)

El virus: influenza A



La grip A

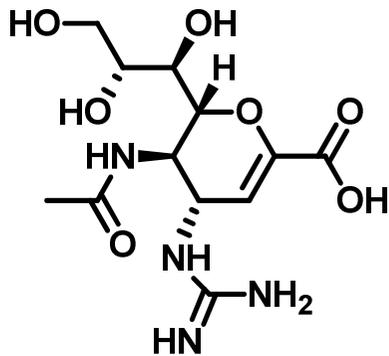
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Tractaments actuals

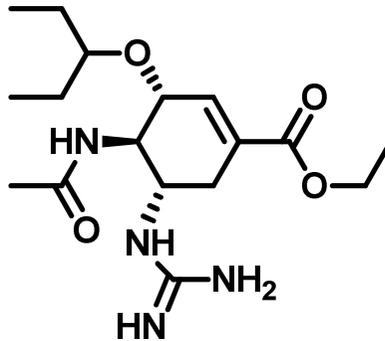
❖ Vacunació

- Vacuna trivalent: grip A (H1N1)+(H3N2) i grip B

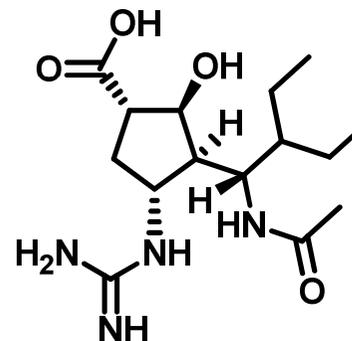
❖ Inhibidors de la neuraminidasa



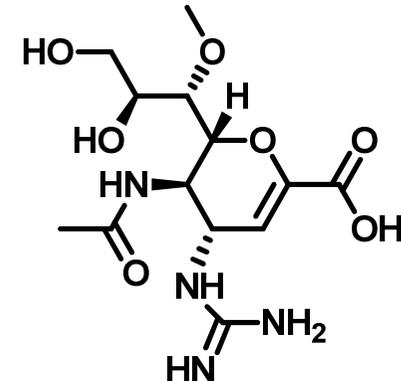
Zanamivir
(Relenza®)



Oseltamivir
(Tamiflu®)



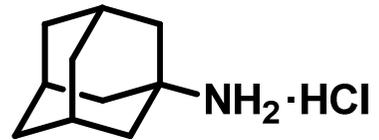
Peramivir
(Rapiacta® and
Peramiflu®)



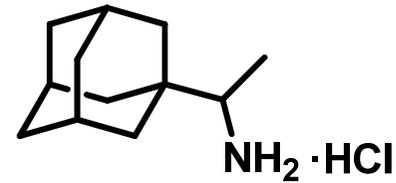
Laninamivir
(Inavir®)

Tractaments actuals

❖ BloCADORS del canal M2

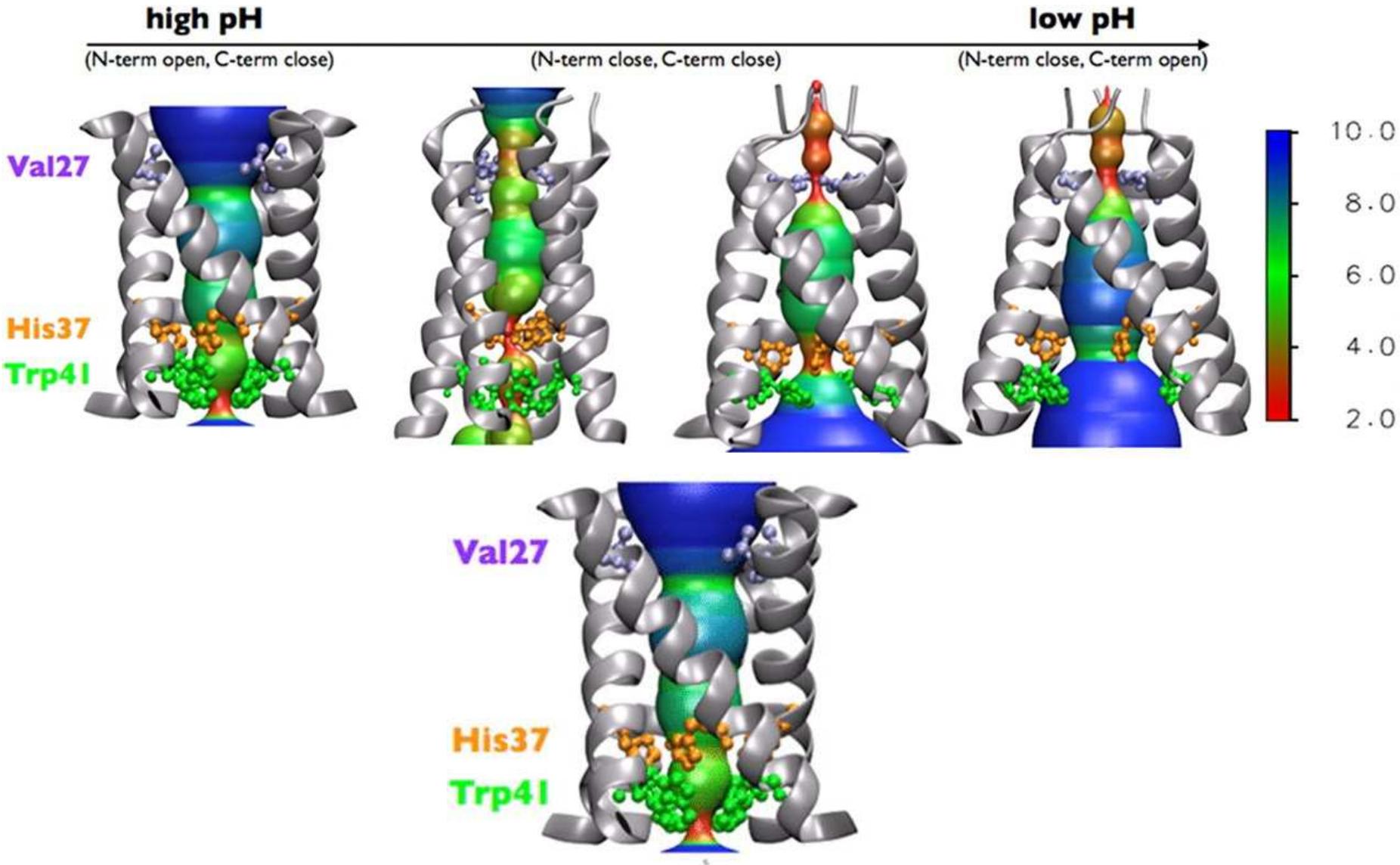


Amantadina
(Symmetrel®)

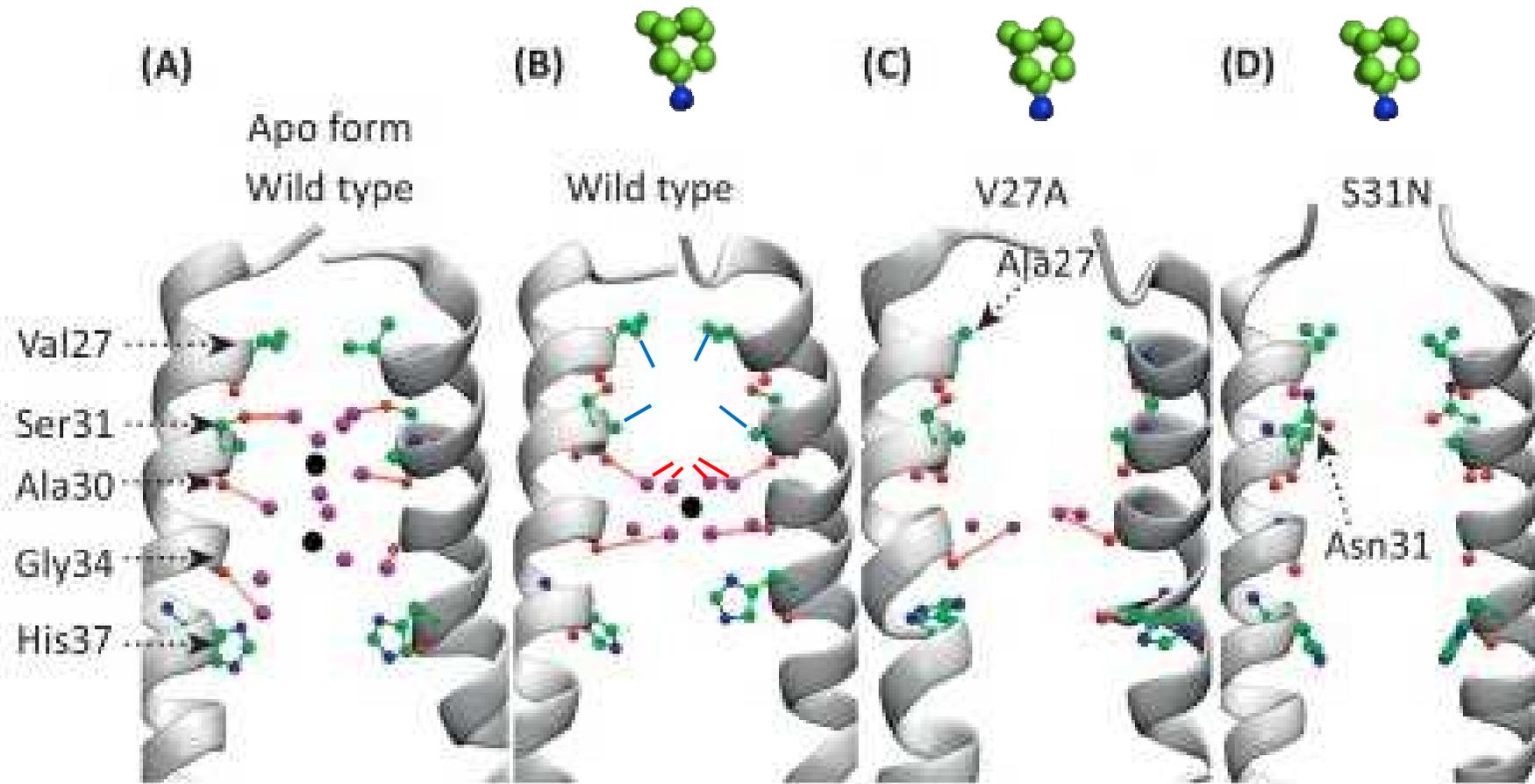


Rimantadina
(Flumadine®)

El canal M2

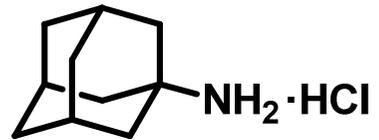


Bloqueig del canal M2

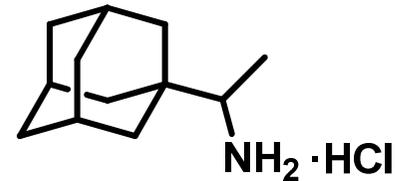


Tractaments actuals

❖ BloCADORS del canal M2



**Amantadina
(Symmetrel®)**



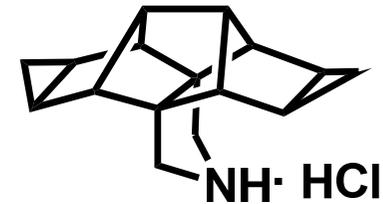
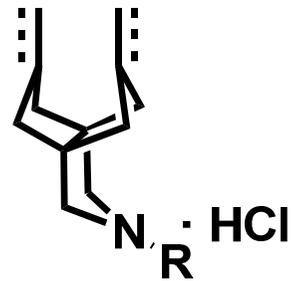
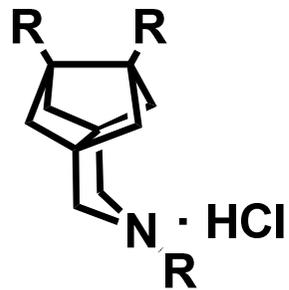
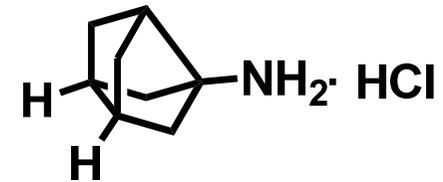
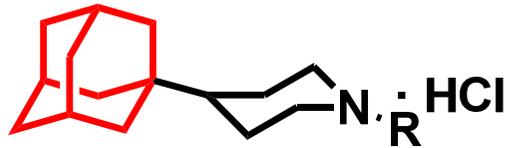
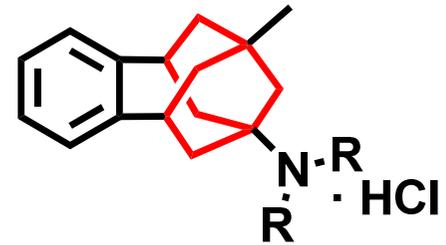
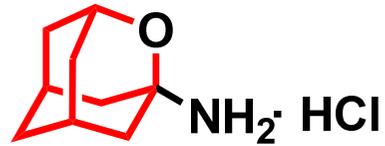
**Rimantadina
(Flumadine®)**

L'OMS desaconsella el seu ús

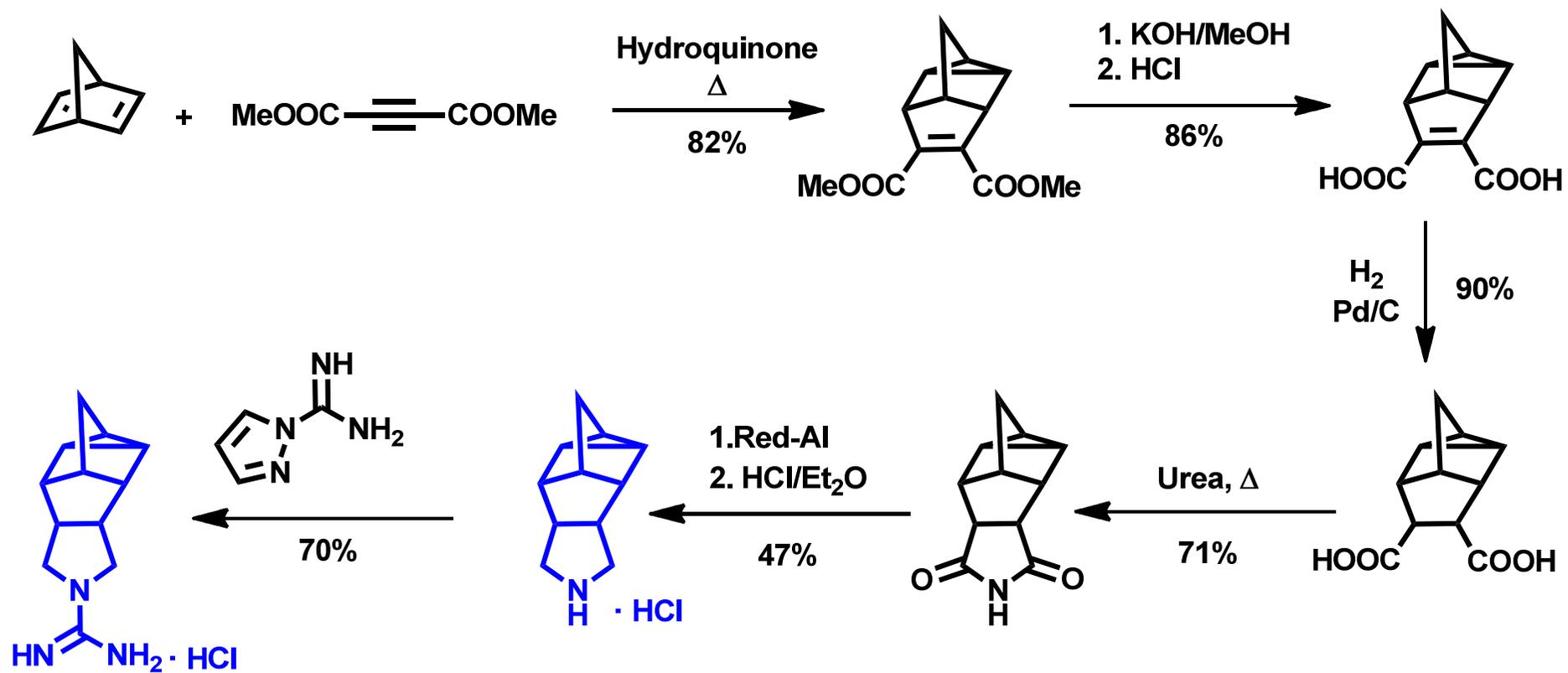
Treball del grup



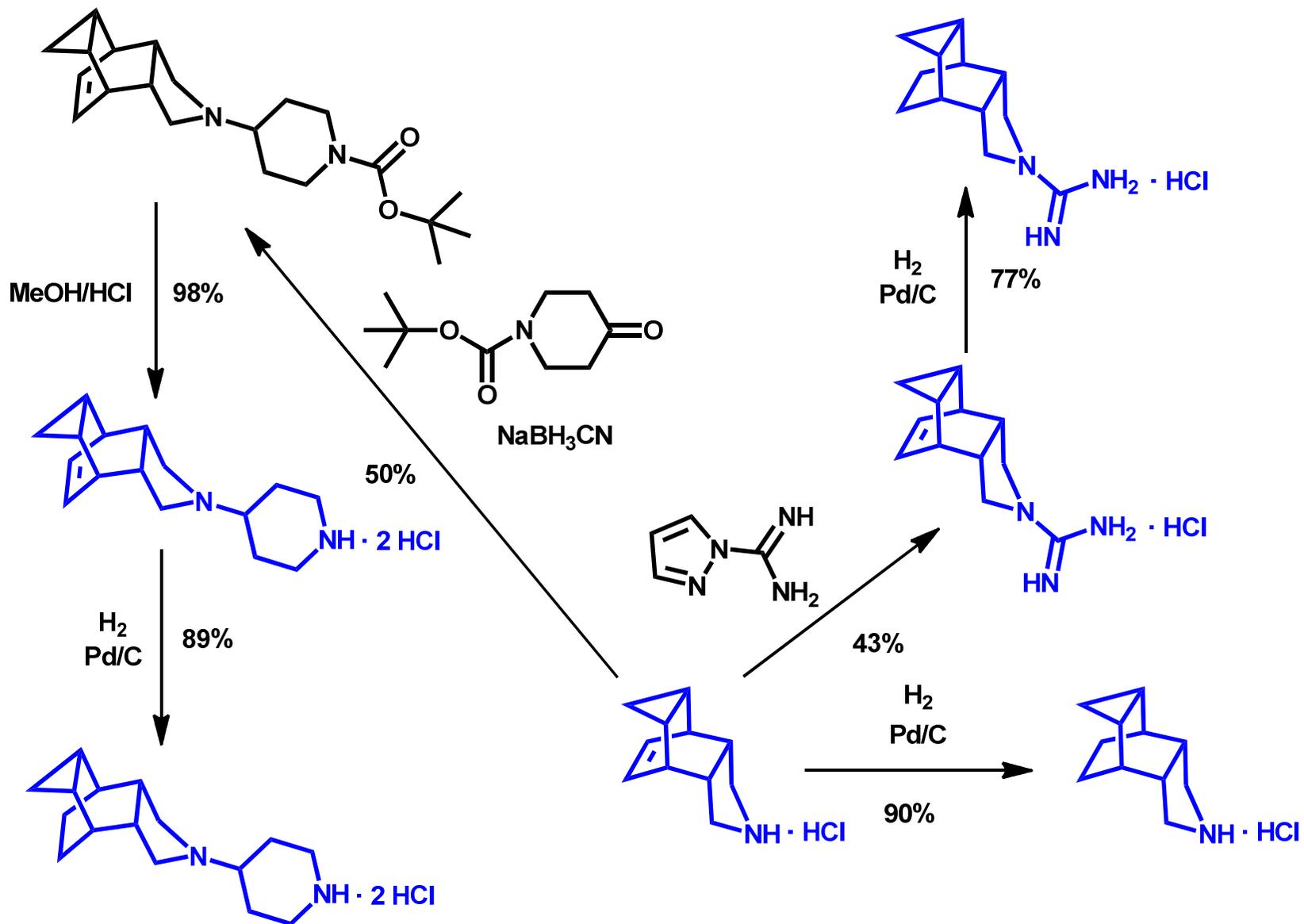
Amantadina



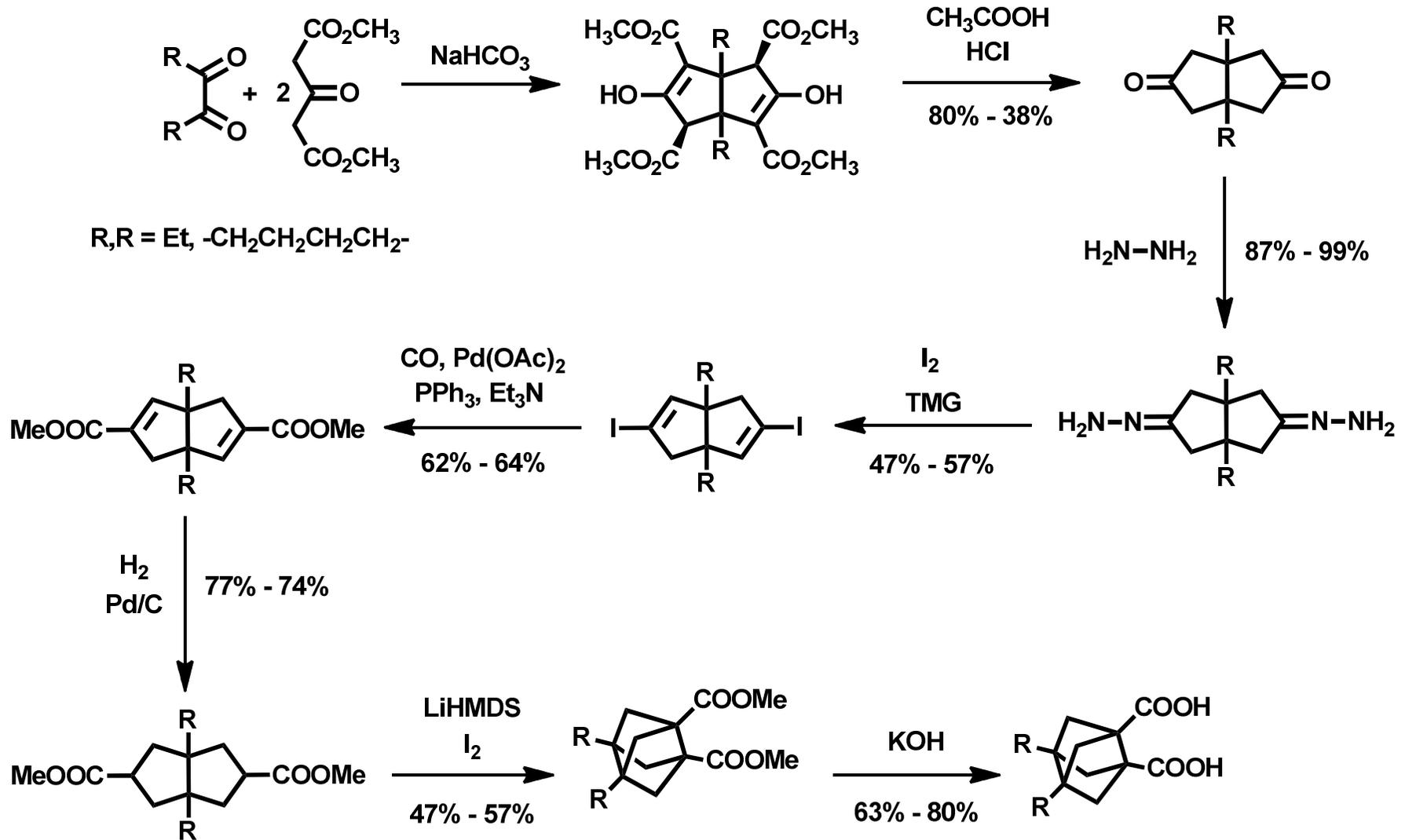
Síntesi



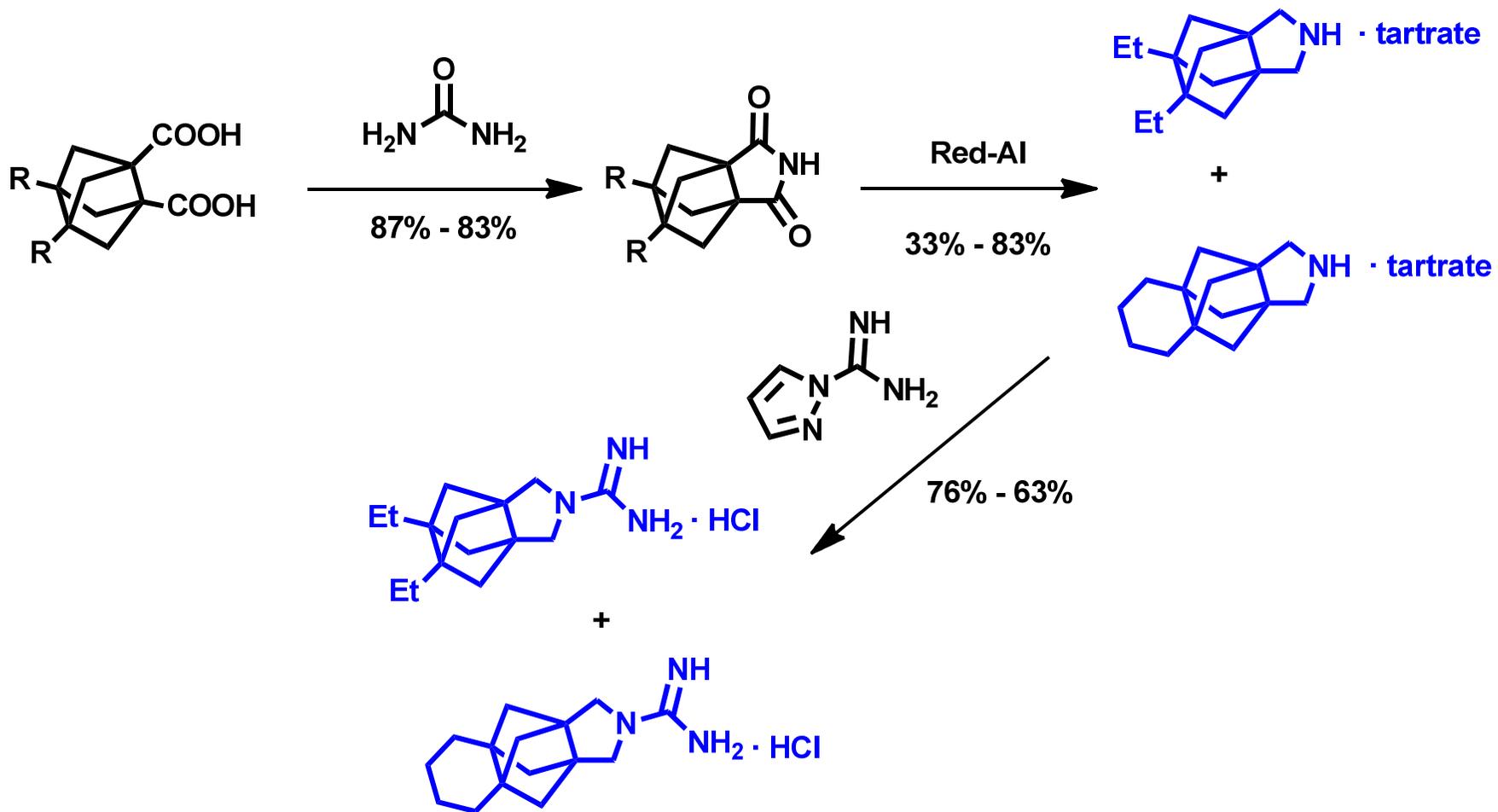
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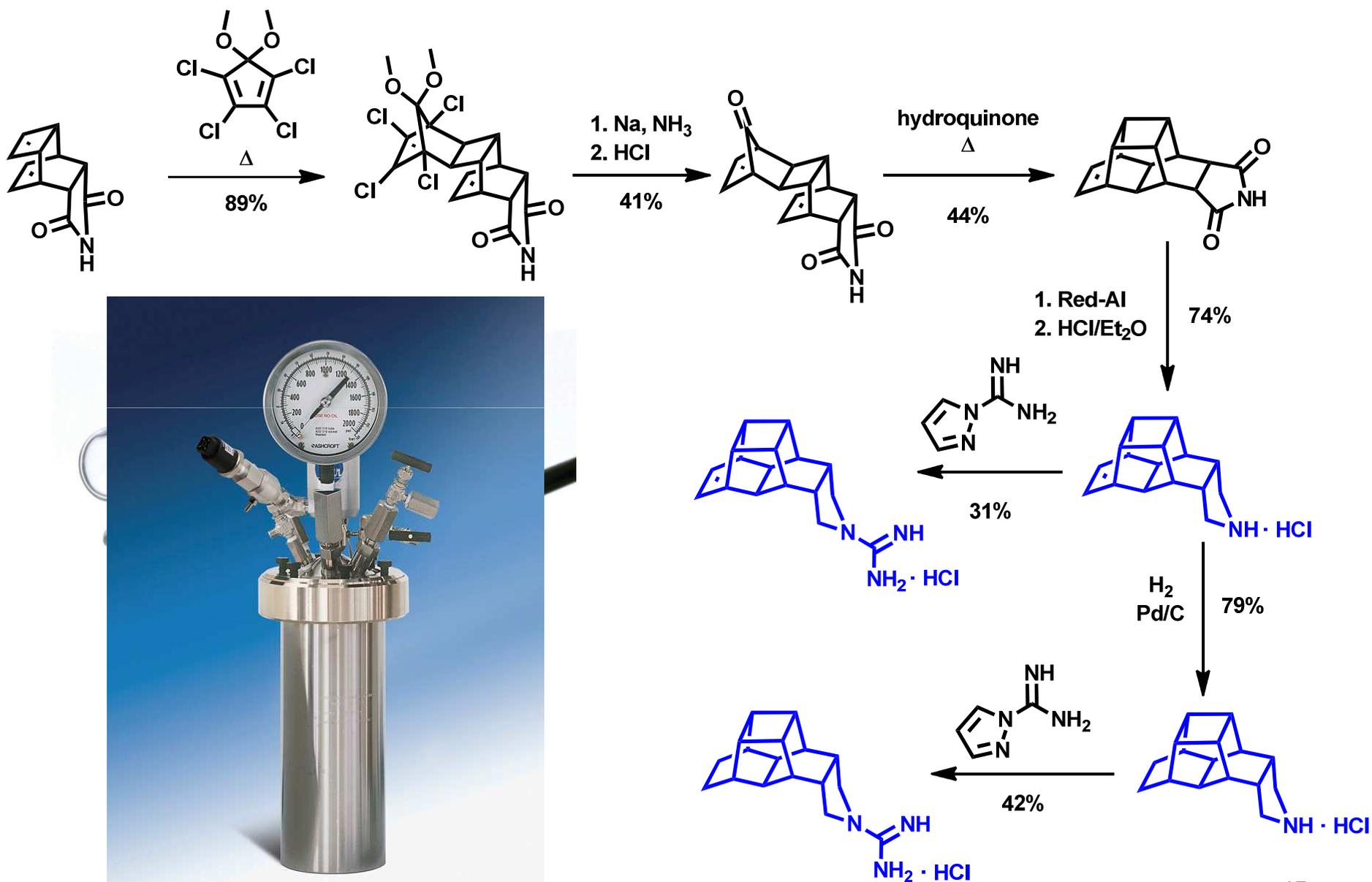
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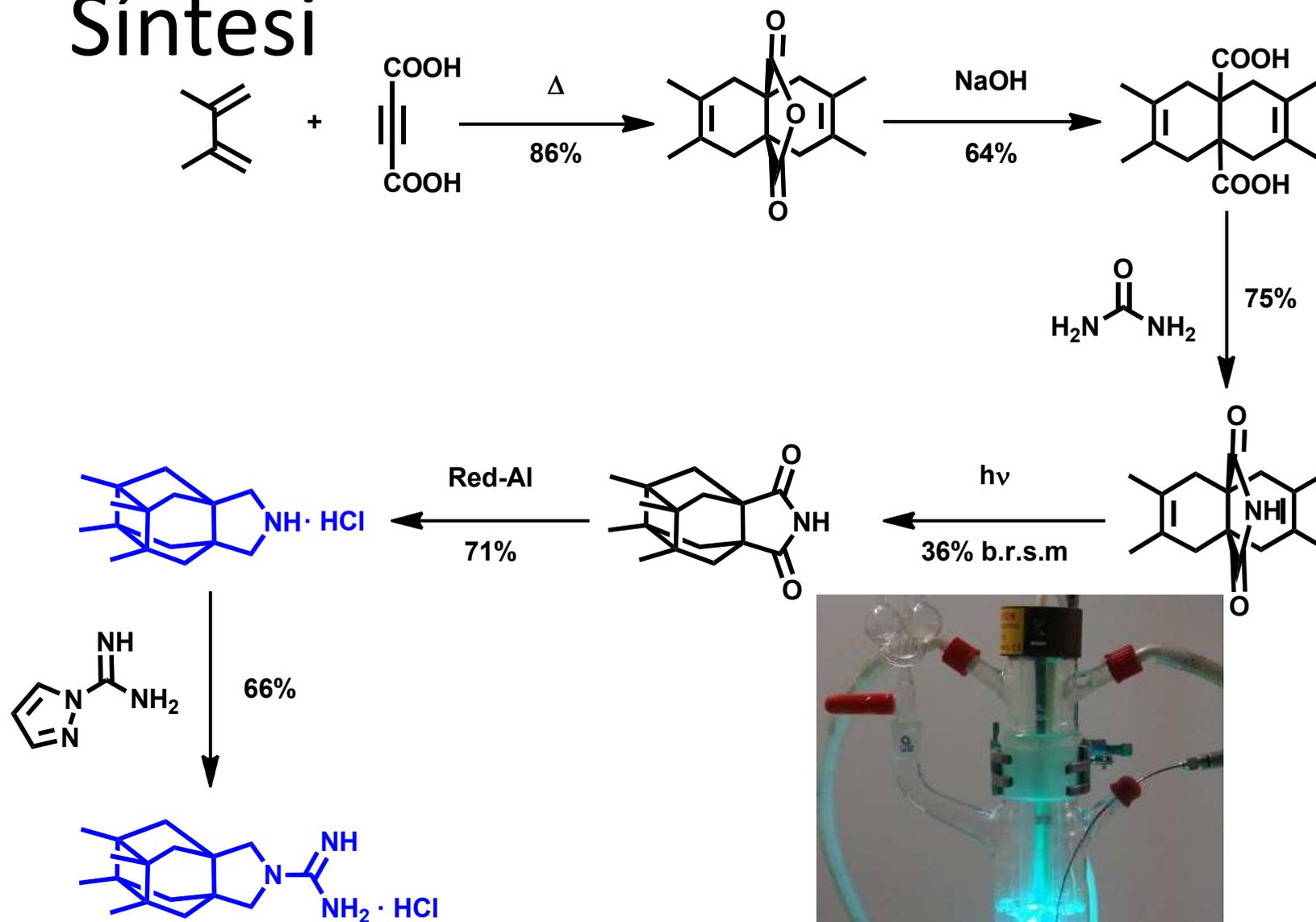
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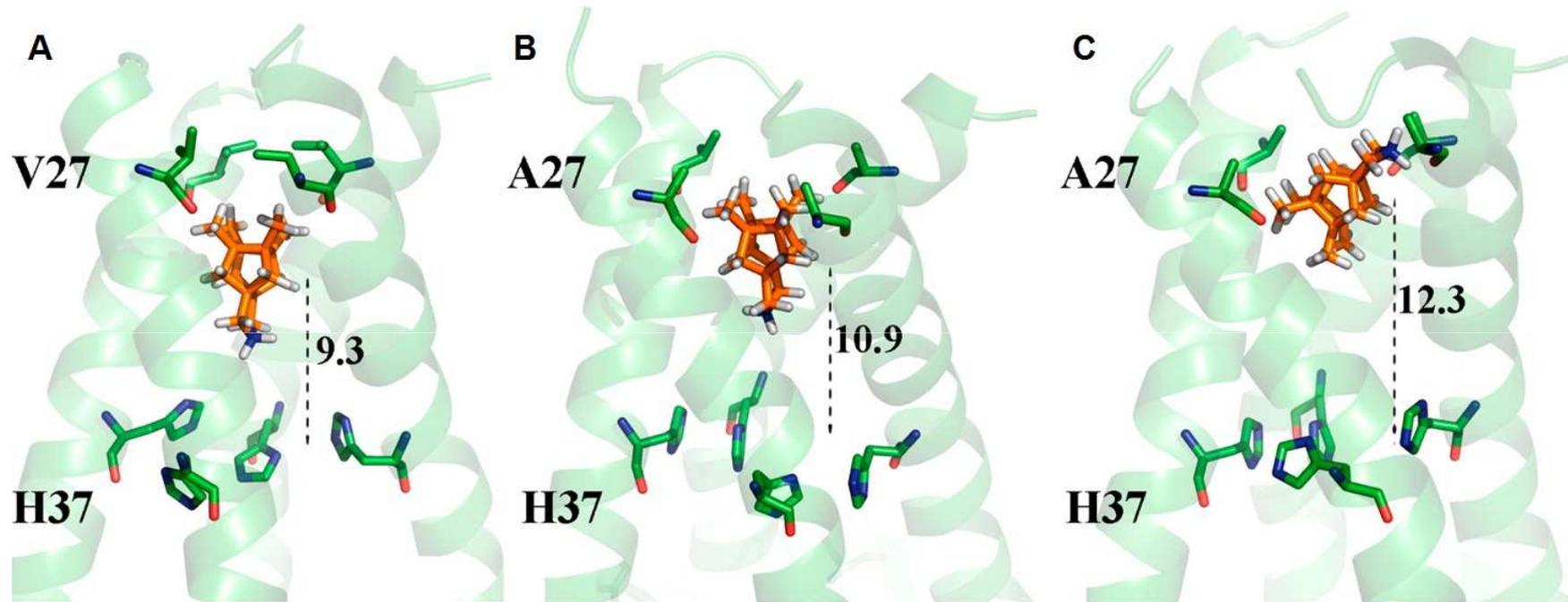
Síntesi



Síntesi



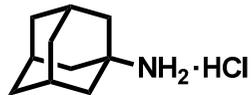
Modelització molecular



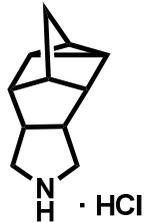
Rey-Carrizo, M.; Barniol-Xicota, M.; Ma, C.; Frigolé-Vivas, M.; Torres, E.; Naesens, L.; Llabrés, S.; Juárez-Jiménez, J.; Luque, F. J.; DeGrado, W. F.; Lamb, R. A.; Pinto, L. H.; Vázquez, S. *J. Med. Chem.* **2014**, *57*, 5738.

Farmacologia

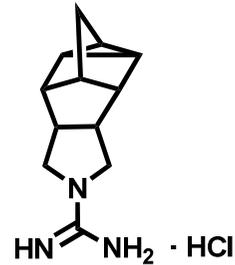
❖ Actius contra la soca salvatge del canal M2



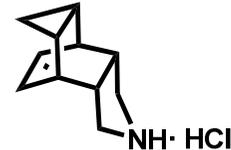
Amantadina
wt $\text{IC}_{50} = 16 \mu\text{M}$
V27A > $200 \mu\text{M}$



wt $\text{IC}_{50} = 3 \mu\text{M}$



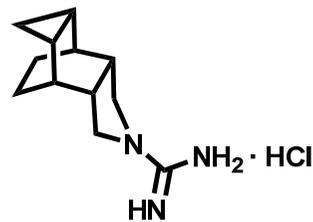
wt $\text{IC}_{50} = 0.8 \mu\text{M}$



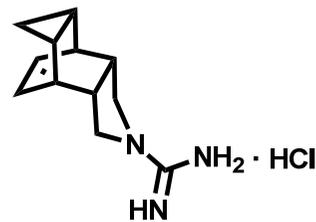
wt $\text{IC}_{50} = 3 \mu\text{M}$



wt $\text{IC}_{50} = 3 \mu\text{M}$



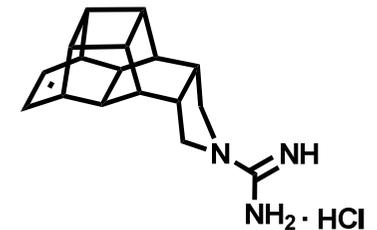
wt $\text{IC}_{50} = 2 \mu\text{M}$



wt $\text{IC}_{50} = 2 \mu\text{M}$



wt $\text{IC}_{50} = 3 \mu\text{M}$



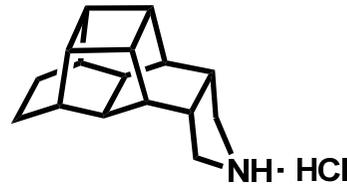
wt $\text{IC}_{50} = 7 \mu\text{M}$

Farmacologia

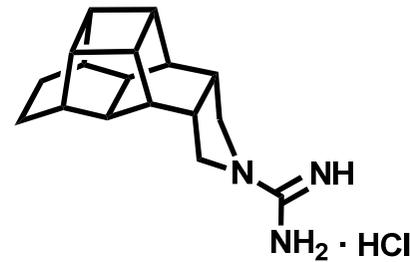
❖ Duals contra la soca salvatge i mutant V27A



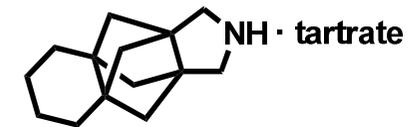
Amantadina
wt $\text{IC}_{50} = 16 \mu\text{M}$
V27A $> 200 \mu\text{M}$



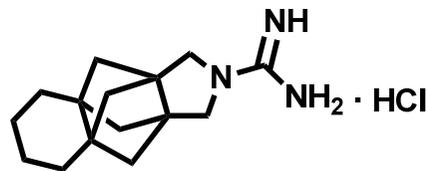
wt $\text{IC}_{50} = 2 \mu\text{M}$
V27A $\text{IC}_{50} = 17 \mu\text{M}$



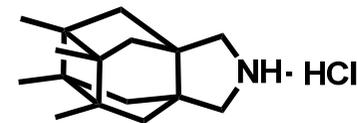
wt $\text{IC}_{50} = 4 \mu\text{M}$
V27A $\text{IC}_{50} = 32 \mu\text{M}$



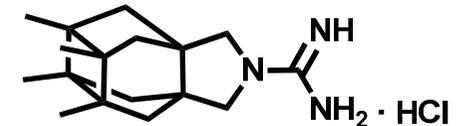
wt $\text{IC}_{50} = 5 \mu\text{M}$
V27A $\text{IC}_{50} = 21 \mu\text{M}$



wt $\text{IC}_{50} = 3 \mu\text{M}$
V27A $\text{IC}_{50} = 0.3 \mu\text{M}$



wt $\text{IC}_{50} = 18 \mu\text{M}$
V27A $\text{IC}_{50} = 0.7 \mu\text{M}$



wt $\text{IC}_{50} = 11 \mu\text{M}$
V27A $\text{IC}_{50} = 0.5 \mu\text{M}$

Publicacions

1. '3-Azatetracyclo[5.2.1.1^{5,8}.0^{1,5}]undecane derivatives: from wild-type inhibitors of the M2 ion channel of influenza A virus to derivatives with potent activity against the V27A mutant.' Rey-Carrizo, M.; Torres, E.; Ma, C.; Barniol-Xicota, M.; Wang, J.; Wu, Y.; Naesens, L.; Degrado, W. F.; Lamb, R. A.; Pinto, L. H.; Vazquez, S. *J. Med. Chem.* **2013**, *56*, 9265.
2. 'Azapropellanes with anti-influenza A virus activity'. Torres, E.; Leiva, R.; Gazzarrini, S.; Rey-Carrizo, M.; Frigolé-Vivas, M.; Moroni, A.; Naesens, L.; Vázquez, S. *ACS Med. Chem. Lett.* **2014**, *5*, 831.
3. 'Easily accessible polycyclic amines that inhibit the wild-type and amantadine-resistant mutants of the M2 channel of influenza A virus'. Rey-Carrizo, M.; Barniol-Xicota, M.; Ma, C.; Frigolé-Vivas, M.; Torres, E.; Naesens, L.; Llabrés, S.; Juárez-Jiménez, J.; Luque, F. J.; DeGrado, W. F.; Lamb, R. A.; Pinto, L. H.; Vázquez, S. *J. Med. Chem.* **2014**, *57*, 5738.
4. 'Dimerization of pyramidalized 3,4,8,9-tetramethyltetracyclo [4.4.0.0^{3,9}.0^{4,8}]dec-1(6)-ene to a hydrocarbon featuring four cyclohexane rings in boat conformations'. Rey-Carrizo, M.; Barniol-Xicota, M.; Font-Bardia, M.; Vázquez, S. *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 8195.
5. 'Exploring new polycyclic scaffolds targeting the V27A mutant M2 channel influenza A virus'. *En redacció*.

Agraïments



Professor Santiago Vázquez

Eva Torres

Marta Barniol

Marta Frigolé

Elena Valverde

Rosana Leiva



Govern d'Andorra

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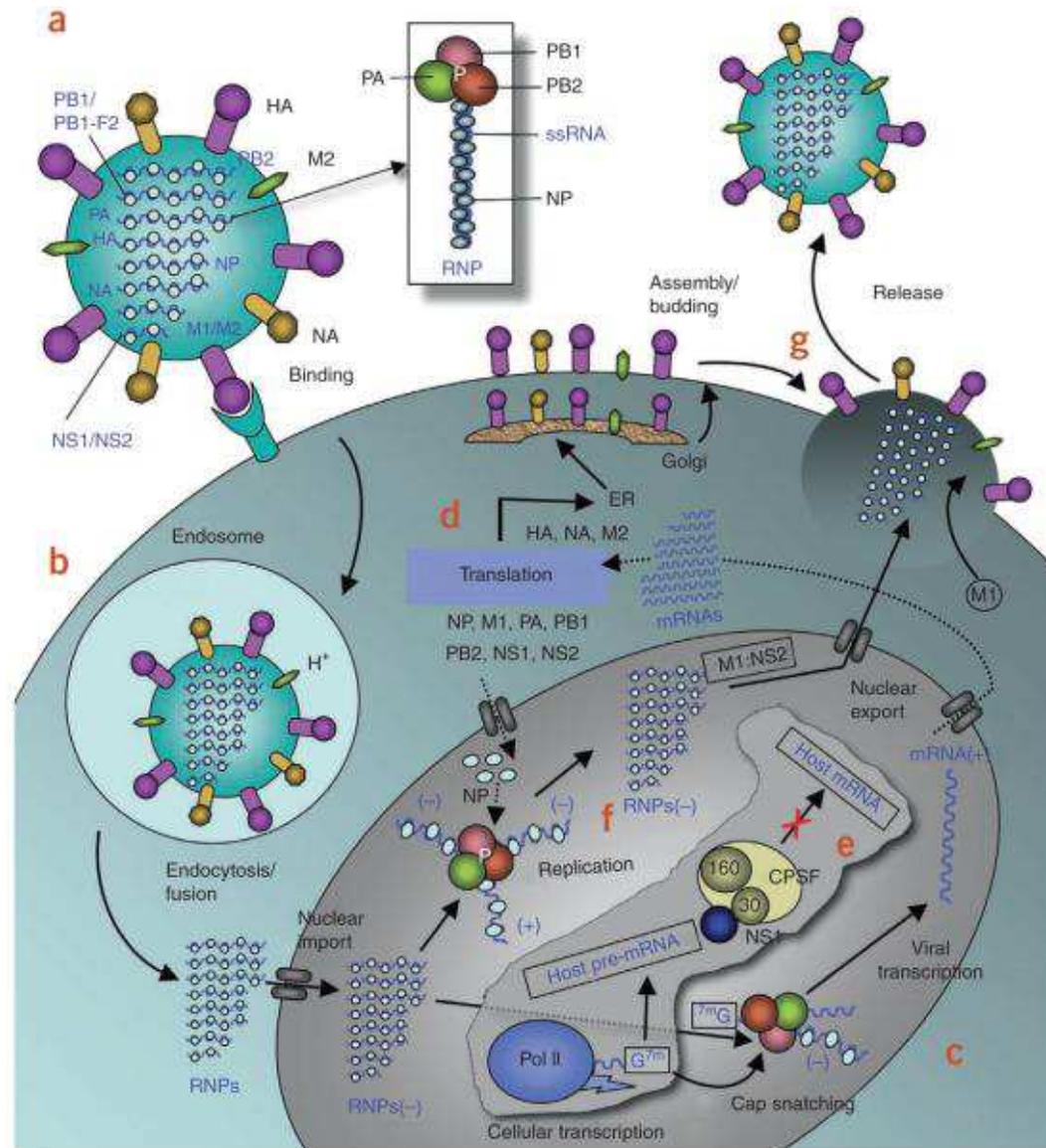
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Mecanisme d'infecció



Sieczkarski, S. B.; Whittaker, G. R. *Curr. Top. Microbiol. Immunol.* **2005**, *285*, 1-23.

Rossman, J. S.; Lamb, R. A. *Virology* **2011**, *411*, 229-236.

Deriva/desplaçament d'antigen

