Drug synthesis II
Lääkeainesynteesit II

Solid Phase Synthesis and Combinatorial Chemistry

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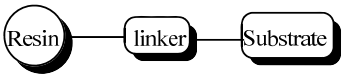
Solid-phase organic synthesis (SPOS)

Organic reactions carried out on substrates that are covalently attached to a polymeric resin

- Advantages of solid phase
  - Synthetic intermediates don't have to be isolated
  - Excess reagents are used - drives reactions to completion
  - Reagents simply washed away each step
  - Overall quicker
  - Can be automated with robots!!
- Disadvantages
  - Cost due to excess reagents and solvents
  - Purification of the cleaved product may be difficult
  - Not all syntheses can be done solid phase
  - Reaction rates can be slower
  - Difficult to monitor the progress of reaction
  - Reaction optimization is difficult

Solid phase synthesis: resins and linkers



Resin

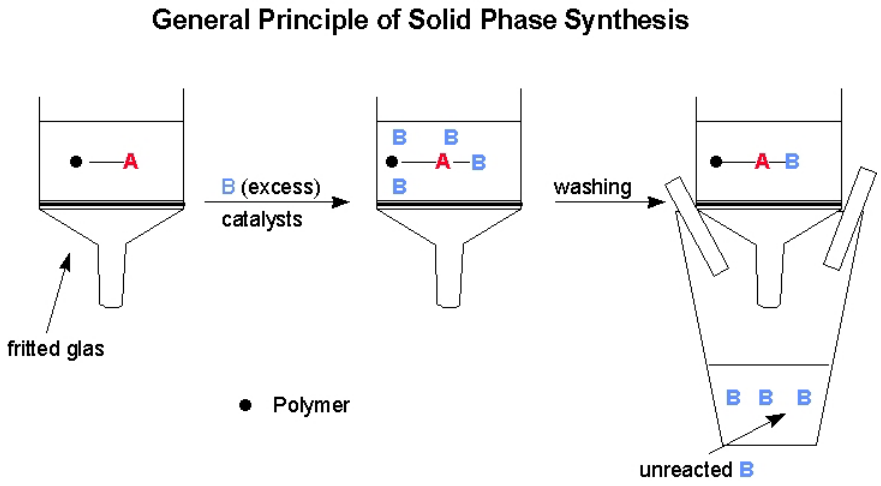
- Polymeric backbone that substrate is anchored to
- Different resins have different swelling properties

  Examples:
  - **Polystyrene (PS): (cheap!) Swells in non-polar solvents**
  - Polyethylene glycol (PEG): Swells in polar and non-polar solvents

Linker

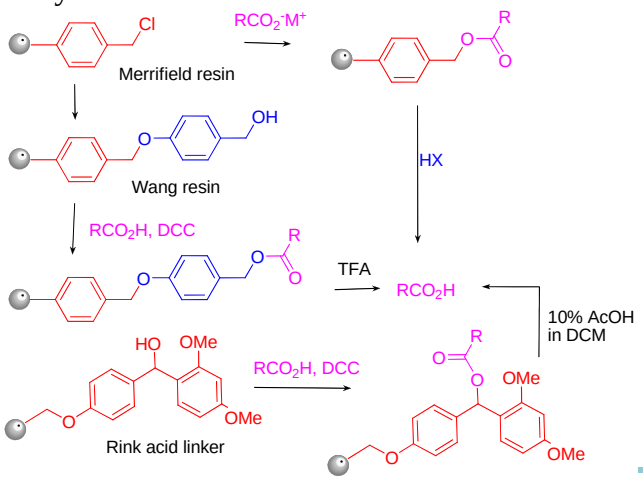
- An intermediate structure between resin and substrate
- Different linkers can be used to unmask different functional groups on the substrate!

Solid phase synthesis



Solid phase synthesis: linkers

- Examples of linkers used in solid phase synthesis for carboxylic acids



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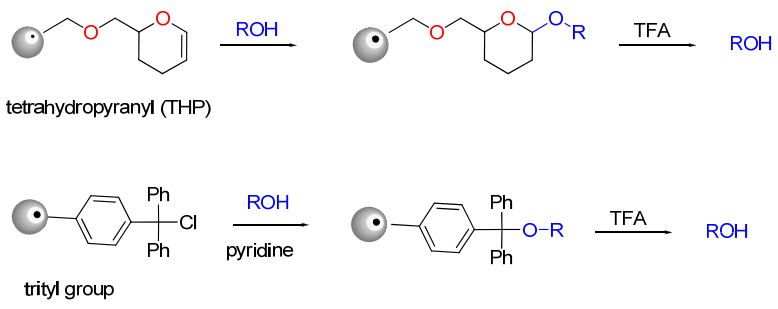
Solid phase synthesis: linkers

- Linkers for alcohols



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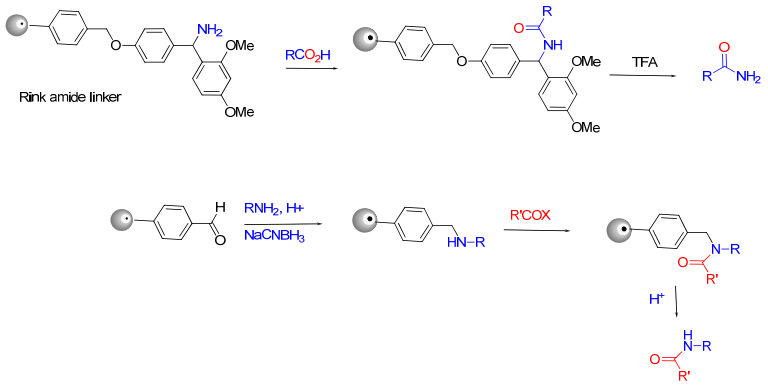
Solid phase synthesis: linkers

- Linkers for amides



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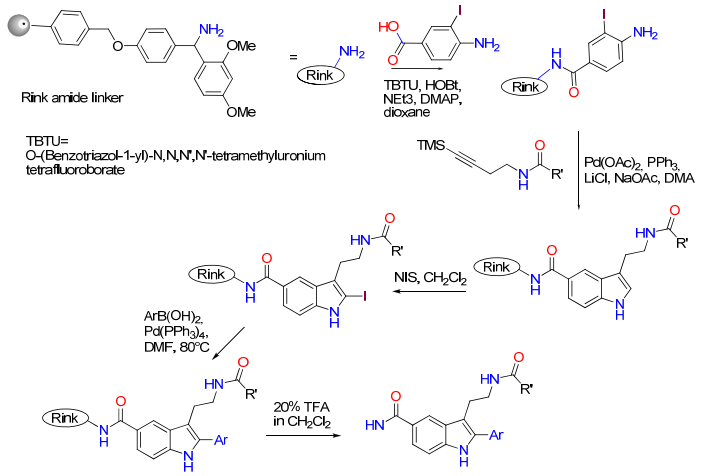
Application of Rink amide resin

- Parallel synthesis of melatonine derivatives



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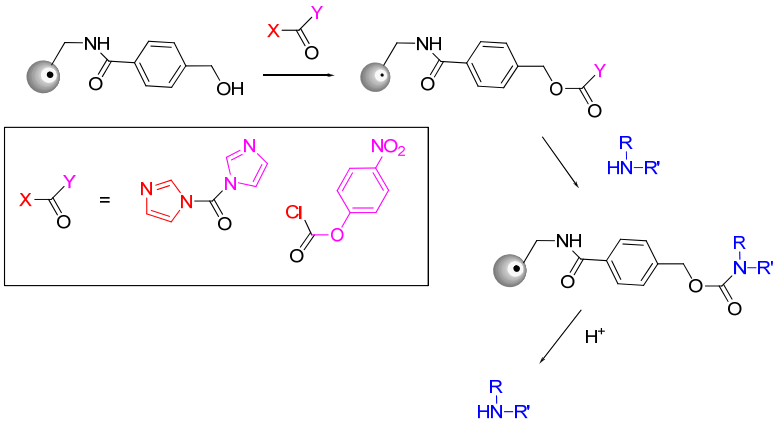
Solid phase synthesis: linkers

- Carbamate linker has been used for the synthesis of amines



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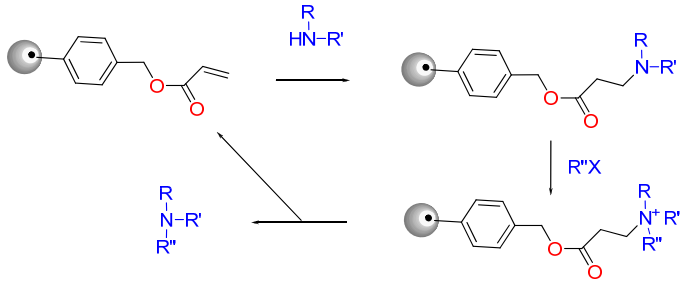
Solid phase synthesis: Linker for tertiary amine

- Primary and secondary amine is introduced to the linker by Michael addition. The amine is alkylated to give a resin-bound quaternary ammonium ion. In mildly basic condition, Hoffmann elimination occurs to give a tertiary amine.



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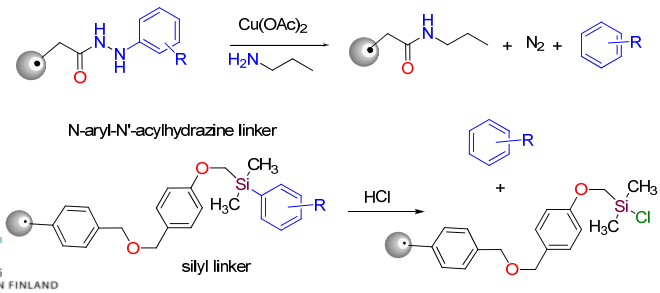
Solid phase synthesis: Linkers for arenes

- Traceless linkers prevent the appearence of additional functional groups (traces) after cleavage
- Oxidation of N-aryl-N'-acylhydrazine linker leads to the formation of N-aryl-N'-acyldiazenes, which, in the presence of nucleophiles, undergo deacylation to yield acid derivatives, arenes and nitrogen.
- The silyl linker linked to a phenyl group can undergo a protodesilylation reaction cleaving the silicon – aryl bond when treated with acid.



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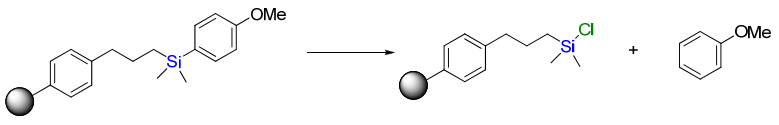
Solid phase synthesis: linkers

- **Ellman linker,** Trialkylsilylchlorid (or triflate) generated from ethoxyphenylsilane
  - Attachment of:
    - alkohols (as silylether)
    - ketones (as silylenolether)
    - arenes (as arylsilanes)



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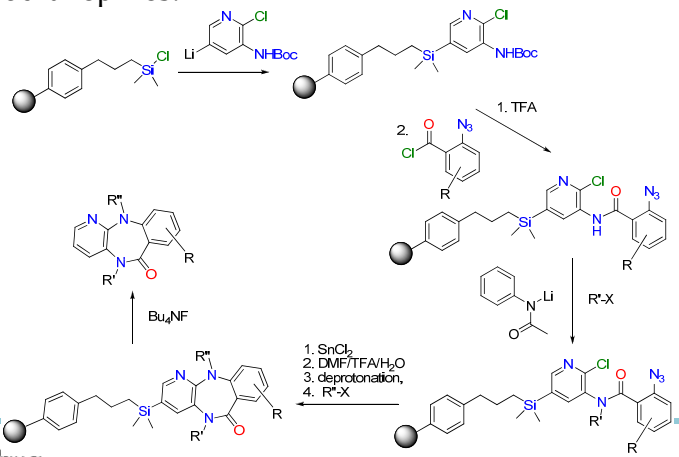
12

Linkers

- Application of the Ellman traceless linker for the SPOS of benzodiazepines:



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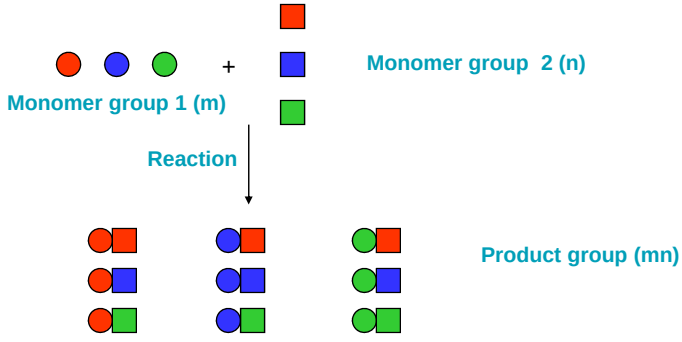
13

Combinatorial synthesis

- Combinatorial synthesis, using a method described as mix and split synthesis, can generate very large numbers of products (generation of large molecule libraries).



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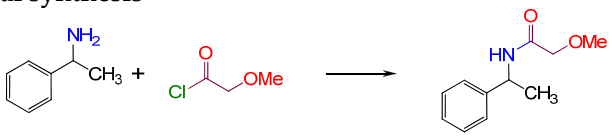
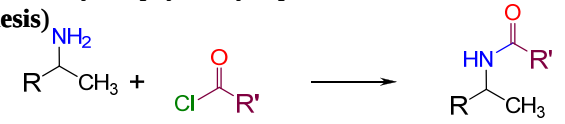
Combinatorial synthesis

- **Traditional synthesis**



lähtöaine lähtöaine = 1 tuote

- **Combinatorial synthesis**
  - Using a combinatorial process to prepare sets of compounds from sets of building blocks (as mixtures or discrete compounds prepared simultaneously in arrays of physically separate reaction vessels = **parallel synthesis**)



50 lähtöainetta 20 lähtöainetta = 1000 tuotetta

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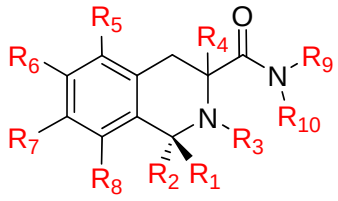
Chemical libraries



- **68 different groups in 10 positions (R1 - R10 are 5, 10, 10, 4, 2, 5, 5, 2, 5 ja 20 different) gives 20 million chemical library.**
- **If configurations of asymmetric carbons are included, the library consists of 80 million chemicals**

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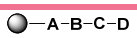
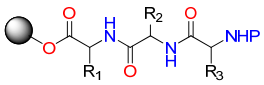
- Linear chemical libraries





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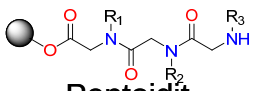
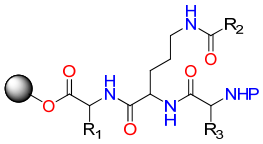
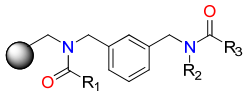


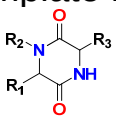
Peptoidit

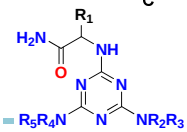
- Branched molecule libraries

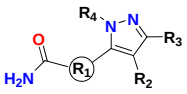




- Template libraries







Felder; Tet. Lett. **1996**, 37(7), 1003

Gordon; *Bioorg. Med. Chem. Lett.*, **1995**, 5, 47

Lebl; *Molecular Diversity*, ***1996***, *2*, *75*

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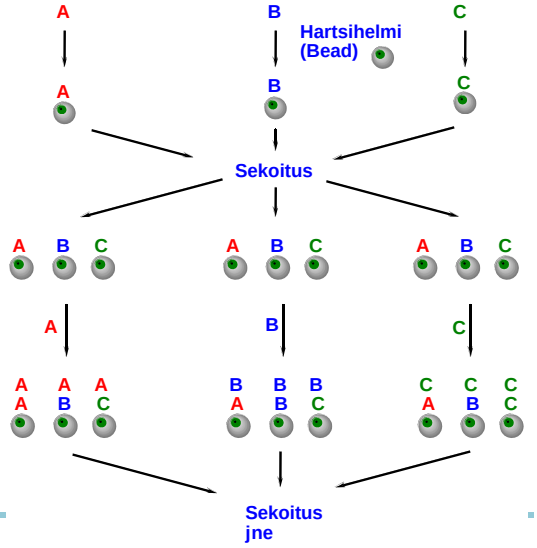
Split and Mix synthesis

(A.Furka et al, *Int. J. Pep. Protein Res*. **199**1, 37, 487.)

1. A sample of resin support material is divided into a number of equal portions (x) and each of these are individually reacted with a single different reagent
2. After completion of the reactions, and subsequent washing to remove excess reagents, the individual portions are recombined, the whole is thoroughly mixed, and may then be divided again into portions.
3. Reaction with a further set of activated reagents gives the complete set of possible dimeric: units as mixtures and this whole process may then be repeated as necessary (for a total of n times).
4. The number of compounds obtained arises from the geometric increase in potential products; in this case x to the power of n.



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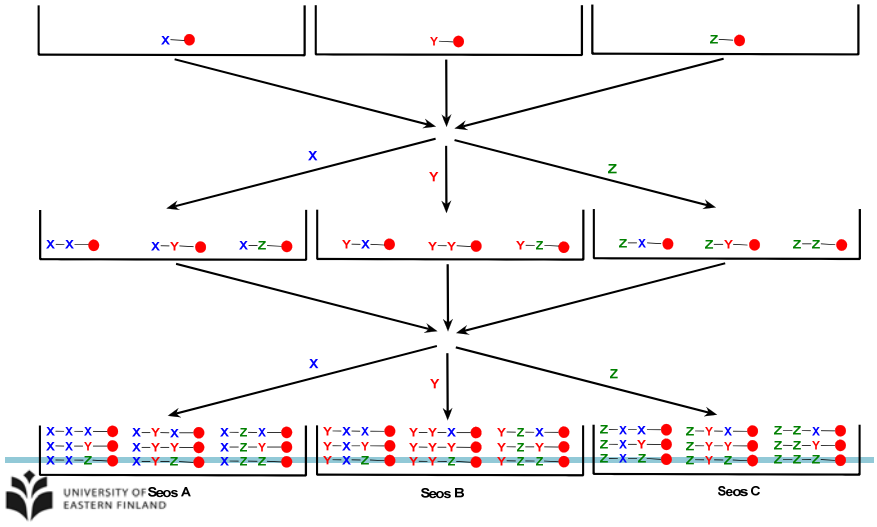
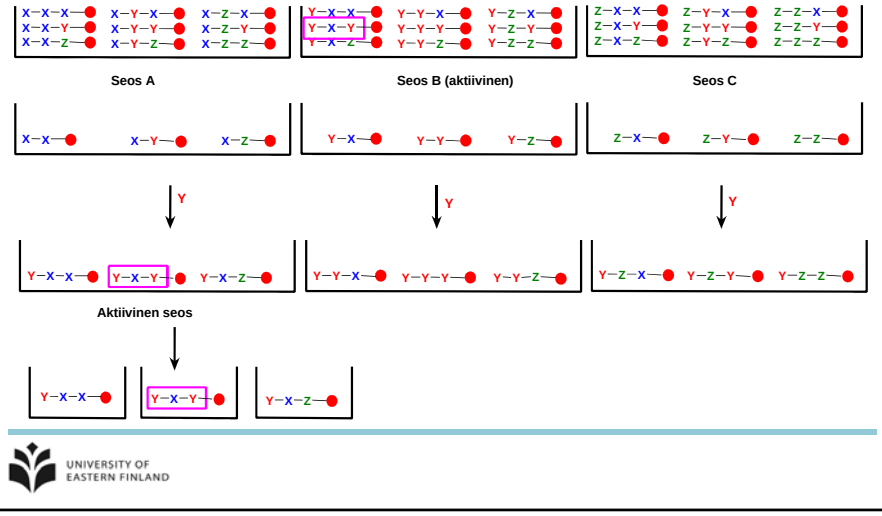
A simple example of a 3 x 3 x 3 library gives all 27 possible combinations of trimeric products

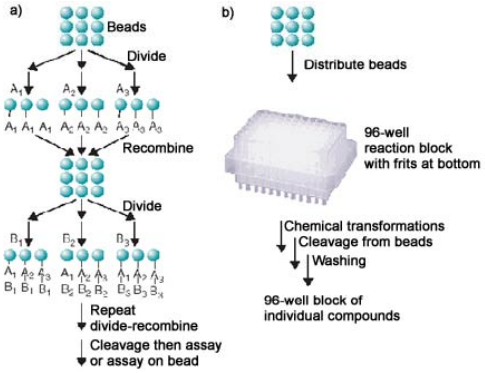


Deconvolution: Process of optimizing an activity of interest by fractionating (normally by resynthesis) a pool with some level of the desired activity to give a set of smaller pools. Repeating this strategy leads to single members with (ideally) a high level of activity and is termed iterative deconvolution.



Parallel synthesis

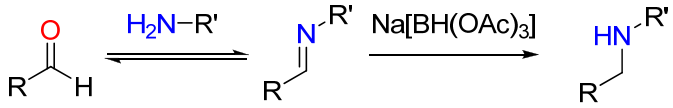
- In the last years, combinatorial chemistry is changed more and more to automated parallel synthesis and parallel purification
- In a parallel synthesis, the reactions are individual isolated in the wells of a plate throughout the synthesis
- Full characterization and biological screening, without the need for laborious identification procedure.



Parallel synthesis

Parallel Synthesis - Reductive Amination of Aldehyde Group

- The solutions of the aldehydes and amines in CH_2Cl_2 were mixed in 24 flasks and shaken for 30 minutes. $Na[BH(OAc)_3]$ was added into each of the 24 tubes .



Parallel Synthesis - Reductive Amination of Aldehyde Group

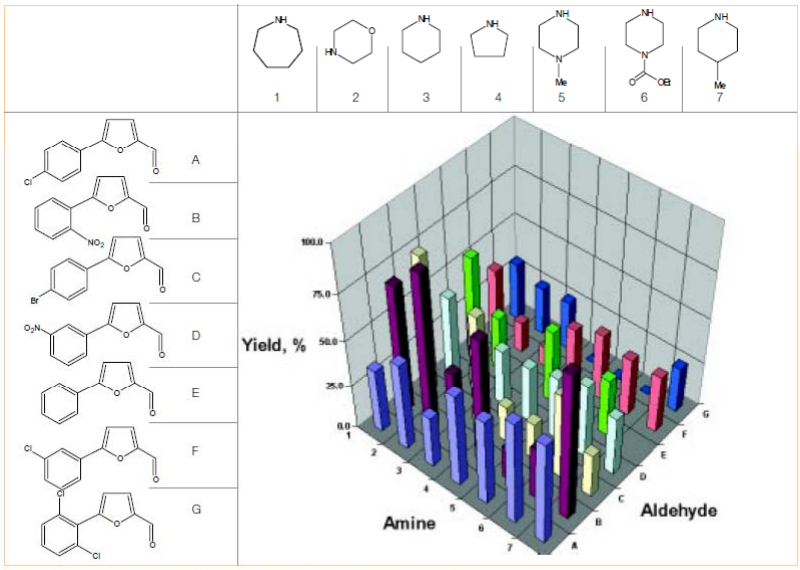


Table 1: Examples of structures of the starting aldehydes and amines with overall yields.

Parallel Synthesis - Reductive Amination of Aldehyde Group

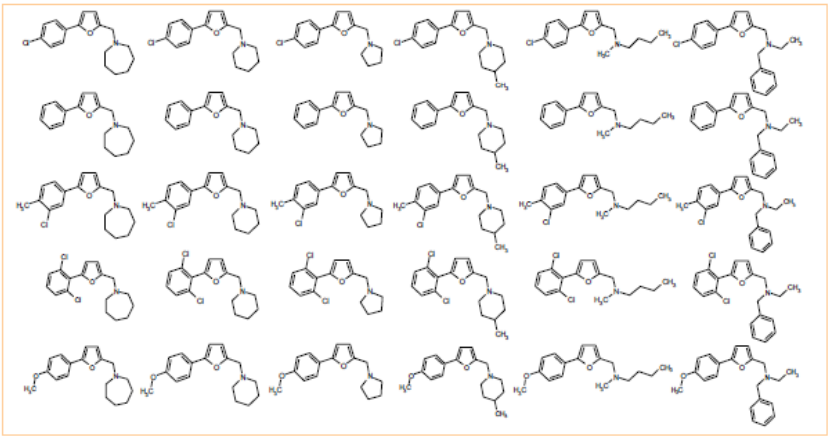


Table 2: Short overview of some synthesized products

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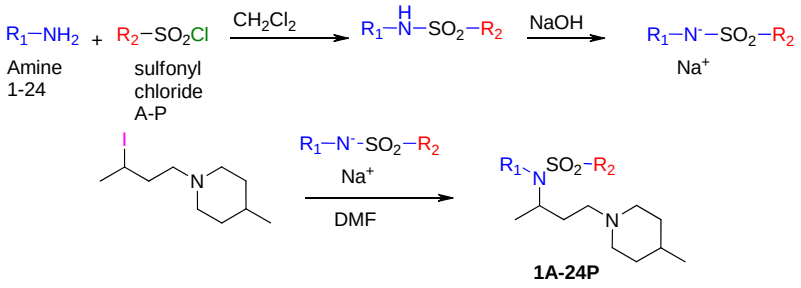
25

Automated parallel synthesis of N-substituted-N-[1-methyl-3-(4-methylpiperidin-1-yl)propyl]-arylsulfonamides

- Library of 384 sulfonamides was prepared with 24 chemically diverse amines **1-24** and 16 sulfonyl chlorides **A-P**



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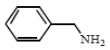
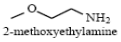
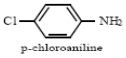
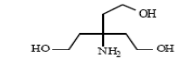
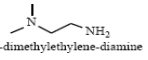
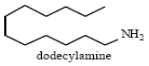
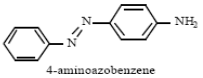
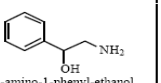
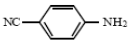
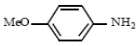
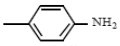
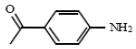
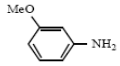
Letters in Drug Design & Discovery, 2006, 3, 49-54

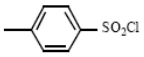
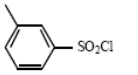
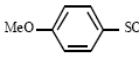
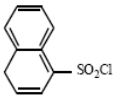
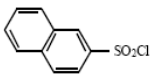
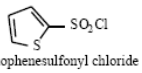
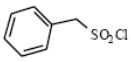
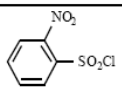
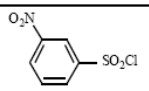
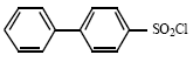
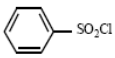
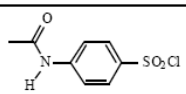
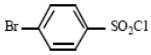
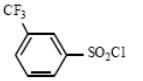
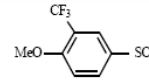
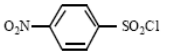
26

Table 1. Overview of Amines Applied to the Combinatorial Synthesis

1  benzylamine	2  tert-butylamine	3  2-methoxyethylamine	4  cyanamide
5  1,1 dimethyl hydrazine	6  p-chloroaniline	7  tris(hydroxymethyl)-aminomethane	8  methylamine
9  N,N-dimethylethylene-diamine	10  dodecylamine	25  4-aminoazobenzene	26  2-amino-1-phenyl-ethanol
13  2-aminopyridine	14  3-aminopyridine	15  2-aminobenzonitrile	16  o-anisidine
17  4-aminobenzonitrile	18  p-nitroaniline	19  p-anisidine	20  p-toluidine
21  aniline	22  4-aminoacetophenone	23  m-anisidine	24  1-naphthylamine

27

Table 2. Selected Sulfonyl Chlorides (A-P)

A	B	C	D
 p-toluenesulfonyl choride	 m-toluenesulfonyl chloride	 p-methoxybenzene-sulfonyl chloride	 1-naphthalene-sulfonyl chloride
E	**F**	**G**	**H**
 2-naphthalenesulfonyl chloride	 2-thiophenesulfonyl chloride	 alpha-toluene-sulfonyl chloride	 2-nitrobenzene-sulfonyl chloride
I	**J**	**K**	**L**
 3-nitrobenzene-sulfonyl chloride	 4-biphenylsulfonyl chloride	 benzenesulfonyl chloride	 4-acetamidobenzene-sulfonyl chloride
M	**N**	**O**	**P**
 4-bromobenzene-sulfonyl chloride	 3-(trifluoromethyl)-benzenesulfonyl chloride	 3,4-dimethoxybenzene-sulfonyl chloride	 4-nitrobenzene-sulfonyl chloride

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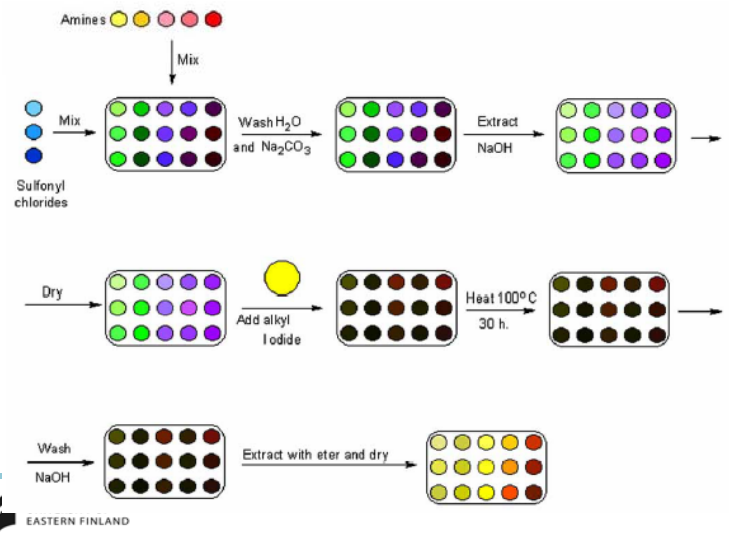
28

Automated parallel synthesis of a chemical combinatorial library of N,N-disubstituted sulfonamides.



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29

5HT-7 Receptor Binding Data Using, [3]H-5-CT.
***) 1 Micromolar **) 100nM ***) 10 nM Binding Affinity**

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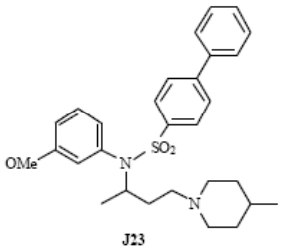
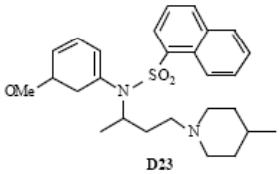
30

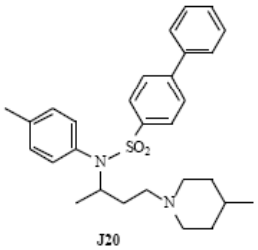
Selected potent 5-HT7 ligands



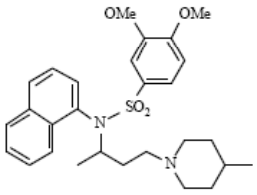
J23



D23

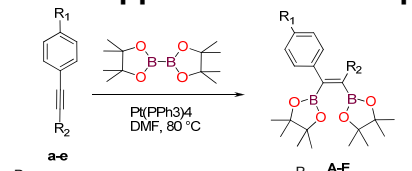


J20

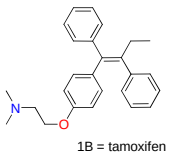


O24

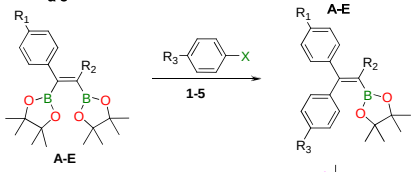
Parallel Synthesis of Tamoxifen and Derivatives on Solid Support via Resin Capture



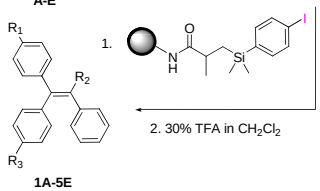
a/A: R1 = H, R2 = Me
b/B: R1 = H, R2 = Et
c/C: R1 = H, R2 = Pr
d/d: R1 = OMe, R2 = Me
e/E: R1 = OMe, R2 = Et



1B = tamoxifen



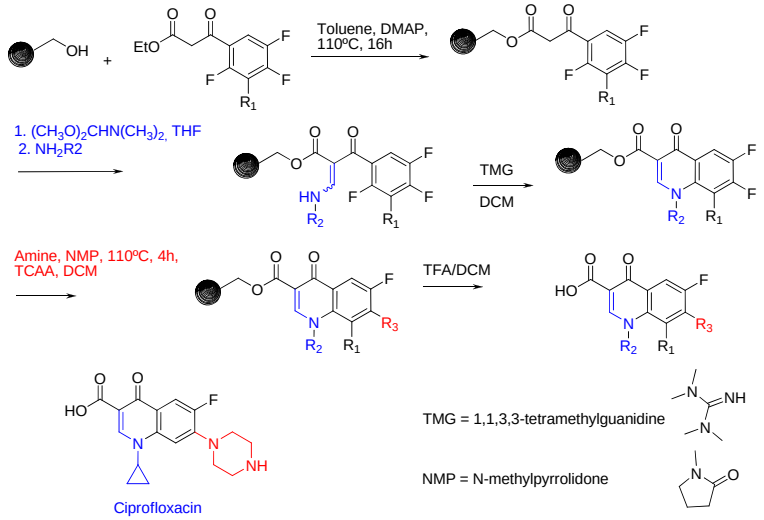
1: X = 1, R3 = $OCH_2CH_2N(Me)_2$
2: X = Br, R_3 = $OCH_2CH_2N(CH_2)_4$
3: X = Br, R3 = $CH_2CH_2N(Me)_2$
4: X = Br, R3 = $CH_2N(i\text{-}Pr)_2$
5: X = Br, R3 = $N(Me)_2$



- The resin was isolated by filtration and purified by washing.

J. Org. Chem., 62 (21), 7076 -7077, 1997

Solid Phase Synthesis of Quinolones



Tetrahedron Letters, 37, 4815-4818, 1996

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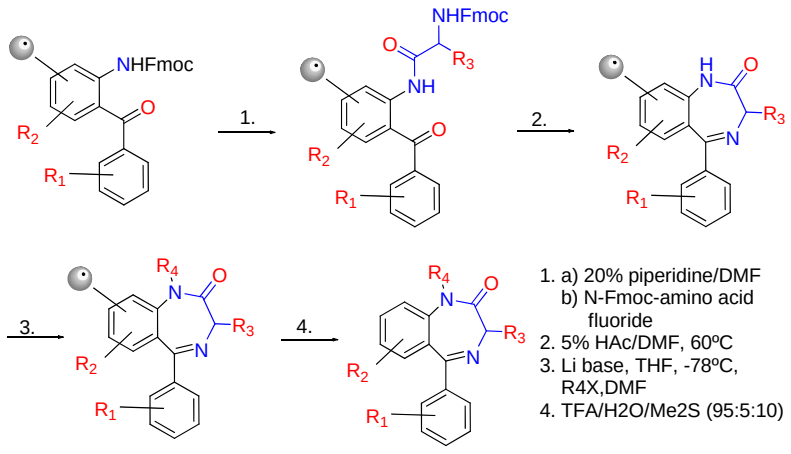
Solid phase synthesis of 1,4-benzodiazepines



1. a) 20% piperidine/DMF
   b) N-Fmoc-amino acid fluoride
2. 5% HAc/DMF, 60ºC
3. Li base, THF, -78ºC, R4X,DMF
4. TFA/H2O/Me2S (95:5:10)

B. A. Bunin and J. A. Ellman, *J. Amer. Chem. Soc*. **1992**, 114, 10997

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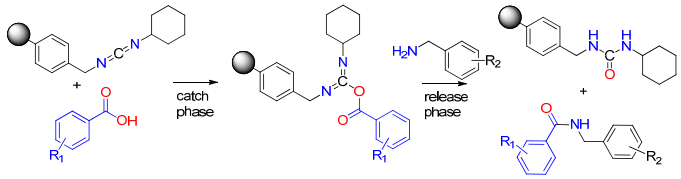
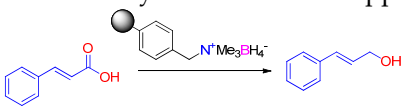
Reagents attached to solid support: catch and release

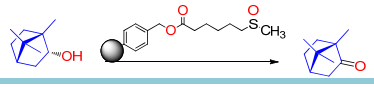
- 'Catch and release' during a coupling reaction



- Reduction of an aldehyde with a solid-supported borohydride reagent.



- Swern oxidation using a solid supported reagent



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35

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