Isosterism and Molecular Modification in Drug Design

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1 Introduction

The idea of isosterism goes back to Langmuir[1] in 1919. At that time the word isosterism was used to describe the similarity of molecules or ions which have the same number of atoms and valence electrons *e.g.* O^{2-}, F^-, Ne. Clearly only those isosteres with the same nett charge show similar chemical and physical properties. Grimm[2] enunciated his hydride displacement law to describe the similarity between groups which have the same number of valence electrons but different numbers of atoms. For example some similarities are present in the sequence: CH_3, NH_2, OH, Hal.

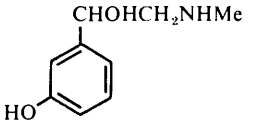
Grimm's hydride displacement law points out some similarities of size in groupings based on elements in the same row of the periodic table. Other similarities to be found in the periodic table are within the groups, where chemical reactivities are similar but with electronegativity decreasing as atomic weight increases and lipophilicity and polarizability increasing with the size of the atom. Other relationships exist in diagonal lines across the periodic table where atoms of similar electronegativity such as nitrogen and sulphur, oxygen and chlorine are found.

In trying to relate biological properties to the physical and chemical properties of atoms, groups, or molecules, many physical and chemical parameters may be involved and the simple relationships mentioned above are clearly inadequate for this purpose. Friedman[3] introduced the term 'bioisosterism' to describe the phenomenon in which compounds which are related in structure have similar or antagonistic properties. The use of the word isosterism has clearly outgrown its original meaning when used in medicinal chemistry and a loose flexible definition could be adopted such as: 'Bioisosteres are groups or molecules which have chemical and physical similarities producing broadly similar biological properties'.

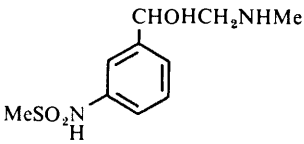
The term non-classical isosterism is also used interchangeably with bioisosterism, particularly in connection with isosteres which do not have the same number of atoms but do produce a similarity in some key parameter of importance in

[1] I. Langmuir, *J. Amer. Chem. Soc.*, 1919, **41**, 868, 1543.
[2] H. G. Grimm, *Z. Elektrochem.*, 1925, **31**, 474; 1928, **34**, 430; 1934, **47**, 53, 594.
[3] H. L. Friedman, 'Influence of Isosteric Replacements upon Biological Activity', National Academy of Sciences—National Research Council Publication No. 206. Washington D.C., 1951, p. 295.

that series. For example[4] the two β-adrenergic stimulants compounds (1) and (2) have similar activity.



(1) pK_a 9.6



(2) pK_a 9.1

The concept of bioisosterism has been described in reviews by Burger,[5a] Schatz,[5b] Foye,[6] Korolkovas,[7] Ariens,[8] and Hansch.[9] This present review collates and extends the earlier observations with more recent reports from the literature and suggests new techniques for exploiting the concept.

The 'classical' isosteres as defined by Burger[5] and Korolkovas[7] are given in Table 1.

Table 1

1) *Univalent atoms and groups*

F	OH	NH_2	Me	Cl
	SH	PH_2		
	I	Bu^t		
	Br	Pr^i		

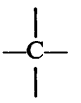
2) *Bivalent atoms and groups*

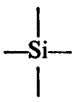
O	S	Se	CH_2	—N(H)—
CO_2R	COSR	$COCH_2R$	CONHR	

3) *Tervalent atoms and groups*

—N=	—CH=
—P=	—As=

4) *Quadrivalent atoms*





5) *Ring equivalents*

—CH=CH—	S	*e.g.* benzene: thiophen
=C(H)—	=N—	*e.g.* benzene: pyridine

—O— —S— $—CH_2—$ —NH—

[4] A. A. Larson and P. M. Lish, *Nature*, 1964, **203**, 1283.

[5a] A. Burger in 'Medicinal Chemistry' 3rd Edn., ed. A. Burger, Wiley-Interscience, New York, 1970.

[5b] V. B. Schatz in 'Medicinal Chemistry' 2nd Edn., ed. A. Burger, Wiley-Interscience, New York, 1960.

[6] W. O. Foye, 'Principles of Medicinal Chemistry', Lea and Febiger, Philadelphia, 1970.

[7] A. Korolkovas, 'Essentials of Molecular Pharmacology: Background for Drug Design', Wiley, 1970.

[8] E. J. Ariens in 'Drug Design', ed. E. J. Ariens, Academic Press, New York, 1971, Vol. 1.

[9] C. Hansch, *Intra-Science Chem. Rep.*, 1974, **8**, 17.

2 Bioisosterism in Molecular Modification

In the process of developing a lead compound, an antagonist to a known agonist, or an anti-metabolite from a known substrate, a large number of systematic molecular modifications will be made. The modern concept of bioisosterism can be an aid to the design of such modifications. In making a bioisosteric replacement the following parameters of the group being changed could be considered:

(*a*) Size.

(*b*) Shape (bond angles, hybridization).

(*c*) Electronic distribution (polarizability, inductive effects, charge, dipoles).

(*d*) Lipid solubility.

(*e*) Water solubility.

(*f*) pK_a.

(*g*) Chemical reactivity (including likelihood of metabolism).

(*h*) Hydrogen bonding capacity.

It is unlikely that any bioisosteric replacement will leave all these parameters undisturbed. The extent to which the replacement is useful will depend upon which of these parameters is important and which ones the bioisostere can best mimic.

The element of a molecule being modified may have one or more of the following roles.

(i) *Structural.* If the moiety has a structural role in holding other functionalities in a particular geometry, parameters such as size and bond angle will be important. The moiety may be buried deep in the molecule and have little contact with the external medium.

(ii) *Receptor interactions.* If the moiety to be replaced is concerned with a specific interaction with a receptor or enzyme its size, shape, electronic properties, pK_a, chemical reactivity, and hydrogen bonding will be the important parameters.

(iii) *Pharmacokinetics.* The moiety to be replaced may be necessary for the absorption, transport, and excretion of the compound. In this case lipophilicity, hydrophilicity, hydrogen bonding, and pK_a are likely to be important.

(iv) *Metabolism.* The moiety may be involved in blocking or aiding metabolism. In this case chemical reactivity will be an important parameter. For example chloro and methyl substituents on a benzene ring may be interchangeable for certain purposes but the toluene derivative can be metabolized to a benzoic acid and may therefore have a shorter half-life or unexpected side effects.

Usually one will not know which role(s) the various parts of the molecule play(s) in its action and this determination will be part of the structure–activity study. However, from the simple considerations listed above it is clear that:–

(A) A given molecular modification may allow some, but probably not all of the parameters (*a*)—(*h*) to be kept the same.

(B) Whether the same or a different biological activity results from the replacement will be governed by the role(s) which that moiety fulfils in the molecule and whether parameters affecting that role have been disturbed.

(C) From (A) and (B) it follows that what proves to be a good bioisosteric replacement in one series of compounds will not necessarily be useful in another.

Completely identical properties are rarely sought and will in any case be difficult if not impossible to achieve. What we are more likely to be seeking is a subtle change in the molecule which will leave some properties the same and some different in order to improve potency, selectivity, absorption, duration, and toxicity. Bioisosteric replacements allow molecular modifications, in which the number of variables changed are limited. Ariens[8] and Korolkovas[7] have tried to introduce the idea of partial bioisosteric groups as those which turn an agonist into an antagonist. Although their lists of groups may be suggestive to the drug designer, the idea is probably incorrect because of the statement (C) above. An 'antagonist' group in one molecule will only antagonize a similar 'agonist' group in another molecule if the agonist groups in both series are performing the same function. If an isosteric replacement results in a molecule which has some properties similar to the parent molecule but some important property has changed, it may be possible to compensate for this undesirable change by modifications elsewhere in the molecule. For example a molecular modification may reduce the lipid solubility of the molecule thereby affecting its absorption, transport, and apparent potency. Optimum activity may be regained by inserting lipophilic groups into the molecule at some sterically undemanding site. Consequently the best compounds in this parallel series of isosteres, such as for example furans and thiophens, are likely to have different substituent patterns.

3 The Mathematical Formulation

The arguments used above can be expressed in the mathematical form used by Hansch[10] for the case where a simple substituent is being varied, for example on a benzene ring. If the potency of a drug is a function of several parameters of the substituent then:

$$\log \frac{1}{c} = A(\pi) + B(\sigma) + C(E_s)$$

where Hansch's π value is used for the lipophilic character, Hammett's σ value for the electronic property, Taft's steric parameter to denote the size of the group and c is the concentration of drug required to achieve a given effect.

If such a relationship were found for a drug series in which the constants B and C were zero then the potency would be a function of π only. In this context groups would be bioisosteric if they have similar π values independent of their

[10] C. Hansch, *Accounts Chem. Res.*, 1969, **2**, 232.

σ and E_s values. If however the three constants A, B, and C are all significant a much more limited range of equivalent groups will be available.

If a series of compounds has more than one property, as is usual, then more than one equation will be needed to describe the effects of changing the substituent:

$$\log \frac{1}{c} = A(\pi) + B(\sigma) + C(E_s)$$

Desired activity

$$\log \frac{1}{c} = D(\pi) + E(\sigma) + F(E_s)$$

Side effects

Clearly if $A = D$, $B = E$, and $C = F$, *etc.*, no selectivity can be found within this limited series. If however $C \ll F$ then for the desired activity E_s is not important and π and σ may be optimized while reducing the value of E_s, thereby reducing the side effects. This phenomenon of increasing selectivity by bioisosteric replacement relies upon the fact that some desirable properties in the molecule can be retained when unimportant parameters can be varied. An unimportant parameter for the biological activity desired *may* be a key parameter in the side effect.

Thus bioisosteric replacements are useful in searching for potency, selectivity, absorption, and duration. Following the Hansch treatment one could produce a modern definition of bioisosterism based upon measurable parameters such as π, σ, E_s, hydrogen bonding properties, pK_a, *etc.*, and Hansch[9] has used the term 'isolipophilic' for groups with the same π value.

Table 2 shows some functional groups with similar electron-withdrawing properties. If electronic effects alone influence the biological activity in a series of drugs then these groups would be equivalent. If, however, the lipophilicity and steric factors are important then absolute identity cannot be achieved.

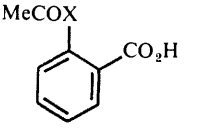
Table 2

Functional Group	σ_m	π	E_s
F	0.34	0.14	0.78
Cl	0.37	0.71	9.27
Br	0.39	0.86	0.08
I	0.35	1.12	−0.16
CF_3	0.43	0.88	−1.16
SCF_3	0.40	1.44	
COMe	0.31	−0.55	
CHO	0.36	−0.65	
CO_2Me	0.32	−0.01	
CH=CH—NO_2	0.32	0.11	

Extensive tables of σ, π, and E_s values are now available.[11] These can be used to gain a more quantitative idea of some aspects of isosterism using the better known functional groups.

4 Chemical Reactivity

Biological effects are generally produced by 'weak' interactions between the drug and the receptor but covalent bonding does occasionally play a part. A series of aspirin isosteres (3) was reported in 1975.[12] The nitrogen, sulphur, and carbon



(3) X = O, NH, S, or CH_2

isosteres were all totally inactive despite the classical purity of the replacements tried. Now that it is known that aspirin is an acetylating agent for prostaglandin synthetase this result is more readily understood.[13] The agents are widely different in their ability to act as acylating agents unless other substantial modifications are made in the molecules.

5 Non-classical Isosteres: Some Further Points

In considering bioisosterism in its widest sense it should be noted that similar effects in two functional groups need not imply atom upon atom overlap. Edwards[14] has pointed out that a common enzyme or receptor interaction involves hydrogen bonding to a carbonyl group. Strong hydrogen bonds may be formed to the carbonyl oxygen by hydrogen atoms within a cone having an angle of about 60° at its apex. Two molecules RXH and RAXH, where A is an additional atom, may be able to bind to the active site without identical positioning of the X or H. In addition the conformational mobility in both the drug and the receptor molecule will allow essentially similar binding of two drugs without the need to consider that the binding groups on the drugs are positioned in space in an identical manner.

Examples of Non-classical Isosteres.—The list shown in Table 3 is drawn from earlier reviews[5–9] and from the examples given in Table 4 at the end of this

[11] Tables of substituent constants can be found in the following papers. C Hansch, S. D. Rockwell, P Y. C. Jow, A. Leo, and E. E. Steller, *J. Med. Chem.*, 1977, **20**, 304; J. G. Topliss, *J. Med. Chem.*, 1972, **15**, 1006, and 1977, **20**, 463; C. Hansch, A. Leo, S. H. Unger, Ki Hwan Kim, D. Nikaitoni, and E. J. Lien, *J Med. Chem.*, 1973, **16**, 1207.

[12] L. Thompkins and K. H. Lee, *J. Pharm. Sci.*, 1975. **64**, 760.

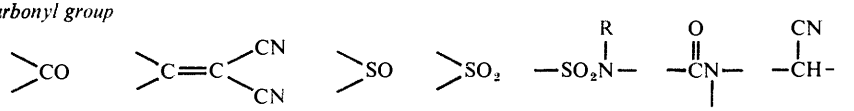
[13] G. J. Roth, N. Stanford, and P. W. Majerus, *Proc. Nat. Acad. Sci, U.S.A.*, 1975, **72**, 3073.

[14] P. N. Edwards, I.C.I. Pharmaceuticals Division, personal communication.

review. In addition a few proposals[15–17] which have not yet been realized in medicinal chemical work are included.

Table 3

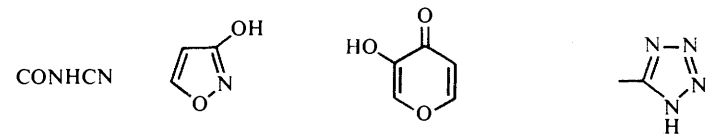
Carbonyl group



ref. 15

Carboxylic acid group

CO_2H SO_2NHR SO_3H $PO(OH)NH_2$ $PO(OH)OEt$



ref. 16

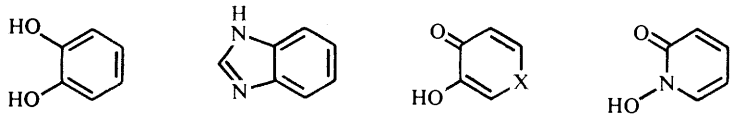
Hydroxy-group

OH NHCOR $NHSO_2R$ CH_2OH $NHCONH_2$

NHCN $CH(CN)_2$

ref. 16 ref. 16

Catechol



X=O
X=NR

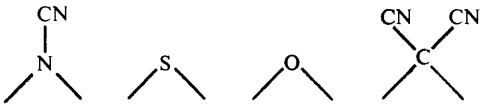
Halogen

Halogen CF_3 CN $N(CN)_2$ $C(CN)_3$ ref. 16, 17

[15] K. Wallenfels, K. Friedrich, J. Rieser, W. Ertel, and H. K. Thieme, *Angew. Chem. Internat. Edn.*, 1976, **15**, 261.
[16] H. von Kohler, B. Eichler, and R. Salewski, *Z. anorg. Chem.*, 1970, **379**, 183, also includes other possibilities in the sulphur and phosphorus and nitro acid series.
[17] K. von Wallenfels, *Chimia*, 1966, **20**, 303.

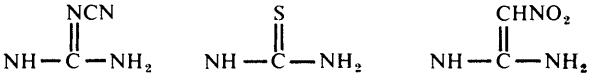
Table 3 *continued*

Thioether



ref. 16

Thiourea



Azomethine

ref. 17

Pyridine

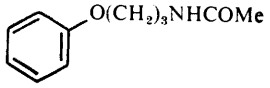
Spacer groups

In addition ring-opened forms of molecules may be considered to be isosteric with the corresponding ring-closed forms although the conformation of the *seco* form will be unlike the parent molecule. However, if in ring opening an atom is removed a conformation similar to the parent molecule may be possible.

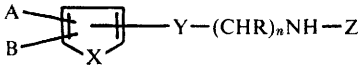
6 Substructure Searching and Bioisosterism

Although the classical Hansch approach is used largely for optimization within a series, molecular modifications based on bioisosterism principles can generate new series or even develop new leads if an agonist is used as the starting point for the design of an antagonist. One aid to this process is the use of a compound collection and computer techniques for doing substructure searches, *e.g.* the

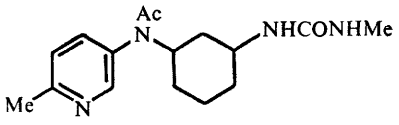
Crossbow suite of programmes.[18] For example suppose that random screening has turned up the lead (4). One may consider bioisosteric replacements for the ring, the oxygen, the polymethylene chain, or the amidic moiety, and design a substructure search for compounds of type (5). A vast number of permutations are possible and from these compounds may be available for tests which result in new leads which have properties worth exploiting, such as perhaps (6).



(4)



(5) X = CH=CH, CH=N, S, O, or NR
Y = O, S, SO, SO_2, Se, NCN, or NCOR
n = 2, 3, or 4
R = H or alkyl, including forming a ring
Z = COR, CO_2R, SOR, SO_2R, or CONHR
A = B = defined substituents



(6)

Examples.—The literature of medicinal chemistry is rich in examples of the use of the concept of bioisosterism and the reader is referred to the reviews mentioned[5–8] and the references quoted therein for examples reported before 1970. There follows a brief discussion of bioisosteres of some indole–amines which has some useful lessons, and Table 4 lists examples culled from the literature since 1970. Only the structures are given in this Table as an illustration of the kinds of change which have been useful. The reader is referred to the original papers for the full details of biological activity and selectivity. The list is not comprehensive but represents some uses of more novel non-classical types. Rudinger[19] has reviewed isosteric replacements in the field of peptide chemistry up to 1971 and some further discussions[20] have been published recently.

Indole-amines.—Campaigne[21] has studied and reviewed the work on bioisosteres of 5-hydroxytryptamine (7) and one or two details of the work are instructive. Whereas (8) was inactive as an agonist or antagonist on the rat uterus preparation, the corresponding tryptophan analogue (9) had weak activity as an enzyme inhibitor for 5-hydroxytryptamine decarboxylase.[22] This type of bioisostere

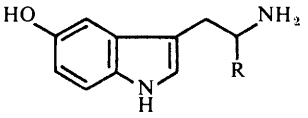
[18] E. E. Townsley and W. A. Warr, 'Chemical and Biological Data; An Integrated On-Line Approach' in 'Retrieval of Medicinal Chemical Information', ed. Howe, Milne, and Pennell (A. C. S. Symposium Series No. 84), American Chemical Society, Washington D.C.

[19] J. Rudinger, in ref. 8, Vol. II, Chapter 9.

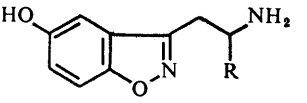
[20] Further discussion of peptide backbone replacement is found in ref. 19 and W. Soudyn and I. van Wijngaarden, in 'Biological Activity and Chemical Structure', ed. J. A. Keverling Buisman, Elsevier, Holland, 1977; a peptide link isostere —CH_2—S— has been reported by J. A. Yankeelov, Kam-Fook Fok, and D. J. Carothers, *J. Org. Chem.*, 1978, **43**, 1623.

[21] E. Campaigne, R. P. Maichel, and T. R. Bosin, Medicinal Chemistry, Specialist Contributions, 3rd International Symposium, 1972, Butterworths, 1973, p. 65.

[22] M. Pigini, M. Gianella, F. Gualtieri, C. Melchiorne, P. Bolle, and L. Angelucci, *European J. Med. Chem.*, 1975, **10**, 29, 33.

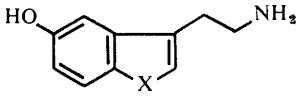


(7) R = H (5-hydroxytryptamine)
(10) R = CO_2H (5-hydroxytryptophan)



(8) R = H
(9) R = CO_2H

loses all affinity for the 5-hydroxytryptamine (5-HT) receptor but retains it in part for an enzyme system. Similarly, in the series of compounds 5-HT, (11), (12), and (13) activity has been measured against the rat fundic strip preparation and on the enzyme caeruloplasmin.[23] Whereas 5-HT is a substrate for the enzyme, compound (11) inhibited caeruloplasmin's oxidation of 5-HT and noradrenaline.



	Rat Fundic Strip		
	X	*Intrinsic activity*	PD_2
5-HT	NH	1	7.6
(11)	CH_2	0.96	5.6
(12)	O	0.84	4.6
(13)	S	1.08	6.1

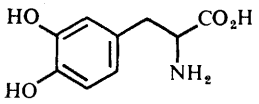
Compound (12) inhibits only 5-HT oxidation and compound (13) was inactive as a substrate or an antagonist. This would appear to demonstrate that for the enzyme system the imino grouping at the 1-position of the ring is essential.

On the rat fundic strip, however, all the analogues have full agonist activity though with reduced potency, demonstrating that the 5-HT receptor has a greater tolerance for loss of the imino nitrogen. These simple experiments demonstrate the role of bioisosteric replacements in exploring selectivity between different receptors and enzymes.

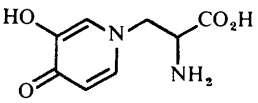
[23] B. C. Barrass, D. B. Goult, R. M. Pinder, and M. Sheels, *Biochem. Pharmacol.*, 1973, **22**, 2891.

Table 4 *Some recent examples of bioisosterism*

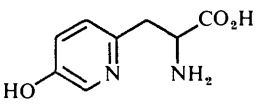
Dihydroxyphenylalanine analogues



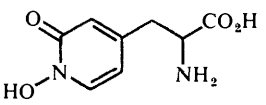
Dopa



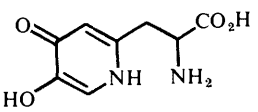
Mimosine ref. 24



ref. 25

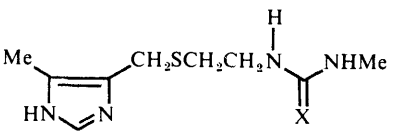


ref. 26

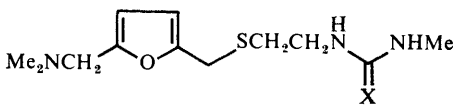


ref. 27

Histamine H-2 antagonists



X = S or NCN ref. 28



X = NCN or $CHNO_2$ ref. 29

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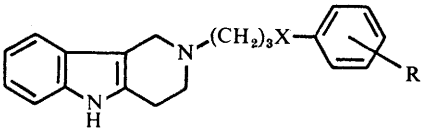
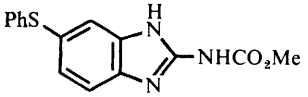
Table 4 *continued*

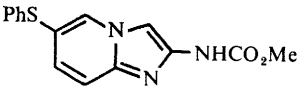
Neuroleptics



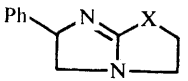
X = C(=O) or CH—CN ref. 30

Anthelmintics



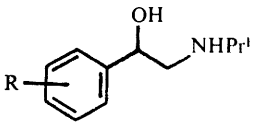


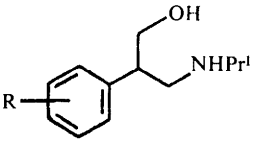
ref. 31



X = S or Se ref. 32

β-Adrenergic blockers





ref. 33

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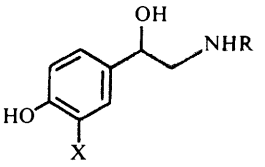
β-Adrenergic stimulants

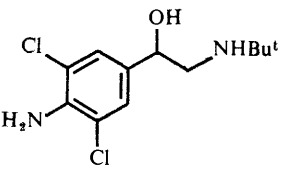


R = Me, X = OH Adrenaline

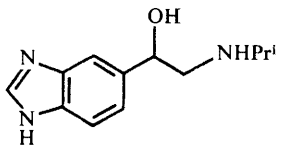
R = Bu^t, X = CH_2OH
Salbutamol ref. 34

R = Bu^t, X = $NHCONH_2$
Carbuterol ref. 35

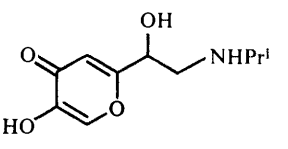
R = Pr^i, X = $NHSO_2Me$
Soterenol ref. 36



Clenbuterol ref. 37



ref. 38



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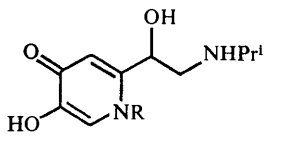

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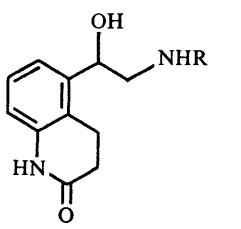

ref. 40

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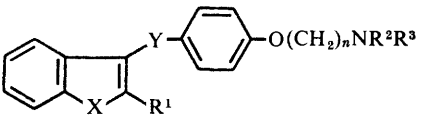
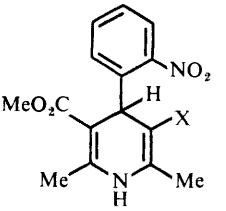
Table 4 *continued*

Vasodilators

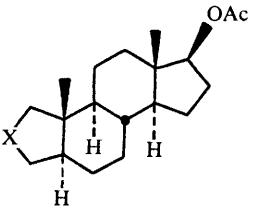


X = O or S, Y = SO_2 ref. 41
X = O, Y = CO ref. 42
X = S, Y = CO ref. 43



X = CO_2Me ref. 44
X = SO_2Me ref. 45

Androgens



X = S or NCN ref. 46

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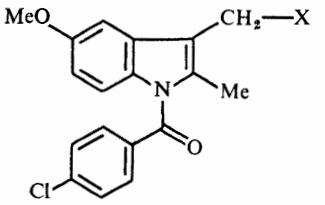
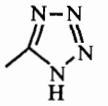
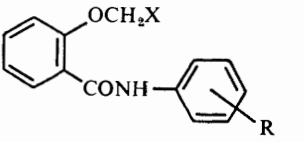
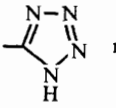
Anti-inflammatory



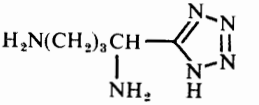
X =  ref. 47

X = CO_2H ref. 48



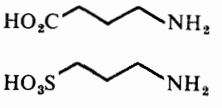
X = CO_2H or  ref. 49

Ornithine decarboxylase inhibitor



ref. 50

Gabergic agents



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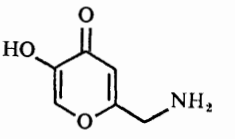

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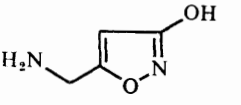

ref. 52

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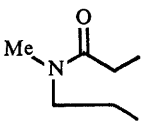
Table 4 *continued*

Prostaglandin ring system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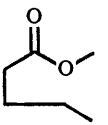
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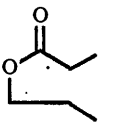
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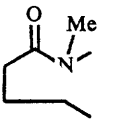
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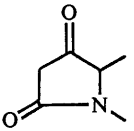
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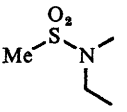
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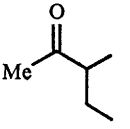
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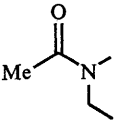

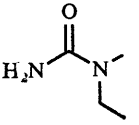

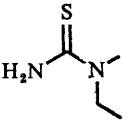
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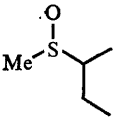
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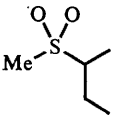
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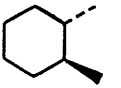
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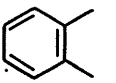

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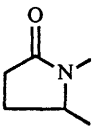

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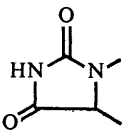

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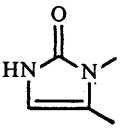

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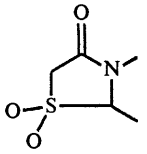

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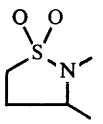

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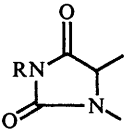

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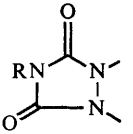

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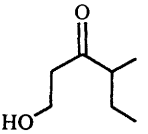

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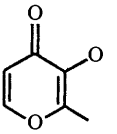

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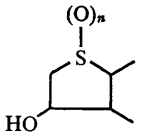

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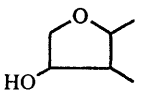

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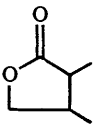

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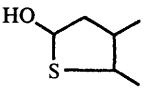

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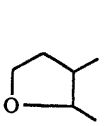
Table 4 *continued*

Prostaglandin ring system (continued)



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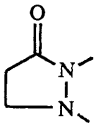

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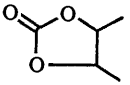

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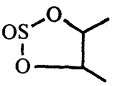

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