Similarities of pharmacophoric patterns revealed by the MEP of metoclopramide, molindone and piquindone, a subgroup of dopamine D-2 receptor antagonists

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Molecular electrostatic potential (MEP) calculations based on ab initio *wave functions have been used to compare three compounds belonging to two distinct chemical series (substituted benzamides (metoclopramide) and indolones (piquindone and molindone)). These compounds have highly similar pharmacological properties at the receptor level (antagonists binding selectively to the dopamine D_2 receptor and in a sodium-dependent manner). The MEPs of these compounds show close similarities and form a common pharmacophoric pattern.*

Keywords: computer aided drug design, molecular electrostatic potential, dopamine receptor antagonists, pharmacophore, metoclopramide, piquindone, molindone

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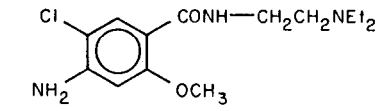
Unlike 'classical (or typical) neuroleptics', the group of novel compounds referred to as 'atypical neuroleptics' are essentially devoid of extrapyramidal side-effects. Atypical neuroleptics include the substituted benzamides[1], and also some newly discovered compounds such as piquindone[2,3], molindone[4] and zetidoline[5]. These compounds appear to be selective inhibitors of a subpopulation of dopamine receptors. This group of receptors, the so-called D_2 receptors[6], are either unconnected or negatively coupled to adenylate cyclase. Orthopramides[7], zetidoline[5], and the indolones piquindone[3] and molindone[3], share the further distinctive feature that their binding to the D_2 receptors is highly sodium-dependent. Stereochemical and/or electronic properties which arise from common structural features must account for these pharmacological similarities.

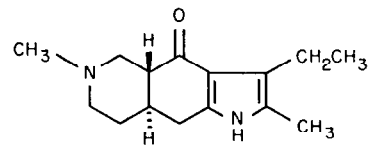
A number of papers have been published on the conformational[8–11] and electronic properties[12–14] of orthopramides. The aim of the work presented in this paper was to find similarities between pharmacologically, but not chemically, related drugs using molecular electrostatic potential (MEP) calculations.

COMPUTATIONAL PROCEDURES

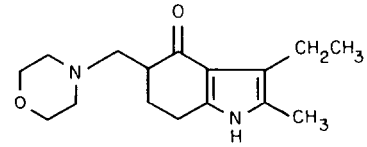
The compounds which formed the basis of this study were metoclopramide, piquindone and molindone (See Figure 1). The Cartesian coordinates of the constituent



Metoclopramide



Piquindone



Molindone

Figure 1. Chemical structure of the studied compounds

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atoms were determined by X-ray crystallography[15–17]. Crystalline neutral metoclopramide had a folded (gauche) conformation[15], (as shown later in Figure 3). But because the active conformation of orthopramides is believed to be the extended one[10,13], MEP plots have also been calculated for an extended form generated by rotation around the N–CH_2–CH_2–C bond. The X-ray structures of (−)−(4aR;8aR)-piquindone[16] and (5R)-molindone[17] were used. A profile view of (4aR;8aR)-piquindone and (5R)-molindone in their crystalline conformation is shown in Figure 2.

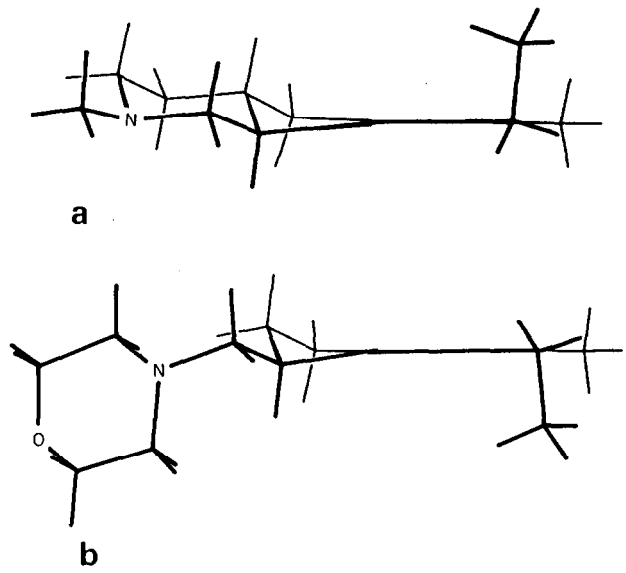

Figure 2. Profile view of (a): (4aR;8aR)-piquindone; and (b): (5R)-molindone

Wave functions and electronic densities were calculated using the *ab initio* Monstergauss 81 program as reported before[12], operating the STO-3G basis set. Preliminary calculations (not shown) using the STO-5G and 4-31G basis sets revealed that no important qualitative differences are observed among these three basis sets. MEPs were obtained with a slightly modified version of DENPOT (QCPE 360). The electrostatic potential at each node in a chosen Cartesian grid was calculated using the equation proposed by Tomasi *et al.*[18]:

$$V(M) = -\int(\rho(N)/r_{N,M}).d\tau(N) + \sum_{\alpha}(Z_\alpha/r_{\alpha,M})$$

MEPs were generated in planes parallel to the aromatic ring, viewing piquindone and molindone from above, when the compounds were positioned as shown in Figure 2. All calculations were performed on the CDC CYBER 170/855 computer of the Federal Institute of Technology in Lausanne. Computing times for a molecule with 40 atoms and 120 orbitals were typically 3000 s for the integrals and the SCF part, and 600 s for a MEP plot.

RESULTS AND DISCUSSION

The MEP plot of folded metoclopramide at 2.5 Å above the plane of the aromatic ring is shown in Figure 3. Extended metoclopramide viewed at distances of 2.5 Å and −2.5 Å from the plane is shown in Figure 4(a) and 4(b).

Extended metoclopramide has MEP plots which differ at distances of 2.5 Å and −2.5 Å in the regions around

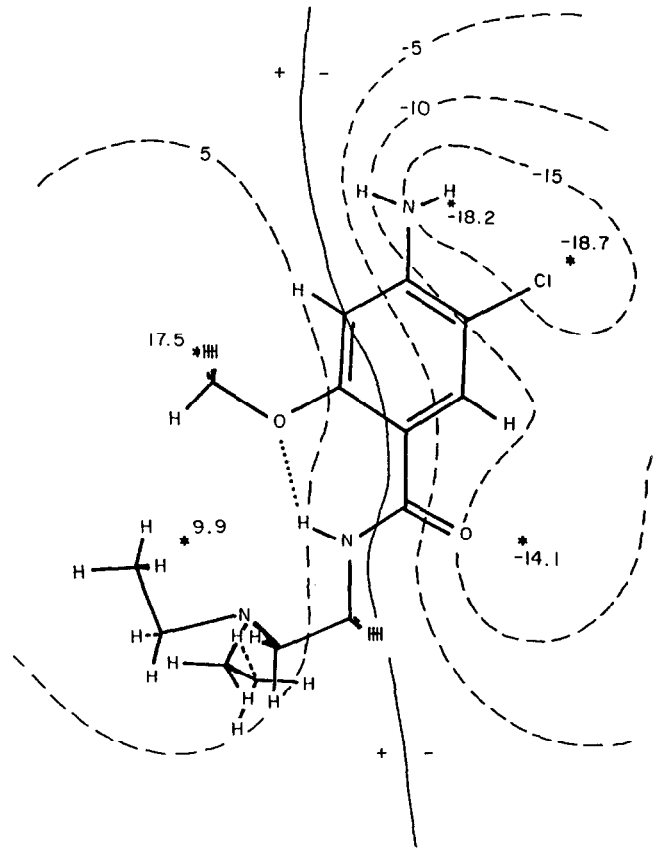

Figure 3. MEP (calculated by the STO-3G ab initio method) of folded metoclopramide. The isoenergy contours (in kcal/mol) are in a plane 2.5 Å above the plane of the aromatic ring

the NEt_2 and NH_2 groups. This is due to the asymmetrical position of these moieties relative to the plane. But, the main features are preserved on both sides of the plane and have already been noted for model compounds[14]. These features include a 'curtain' separating the positive and negative zones and crossing the aromatic ring, there is a strong positive region generated by the methoxy group, and a strong negative region generated by the chlorine atom and by the carbonyl oxygen. These features are also apparent for the folded conformation of metoclopramide (see Figure 3), but their position relative to the basic nitrogen is significantly different.

When piquindone and molindone are compared it is found that at distances 2.5 Å and −2.5 Å away from the plane of the aromatic ring (see Figure 5(a) and 5(b), and Figure 6(a) and 6(b), respectively) there are differences near the basic nitrogen atom and the ethyl substituent. This is due to the non-symmetrical position of these groups. However, other features are observed; these include a curtain separating the positive and negative zones which cut through the ring systems, a strong positive region generated by the pyrrolyl N–H group, and a strong negative region generated by the carbonyl oxygen.

The MEPs of metoclopramide, piquindone and molindone share common features, including a positive maximum generated by the OMe or N–H group, a negative minimum generated by the carbonyl oxygen, and a curtain separating the positive and negative zones. In addition, the three drugs have a basic nitrogen atom.

It is interesting that when metoclopramide is consid-

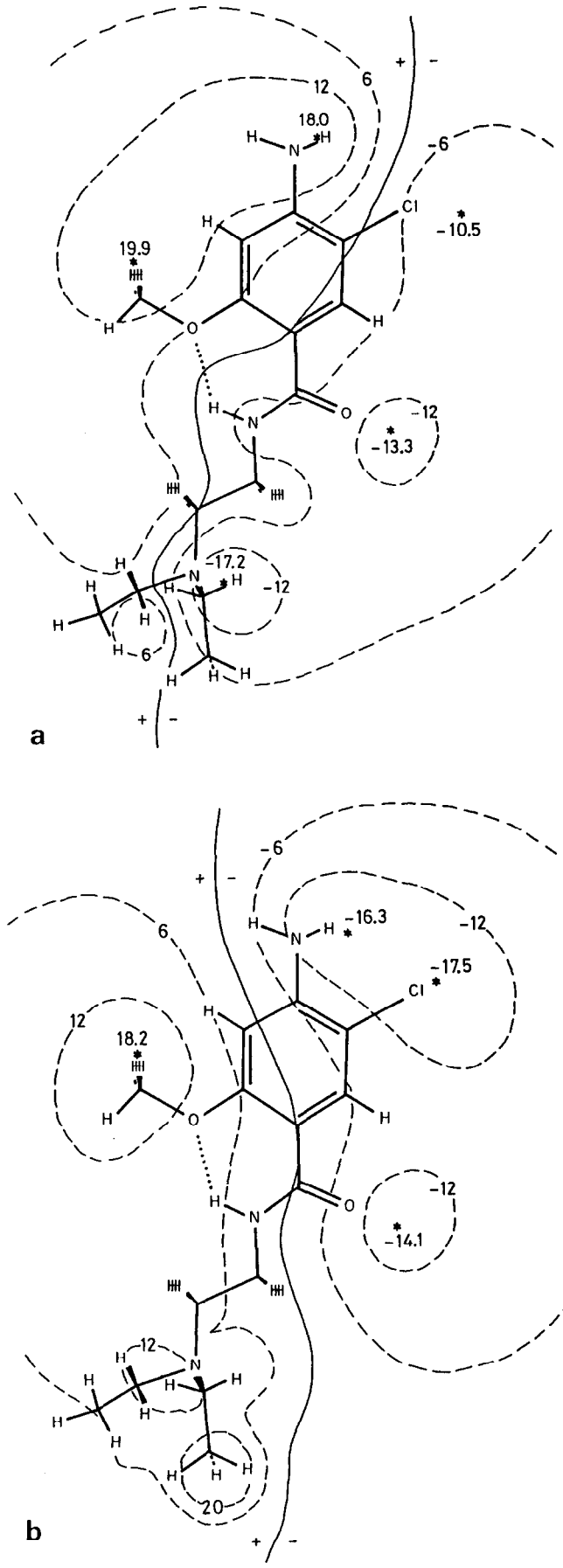

Figure 4. MEP (calculated by the STO-3G ab initio *method) of extended metoclopramide. The isoenergy contours (in kcal/mol) are in planes (a): 2.5 Å; and (b): −2.5 Å away from the plane of the aromatic ring.*

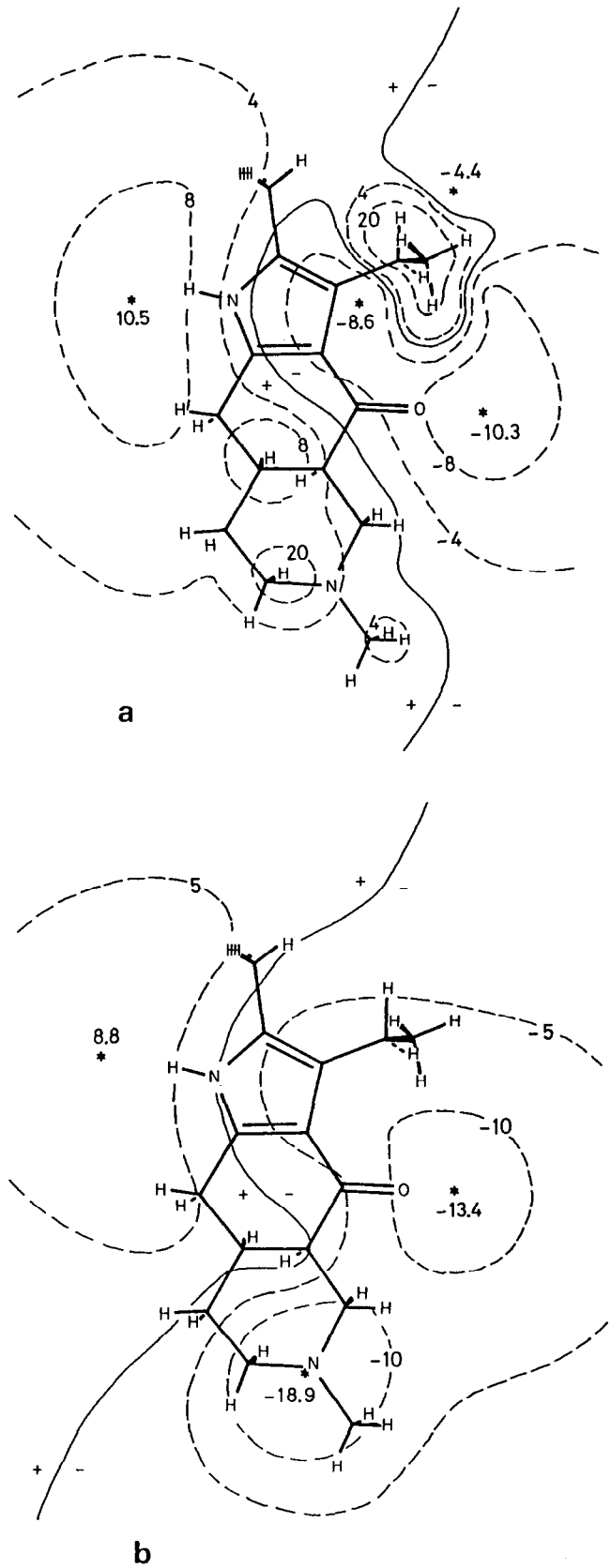

Figure 5. MEP (calculated by the STO-3G ab initio *method) of piquindone. The isoenergy contours (in kcal/mol) are in planes (a): 2.5 Å; and (b): −2.5 Å away from the plane of the aromatic ring*

ered in its extended, active conformation, the similarities between the three drugs become quantitative. The topographical position of the nitrogen atom, the positive

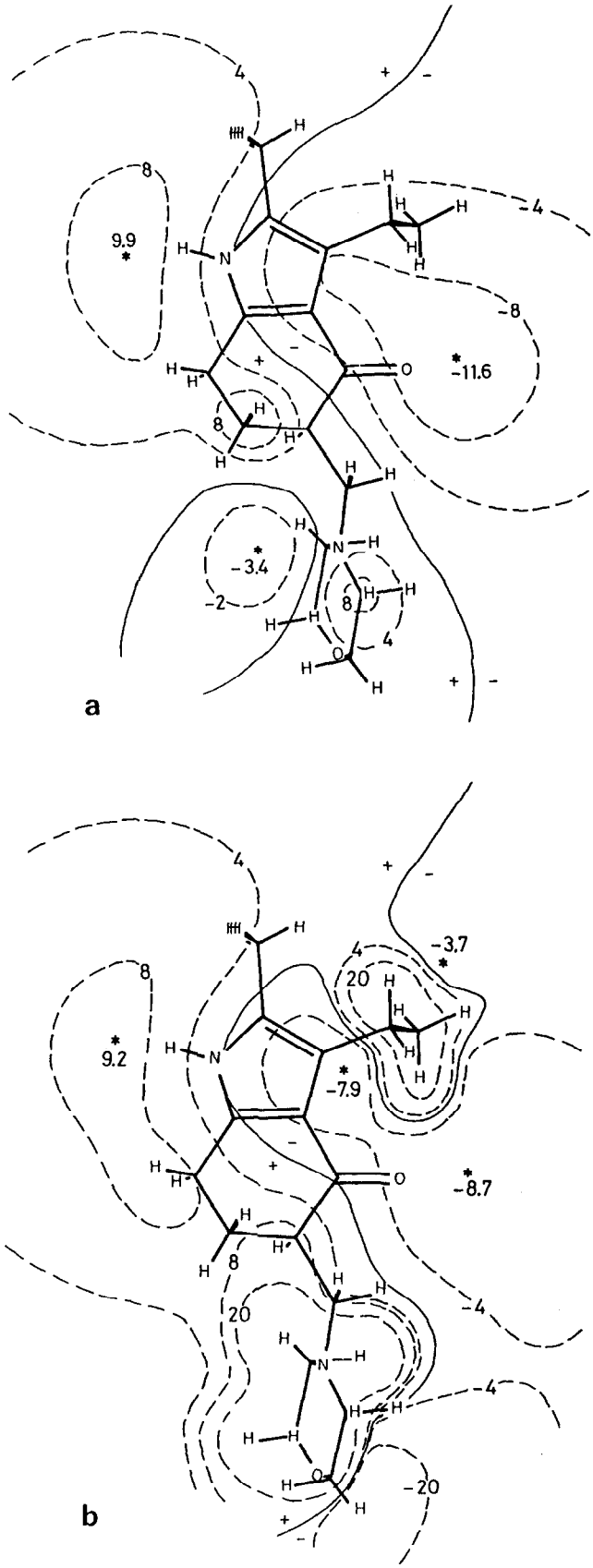

Figure 6. MEP (calculated by the STO-3G ab initio *method) of molindone. The isoenergy contours (in kcal/mol) are in planes (a): 2.5 Å; and (b): −2.5 Å away from the plane of the aromatic ring*

maximum and the negative minimum are practically superimposable in the three drugs, as shown in Figure 7.

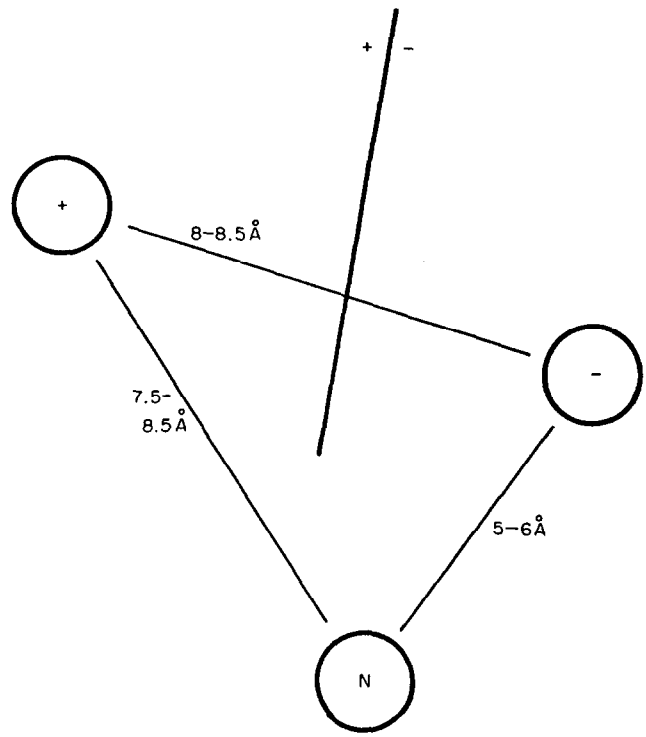

Figure 7. Pharmacophoric pattern generated by superposition of the MEPs of molindone, piquindone and extended metoclopramide

CONCLUSION

Extended metoclopramide, piquindone and molindone share very similar topographical features in their electronic structure. It is postulated that these features represent the main pharmacophore of antagonists which bind to the D_2 receptor in a sodium-dependent manner. This pharmacophore has some similarities to a more general pharmacophore which has been postulated for dopamine antagonists.

ACKNOWLEDGEMENTS

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REFERENCES

1 **Jenner, P and Marsden, C D,** *Life Sci.* Vol 25 (1979) pp 479–486
2 **Olson, G L, Cheung, H C, Chiang E and Berger, L,** *ACS Symp. Ser.* Vol. 114 (1983) pp 251-274
3 **Nakajima, T and Iwata, K,** *Mol. Pharmacol.* Vol 26 (1984) pp 430–438
4 **Koe, B K,** in **Usdin, E, Kopin, I J and Barchas, J(Eds.)** *Catecholamines; Basic and Clinical Frontiers* Vol 1 (1979), Pergamon, New York, p 740
5 **Barone, D, Assandri, A, Galliani, G, Glasser, A and Tarzia, G,** *J. Pharm. Pharmacol.* Vol 37 (1985) pp 180–187; **Harris, N, Dorey, P G, Woodruff, G N,** *J. Pharm. Pharmacol.* Vol 35 (1983) pp 599–600
6 **Kebabian, J W and Calne D B,** *Nature* Vol 277 (1979) pp 93–96
7 **Theodorou A E, Hall, M D, Jenner, P and Marsden, C D,** *J. Pharm. Pharmacol.* Vol 32 (1980) pp 441–444
8 **Pannatier, A, Anker, B, Testa, B and Carrupt, P A,** *J. Pharm. Pharmacol.* Vol 33 (1980) pp 145-149

9 **van de Waterbeemd, H and Testa, B,** *Helv. Chim. Acta* Vol 64 (1981) pp 2183-2188
10 **van de Waterbeemd, H and Testa, B,** *J. Med. Chem.* Vol 28 (1983) pp 203-207
11 **Anker, L, Lauterwein, J, van de Waterbeemd, H and Testa, B,** *Helv. Chim. Acta* Vol 67 (1984) pp 706–716
12 **van de Waterbeemd, H, Carrupt, P A and Testa, B,** *Helv. Chim. Acta* Vol 68 (1985) pp 715–723
13 **Testa, B, van de Waterbeemd, H and Carrupt, P A,** *Theochem.* in press
14 **van de Waterbeemd, H, Carrupt, P A, and Testa, B,** *J. Med Chem.* in press
15 **Cesario, M, Pascard, C, El Moukhtari, M and Jung, L,** *Eur. J. Med. Chem.* Vol 16 (1981) pp 13–17
16 **Olson, G L, Cheung, H C, Morgan, K D, Blount, J F, Todaro, L, Berger, L, Davidson, A O and Boff, E,** *J. Med. Chem.* Vol. 24 (1981) pp 1026–1034
17 **Olson, G L** (1984) personal communication
18 **Bonaccorsi, R, Scrocco, E and Tomasi, J,** *J. Chem. Phys.* Vol 52 (1970) pp 5270–5284