12

MOLECULAR VARIATIONS IN HOMOLOGOUS SERIES: VINYLOGUES AND BENZOLOGUES

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Methyl, ethyl, propyl, butyl … futile **Old adage**

I HOMOLOGOUS SERIES

The concept of a homologous series was introduced into organic chemistry by Gerhardt.[1] In medicinal chemistry the term has the same meaning, namely molecules differing one from another by only a methylene group.

II CLASSIFICATION OF THE HOMOLOGOUS SERIES

The most frequently encountered homologous series in medicinal chemistry are monoalkylated derivatives, cyclopolymethylenic compounds, straight chain difunctional systems, polymethylenic compounds and substituted cationic heads.

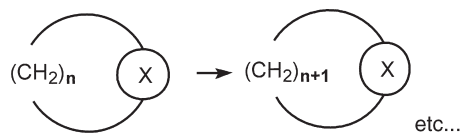
A Monoalkylated derivatives

$$R{-}X \rightarrow R{-}CH_2X \rightarrow R{-}CH_2{-}CH_2{-}X, \text{ etc...}$$

An example is provided by a series of neuraminidase inhibitors with a cyclohexene scaffold containing lipophilic side chains.[2]

As shown in Fig. 12.1, a 6300-fold increase in potency is observed when the hydroxylic hydrogen is replaced by a diethyl-methyl side chain. A comparable increase in potency is observed in a series of 1-methyl-1,2,3,4-tetrahydro-pyridyl-pyrazines described by Ward *et al.*[3] exhibiting M_1 muscarinic agonists. In changing from *O*-methyl to *O*-butyl, the affinity for the M_1 receptor varies from 850 nM to 17 nM. Another example is found in a series of 2-pyrone-derived elastase inhibitors.[4]

B Cyclopolymethylenic compounds



Examples of such structures with regularly increasing ring sizes are found for guanethidine (see Chapter 14), or for enalaprilat analogues (Fig. 12.2).[5] In the latter example, a

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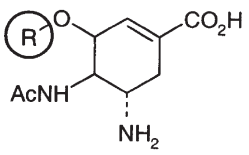
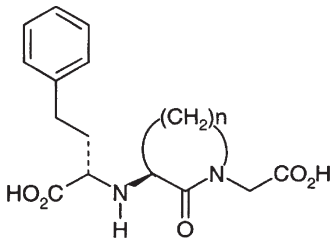


Neuraminidase inhibition	
R =	IC50 (nM)
H	6.300
CH_3 -	3.700
CH_3 - CH_2 -	2.000
CH_3 - CH_2 - CH_2 -	180
CH_3 - CH_2 - CH_2 - CH_2 -	300
$(CH_3)_2$ -CH_2 - CH_2-	200
CH_3 - CH_2 - $CH(CH_3)$ -	10
$(CH_3$ - $CH_2)_2$ - CH -	1
(CH_3 - CH_2 - CH_2) CH -	16
Cyclopentyl	22
Cyclohexyl	60
Phenyl	530

Fig. 12.1 Monoalkylated, cyclohexene-derived, neuraminidase inhibitors.



Size	IC_{50} (nM)
n = 2	19.000
n = 3	1.700
n = 4	19
n = 5	4.8
n = 6	8.1

Fig. 12.2 Angiotensine-convertase inhibiting potency of enalaprilat analogues.[5]

4000-fold increase in inhibition of angiotensin converting enzyme is obtained when changing from the five-membered ring ($n = 2$) to the eight-membered ring ($n = 5$).

Another example, published by scientists from Parke-Davis, relates to a series of 'dipeptoid' analogues of cholecystokinin.[6] These compounds are α-methyl-tryptophan derivatives, *N*-substituted by carbamic esters of cyclanols with ring sizes increasing from cyclobutyl to cyclododecyl (Fig. 12.3). Here again an optimal size was found (cyclononyl).

C Open, difunctional, polymethylenic series

$$X—(CH_2)_n—Y \rightarrow X—(CH_2)_{n+1}—Y$$

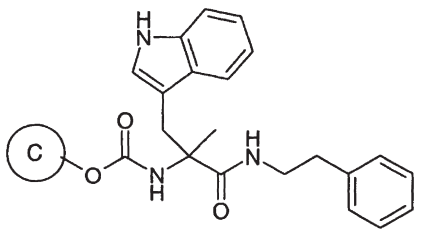
In the above general formula, X and Y can represent very diverse functional elements. The compounds can be symmetrical ($X = Y$; 'dimers') or non-symmetrical ($X \neq Y$); see Chapter 15. Usually, X and Y represent *polar functions* or *functionalized cyclic systems*.

When X and Y are polar functions, they are made essentially from functional groups such as alcohols, amines, acids, amides, amidines or guanidines (Fig. 12.4). A classical representative of a difunctionalized, symmetrical compound is decamethonium.

When X and Y are functionalized cyclic systems, they can be alicyclic or aromatic, as well as homocyclic or heterocyclic (Fig. 12.5). In any case they bear some polar function or polar element. An example of this type of compound is pentamidine.

Other examples are symmetrical bradykinine antagonists[7] and symmetrical lexitropsines (netropsine, distamycine), active against HIV-I viruses.[8] Non-symmetrical polymethylenic thromboxane synthetase inhibitors are described by Press *et al.*[9] The compounds contain a thiophen-2-carboxamide moiety, separated from an imidazole ring by 3 to 8 methylene units. Surprisingly, whereas most of the compounds show similar thromboxane-synthetase inhibiting activities, only the two medium-sized ones ($n = 3$ and $n = 4$) showed hypotensive effects in spontaneously hypertensive rats (Fig. 12.6).

In a series of benzimidazole-derived thromboxane A_2 receptor antagonists described by Nicolaï *et al.*,[10] the crucial element is the distance between the carboxylic group and the benzimidazole ring. A 200-fold increase in affinity was observed when changing from propionic to a butyric side chain (Fig. 12.7).



C	log P	IC_{50} (nM)
cyclobutyl	3.88	12100
cyclopentyl	4.44	5170
cyclohexyl	5.00	520
cycloheptyl	5.55	190
cyclooctyl	6.11	125
cyclononyl	6.67	85
cyclodecyl	7.23	247
cyclododecyl	8.34	1437

Fig. 12.3 Optimal ring size for a series of cyclanol carbamates.[6]

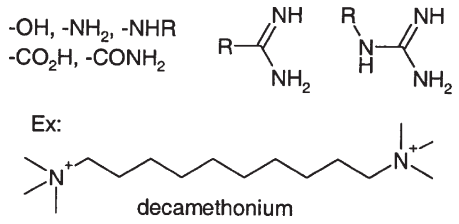


Fig. 12.4 Examples of functional groups encountered in open, difunctional, polymethylenic compounds and structure of decamethonium.

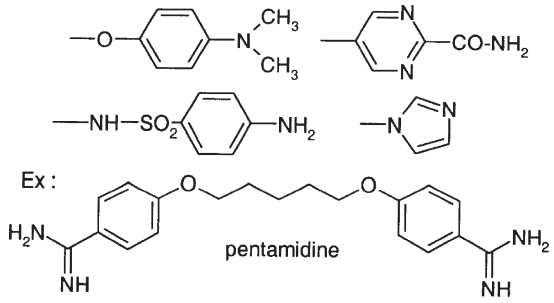
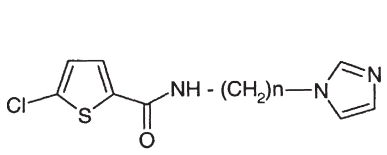
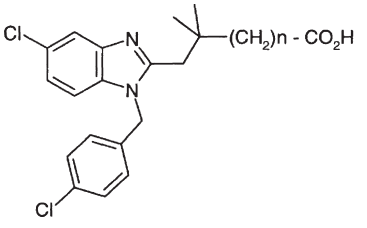


Fig. 12.5 Examples of functionalized rings found in straight chain, difunctional, polymethylenic compounds. Structure of pentamidine.



Size	IC_{50} (nM)
n = 3	600
n = 4	200
n = 5	200
n = 6	200
n = 8	70

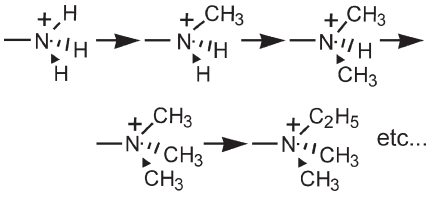
Fig. 12.6 Thromboxane synthetase inhibiting activity of a series of *N*-(imidazolyl-alkyl)-thiophene-5-carboxamide.[9]



Size	IC_{50} (nM)
n = 0	1700
n = 1	7.8
n = 2	20

Fig. 12.7 Affinity for the thromboxane A_2 receptor.[10]

D Substituted cationic heads



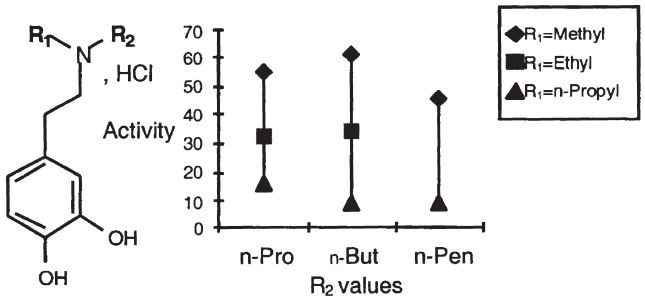


Fig. 12.8 Anticataleptic activity of substituted dopamines.[11]

With cationic head groups, homology simultaneously achieves a progressive increase in bulkiness and in lipophilicity. Figure 12.8 illustrates the influence of increasing bulkiness around the dopamine nitrogen in the antagonism of reserpine-induced catalepsy in mice.[11]

III SHAPES OF THE BIOLOGICAL RESPONSE CURVES

The most common curves are bell-shaped, the peak activity corresponding to a given value of the number *n* of carbon atoms (curve A, Fig. 12.9). However, many other relationships were found among homologous series:

(1) The activity can increase, without any particular rule, with the number of carbon atoms (curve B).
(2) The biological activity can alternate with the number of carbon atoms, resulting in a zigzag pattern (curve C).
(3) In other series the activity increases first with the number of carbon atoms and then reaches a plateau (curve D).
(4) The activity can also decrease regularly, starting with the first member of the series (curve E). This was found for the toxicity of aliphatic nitriles or for the antiseptic properties of aliphatic aldehydes.
(5) A last possibility resides in inversion of the pharmacological activity accompanying the increase in the number of carbon atoms (not shown in Fig. 12.9; this will be discussed below).

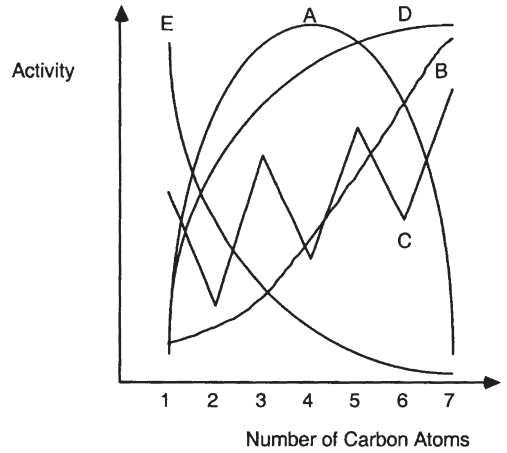


Fig. 12.9 Shapes of the biological response curves in homologous series.

IV RESULTS AND INTERPRETATION

A Curves with a maximum activity peak (bell-shaped curves) and curves with a continuous increase of activity

In such series the continuous growth of an alkyl chain or of methylene units increases the hydrophobic part of the molecule. Various physicochemical parameters, such as solubility in water, partition coefficients, chromatographic R_f values, and critical micellar concentration, are precisely governed by the same fundamental property: the hydrophobic character.

Bell-shaped curves

Curves with an activity maximum are the most common ones, it is currently admitted that they reflect the existence of an optimal partition coefficient associated with the easiest crossing of the biological membranes. The relationship between the biological response and the partition coefficient is then illustrated by a parabolic curve. An example is found in structural analogues of PAF-acether.[12] In varying the length of the alkoxy chain from *n*-butyl to *n*-eicosanyl, the authors observed the peak activity for the *n*-hexadecyl chain, with a 1200-fold interval between the most and the least active compounds (Fig. 12.10). The drop in activity observed for the descending branch, is usually attributed to insufficient solubility in water (incapability to cross the aqueous biophases), but can also be due to the formation of micelles. In this case, the concentration of the free drug, which represents the directly available form, lies under the critical threshold level. Bell-shaped curves are also seen when using isolated cells for which it can be demonstrated that the receptor is outside the membrane. In this case the dominant factor is probably not the crossing of biological membranes. Changes in critical micellar concentration with increasing chain length could explain the effect in some cases, however the curve is often too steep for this to be an acceptable explanation. Another possibility is that there is a lipophilic pocket of finite size. In many cases this pocket is not actually in the receptor protein. An argument in favour of this explanation is that the top of the bell is at C_{16} or C_{18} which fits with the length of the alkyl chains making up part of the bilayer, examples being PAF-acether analogues[12] and leucotriene D_4 agonists/antagonists. Another bit of evidence that supports this idea is the observation that the position of the peak of the curve can vary depending on which cell type is expressing the same receptor protein.

The study of the activities of *some* homologous compounds, can, through interpolation, identify which term is associated the highest potency. The optimization method proposed by Bustard,[13] makes use of the Fibonacci numbers, and allows the identification of the most active compound (presumed to exist in a given interval) with the smallest possible number of syntheses (see also References 14 and 15).

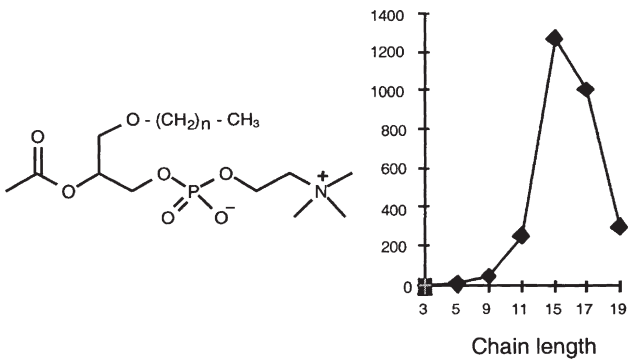


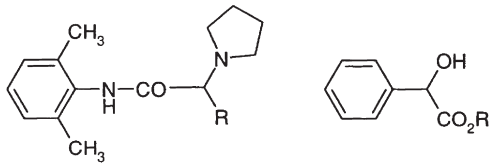
Fig. 12.10 Antiaggregant activity of structural analogues of PAF-acether.[12]

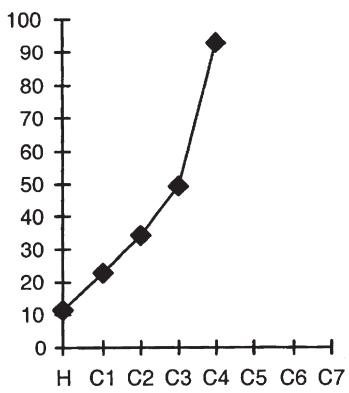
Apparently continuous increase

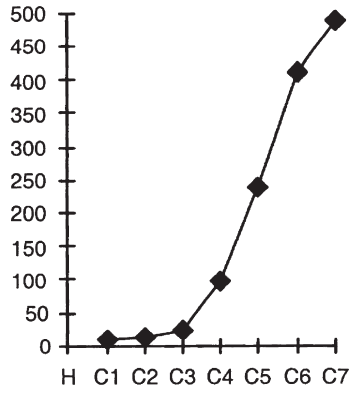
Actually, an apparently continuous increase of activity may correspond simply to the ascendant branch of the parabola (see the two curves in Fig. 12.11). The observed 'pseudo-linear' curve usually occurs in an insufficiently explored series. A true linear correlation would imply the existence of compounds of infinite potency!

B Non-symmetrical curves with a maximum activity peak

In some instances curves with maximum activity peaks are not symmetrical and one side shows very sharp activity







R	Duration of Anaesthesia in Rabbit Cornea (min.)
Hydrogen	11
Methyl	23
Ethyl	34
Propyl	49
Butyl	93

R	Spasmolytic Activity on Guinea-Pig Isolated Gut
Methyl	8
Ethyl	12
Propyl	24
Butyl	98
Pentyl	240
Hexyl	410
Heptyl	490

Fig. 12.11 Local anaesthetic activity[16] and spasmolytic activity[17] in homologous series.

variations, whereas the other one corresponds to a progressive variation. The shape of such a curve is represented on Fig. 12.12.

For the $GABA_A$ antagonists represented in Fig. 12.13, the peak activity corresponds to the branching of a *butyric* side chain on the aminopyridazine system. The affinity diminishes drastically for shorter chains, but very progressively for longer chains.[18]

The particular case of polymethylenic bisammonium compounds

Compounds having the general formula $(CH_3)_3N^+—(CH_2)_n—N^+(CH_3)_3$ usually have high affinity for the cholinergic receptors. When the values of n are intermediary ($n = 5$ or 6: penta- or hexamethonium), such compounds behave like cholinergic *agonists* (towards the sympathic ganglions). For higher values ($n = 10$: decamethonium)

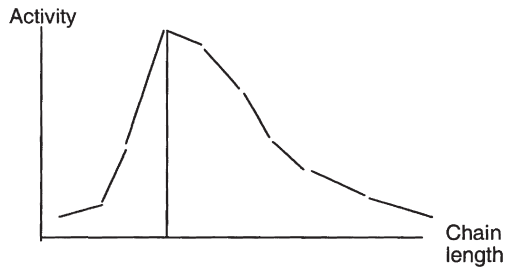


Fig. 12.12 Non-symmetrical curve with a maximum activity peak.

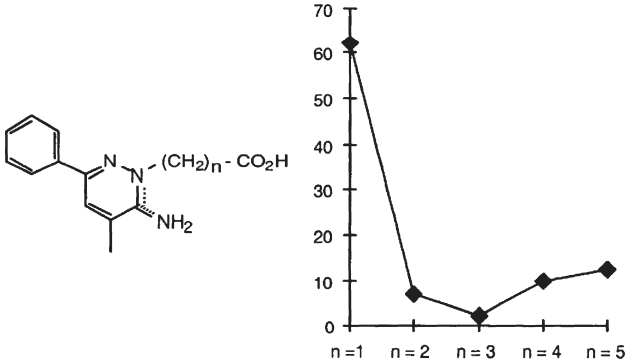


Fig. 12.13 Affinity of $GABA_A$ antagonists for the $GABA_A$ receptor site.[18]

the compounds become *antagonists* of acetylcholine (at the muscular end plate). In both cases increasing acetylcholine levels displace them from their binding sites. When considering the neuro-muscular blockade, one observes again a curve with an asymmetric profile: sudden changes between $n = 6$ and $n = 8$, and then progressive diminution between $n = 9$ and $n = 12$.

To explain this, if we suppose that compounds of general structure X—$(CH_2)_n$—Y interact by means of their polar groups X and Y with complementary groups at the receptor, four interaction schemes can be envisaged, depending on the value of n (Fig. 12.14: (1–5)):

(1) *n is small:* The molecule is too short and only one of its polar ends can establish an interaction with the complementary sites of the receptor (Fig. 12.14: (1)). The molecule will be inactive or poorly active. This is the case for the pyridazinyl-glycine of Fig. 12.13.

(2) *n possesses sufficient length:* A good interaction can be established with complementary sites of the receptor and trigger off the biological response (Fig. 12.14: (2)). This represents the optimal case.

(3) *n is too great:* Two situations are foreseeable. If the molecule is rigid or if there is steric hindrance, the interaction is not possible for Y (Fig. 12.14: (3)). If the molecule is flexible and if the steric tolerance is sufficient, the fit can be entirely satisfactory (Fig. 12.14:(4)).

(4) *n is very great:* In this case (Fig. 12.14: (5)), the fit with the receptor is again very good, but with a further located subsite Y$''$ instead of Y$'$, the substance can then behave as an *antagonist* (this was the case discussed above of decamethonium).

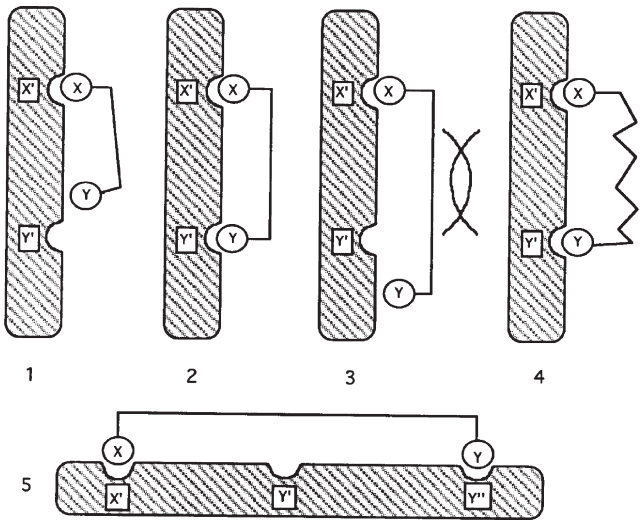


Fig. 12.14 Different modes of interaction of bifunctional molecules according to their length.

C Serrated variations

One sometimes observes alternating (serrated) variations of activity (zig-zag curves) according to whether the number of atoms of carbon is even or odd. Such an example is found for antimalarials derived from methoxy-6-amino-8-quinoline (Fig. 12.15).

For these derivatives the antimalarial activity is greater if n represents an odd number (for studied values that vary from $n = 4$ to $n = 10$).[19] Another example is provided by leukotriene B_4 antagonists derived from hydroxyacetophenones[20] (Table 12.1).

For both cases, the findings are a reflection of the rotational energy curves for adjacent CH_2 groups. Similar observations were made in a series of 4,4$'$-dimethylaminodiphenoxyalkanes tested as potential schistosomicides.[21] For diamines where $n = 4$ to $n = 10$, the activity on the schistosomes varies in alternate manner (Fig. 12.16). Alkyl-linked bis(amidinobenzimidazoles) with an even number of methylenes connecting the benzimidazole rings have a higher affinity for the minor groove of DNA than those with an odd number of methylenes (Fig. 12.16).[22] Serrated variations of acetylcholinesterase inhibiting activity were also observed for donepezil analogues (Fig. 12.16).[23]

Zig-zag variations are well known in homologous series for physical properties such as melting points and solubilities. Thus, propane, with an odd number of carbon atoms, melts at $-189.9\,°C$ whereas butane, with an even number, melts 51.6 °C higher at $-138.3\,°C$. However, odd-numbered pentane melts at $-129.7\,°C$, only 8.6 °C higher than butane. Boese[24] studying X-ray structures of *n*-propane to *n*-nonane at $-90°C$ indicate that the methyl groups on chains lying end-to-end are the culprits. In even-numbered

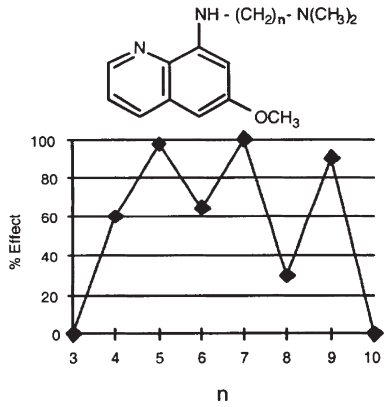
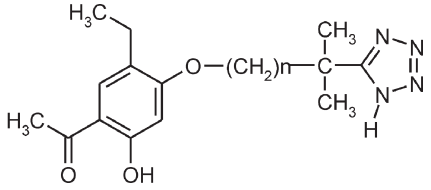


Fig. 12.15 Antimalarial activity in a homologous series of bifunctional methoxy-6-amino-8-quinolines (after Magidson and Strukov[19]).

Table 12.1 *Zig-zag variations of the affinity of hydroxyacetophenone derivatives for the human peripheral neutrophils. Inhibition of [^{3}H] LTB$_4$ binding at 0.1 mM*[20]



n = length of the methylene chain	% inhibition of [^{3}H] LTB_4 binding at 0.1 μM
3	28
4	17
5	56
6	13
7	49

chains the methyl groups dovetail nicely and stay out of one another's way. However in odd-numbered chains methyl groups on one end can only avoid one another by increasing the distance between chain ends. This less-than-tight packing in odd-numbered chains apparently results in their anomalous melting points. In the examples above, the alkyl chain represents a spacer group between two binding groups. In some cases it can be shown that the energy required to fold the molecule to obtain the required separation should change in a zig-zag manner with increasing chain length.

In the biological domain, variations of activity are not necessarily linked to the induction of effects at the level of a given receptor, but could have come from a pharmacokinetic factor (urinary or biliary excretion, plasma protein binding, differential metabolism). A case of differential metabolism is illustrated by the comparison of the toxicities of odd and even ω-fluoro acids.[25] The β-oxidation of odd chain length compounds leads to the extremely toxic fluoroacetic acid, while that of the acids with even numbers of carbon atoms generates β-fluoropropionic acid which is clearly less toxic (Table 12.2).

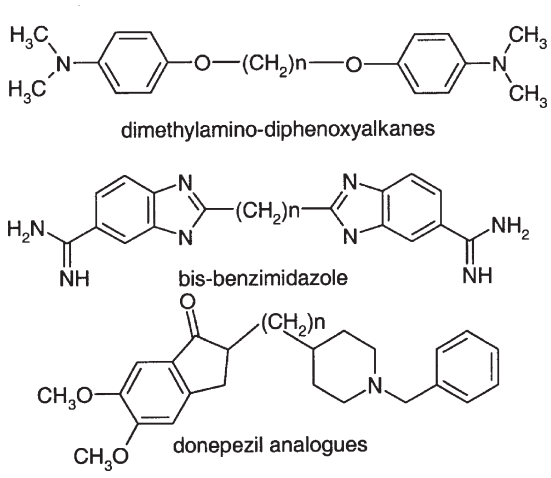


Fig. 12.16 4,4′-Dimethylamino-diphenoxyalkanes,[21] alkyl-linked bis(amidinobenzimidazoles),[22] and donepezil analogues.[23]

D Inversion of the activity

It can happen that the lower members of a series possess one activity profile and that the higher terms possess a different activity, which contrasts with that of the lower members.

This phenomenon is particularly observed when the bulkiness of cationic heads is progressively increased. In *N*-alkylated derivatives of norepinephrine,[26] progressive alkylation reduces the hypertensive activity according to the sequence: —NH_2, —NHMe, —NHEt, —NH-NPro. Finally, the molecules become hypotensive for the values: —NH-IsoPro, —NH-nBu and —NH-IsoBu (Table 12.3).

This anomaly is explained by the fact that norepinephrine can interact with two subclasses of receptors (α- and β-adrenergic receptors). The less hindered derivatives are able to bind to both α- and β-receptors, hindered ones solely to β-receptors. A similar inversion of properties is observed when the cholinergic agonist carbachol is modified by dibutylation at the carbamate function and exchange of one of its methyl groups for an ethyl group (Fig. 12.17). The analogue, dibutoline, is a powerful cholinolytic.

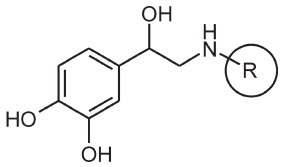
In morphine (agonist), the replacement of the *N*-methyl group by a more bulky radical such as *N*-allyl, *N*-cyclopropyl-methyl or *N*-cyclobutyl-methyl leads to powerful antagonists of the opiate receptors (see Chapter 19: Unsaturated Groups).

Introduction of bulkiness in a cationic head does not always cause a change from agonist to antagonist.

Table 12.2 *Zig-zag variations of the toxicity of aliphatic ω-fluoro derivatives (LD_{50} for mice in mg kg^{-1} intraperitoneally)*[25]

n	$F(CH_2)_nCOOH$		$F(CH_2)_nCO$		$F(CH_2)_nCOH$		$F(CH_2)_nCH_3$	
	Odd	Even	Odd	Even	Odd	Even	Odd	Even
1	6.6		6		10			
2		60				46.5		
3	0.65		2		0.9			
4		>100		81		>100		
5	1.35		0.58		1.2		1.7	
6		40		>100		80		35
7	0.64		2		0.6		2.7	
8		>100		53		32		21.7
9	1.5		1.9		1		1.7	
10		57		>40		>100		15.5
11	1.25				1.5		2.5	

Table 12.3 *Gradual inversion of the activity in a homologous series*[26]



	Blood pressure of the cat	
R	Hypertensive	Hypotensive
Hydrogen	++	−
Methyl	++	−
Ethyl	+	+
Propyl	−	+
Isopropyl	−	++
Butyl	−	++
Isobutyl	−	++

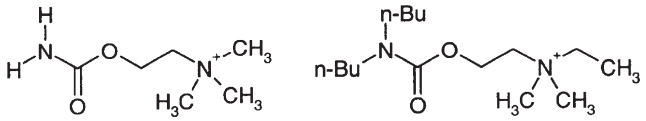


Fig. 12.17 Carbachol (left) and dibutoline (right).

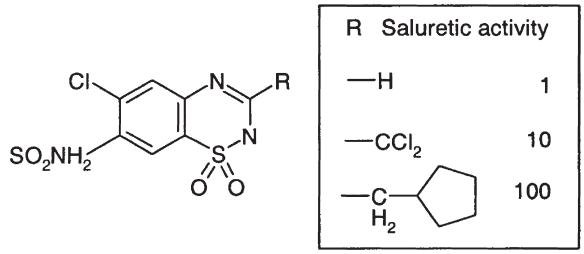


Fig. 12.18 Tolerance to bulkiness.[27]

Thus the analogue *N*-propyl-apomorphine is a more powerful dopaminergic agonist than the apomorphine itself. The creation of bulkiness is obviously not limited to cationic head groups and lipophilic groups can be attached to any other part of the molecule (Fig. 12.18).[27]

E Conclusion

Variations in homologous series generally relate to the search for optimal lipophilicity. In the cyclo-polymethylenic series, conformational problems may be added. For difunctional polymethylenic derivatives, intercharge distances and, possibly, elements of symmetry (see Chapters 16 and 28) can take over. Whereas the activity profile is generally preserved during homology changes, very large differences in potency can be found, that confound the old adage 'methyl, ethyl, propyl, butyl … futile'.

V VINYLOGUES AND BENZOLOGUES

The vinylogy principle was first formulated by Claisen in 1926,[28] who observed for formylacetone acidic properties similar to that of acetic acid. The vinyl group plays the role of an electron-conducting channel between the carbonyl and the hydroxyl group. The same effect explains the acidity of ascorbic acid (Fig. 12.19).

Today the vinylogy principle is explained by the mesomeric effect and it applies to all conjugated systems: imine and ethynyl groups, phenyl rings, aromatic heterocycles (Fig. 12.20). For a review of the chemical aspects of the vinylogy principle see Krishnamurthy.[29]

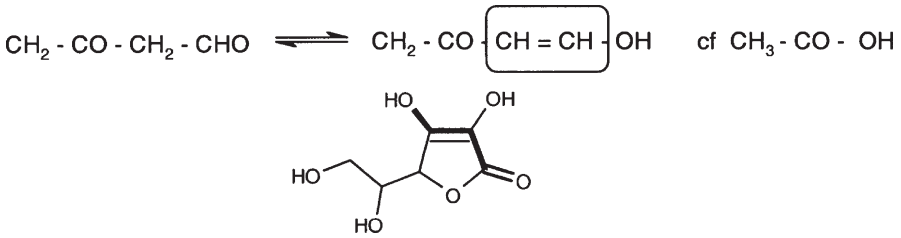


Fig. 12.19 Formylacetone (enolic form) and vitamin C are comparable in acidity to carboxylic acids.

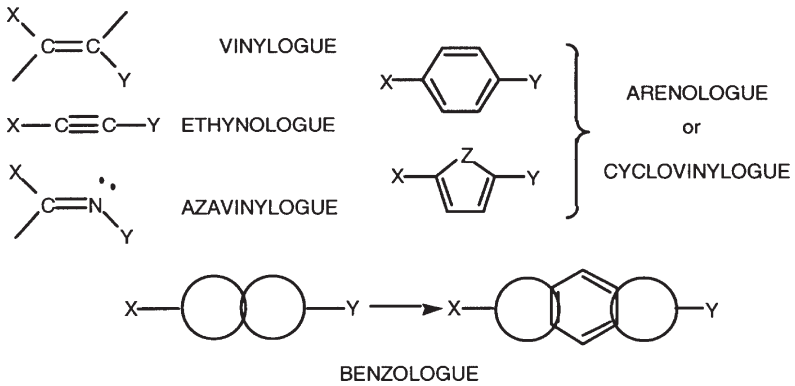


Fig. 12.20 Vinylogy and its extensions.

A Applications of the vinylogy principle

Although numerous applications of the vinylogy concept are found in the medicinal chemistry literature, only a very few of them are of practical interest, mainly because the preparation of vinylogues usually leads to compounds which are more sensitive to metabolic degradation and more toxic (reactivity of the conjugated double bond) than the parent drug, without being more active.

Authentic vinylogues

The vinylogues of phenylbutazone,[30] and of pethidine (C. G. Wermuth, unpublished results) have the same type of activity as the parent drug, but the duration of action, especially for the pethidine analogue, is notably shorter than that of the initial molecule (Fig. 12.21). This is probably due to the easier metabolic degradation of the styryl double bond.

In preparing the vinylogues of acetylcholine (Fig. 12.21), Tenconi and Barzaghi[31] succeeded in separating the nicotinic from the muscarinic activity (Table 12.4).

Tolcapone (Fig. 12.22) was designed as an inhibitor of the enzyme catechol *O*-methyltransferase useful in the L-DOPA treatment of Parkinson's disease.[32] In avoiding the methylation of L-DOPA, as well as that of dopamine it prolongs the beneficial activities of these molecules.

Catechol *O*-methyltransferase inhibition therefore represents a valuable adjuvant to L-DOPA decarboxylase inhibition. Unfortunately, tolcapone exhibited severe liver damage and had to be removed from the market. The corresponding vinylogue entacapone is devoid of these side-effects.[33]

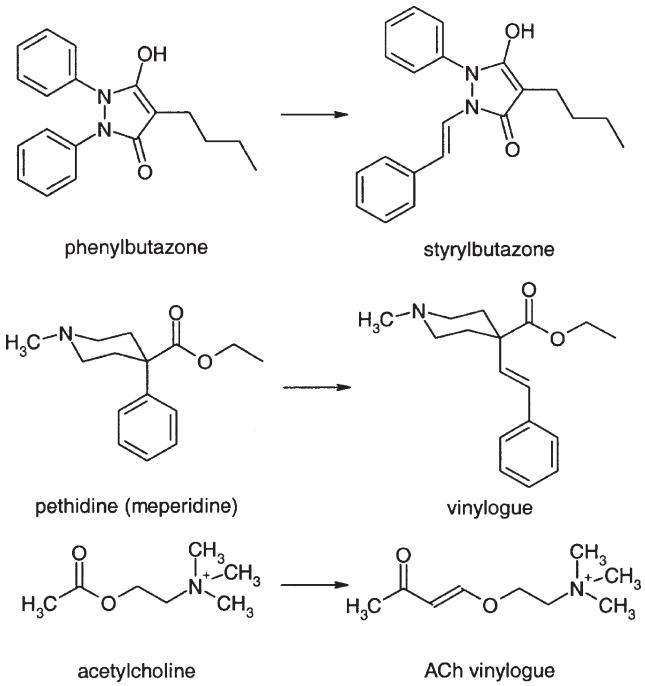


Fig. 12.21 Vinylogues of phenylbutazone, pethidine and acetylcholine.

Table 12.4 *Cholinergic profile of the vinylogue of acetylcholine*[31]

Compound	Nicotinic activity	Muscarinic activity	Sensitivity to ACh-esterase
ACh	+	+	Sensitive
Vinylogue	+	Insensitive	Insensitive

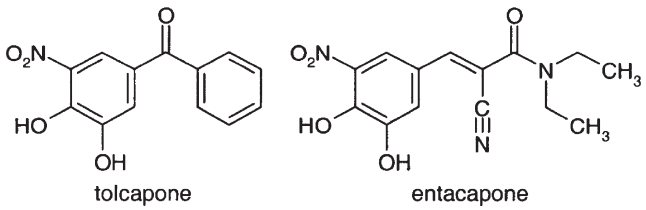


Fig. 12.22 The vinylogy principle applied to the catechol *O*-methyltransferase inhibitor tolcapone.

Wright *et al.*[34] describe a series of hydroxamic acid vinylogues acting as dual inhibitors of 5-lipoxygenase (5-LO; $IC_{50} = 0.15 \times 10^{-6}$ M) and of interleukin-1β (IL-1β) biosynthesis ($IC_{50} = 2.8 \times 10^{-6}$ M) which might be useful as anti-inflammatory drugs (Fig. 12.23).

For such compounds several possible isomeric and tautomeric forms can be considered. These include the (E) and (Z) geometrical isomers (a and b), as well as the tautomers nitrone (c), 5-hydroxy-isoxazolidine (d), and oxaziridine (e). Examination of the ^{1}H and ^{13}C NMR spectra of the vinylogues revealed that each of the tautomeric possibilities are present in solution in varying proportions. The relative proportion of each isomer was found to be dependent upon the solvent, the pH, and its chemical structure.

In order to design compounds able to react covalently with the nucleophilic cysteine of human 3C rhinovirus protease, scientists from Agouron designed vinylogous derivatives of the prototype inhibitor 3-carbamoyl-benzaldehyde (Fig. 12.24). In this particular case Michael acceptor reactivity is eventually the wanted feature.[35]

Ethynologues

Some ethynologues of biologically active compounds were prepared by Dunoguès and his group, unfortunately they did not describe their biological activity: aspirin ethynologue,[36] nicotinamide and isoniazide ethynologues,[37] chalcones ethynologues.[38] In some way the cholinergic antagonist oxotremorine can be considered as an ethynologue of the acetylcholine pharmacophore (Fig. 12.25).

Azavinylogues

As a rule, simple azavinylogues are unstable compounds, due to the easy hydrolysis of the imino bond. However the particular case of *O*-alkylated oximes (X—CH=N—O—Y; with Y=R or Ar) can be interesting insofar as the oximic imino bond was shown to be biostable.[39] Preparing azavinylogues of β-blocking agents (Fig. 12.26) led to some active compounds.[40–42] The proposal was made that the stable oxime C—$NOCH_2$ could mimic a portion of an aromatic ring, thus simulating an aryl or an aryloxymethylene group.[43]

Reduction of the imino bond results in a decrease but not a loss of activity and ether derivatives retain activity.[42] Tricyclic oxime β-blockers showed high selectivity for β_2 receptors.[40,41] Noxiptyline (Agedal®, Bayer) is the oximic equivalent of amitriptyline (for review see Hoffmeister;[39,44] for crystal structure see Bandoli[45]).

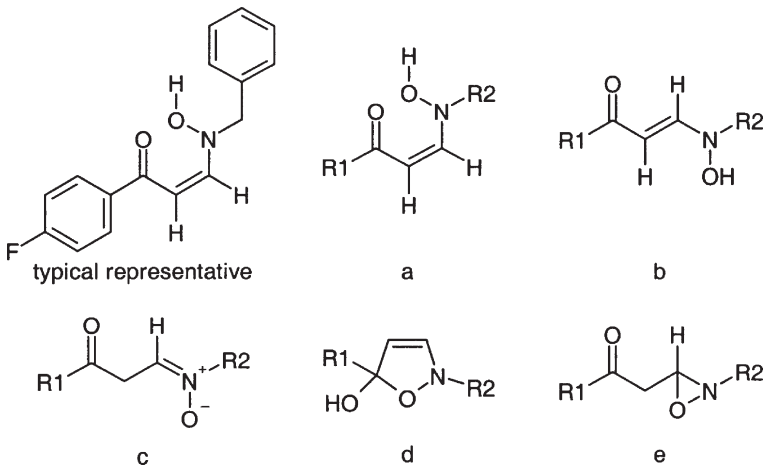


Fig. 12.23 Hydroxamic acid vinylogues and their various isomeric forms.[34]

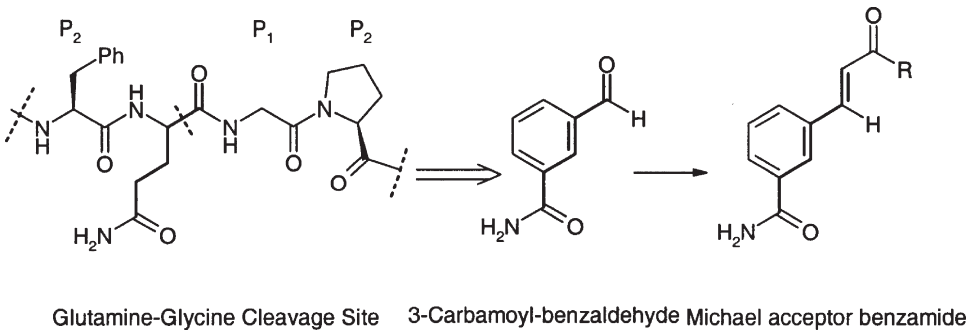


Fig. 12.24 Cinnamic derivatives as vinylogues of benzaldehyde.[35]

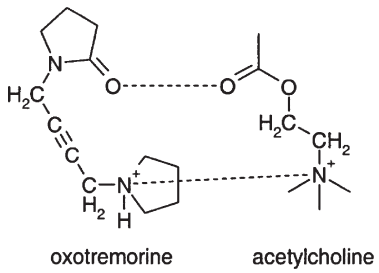


Fig. 12.25 Oxotremorine is an ethynologue of the acetylcholine pharmacophore.

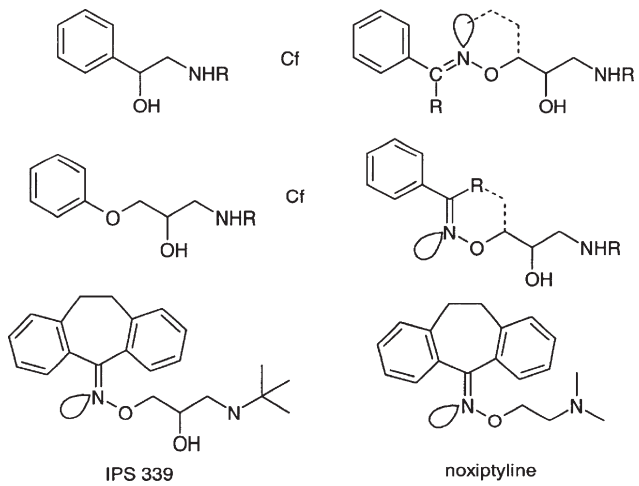


Fig. 12.26 Oxime ethers as azavinylogues.

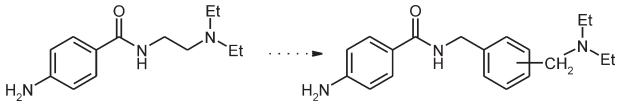
Cyclovinylogues

These vinylogues have the advantage of being more stable towards *in vivo* metabolism. In addition they allow molecular variations with *ortho*, *meta* and *para* positional isomers. Thus, for cyclovinylogues of procainamide, the highest local anaesthetic activity was found with the *meta* derivative, which also showed the best dissociation between local anaesthetic and antiarrhytmic activity (Table 12.5).[46]

Similar results were observed with cyclovinylogues of lidocaine.[47] For other references, see Valenti *et al.*[48] Compound TA-1801 (Ethyl 2-(4-chlorophenyl)-5-(2-furyl)-4-oxazoleacetate),[49] can to some extent be considered as an arenologue of clofibrate (Fig. 12.27).

Pyrroline-3-ones were used as peptidic bond surrogates by Hirshman and his group.[50] In such compounds (Fig. 12.28), thanks to vinylogy, the carbonyl and the

Table 12.5 *Cyclovinylogues of procainamide, relative activity with regard to procainamide*[46]



Compound	Local anaesthetic power	Antiarrhytmic activity
Procainamide	1	1
Ortho-cyclovinylogue	~0	0.17
Meta-cyclovinylogue	47	0
Para-cyclovinylogue	35	0

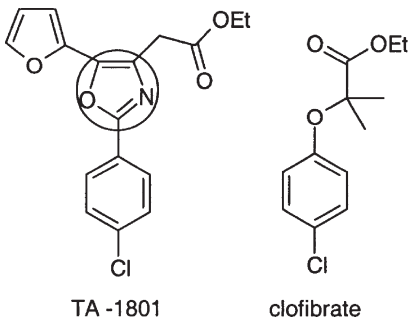


Fig. 12.27 TA-1801, an arenologue of clofibrate.[49]

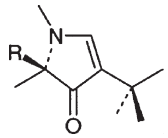


Fig. 12.28 The vinylogous relationship between the carbonyl and the amino group in pyrroline-3-ones gives them the reactivity of secondary amides.[50]

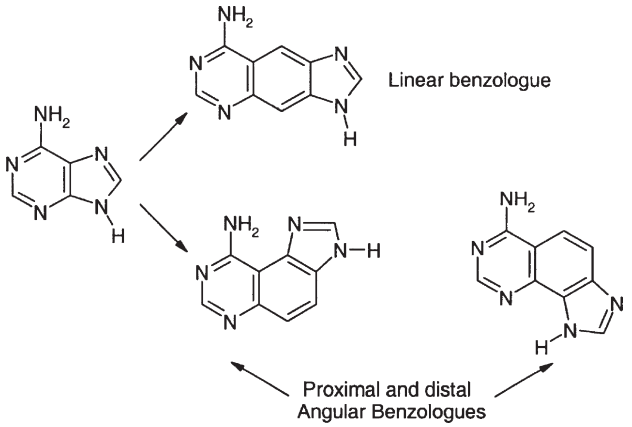


Fig. 12.29 Linear and angular adenine benzologues.

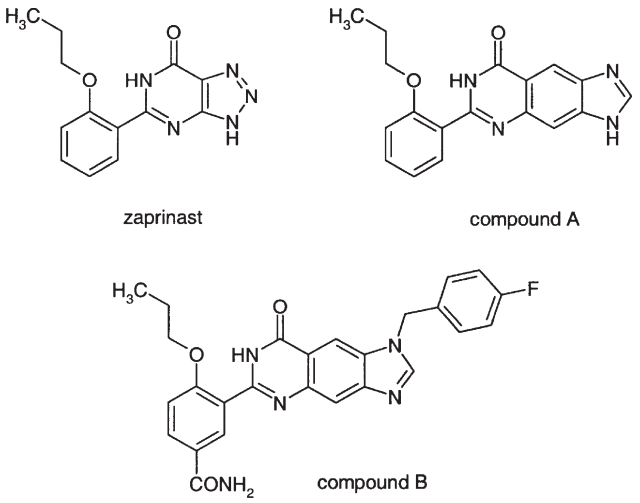


Fig. 12.30 Linear benzologues derived from zaprinast.[58]

amino group show the same chemical reactivity to that of a secondary amide.

Benzologues

Linear and angular benzologues of guanine[51] and adenine,[52–54] were published without any indication of biological activity (Fig. 12.29). A review article on chemistry and biochemistry of benzologues was published by Leonard and Hiremath.[55] More recently, linear and angular benzologues of xanthines showed submicromolar affinities for rat brain A_1 and A_2 adenosine receptors[56] and benzologues of quinolone antibacterials maintained high antimicrobial activity.[57]

A very convincing example of the usefulness of benzologues is provided by the synthesis of compound 'A', a linear benzologue of the prototypical PDE-5 inhibitor zaprinast and its optimization to potent and selective PDE5 inhibitors such as 'B'(Fig. 12.30).[58]

B Comments

Due to important changes in geometry, vinylogues often have unpredictable activity. For this reason vinylogues play a minor role in medicinal chemistry. In addition, their metabolic vulnerability or their increased toxicity may represent a significant drawback.

However, the vinylogy principle is sometimes applied to the design of bioisosteres. Thus the guanidinic group of the benzimidazole fenbendazole[59] can be compared with its vinylogue[60] in the corresponding imidazo[1,2-*a*]pyridine (Fig. 12.31). Both compounds are anthelminthics of similar potency.

The vinylogy principle can account for unexpected chemical reactivity that is not always recognized at first glance (Fig. 12.32). So, for example the basicity of the N1 nitrogen is strengthened in compound CGS 8216 thanks to the vinylogous influence of the quinoline nitrogen. For a similar reason, the carbonyl group of benzopiperidones or of 3-acyl-indoles behaves chemically more like an amidic carbonyl than a ketonic one. In 2-methoxy-*para*-benzoquinone the reactivity of the methoxy group is that of a carboxylic ester, rendering it susceptible to attack by secondary amines.

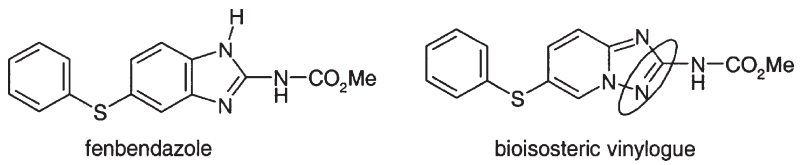


Fig. 12.31 Application of the vinylogy principle to the design of a fenbendazole bioisostere.[60]

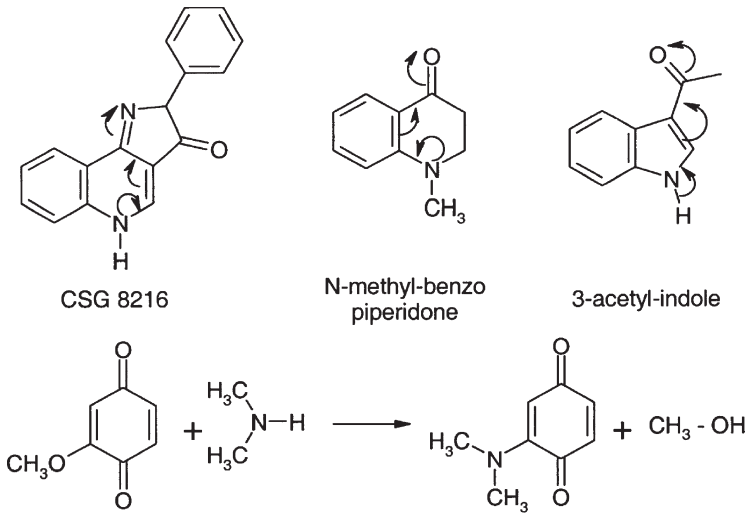


Fig. 12.32 Unexpected chemical reactivities attributable to vinylogy.

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