Chapter 6: Combinatorial and parallel synthesis

Question 6.1
Identify three stages of the drug discovery, design, and development process where combinatorial chemistry or parallel synthesis is of importance.

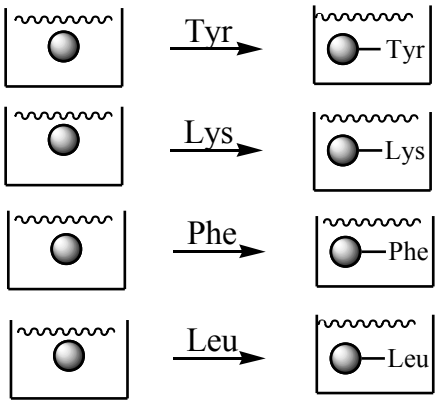
Answer
The identification of a lead compound; the generation of analogues for a study into structure-activity relationships; the generation of analogues aimed at optimising activity and other properties.

Question 6.1
A pharmaceutical laboratory wishes to synthesize all the possible dipeptides containing the amino acids tyrosine, lysine, phenylalanine, and leucine. Identify the number of possible dipeptides and explain how the lab would carry this out using combinatorial techniques.

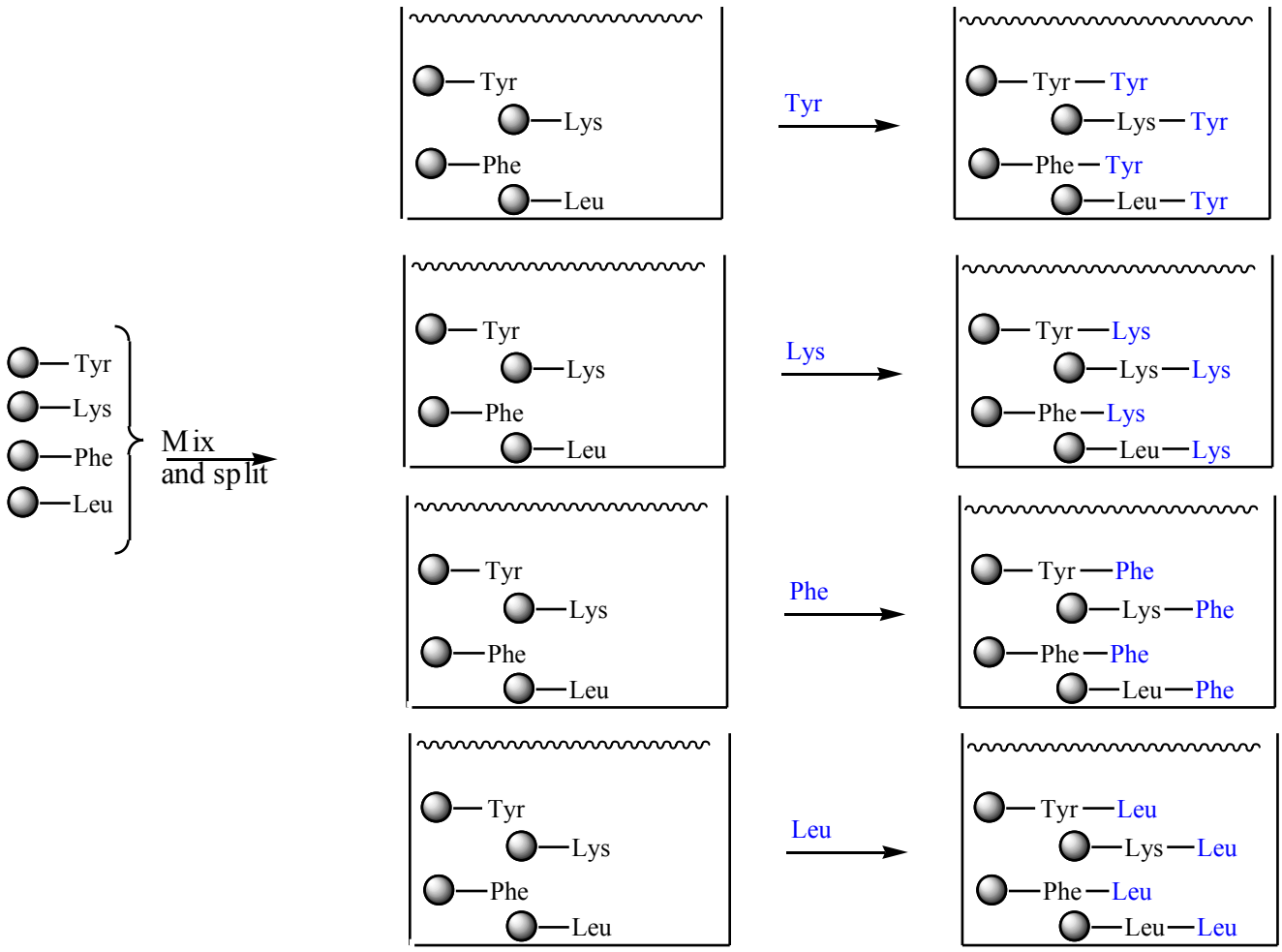
Answer
There are 16 possible dipeptides as follows
Tyr-Tyr; Tyr-Lys; Tyr-Phe; Tyr-Leu
Lys-Tyr; Lys-Lys; Lys-Phe; Lys-Leu
Phe-Tyr; Phe-Lys; Phe-Phe; Phe-Leu
Leu-Tyr; Leu-Lys; Leu-Phe; Leu-Leu

These could be synthesised by a parallel combinatorial synthesis where each dipeptide is made in a separate flask.
Alternatively, the 16 dipeptides could be generated by a mixed combinatorial synthesis using mix and split procedures. This would involve the following stages:

Add the four amino acids to resin in four separate reaction flasks.



Mix and split the beads amongst four separate reaction flasks. Each flask contains the same mixture. Add a different amino acid to each flask



All 16 peptides are now present in four separate reaction flasks. No two flasks contain the same dipeptide.
(Note that the peptide synthesis used would involve protection, coupling and deprotection stages, for example see figure 16.2))

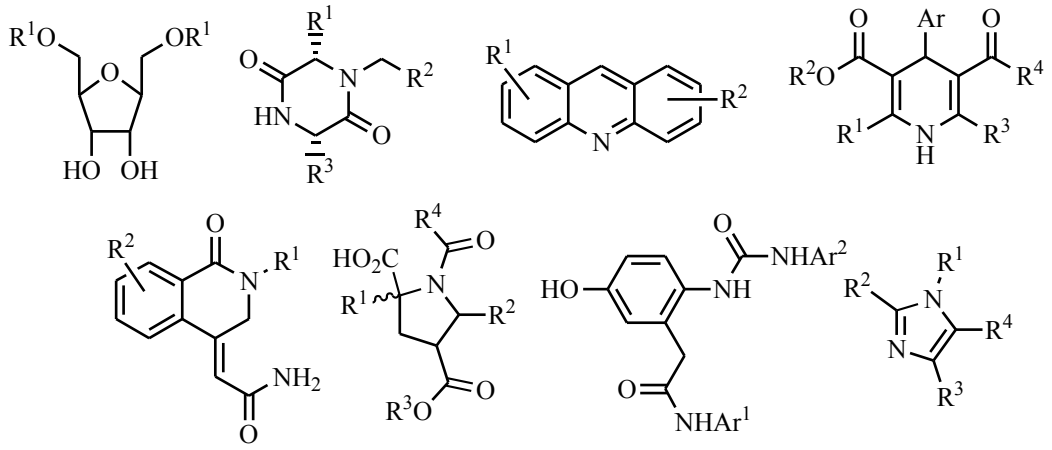
Question 6.3
What particular precautions have to be taken with the amino acids tyrosine and lysine in the above synthesis?

Answer
As stated in the previous question, normal procedures of peptide synthesis would be employed, involving protection, coupling and deprotection stages. Additional protection

strategies may be necessary for the amino acids tyrosine and lysine since these contain functional groups on their side chains. Tyrosine has a phenol group, while lysine has a primary amino group. Failure to protect these functional groups may lead to alternative reactions.

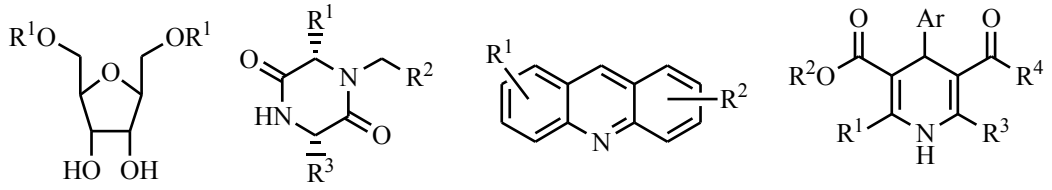
Question 6.4

Identify the advantages and disadvantages of the following structures as scaffolds.



Answer

In the following structures, it is assumed that the only variation allowed are the groups R^1-R^4.



I II III IV

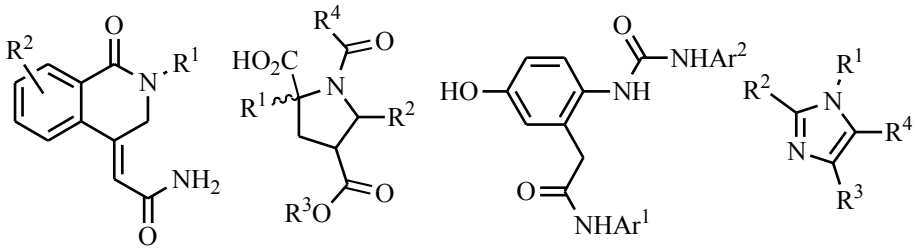
Structure I as illustrated is a poor scaffold since there is only limited variation allowed. There are two locations where variation can occur but the groups are identical. Moreover, the bottom half of the molecule is not varied at all. This is an example of a tadpole scaffold. If a synthesis could be devised that could lead to four different groups on all of the alcohol groups present in the structure, it would be a far better scaffold. However, distinguishing between four alcohol groups would not be easy.

Structure II is a good scaffold. The scaffold has a low molecular weight allowing flexibility in the sort of substituents that can be introduced. Three different substituents are allowed and they are not confined to one region of the molecule.

Structure III is not an ideal scaffold. Two different substituents are allowed at either end, and there are a variety of substituent positions allowed. However, the scaffold itself is

planar which places quite a restriction on the conformational space that can be explored round the molecule.

Structure IV is an excellent scaffold. It has a low molecular weight allowing a variety of substituents to be added. There are five variable substituents located right round the molecule, allowing an extensive search of the conformational space around it.



V VI VII VIII

Structure V is not ideal. There are only two variable positions and this limits the conformational space that can be explored. Moreover, the aromatic substituent must be in the plane of the aromatic ring.

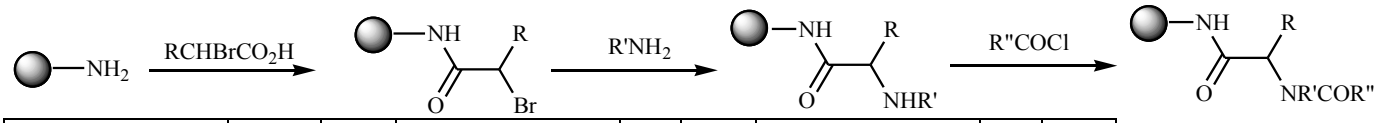
Structure VI is a good scaffold. The scaffold itself is small, and there are four variable positions evenly distributed around the molecule, allowing an extensive search of conformational space.

Structure VII is a poor scaffold. The molecule only has two variable positions. Both of these have to be aromatic rings and so the molecular weight of the molecule may be an issue.

Structure VIII is a good scaffold. The scaffold itself is small with a low molecular weight, and there are four variable substituents distributed round the ring.

Question 6.5
You wish to carry out the combinatorial synthesis shown in Fig. 6.40 using bar coding techniques rather than the conventional tagging scheme shown in the figure. You have nine molecules suitable for tagging purposes (A-I), seven bromo acids (B1-B7), seven amines (A1-A7), and seven acid chlorides (C1-C7). Construct a suitable coding system for the synthesis.

Answer



Bromoacid (R)	Tag	Code	Amine (R')	Tag	Code	Acid chloride (R")	Tag	Code
B1	A	100	A1	D	100	C1	G	100
B2	B	010	A2	E	010	C2	H	010
B3	C	001	A3	F	001	C3	I	001
B4	AB	110	A4	DE	110	C4	GH	110
B5	AC	101	A5	DF	101	C5	GI	101
B6	BC	011	A6	EF	011	C6	HI	011
B7	ABC	111	A7	DEF	111	C7	GHI	111

Question 6.6

Based on your coding scheme from Question 5, what product is present on the bead if the released tags resulted in the gas chromatograph shown in Fig. 6.41.

Answer

The code in figure 6.41 is 101, 110, 111

Based on the table above, this shows that the bromoacid used was B5, the amine used was A4, and the acid chloride used was C7