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The Concept of a Supporting Moiety as Applied to the Synthesis of Anti-viral Compounds

G. CAVALLINI and E. MASSARANI

Medicinal Chemistry Research Laboratories, Vister-Casatenovo (Como), Italy

Theory

Our investigations into the synthesis of medicinal products, based on the concept of a 'supporting' moiety, have been discussed in detail by one of us in a lecture presented before the 2nd Convention of the Italian Society of Pharmaceutical Sciences, 27–29 May 1955.[1] The theory of the 'supporting' moiety may be explained as follows:

(1) There are certain molecules, which we call 'supporting' moieties, which can be modified by the introduction of certain radicals. These radicals direct the activity of the molecule.

(2) The 'supporting' moiety must have a distinct affinity for the biological substrate and, therefore, molecules which already possess significant biological activity are most suitable for use as 'supporting' moieties.

(3) The introduction of particular chemical radicals on these so-called 'supporting' moieties, which have their own well defined metabolic cycle and exert significant physiological actions, can lead to compounds pre-determined to display new biological activities.

The first step towards the development of this concept was the synthesis of the vinyl homologue of 4-diethylaminoethoxybiphenyl,[2] a substance displaying sympatholytic activities. The new compound, 4-diethylaminoethoxystilbene, and its reduction product display coronary dilating actions superior to those of the corresponding biphenyl derivative.[3] We considered these substances to be formed from two essential components; the biologically active 'supporting' molecule (4-oxybiphenylethane) and the

R, R1 = H
R, R1 = CH2CH2N(C2H5)2
R = CH2CH2N+(C2H5)3 · I−
R1 = CH2CH2N+(C2H5)3 · I−
Hormonal activity
Coronary dilators
Curariform agents
Ganglionic blocking agents

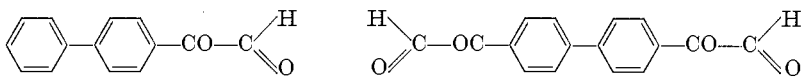
radical, which modifies activity, in this case the diethylaminoethyl group.

Since these molecules intrinsically possess minor estrogenic properties, we selected two synthetic estrogens to form the 'supporting' molecule: hexestrol and stilbestrol. The introduction into these two molecules of the diethylaminoethyl radical eliminated the estrogenic action of the 'supporting' molecule, conferring instead a specific vasodilator activity.[4] In order to further confirm these early findings, we introduced the trialkylammonium radical into the 'supporting' molecule of hexestrol and stilbestrol. Other investigators[5] have also introduced this radical into the 4,4′-dihydroxybiphenyl molecule and have thus obtained powerful synthetic curariform compounds. The importance of the radicals activating the supporting moiety is demonstrated even more clearly by the fact that the introduction of a single tetra-alkylammonium radical has resulted in products with ganglionic blocking properties.[7] The significance of tetraethylammonium salts is well known in the field of ganglionic blocking agents. Other compounds such as 4,4′-ethylenedioxy-α,β-diethylstilbene bis(diethylmethylammonium)diiodide and its reduction product are substances which lack any estrogenic activity but which possess curariform properties superior to those of the corresponding biphenyl derivatives.[6] The importance of the biological activity of the 'supporting' moieties may be concluded from these data, and for this reason we have selected the specific hormones as biologically active 'supporting' molecules. We have introduced the diethylaminoethyl radical and the tetra-alkylammonium group into estrone, testosterone, androstenediol and dihydroandrosterone.[8] As outlined in Table I, we obtained in this manner a series of coronary dilators, anti-nicotinic agents, ganglionic blockers and synthetic curariform compounds, while the hormonal activity of the 'supporting' molecules was eliminated.

Further Research

Subsequently, this research was directed to anti-lipaemic and anti-hypercholesteraemic compounds and, recently, also to anti-viral agents. We selected biphenyl as the 'supporting' molecule

for a first series of products. Since hyperlipaemia and hypercholesteraemia are expressions of an abnormal metabolism, we selected a radical, which was to modify the activity, contained in substances which interfere at different levels with the most important metabolic cycles, with the hope that the new entity ('supporting' moiety plus radical) would function as a metabolic antagonist. With this viewpoint, we synthesized a series of biphenyl derivatives, which displayed a high degree of anti-hypercholesteraemic and anti-lipaemic activity.[9,10] Recently, several authors,[11–13] have tried a series of glyoxals as anti-viral agents in the embryonated chicken egg against influenza virus (A–PR8) and Newcastle virus (NJKD). These glyoxals displayed a more or less pronounced activity; however, their anti-viral properties could not be confirmed in animals.[15] We felt that these substances were only activating radicals, and it would then only remain to find the suitable 'supporting' moiety so that compounds, also active *in vivo*, could be developed. Biphenyl was then chosen as 'supporting' moiety and an initial series of derivatives was synthesized whose formulae are shown below:



Compounds synthesized according to this concept have been tried in experimental animals subjected to different viral infections. The results so obtained are the subject of a series of studies performed in collaboration with Magrassi and co-workers.

The screening tests were performed on 8 Swiss strain mice, weighing 15–20 g on the average. The drugs were given in aqueous suspension with 3 per cent gum arabic. The suspension for oral and subcutaneous administration is prepared in a way that 0·10 ml contains the stabilized dose of the drug. The compounds were given for 10 days in doses equimolecular to 500 mg of 4-biphenylglyoxal hydrate orally and to 250 mg of the same substance parenterally. All the viruses were inoculated 24 h after the beginning of the treatment. The compounds which produced a survival of at least 50 per cent were considered to be significantly active.

Table II

Drug	Influenza Virus A–PR8 inoculation: nasal 5 LD50 ($LD50 = 10^{-2.13}$) % of survivals route administration		Virus MHV_3 inoculation: s.c. 60 LD50 ($LD50 = 10^{-3.4}$) % of survivals route administration		LD50* mg/kg
	s.c.	p.o.	s.c.	p.o.	
$C_6H_5COCHO.H_2O$	25	12	25	12	500
$C_6H_5COCHO.NaHSO_3$†	37	14	37	25	>1,200
4-$C_6H_5C_6H_4COCHO.H_2O$	42	37	50	25	1,300
4-$C_6H_5C_6H_4COCHO.NaHSO_3$†	91	63	78	62	1,000
4,4′-$OHCCOC_6H_4C_6H_4COCHO.2H_2O$	16	0	62	62	>1,500
4,4′-$OHCCOC_6H_4C_6H_4COCHO.2NaHSO_3$†			57	43	>1,500
4,4′-$CH_3OC_6H_4C_6H_4COCHO.H_2O$	25	12	50	37	>1,500
4,4′-$CH_3OC_6H_4C_6H_4COCHO.NaHSO_3$†	25	0	50	25	>1,500
4-(4′-CH_3O, 3′-ClC_6H_3)$C_6H_4COCHO.H_2O$	20	0	62	50	>1,500

* Determined in mice weighing 15–20 g. Administration of the compounds in aqueous suspension with 3% gum arabic.

† The sodium bisulphite was found to be completely inactive.

Summary. Based on the concept of 'supporting' molecular moieties, a number of glyoxal derivatives of biphenyl were tested as anti-viral agents. Whereas simpler glyoxals show activity only in embryonated chicken eggs, the derivatives of biphenyl were active in infected mice.

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