Laurea Magistrale in Chimica

Laboratorio di Chimica Bioorganica

anno accademico 2015 – 2016

Prima esperienza

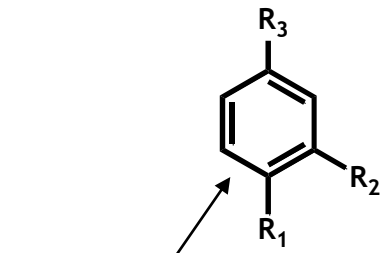
Due librerie ortogonali di inibitori della β-secretasi a scaffold diidropirimidinico: sintesi per reazione di Biginelli supportata e valutazione dell'attività biologica.

Introduzione alla chimica combinatoriale

$P_1—P_2—P_3$ 20^3 = 8000 tripeptidi

$P_1 \cdots P_{100}$ $20^{100} = 1 \times 10^{130}$ peptidi

Una libreria di origine biologica, ad es. fagica: $10^6 – 10^8$ membri



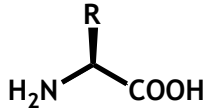
R_1	R_2	R_3
Me	F	OH
Et	Cl	NH_2
Pr	Br	SH
i-Pr	I	$NHCOCH_3$

64 composti: una libreria di sintesi

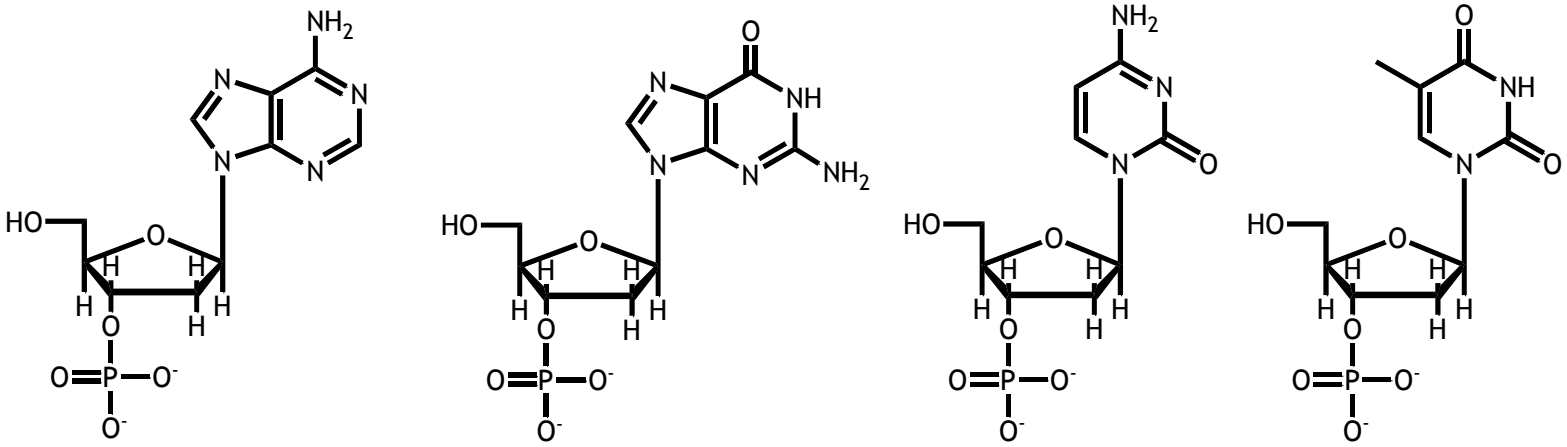
Scheletro (scaffold) non polimerico

gruppi funzionali

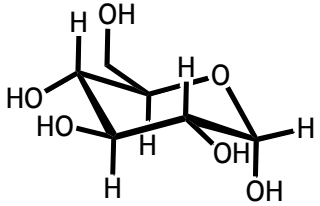
Scheletro polimerico: il gruppo funzionale fa parte del monomero che partecipa alla eteropolimerizzazione.



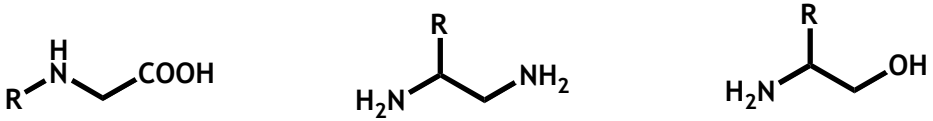
Peptidi: variabilità in R



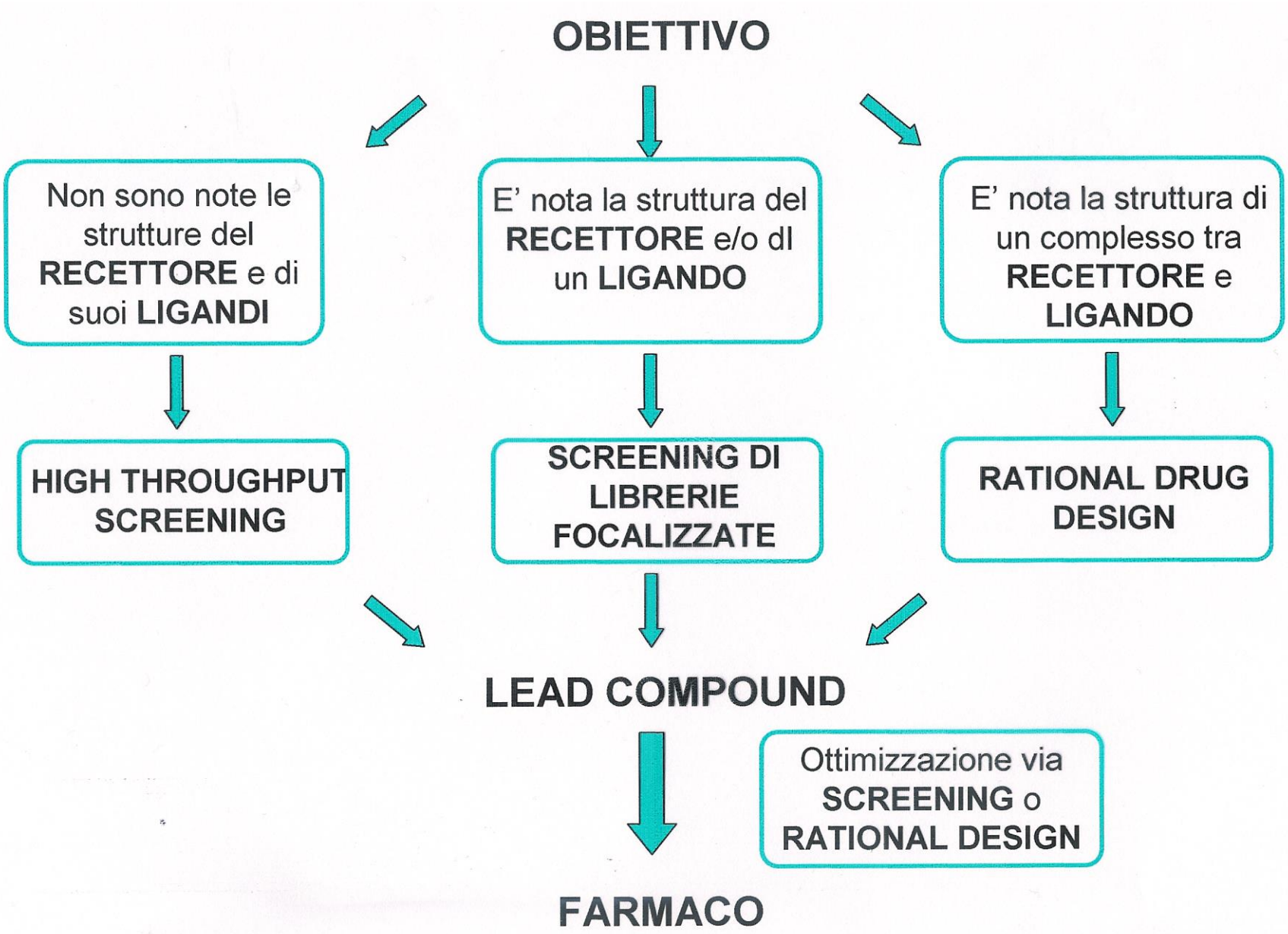
Acidi nucleici: variabilità in base



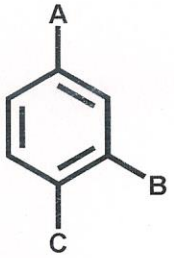
Polisaccaridi: variabilità in struttura, stereochimica, legame glicosidico



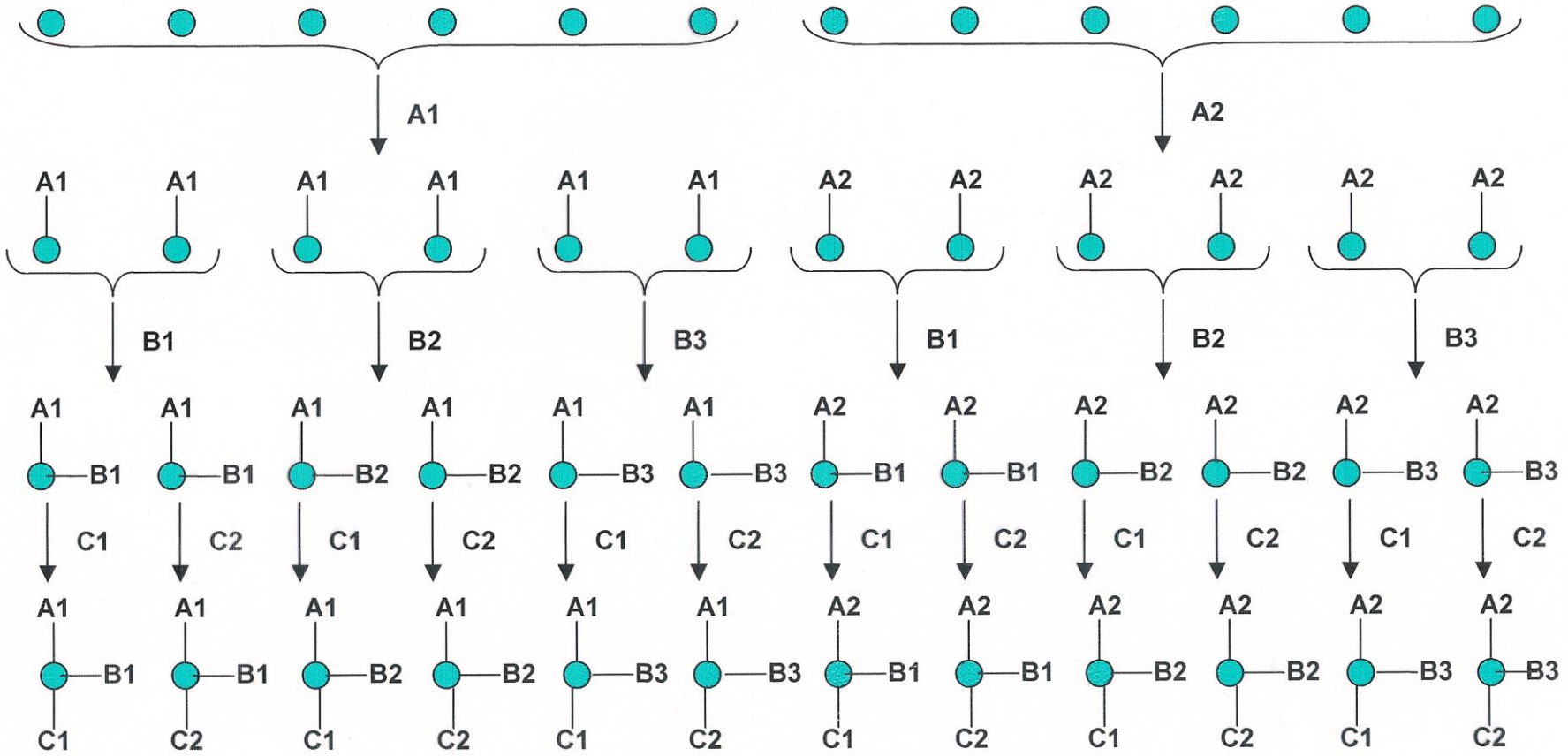
Scheletri polimerici artificiali: peptoidi, poliuree, poliuretani


OBIETTIVO
Non sono note le strutture del RECETTORE e di suoi LIGANDI
E' nota la struttura del RECETTORE e/o dl un LIGANDO
E' nota la struttura di un complesso tra RECETTORE e LIGANDO
HIGH THROUGHPUT SCREENING
SCREENING DI LIBRERIE FOCALIZZATE
RATIONAL DRUG DESIGN
LEAD COMPOUND
Ottimizzazione via SCREENING o RATIONAL DESIGN
FARMACO

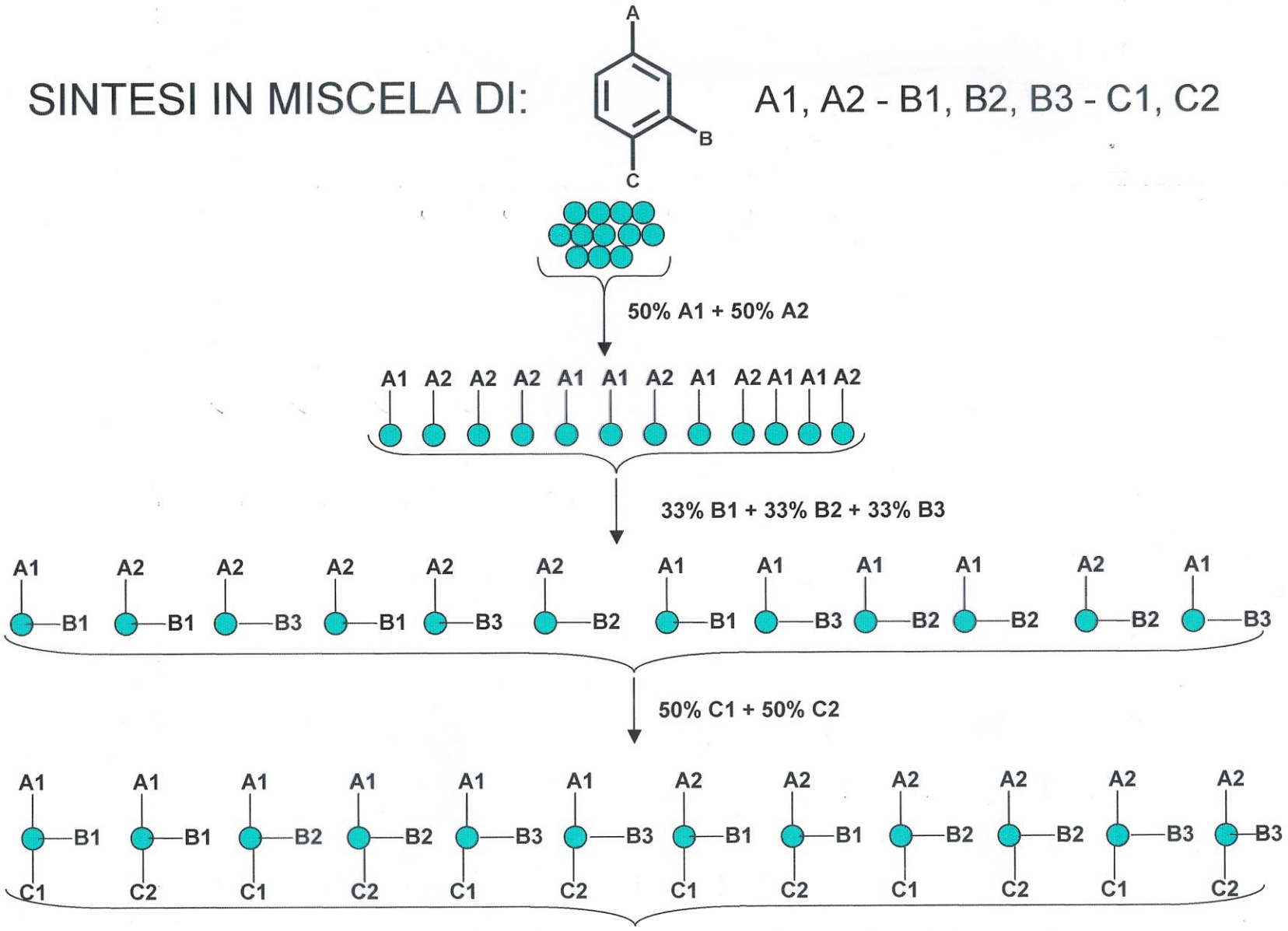
SINTESI PARALLELA DI:



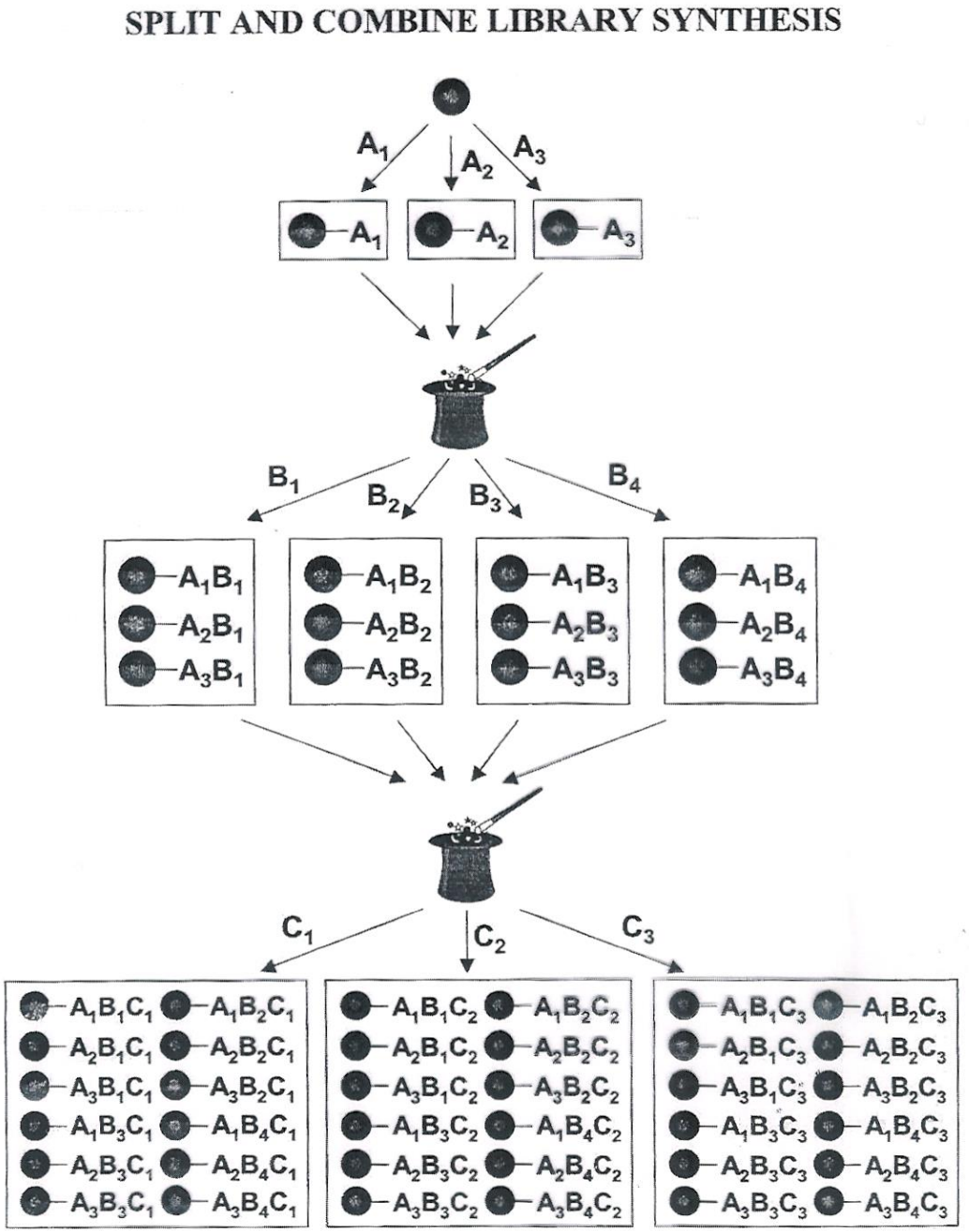
A1, A2 - B1, B2, B3 - C1, C2



2+6+12=20 reazioni per 12 composti

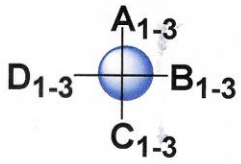


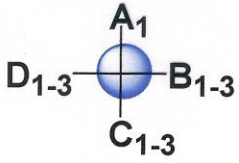
Tre reazioni per una libreria di 12 composti

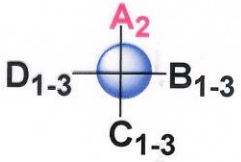


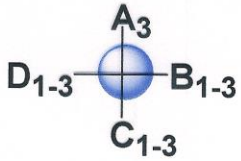
Sintesi in miscela di una libreria composta di una gerarchia di sottolibrerie

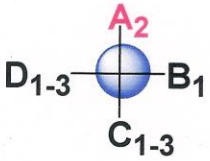
DECONVOLUZIONE ITERATIVA

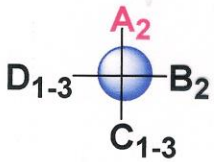


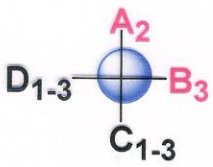


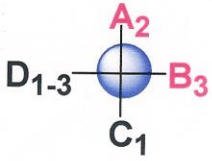


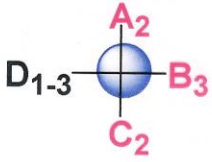


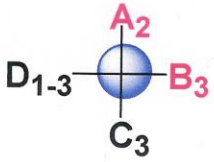


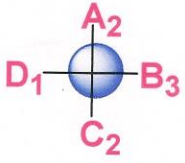


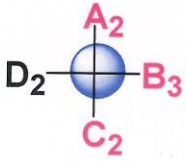


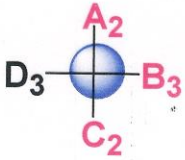




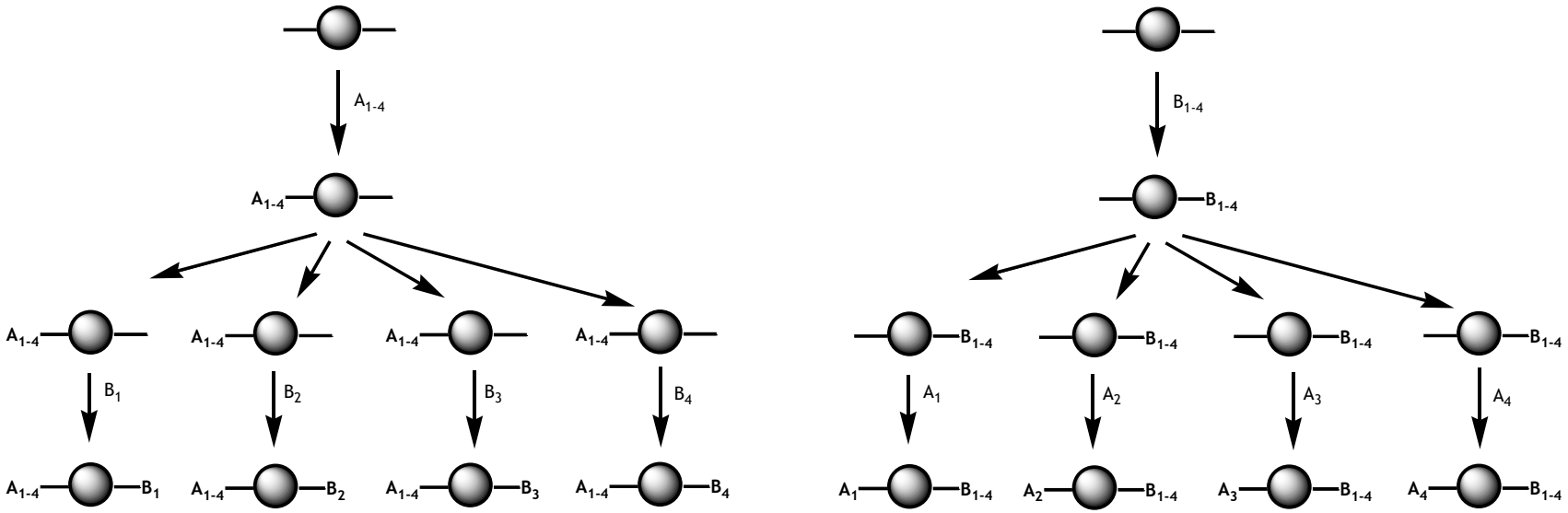






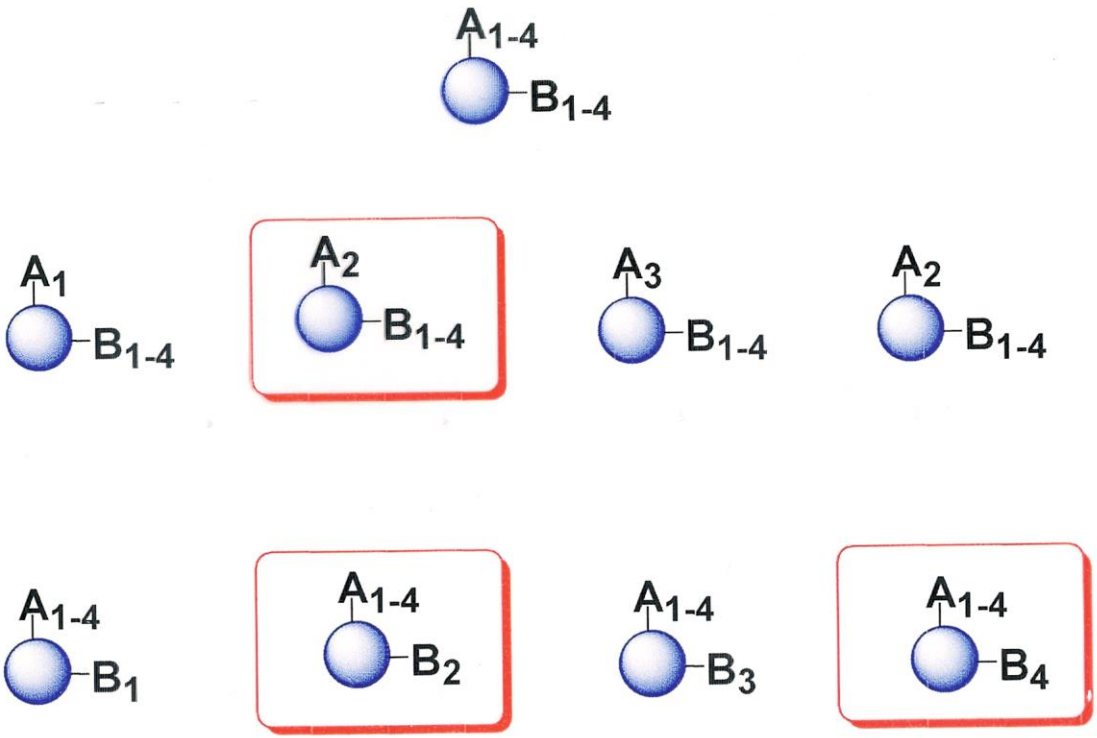


Sintesi in miscela di librerie ortogonali

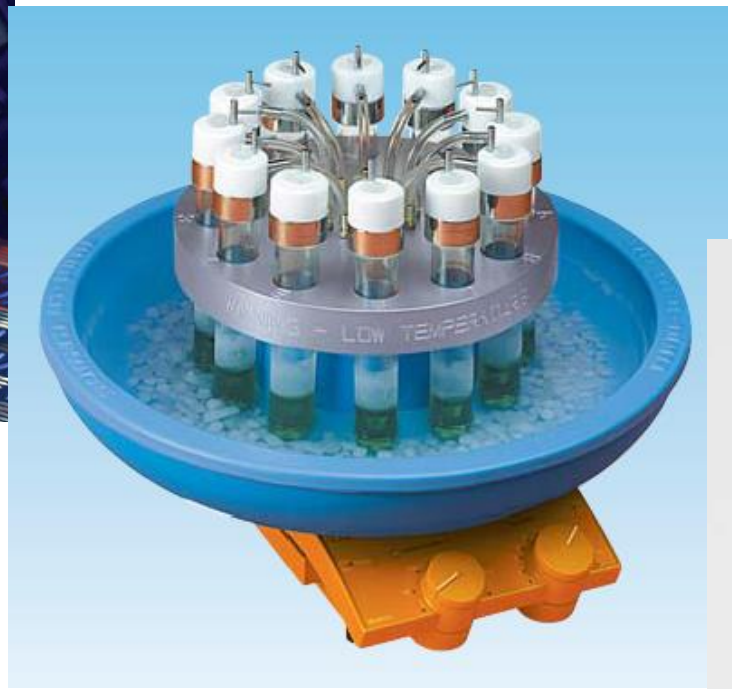


100 A, 100 B: 10000 composti, 10000 reazioni per la sintesi parallela pura. 202 reazioni in quattro passaggi per la sintesi di librerie ortogonali.

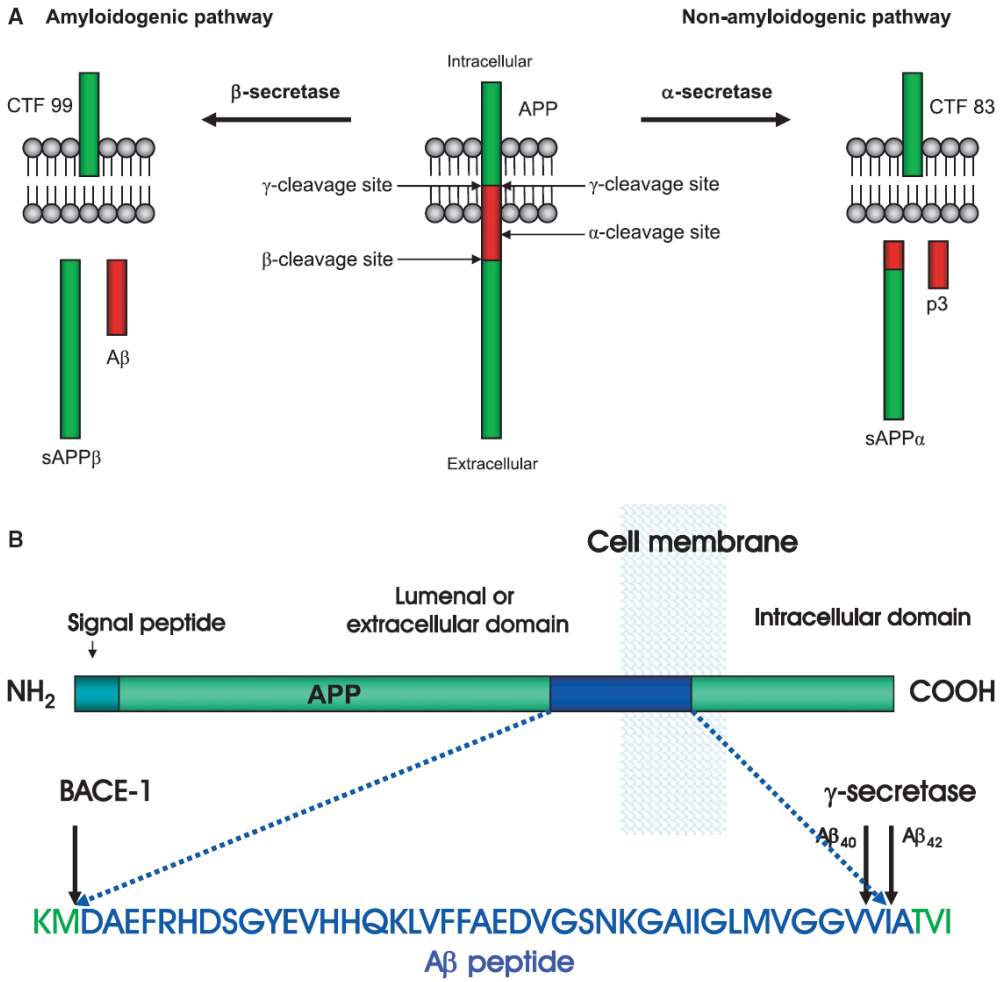
Deconvoluzione di librerie ortogonali



Attivi: A_2B_2 e A_2B_4



La β-secretasi



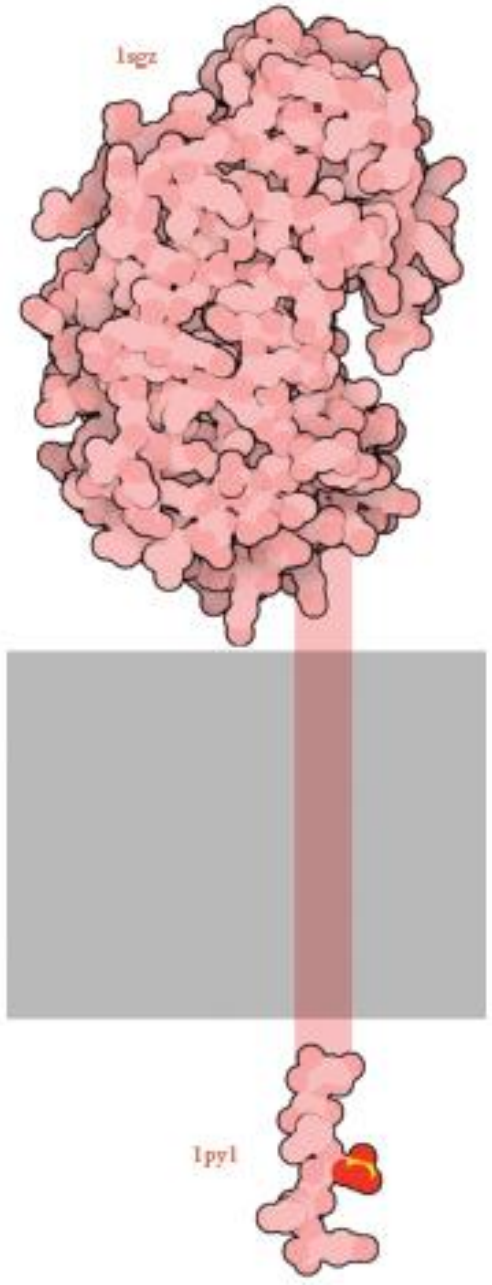
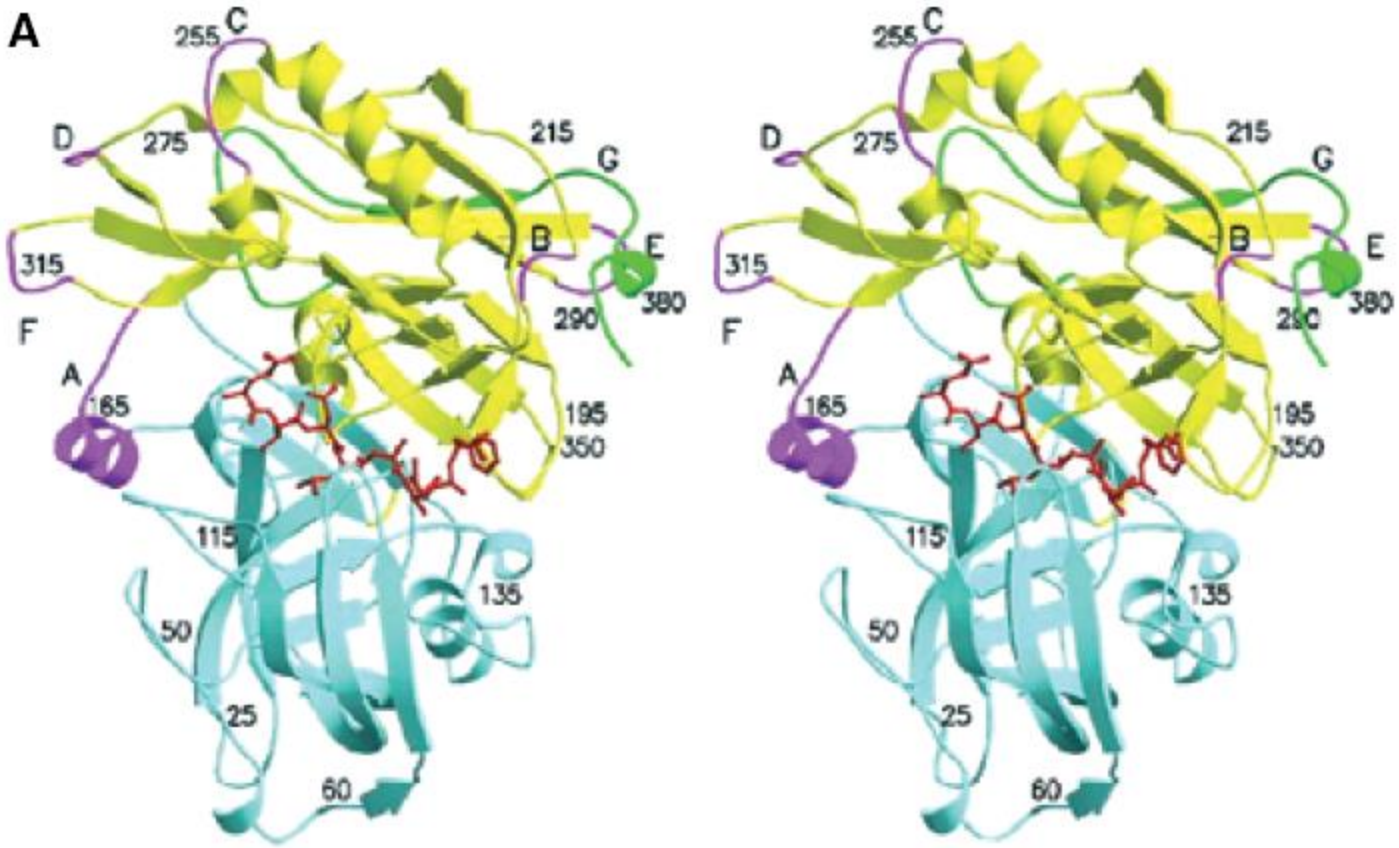
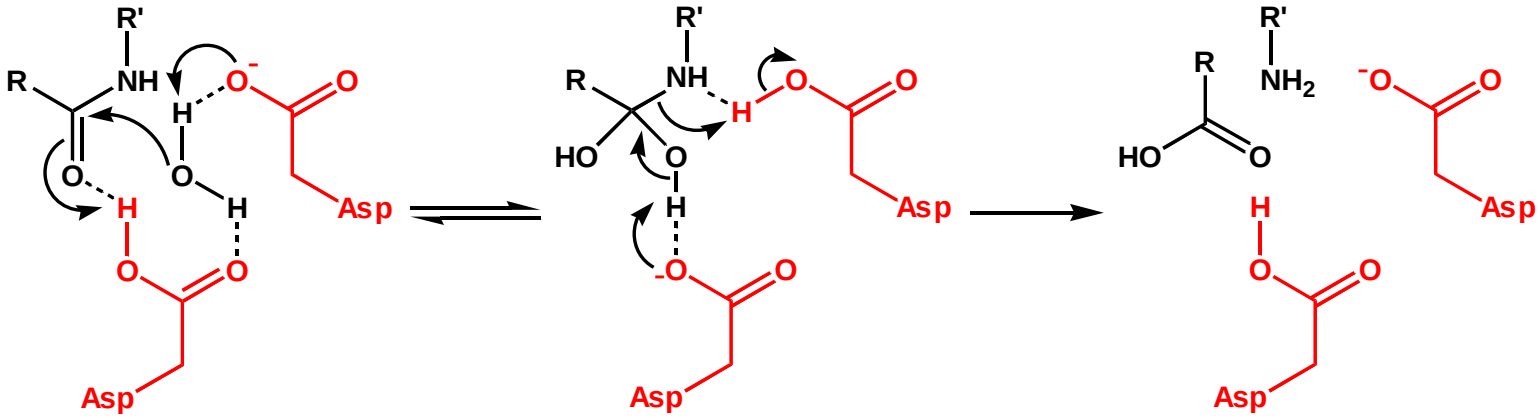
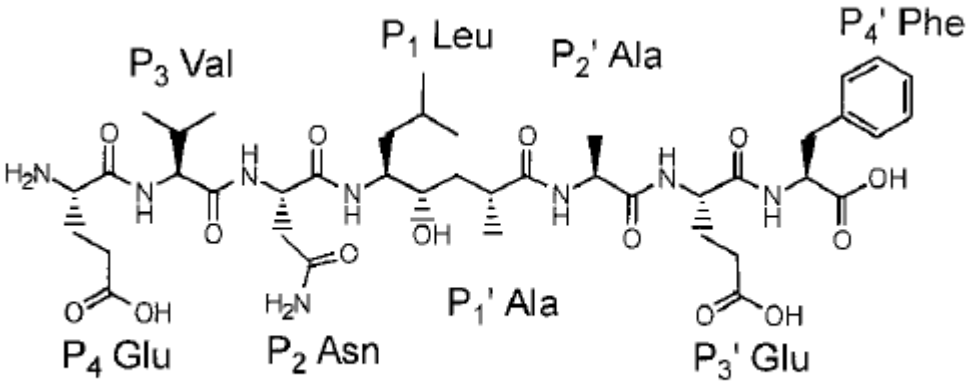


Fig. 1. Processing of APP to form Aβ peptides. (A) Schematic diagram of the alternative processing pathways of APP. The transmembrane APP undergoes two alternative and competing pathways of metabolism. The major and non-amyloidogenic, or α-secretase, pathway precludes the formation of Alzheimer's Aβ peptide. The amyloidogenic, or β-secretase, pathway initiates the formation of Aβ, which is completed by the action of the γ-secretase. α-Secretase has been identified as a zinc metalloproteinase of the ADAMs family, whereas both β- and γ-secretases are membrane-bound aspartic proteinases (see text for full details). (B) Sites of cleavage of APP by β- and γ-secretases to form Aβ peptides. The sites of the juxtamembrane and intramembrane cleavages of transmembrane APP by β- and γ-secretases, respectively, are indicated by arrows. The γ-secretase cleavages are heterogeneous, mainly producing Aβ peptides of 40 and 42 amino acids. The amino acid sequences of Aβ and around the scissile bonds are indicated by the one letter code for amino acids. The sequence shown is the wild-type sequence. The 'Swedish mutant' APP sequence around the β-secretase cleavage site is …NL/DAEF… rather than …KM/DAEF… The development of many BACE-1 inhibitors has used the sequence around the scissile bond in the Swedish mutant as the lead for synthetic chemistry to produce potent and selective compounds.

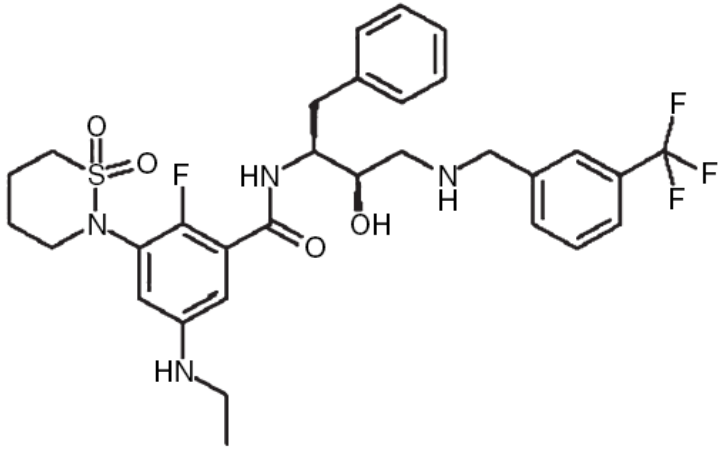

A
255
C
D
275
215
G
B
E
315
380
290
F
A
165
195
350
115
135
50
25
60
255
C
D
275
215
G
B
E
315
380
290
F
A
165
195
350
115
135
50
25
60

Le proteasi aspartiche

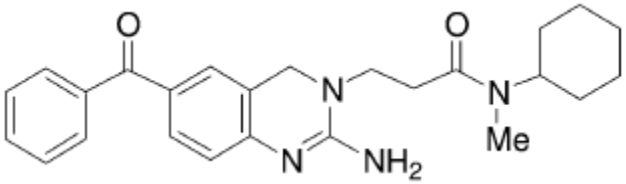




Design of potent inhibitors for human brain memapsin 2 (β-secretase). A. Ghosh *et al.*, *J. Am. Chem. Soc.* **2000**, *122*, 3522.



Oral administration of a potent and selective non peptidic BACE-1 inhibitor decreases β-cleavage of amyloid precursor protein and amyloid-β production in vivo. I. Hussain et al. *J Neurochem* **2007**, *100*, 802.



2-Amino-3,4-dihydroquinazolines as Inhibitors of BACE-1 (β-Site APP Cleaving Enzyme): Use of Structure Based Design to Convert a Micromolar Hit into a Nanomolar Lead. E. W. Baxter et al., *J. Med. Chem.* **2006**, *50*, 4262.

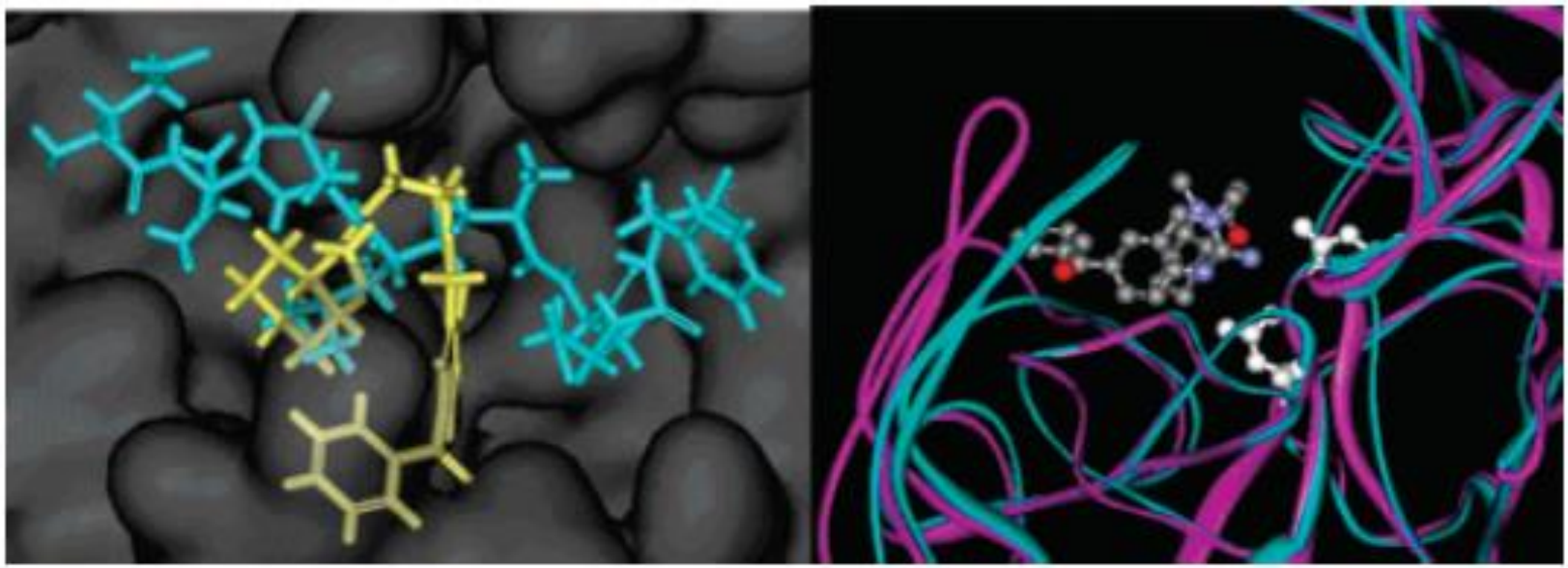


Figure 1. Left: superposition of OM99-2 (peptidic inhibitor) and **1** in the active site of BACE-1. Right: ribbon diagram representation of **1** with the two catalytic aspartic acids highlighted bound into BACE-1 (maroon), showing the flap over the active site moved when compared with BACE-1 when OM99-2 is bound in (turquoise).

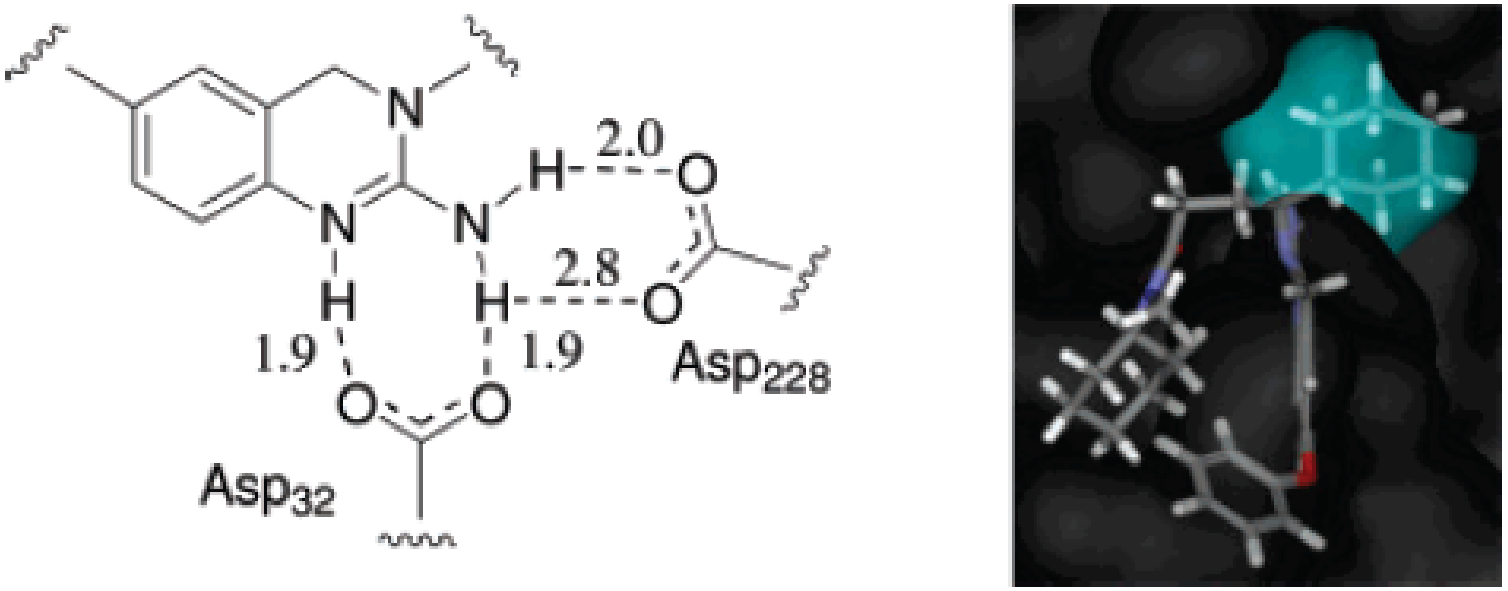


Figure 2. Left: the 2-amino-3,4-dihydroquinazoline fragment of **1** and the Asp_{32} and Asp_{228} sidechains of BACE-1, with H-bond distances in Å between the Asp carboxylate oxygens and the hydrogens. Right: the X-ray structure of **3a** bound in to BACE-1, showing the α-cyclohexyl substituent filling the S_1' pocket.

La reazione multicomponente di Biginelli

Biginelli P. Derivati aldeiduredici degli eteri acetil- e dossal-acetico, *Gazzetta Chimica Italiana*, **1893**, *23*, 360 – 416

The Generation of Dihydropyrimidine Libraries Utilizing Biginelli Multicomponent Chemistry

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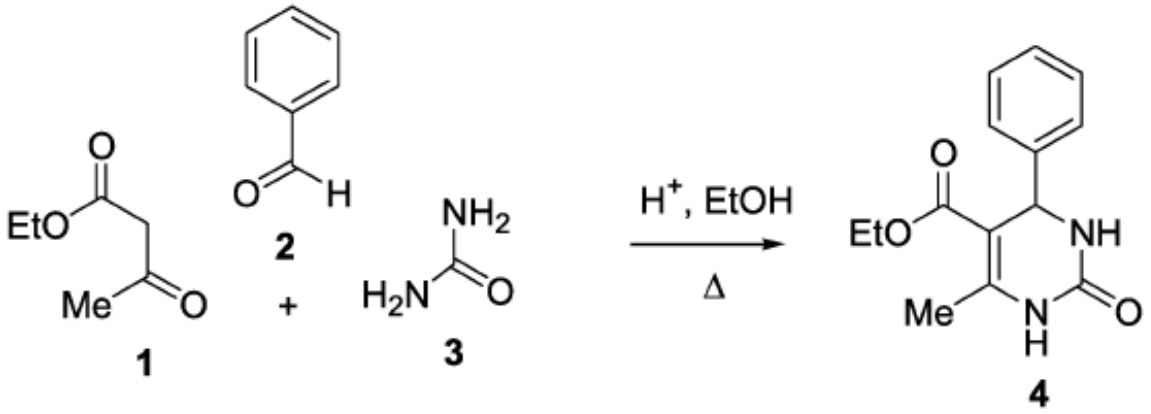
QSAR Comb. Sci. *22* (2003) DOI: 10.1002/qsar.200320001



Scheme 1. The original Biginelli dihydropyrimidine synthesis (1893).

Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 49–51

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Highly Versatile Solid Phase Synthesis of Biofunctional 4-Aryl-3,4-dihydropyrimidines Using Resin-Bound Isothiourea Building Blocks and Multidirectional Resin Cleavage†

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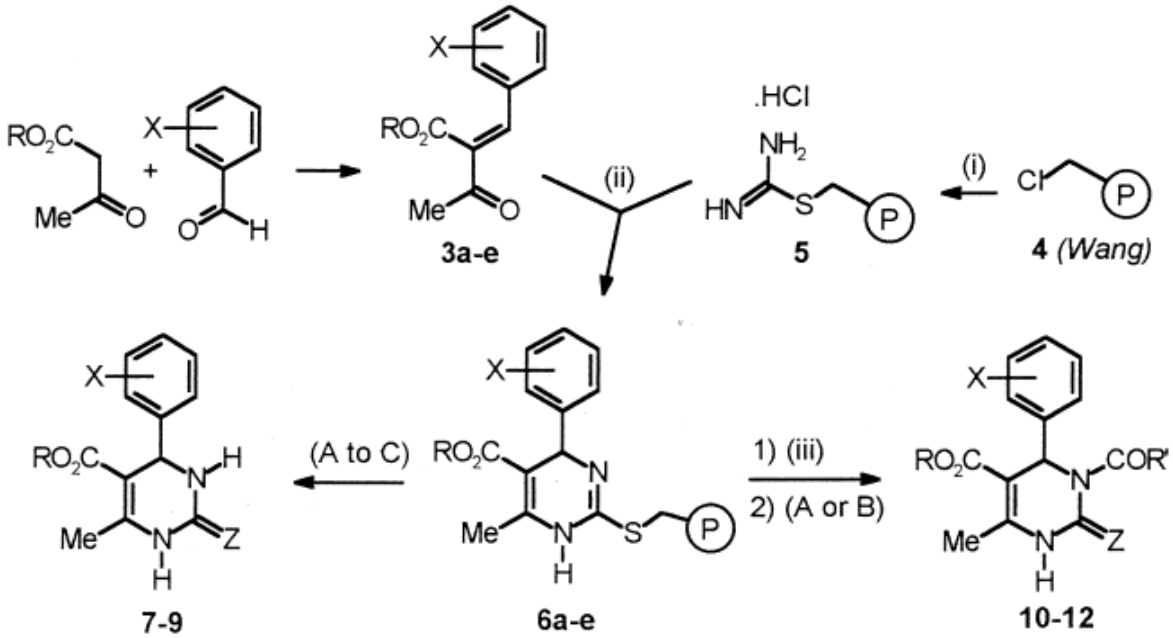

Scheme 2. Reagents and conditions:[24] (i) thiourea, NMP, 75 °C, 16 h; (ii) NMP, Cs_2CO_3, 90 °C, 16 h; (iii) Cl-COR′, pyridine, CH_2Cl_2, 0 °C→rt, 6 h; (A) dioxane, ethanol, AcOH, H_2O, reflux, 16 h; (B) TFA, EtSH, CH_2Cl_2, rt, 16 h; (C) dioxane, MeCN, NH_4OAc, reflux, 8 h.

Pergamon

Tetrahedron Letters 40 (1999) 7031–7033

TETRAHEDRON LETTERS

New solid phase Knoevenagel catalyst

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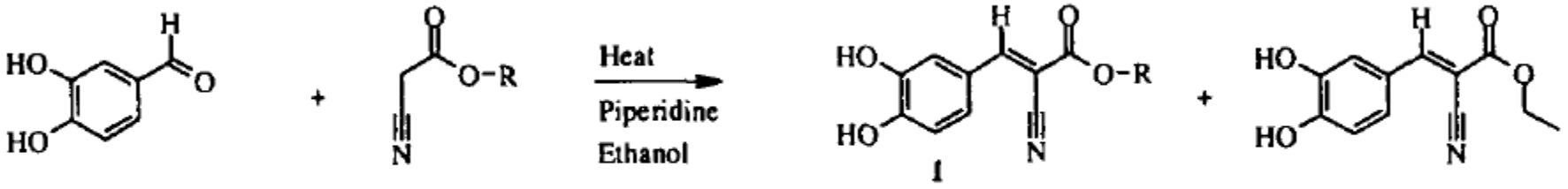
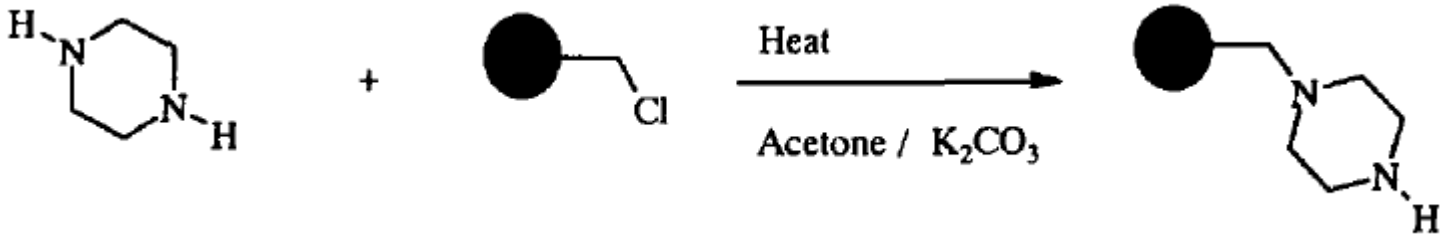
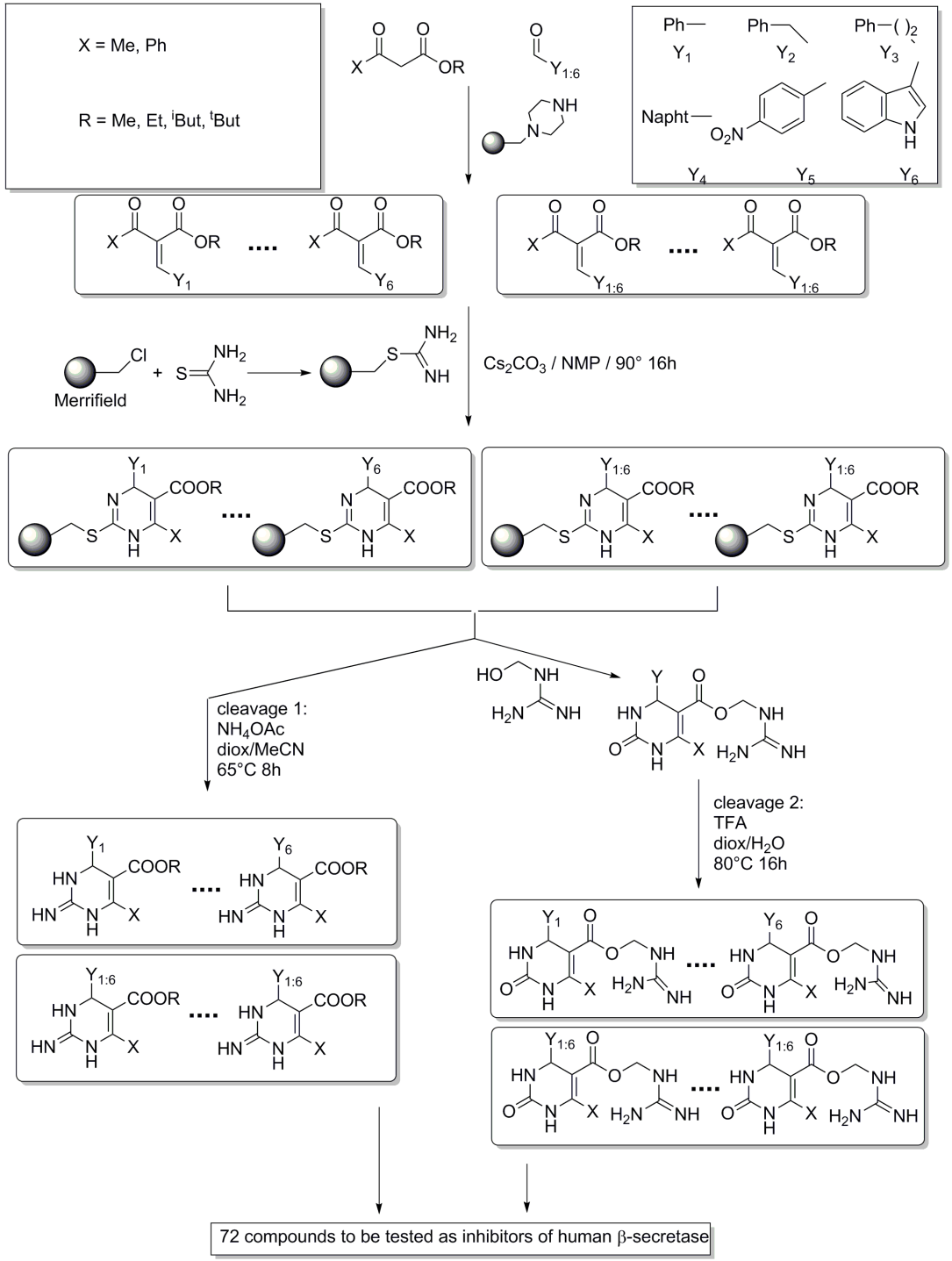
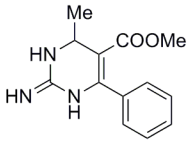
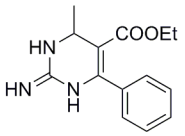
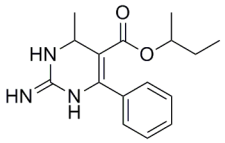
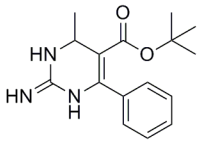
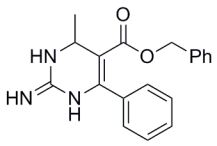
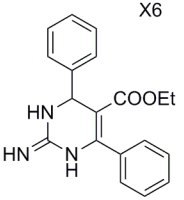
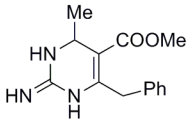
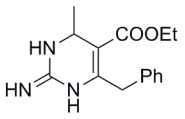
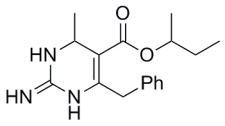
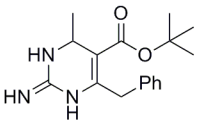
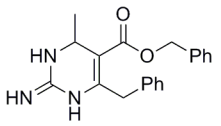
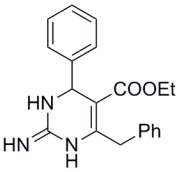
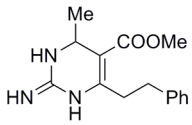
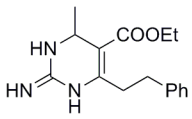
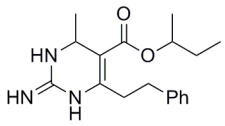
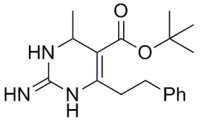
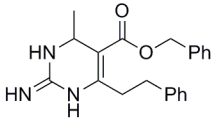
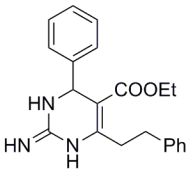
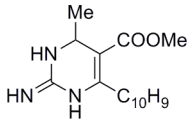
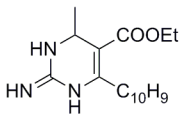
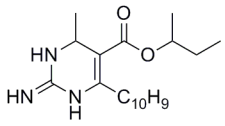
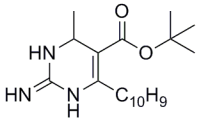
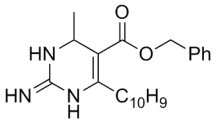
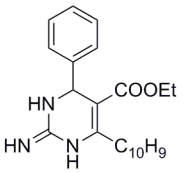
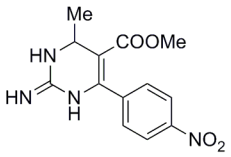
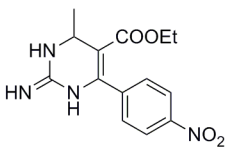
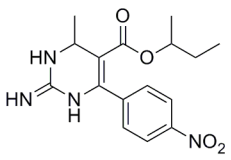
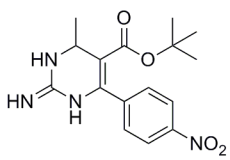
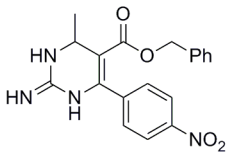
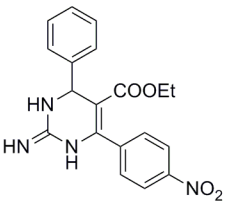
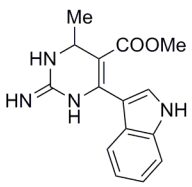
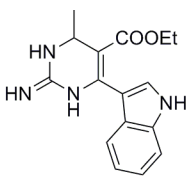
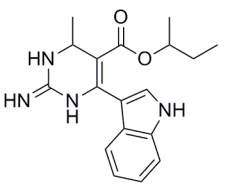
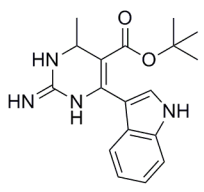
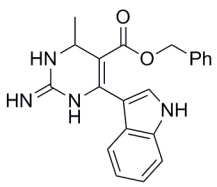
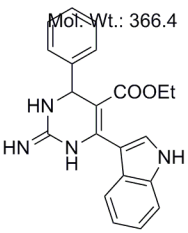
Received 27 May 1999; revised 22 July 1999; accepted 27 July 1999



R = Simple and functionalised alkyl groups




X = Me, Ph
R = Me, Et, iBut, tBut
Ph— Y1
Ph— Y2
Ph—( )2 Y3
Napht— Y4
O2N Y5
NH Y6
Merrifield
Cs2CO3 / NMP / 90° 16h
cleavage 1:
NH4OAc
diox/MeCN
65°C 8h
cleavage 2:
TFA
diox/H2O
80°C 16h
72 compounds to be tested as inhibitors of human β-secretase

	X1	X2	X3	X4	X5	X6
Y1	 Mol. Wt.: 245.3	 Mol. Wt.: 259.3	 Mol. Wt.: 287.4	 Mol. Wt.: 287.4	 Mol. Wt.: 321.4	 Mol. Wt.: 321.4
Y2	 Mol. Wt.: 259.3	 Mol. Wt.: 273.3	 Mol. Wt.: 301.4	 Mol. Wt.: 301.4	 Mol. Wt.: 335.4	 Mol. Wt.: 335.4
Y3	 Mol. Wt.: 273.3	 Mol. Wt.: 287.4	 Mol. Wt.: 315.4	 Mol. Wt.: 315.4	 Mol. Wt.: 349.4	 Mol. Wt.: 349.4
Y4	 Mol. Wt.: 295.3	 Mol. Wt.: 309.4	 Mol. Wt.: 337.4	 Mol. Wt.: 337.4	 Mol. Wt.: 371.4	 Mol. Wt.: 371.4
Y5	 Mol. Wt.: 290.3	 Mol. Wt.: 304.3	 Mol. Wt.: 332.4	 Mol. Wt.: 332.4	 Mol. Wt.: 366.4	 Mol. Wt.: 366.4
Y6	 Mol. Wt.: 284.3	 Mol. Wt.: 298.3	 Mol. Wt.: 326.4	 Mol. Wt.: 326.4	 Mol. Wt.: 360.4	 Mol. Wt.: 360.4