agreed well with the measured affinity constants. The resolution of the electron density did not clearly define the conformation of the alkoxy linkage of **7**, but an approximately helical folded conformation, as shown in Figure 2, accommodated the electron density.

In summary, we have used three-dimensional molecular models of the *E. coli* DHFR–MTX complex to design analogues of TMP that not only had significantly higher affinity for DHFR than that of TMP but also furnished useful information on the binding mode of this class of inhibitor in solution. The postulated binding mode was then verified by X-ray crystallographic studies of TMP and two of these analogues in complex with *E. coli* DHFR. Although these analogues were not as effective as TMP as broad-spectrum antibacterials, we feel that this study amply demonstrates the considerable potential of this approach to inhibitor design.

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Two Clonidine-like Compounds with Substituents at the 2-, 3-, and 6-Position of the Phenyl Ring Possessing Pronounced Hypotensive Potencies

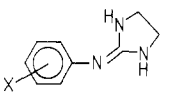
Sir:

The discovery of clonidine (1; Chart I) as a potent, centrally acting, hypotensive drug[1-4] has led to detailed studies on the relationship between structure and hypotensive activity in the class of 2-(phenylimino)-imidazolidines of the clonidine type. The majority of these investigations has considered variations of the substitution in the phenyl moiety of the molecules.[5-17] An interesting observation has been the approximately equal hypotensive activities found for 2,3- and 2,6-disubstituted analogues,[7,11-17] of which clonidine itself is one of the most active representatives. This knowledge has prompted us to synthesize 2,3,6-trisubstituted derivatives with the objective of obtaining potent hypotensive drugs in the clonidine series.

The present communication reports on the hypotensive activities of 2-[(2,3,6-trichlorophenyl)imino]imidazolidine (**2**) and 2-[(2,3-dichloro-6-methylphenyl)imino]-imidazolidine (**3**), demonstrating the potential of this newly substituted class of centrally acting, hypotensive imidazolidine compounds.

The trisubstituted 2-(phenylimino)imidazolidines **2**[18] and **3**[18] resulted from a reaction of the corresponding *N*-(di-

Chart I. Structural Formulas of Clonidine and Two of Its 2,3,6-Trisubstituted 2-(Phenylimino)imidazolidines[a]



1 (X = 2,6-Cl_2; Clonidine)
2 (X = 2,3,6-Cl_3)
3 (X = 2,3-Cl_2,6-CH_3)

[a] The numbering refers to Table I.

Table I. Hypotensive Activities, pC_{20}, and Apparent Partition Coefficients, Log P', of Clonidine and Two of Its 2,3,6-Trisubstituted Derivatives

compd	pC_{20}[a] anesthetized normotensive rat[b]	pC_{20}[a] anesthetized cat[c]	log P'[d]
1[e]	7.96	8.72	0.91
2	8.39	9.17	1.71
3	7.79	7.92	1.06

[a] -Log dose (moles/kilogram) required for 20% decrease in mean arterial pressure following systemic administration. The data reported were calculated from log dose-depressor response curves. At least six animals were used for each dose level, and a minimum of five dose levels was employed for determination of a dose-response curve. [b] Artificially ventilated, male Wistar, normotensive rats (200-250 g) anesthetized with pentobarbital (75 mg/kg, intraperitoneally) were used. The compounds dissolved in saline were administered as single bolus injections (0.5 mL/kg) via a cannulated jugular vein (see ref 12 and 16). [c] Artificially ventilated mongrel cats of either sex (2-4.5 kg) anesthetized with α-glucochloralose (60 mg/kg, intraperitoneally) were used. The compounds dissolved in saline were infused via the left vertebral artery in a volume of 140 μL over a period of 1 min (see ref 13). [d] Octanol/buffer (pH 7.4; 37 °C) partition coefficients (see ref 16 and 21). Mean P' values were obtained from six partition experiments (SEM < 5%). [e] Clonidine.

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(18) Compound **2** (base), formula $C_9H_8Cl_3N_3$: mp 153–156 °C (uncorrected); compound **3** (HCl salt), formula $C_{10}H_{12}Cl_3N_3$: mp 241–243 °C (uncorrected); both substances were analyzed for C, H, and N, and the results were within ±0.4% of theory.

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chloromethylene)anilines with ethylenediamine in ethyl acetate in the presence of triethylamine. The *N*-(dichloromethylene)anilines were prepared from the formamides with thionyl chloride in sulfuryl chloride. The formamides became available by formylation of the corresponding anilines. For information on the general synthesis of substituted 2-(phenylimino)imidazolidines, see ref 15, 17, and 19.

Compounds **2** and **3**, as well as clonidine, were studied for their ability to decrease mean arterial pressure in pentobarbital-anesthetized normotensive rats.[12,16] Upon intravenous administration, clonidine (1–10 μg/kg), **2** (0.3–6 μg/kg), and **3** (1–30 μg/kg) elicited the common biphasic response on arterial pressure. After a short-lasting hypertensive effect, a more persistent fall in pressure was obtained. When the maximal decrease in mean arterial pressure (percent of preinjection value) was plotted against log dose (moles/kilogram), log dose–depressor response curves were constructed, from which the –log doses for 20% decreases, pC_{20}, were calculated. As reported in Table I, compound **2** was found to be approximately 3 times more potent than clonidine in decreasing mean arterial pressure of anesthetized normotensive rats by 20% after intravenous injection. Derivative **3** had hypotensive activity comparable to clonidine.

Acute central hypotensive effectiveness of the congeners was determined by infusing them via the left vertebral artery of chloralose-anesthetized cats.[13] Accordingly, clonidine (0.1–2 μg/kg), **2** (0.1–1 μg/kg), and **3** (0.5–10 μg/kg) immediately caused a sharp fall in arterial pressure without a preceding hypertensive effect. Log dose–response curves were constructed for the maximal decrease in mean arterial pressure (percent of initial value), and –log dose for 20% decrease, pC_{20}, was calculated. As listed in Table I, the 2,3,6-trichloro-substituted molecule **2** was 3 times more effective than clonidine, whereas the 2,3-dichloro-6-methyl derivative **3** was less active than clonidine.

The results show that the introduction of a third substituent at the meta position of the phenyl ring of 2,6-disubstituted clonidine-like imidazolidines does not necessarily hamper hypotensive activity following systemic application, as has been generally observed for all 2,4,6-trisubstituted 2-(phenylimino)imidazolidines.[7,11-15,20] The para position allows only for small substituents, like OH and NH_2, for high hypotensive activity.[14,15,20] However, these groups profoundly affect lipophilicity, so that the increase in activity at the receptor level is overwhelmed by poor penetration into the central nervous system, resulting in moderate overall hypotensive potency. To our knowledge, compound **2** is the most effective hypotensive clonidine-like imidazolidine reported. The increase in hypotensive activity of compound **2** over clonidine may be due to more favorable penetration abilities of the former, as illustrated by its log P' value (Table I), which is closer to the ideal value of 2.16 determined for this series of drugs.[21]

In summary, members of 2,3,6-trisubstituted clonidine-like 2-(phenylimino)imidazolidines show potential for pronounced hypotensive activity following systemic administration. This new class of derivatives needs further exploration with respect to their substituent allowance on the phenyl ring.

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Sparsophenicol: A New Synthetic Hybrid Antibiotic Inhibiting Ribosomal Peptide Synthesis

Sir:

Recently, we suggested[1] that the biological activity of chloramphenicol (**1a**)—an antibiotic inhibiting procaryotic ribosomal protein synthesis—can be explained in terms of retro-inverso relationship[2] to the amino acid moiety of another strong inhibitor puromycin.[3] It should be possible to extend this hypothesis to other antibiotics, for example, sparsomycin,[4] that carry an acylamido function attached to the asymmetric (D) carbon of the substituted propanol moiety and interfere with ribosomal protein synthesis. This approach would lead to novel synthetic antibiotics by a simple interchange of the relevant *N*-acyl residues.

We now report on the first case[5] of such a hybrid antibiotic (**1b**) derived from a combination of chloramphenicol (**1a**) and sparsomycin (**1c**)—hence, the suggested name sparsophenicol—which is indeed a strong inhibitor of ribosomal peptide synthesis.

β-(*E*)-1,2,3,4-Tetrahydro-6-methyl-2,4-dioxo-5-pyrimidineacrylic acid[6] (**2b**; 0.5 g, 2.5 mmol) was converted to the corresponding mixed anhydride by reaction with triethylamine (0.35 mL, 2.5 mmol) and isobutyl chloroformate (0.32 mL, 2.5 mmol) in acetonitrile (20 mL).[7] A solution of chloramphenicol base (**1d**; 0.53 g, 2.5 mmol) in

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