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The use of quantum chemistry in pharmaceutical research as illustrated by case studies of indometacin and carbamazepine

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Abstract

A number of case studies that illustrate how quantum chemistry may be used in studying pharmaceutical systems are reviewed. A brief introduction to quantum methods is provided and the use of these methods in understanding the structure and properties of indometacin and carbamazepine is discussed. The use of calculated structures and molecular electrostatic potentials in developing quantitative structure–activity relationships is discussed along with the use of computation chemistry to predict spectroscopic properties.

Introduction

The purpose of this paper is to provide a group of case studies that illustrate how quantum chemistry may be used in studying pharmaceutical systems. Rather than presenting an exhaustive literature survey, the focus is on a number of commonly used drugs; namely the anti-inflammatory drug indometacin and the antiepileptic drug carbamazepine, and how they have been studied using quantum chemistry. Importantly we focus on existing and well-established quantum methods. The final section looks forward to how spectroscopic methods that may be readily applied to solid-state samples, particularly vibrational methods, may play a role in the future of pharmaceutical research and development.

We are particularly interested in trying to model the properties of molecules, such as structures, vibrational spectra and charge distributions; for these properties there are an array of methods and commercial program packages available to researchers (Young 2001). For example, there are comparatively simple molecular mechanics and semi-empirical methods that may be applied to large molecular systems. These methods have been successful in many areas (e.g., a recent review by Taskinen et al (2003) highlighted the use of semi-empirical calculations to predict the octanol–water partition coefficients for a variety of compounds). AM1 calculations may be used to screen tens of thousands of compounds for the purposes of drug design as exemplified in the study of ligands for the retinoic acid receptor by Silva et al (2005). However, as we are interested in molecular properties such as vibrational spectra it is often necessary to use more sophisticated and more limited computational methods than offered by semi-empirical approaches. For this reason we will focus on the use of quantum calculations applicable to these types of problems.

Hartree-Fock (HF) methods increase accuracy of prediction for vibrational spectra but scale as a function of the number of electrons in the system and become unwieldy for large systems (Young 2001). Density functional theory calculations improve on the accuracy of HF methods but are similarly unwieldy for many-atom (>100 atoms) systems. It is useful for an appreciation of the utility of these calculations to briefly examine how these methods accomplish prediction of molecular properties, how they can improve the accuracy of such predictions and what limitations exist on using such calculations.

Fundamentally the calculations try to determine the energy of the molecule. HF is an ab-initio method that accomplishes this by getting as close as possible to a solution of the Schroedinger equation for the molecular system of interest. The Schroedinger equation is given as:

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$$\hat{H}\Psi = E\Psi \quad (1)$$

This deceptively simple-looking equation states that the energy of the system (E) is derived from the operation of the Hamiltonian operator ($\hat{H}$) on the wavefunction (ψ), a function of the nuclei and electrons in the system. An advantage of the quantum methods is that they provide insight into electronic structure in the sense of electron distributions; these are often very important in terms of reactivity of the system of interest. The output of calculations describes the electronic structure in terms of molecular orbitals. The orbitals are constructed from mathematical functions, called basis functions, that when grouped for the purposes of the calculation are called a basis set. The more functions present in the basis set the better the representation of the orbitals. However, the greater the number of functions in the calculation the greater the resources required to accomplish the output. In fact, calculations scale as the number of basis functions to the fourth power – thus the more basis functions employed the more resources the calculation requires (Jensen 1999). The Hamiltonian operator ($\hat{H}$) yields the energy by considering the energy in a molecule to be made up of a series of interactions:

$$\begin{aligned}\hat{H} = &-\text{Kinetic energy of the electrons}\\ &-\text{potential energy between electrons and nuclei}\\ &+\text{potential energy between electrons}\\ &+\text{potential energy between nuclei}\end{aligned} \quad (2)$$

The attractive forces are negative and the repulsive forces are positive in this equation. The HF method, however, has an intrinsic weakness in its approach. This lies in the way in which the potential energy between electrons (a repulsive force) is determined. HF methods use the central field approximation, which takes an average value for the electron–electron repulsion and uses that value in $\hat{H}$ and does not determine the specific electron–electron interactions. This means that the wavefunction for a system with many electrons is determined by the nuclei to electron distances (d_1 and d_2 for two of the many electrons, Figure 1) and is invariant with the closeness of approach of the electrons to each other. Thus the energies of such a system depicted in Figure 1 are calculated to be the same with HF methods.

This is clearly not physically realistic. The situation where the electrons are far from each other should be more probable as the electron–electron repulsion is less; the consideration of the explicit interactions between electrons is called electron–electron correlation. The absence of this correlation means that HF methods always carry an error. There are a number of ways to include correlation; one is to use more sophisticated methods such as coupled cluster, as reviewed by Ratner & Schatz (2001) or configuration interaction (CI) methods, as reviewed by Ratner & Schatz (2001). Both of these methods are some way off being useful for medium-to-large-size molecular systems and are presently the domain of small-molecule chemical physics.

A more practical approach to improving accuracy of calculations for the medium-to-large systems is density function theory (DFT) (Jensen 1999). In such calculations some aspects of electron–electron correlation are included. Over the past 5 years DFT has come to dominate computational chemistry of medium-to-large molecules, including pharmaceuticals (Young 2001).

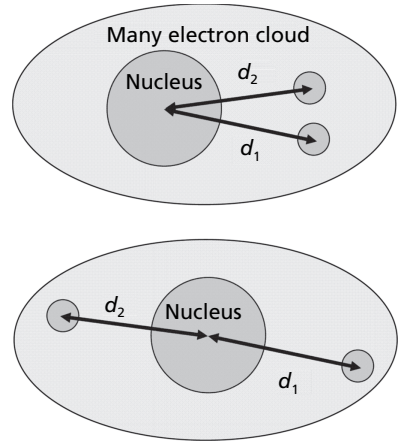


Figure 1 Two differing electronic situations for a many-electron system. Within the HF method these have the same probability event though the upper situation is less likely due to Coulombic interactions.

These three classes of methods all approach the determination of energy in different ways – however, in determining geometries they use similar strategies – the molecule is varied until a local or global energy minimum is obtained. Once the structure is calculated it is possible to test if the calculation is accurate. One way to do this is to compare the calculated structure with a known crystal structure. Generally DFT and HF methods perform well in structural comparisons with experimental data. Another way is to use the information from the calculation to evaluate other observables, such as the dipole moment or vibrational spectra of the compound of interest. The vibrational spectrum is a rather useful observable because it is easy to measure on samples for which crystallographic data may be absent (Foresman & Frisch 1995).

Vibrational spectroscopy offers a good method of determining how accurate a calculation is for a number of reasons. Firstly, the values for band frequencies are evaluated through the gradients of the energy (E) of the nuclear potential energy surfaces (PES) for the vibrational modes of the molecule (q), that is $\delta E/\delta q$. For this to correlate with experimental data, the calculation must reproduce the stiffness of the bonds in the molecule. Secondly, the relative intensities of vibrational spectra are related to the PES and its interaction with external electric fields and geometry changes caused by vibrational motion. For example the infrared intensities are determined by the change in dipole moment (μ) with vibrational mode ($\delta\mu/\delta q$). To calculate this correctly the modelling must not only accurately predict the dipole but also how it changes with vibrational modes (e.g. bond stretching). For Raman spectroscopy the test is more rigorous. The Raman intensity is related to the change in polarizablity (α) with vibrational mode ($\delta\alpha/\delta q$). The polarizability of the molecule is related to the elasticity of the electron field in the system. These are related to the energy of the system in the following ways (Jensen 1999).

For infrared (IR) intensity $(\delta\mu/\delta q)^2=(\delta^2 E/\delta R\delta F)^2$, where R is the change in geometry and F is the electric field strength. For Raman intensity $(\delta\alpha/\delta q)^2=(\delta^3 E/\delta R\delta F^2)^2$, thus the Raman intensities require the energy of the system to be known with respect to geometry change and the effect of external electric field. These are formidable tasks for the calculation. Importantly if there is good correlation between the calculated properties and those observed, this indicates that the other calculated parameters, such as electrostatic potentials and molecular orbitals (MOs), may also be good representations and thus provide predictive power to the researcher examining these data. The nature of MOs and electrostatic potentials are important parameters used to study pharmaceuticals and the properties of such compounds.

Case studies

Two drugs are chosen in this paper to exemplify how quantum chemistry has been used to investigate pharmaceuticals – these are indometacin and carbamazepine.

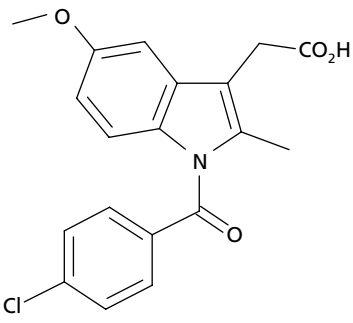
Indometacin ([1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid) is an indole acetic acid derivative (Figure 2). It is classified therapeutically as a nonsteroidal anti-inflammatory drug (NSAID), and thus is used in the symptomatic management of painful and inflammatory conditions, especially musculoskeletal and joint disorders. Carbamazepine has antiepileptic and psychotropic properties, and is used to control secondarily generalized tonic–clonic seizures and partial seizures. It is also used in the treatment of trigeminal neuralgia, other neurological syndromes associated with severe pain and as a mood stabilizer in the treatment of bipolar disorder unresponsive to lithium.

Studies of indometacin

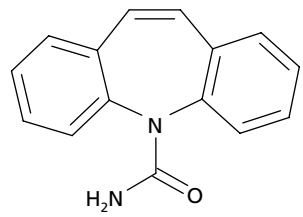
A recent example of the use of quantum-mechanical calculations in attempting to understand the efficacy of an active pharmaceutical ingredient was the study of indometacin and a series of structurally similar arylalkanoic acids (Santana et al 1999). Compounds containing this type of acid group are known to have interesting anti-inflammatory properties. The anti-inflammatory activity was believed to be due to inhibition of cyclooxygenase (COX) and subsequent disruption of prostaglandin synthesis (Garret & Grisham 2005). However, a detailed picture of the interaction between the alkanoic acid and the receptor was not evident (Guarnieri et al 1998). The aim of this paper was to attempt to provide a structure–activity relationship for arylalkanoic acids and anti-inflammatory response. Previous studies suggested that the charge distribution within the active compound may correlate with drug efficacy (Guarnieri et al 1998). To explore this possible correlation, Santana et al (1999) synthesized a series of structurally similar benzofurylacetic acids in which electron-donating and -withdrawing groups were substituents on the benzyl ring (Figure 3).

These compounds were investigated for anti-inflammatory response by testing the inhibition of prostaglandin synthesis via measurement of malondialdehyde (MDA) production spectrophotometrically. The electronic properties of the compounds were modelled using the semi-empirical AM1 method. It was found that the general shape in terms of wavefunction amplitude and node disposition of the frontier molecular orbitals (FMOs) was similar for the series of arylalkanoic acids. Changes were observed that appeared systematic (e.g., the electron density of the aromatic ring was greater for the methyl-substituted system compared with the hydroxy-substituent compound). Furthermore, the electronic structures and FMOs for the series of arylalkanoic acids appeared similar to those of the active drug naproxen and calculations on a fragment (with the chorobenzene substituent absent) of the active drug indometacin. Studies of the efficacy of these materials revealed that naproxen and indometacin were the only active compounds, with indometacin having an IC50 value 1000 times that of naproxen. More detailed calculations on the complete indometacin molecule revealed that the chlorobenzene substituent had a considerable effect on the electronic structure of the compound. The lack of activity from any of the arylalkanoic acid series meant that no electronic structure-to-function relationship could be identified.

The importance of the indometacin structure and the chlorobenzene substituent was further examined in a subsequent study. More sophisticated computational methods were used to understand the inhibition of COX by NSAIDs such as indometacin (Lozano et al 1997). In this study the molecular electrostatic potentials (MEPs) were calculated and these MEP properties

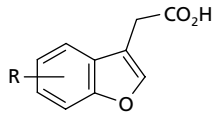


Indomethacin



Carbamazepine

Figure 2 Chemical strucuture of indometacin and carbamazepine.



R = 6-OH; 6-OH, 7-CH_3; 5-CH_3; 5-OCH_3

Figure 3 Structure of benzofurylacetic acids and derivatives.

related to the observed COX inhibition. There are two isoforms of COX, termed COX-1 and COX-2. COX-1 is responsible for the normal physiological production of prostaglandins and it is COX-2 that is induced by cyctokines, mitogens and endotoxins in inflammatory cells to produce the prostaglandins in inflammation. Indometacin belongs to the class of NSAIDs that inhibit both COX-1 and COX-2. Such drugs are thus effective in reducing the inflammatory response from COX-2 but also may result in stomach lesions and renal toxicity through inhibition of COX-1. It has been recognized that indometacin and a number of other drugs, including flurbiprofen, cause a slow, time-dependent inhibition of COX-1 and COX-2, whereas other NSAIDs are competitive inhibitors of substrate binding (ibuprofen, pirprofen and naproxen, Figure 4) (Tomlinson et al 1972; Bray & Gordon 1978; Garret & Grisham 2005). The aim of the study was to establish if there was a pattern to the effectiveness of the drugs and their MEPs as the drugs were not structurally closely related.

Over eight active drugs were studied along with numerous related compounds. The analysis of the spatial volume distribution of the MEPs was instructive in that it showed that the time-dependent inhibitors were electronically distinct from the non-time-dependent (simple competitive) inhibitors. The MEP for the time-dependent inhibitors was a cone of negative potential; the point of the cone started at the carboxy group (Figure 5). The simple inhibitors did not possess this electronic structure. On the basis of these results the authors predicted that (*S*)-pirprofen would act as a time-dependent inhibitor, and studies demonstrated this to be correct (Rome & Lands 1975; Dionne & Webber 1983).

Studies of carbamazepine

It had been recognized from the late 1990s that there existed a correlation between the activity of drugs, such as carbamazepine, and their ring topology (Marone et al 1999). In a detailed study of ring topology and activity, Marone et al (1999) used semi-empirical methods to examine the suite of possible conformers that existed for a group of tricyclic antidepressant, antipsychotic and anticonvulsant drugs,

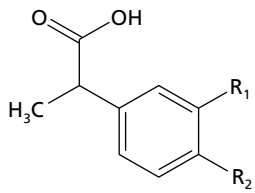


Figure 4 Selected compounds used in the study of Lozano et al (1997). Flurbiprofen: $R_1 = F$, $R_2 = C_6H_5$. Ibuprofen: $R_1 = H$, $R_2 = CH_2$-$CH(CH_3)_2$. Pirprofen: $R_1 = Cl$, $R_2 = NC_4H_6$.

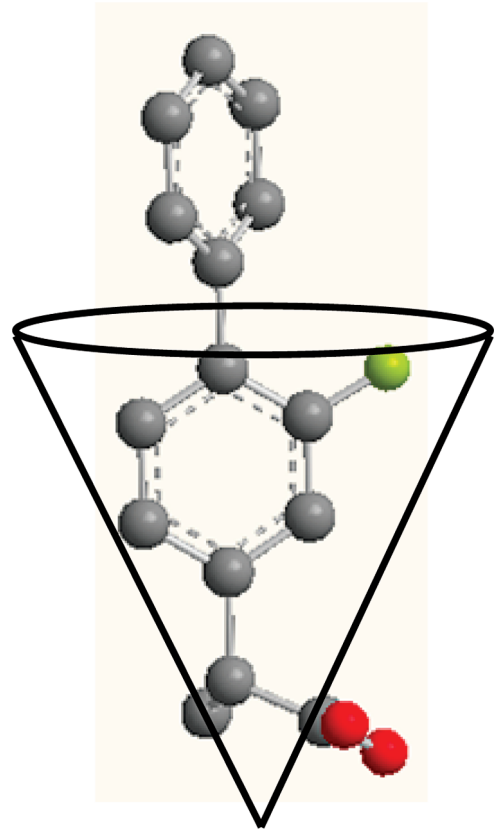


Figure 5 Depiction of MEP isopotential surface (dark line cone) for flurbiprofen, adapted from Lozano et al (1997).

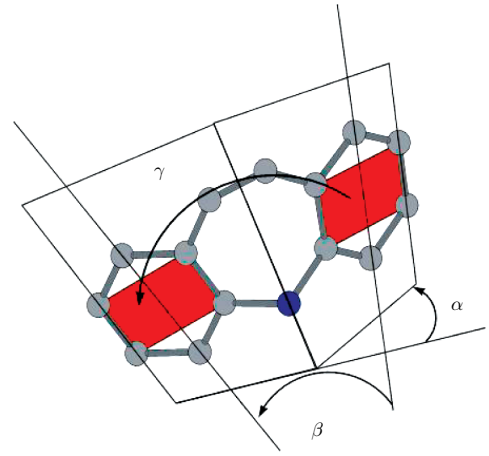


Figure 6 Carbamazepine structure with angular descriptors included, adapted from Marone et al (1999).

including carbamazepine. The tricyclic ring system may be structurally described by three angular descriptors (Figure 6). These descriptors were characteristic of the type of neuroactive drug. Indeed, some of the drugs showed activity in more than one treatment – such drugs had borderline angular descriptor values. The best differentiating parameter between anticonvulsants and antidepressants was the γ angle.

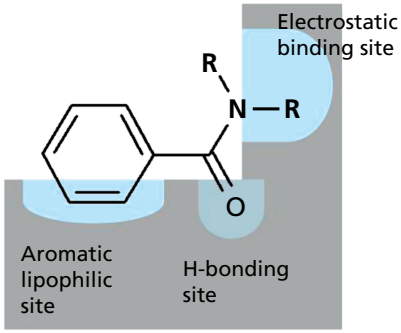


Figure 7 Depiction of the binding site for anticonvulsants and anaesthetic binding site, adapted from Carter et al (2003).

Semi-empirical methods were used to develop a better quantitative structure–activity relationship (QSAR) understanding of anticonvulsant drugs, including carbamazepine (Tasso et al 2000). A number of important structural parameters and electronic properties were recognized from this study. Firstly, the classical parameter of lipophilicity was a poor indicator of activity. However, quantum parameters, such as the energies of the FMOs, were more closely correlated to activity. The importance of the carbonyl group in the carboxamide moiety was observed and this led to the hypothesis that these types of drugs interact through an initial electrostatic interaction.

The examination of the direct interaction between carbamazepine and an enzyme CYP3A4 (a type of cytochrome P450, expressed in the liver) was undertaken using theoretical calculations and activity studies (Torimoto et al 2003). Of particular interest was the epoxidation of carbamazepine to carbamazepine 10,11-epoxide in the presence of steroids. The active site was modelled using molecular mechanics and density functional theory. Modeling of the active site of CYP3A4 showed that is was large enough to accommodate two substrate molecules and theoretical calculations supported the concept that the carbamazepine could be present with steroid, thus facilitating the epoxidation of the former.

An interesting study examined the structural relationship between anticonvulsants and anaesthetics (Carter et al 2003). Using density functional theory, the structures of individual molecules were calculated. The compounds examined had structural similarity in terms of the separation between the carbonyl group and phenyl ring (which all systems possessed); the phenyl–carbonyl oxygen separation for anticonvulsants lay at 4.2 ± 0.2 Å, while that of the anaesthetics was shorter (3.6 ± 0.4 Å) (Figure 7). This and other evidence suggests that the two classes of drugs bind at the same sodium ion channel (Ragsdale et al 1996; Ragsdale & Avoli 1998).

Spectroscopy of pharmaceuticals

Vibrational spectroscopy has been widely used in the study of pharmaceuticals, ranging from quantification of polymorph mixtures using near IR or Raman spectroscopy (McMahon et al 1996; Taylor & Zografi 1997, 1998; Bell et al 2000; Gabrielli et al 2000; Rustichelli et al 2000; Patel et al 2001; Pratiwi et al 2002; Anquetil et al 2003; Auer et al 2003; Santesson et al 2003; Schmidt et al 2003; Strachan et al 2004a) through to terahertz spectroscopy (Gordon & Rades 2002; Taday et al 2003; Strachan et al 2004b, 2005). However, there have been comparatively few studies that have attempted to combine computational methods with spectroscopic data (Strachan et al 2004a; Jubert et al 2005; Williams et al 2005; Zeitler et al 2005). One reason to combine these techniques is that spectroscopy provides a method of testing the efficacy of the calculation. The accurate prediction of the frequency and intensity of vibrational bands suggests a well-modelled potential energy surface. This in turn provides more confidence in other predicted parameters, such as electrostatic potentials, which may be much more difficult to verify. An excellent example of the combination of spectroscopy and computational chemistry is provided in a study of indometacin and a number of related structures (niflumic acid and diclofenac) (Jubert et al 2005). The primary interest in these structures was their electrostatic potentials, as this is of particular use in identifying sites of electrophilic or nucleophilic attack. This potential represents the first interaction between substrate and enzyme in pharmaceutical action.

The structures and vibrational spectra of the compounds were determined using density functional theory (B3LYP/6-311++G*) (this notation represents the method and basis set used, respectively; detailed explanation of this notation may be found in Young (2001)) starting from the lowest energy conformers, determined by molecular modelling using force fields. The electrostatic potentials across each of the molecules were then determined. Vibrational infrared data were measured at 298 and 77 K and compared with the calculated spectra. The conclusion of this study was that the carboxylate groups of NSAIDs, such as indometacin, play a key role in the interaction of the drugs with prostaglandin producing enzyme in the human body. This work demonstrated similar findings to that of Lozano et al (1997) but with greater quantification through the use of more precise electrostatic potential modelling and vibrational spectroscopy to confirm structural predictions.

Density functional theory calculations were used to understand spectral changes in carbamazepine (Strachan et al 2004a). B3LYP/6-31G(d) level calculations on the isolated carbamazepine molecule proved to be rather poor at predicting the observed IR and Raman spectral data. This was particularly true for modes involving the $CONH_2$ groups. A much improved correlation for experimental to calculated spectral data was attained when the hydrogen bonded dimer of carbamazepine was studied (Figure 8).

New experiments: where to now?

One of the most exciting developments in recent years in the area of quantum calculations with respect to solid-state forms of pharmaceuticals has been the impressive improvement in the ability of researchers to use quantum calculations for larger and larger systems. It is a tribute to software developers that many packages now exist that allow scientists with little experience in programming to delve into quantum calculations (Young 2001). It is now possible to predict the vibrational spectra of large systems reasonably easily and with some confidence that the calculations will be effective. Although this is a great advance there are some new challenges that have

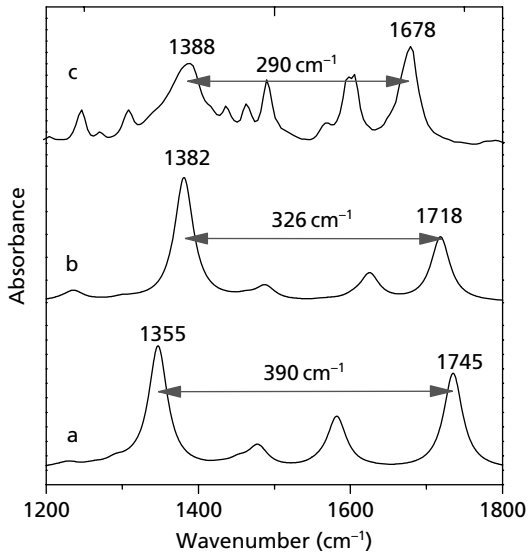


Figure 8 Infrared spectra of carbamazepine; calculated for monomer species (a); calculated for dimer (b); experimental data for form III (c). Arrows indicate the wavenumber separation between $CONH_2$ modes, adapted from Strachan et al (2004a).

become worth exploring. Within the confines of polymorphism, for example, the solid-state interactions between molecules in differing crystal forms or with excipients are extremely important. This manifests itself in spectral data and can now be modelled, albeit with rather limited success at this point. A recent study used density functional theory to model the low frequency modes of carbamazepine (Zeitler et al 2005). The level of correspondence between theory and experimental spectra was of sufficient qualitative agreement to support the assertion that the solid-state sample was better modelled by using a carbamazepine dimer rather than single molecule.

Conclusions

Quantum chemistry has played a significant role in understanding pharmaceutical systems and their interactions with the human body. The improvements in computer power and software mean that this contribution will continue and become more commonplace. The development of coding that can readily handle more complex systems, such as unit cells and many-molecule problems, suggests that in the future polymorphic and amorphic states may be modelled using these quantum techniques. In this way it may be possible for quantum chemistry to assist process control development in the same way that it has facilitated drug discovery for many years.

References

Anquetil, P. A., Brenan, C. J. H., Marcolli, C., Hunter, I. W. (2003) Laser Raman spectroscopic analysis of polymorphic forms in microliter fluid volumes. *J. Pharm. Sci*. **92**: 149–160

Auer, M. E., Griesser, U. J., Sawatzki, J. (2003) Qualitative and quantitative study of polymorphic forms in drug formulations by near infrared FT-Raman spectroscopy. *J. Mol. Struct*. **661–662**: 307–317

Bell, S. E. J., Burns, D. T., Dennis, A. C., Speers, J. S. (2000) Rapid analysis of ecstasy and related phenethylamines in seized tablets by Raman spectroscopy. *Analyst (Cambridge, United Kingdom)* **125**: 541–544

Bray, M. A., Gordon, D. (1978) Prostaglandin production by macrophages and the effect of antiinflammatory drugs. *Br. J. Pharmacol*. **63**: 635–642

Carter, M. D., Stephenson, V. C., Weaver, D. F. (2003) Are anticonvulsants two thirds of local anesthetics? A quantum pharmacology study. *Theochem* **638**: 57–62

Dionne, R. E., Webber, S. S. (1983) Pirprofen. *Drug Intell. Clin. Pharm*. **17**: 894–897

Foresman, J. B., Frisch, A. (1995) *Exploring chemistry with electronic strucuture methods*. 2nd edn., Gaussian Inc., Pittsburgh

Gabrielli, C., Jaouhari, R., Joiret, S., Maurin, G. (2000) In situ Raman spectroscopy applied to electrochemical scaling. Determination of the structure of vaterite. *J. Raman Spectrosc*. **31**: 497–501

Garret, R. H., Grisham, C. M. (2005) *Biochemistry*. 3rd edn, Thomson Brookes/Cole, Australia

Gordon, K., Rades, T. (2002) Spectroscopy and solid state properties of drugs: will femtochemistry meet pharmacy? *Chem. N. Z*. **66**: 43–47

Guarnieri, F., Schmidt, A. B., Mehler, E. L. (1998) Screened Coulomb potential based implicit solvent model: formulation and parameter development. *Int. J. Quantum Chem*. **69**: 57–64

Jensen, F. (1999) *Introduction to computational chemistry*. 1st edn, John Wiley & Sons, Chichester

Jubert, A., Massa, N. E., Tevez, L. L., Okulik, N. B. (2005) Vibrational and theoretical studies of the non-steroidal anti-inflammatory drugs niflumic [2–3((3-trifluoromethyl)phenylamino)-3-pyridinecarboxylic acid]; diclofenac [[2-(2,6-dichlorophenyl)amino]-benzeneacetic acid] and indometacin acids [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid]. *Vibrational Spectrosc*. **37**: 161–178

Lozano, J. J., Pouplana, R., Ruiz, J. (1997) Molecular electrostatic potential in differential inhibition of prostaglandin endoperoxide synthase (cyclooxygenase) by non-steroidal antiinflammatory drugs. *Theochem* **397**: 59–77

Marone, S., Rozas, I., Weaver, D. F. (1999) Theoretical structural analyses of tricyclic neuroactive drugs: quantum pharmacologic descriptors for clustering anticonvulsant, antidepressant, and antipsychotic activities. *Theochem* **467**: 25–30

McMahon, L. E., Timmins, P., Williams, A. C., York, P. (1996) Characterization of dihydrates prepared from carbamazepine polymorphs. *J. Pharm. Sci*. **85**: 1064–1069

Patel, A. D., Luner, P. E., Kemper, M. S. (2001) Low-level determination of polymorph composition in physical mixtures by near-infrared reflectance spectroscopy. *J. Pharm. Sci*. **90**: 360–370

Pratiwi, D., Fawcett, J. P., Gordon, K. C., Rades, T. (2002) Quantitative analysis of polymorphic mixtures of ranitidine hydrochloride by Raman spectroscopy and principal components analysis. *Eur. J. Pharm. Biopharm*. **54**: 337–341

Ragsdale, D. S., Avoli, M. (1998) Sodium channels as molecular targets for antiepileptic drugs. *Brain Res. Brain Res. Rev*. **26**: 16–28

Ragsdale, D. S., McPhee, J. C., Scheuer, T., Catterall, W. A. (1996) Common molecular determinants of local anesthetic, antiarrhythmic, and anticonvulsant block of voltage-gated Na+channels. *Proc. Natl Acad. Sci. USA* **93**: 9270–9275

Ratner, M. A., Schatz, G. C. (2001) *Introduction to quantum mechanics in chemistry*. 1 edn, Prentice-Hall Inc., Upper Saddle River, NJ, p. 305

Rome, L. H., Lands, W. E. (1975) Structural requirements for time-dependent inhibition of prostaglandin biosynthesis by antiinflammatory drugs. *Proc. Natl Acad. Sci. USA* **72**: 4863–4865

Rustichelli, C., Gamberini, G., Ferioli, V., Gamberini, M. C., Ficarra, R., Tommasini, S. (2000) Solid-state study of polymorphic drugs: carbamazepine. *J. Pharm. Biomed. Anal*. **23**: 41–54

Santana, L., Teijeira, M., Uriarte, E., Teran, C., Linares, B., Villar, R., Laguna, R., Cano, E. (1999) AM1 theoretical study, synthesis and biological evaluation of some benzofuran analogs of anti-inflammatory arylalkanoic acids. *Eur. J. Pharm. Sci*. **7**: 161–166

Santesson, S., Johansson, J., Taylor, L. S., Levander, I., Fox, S., Sepaniak, M., Nilsson, S. (2003) Airborne chemistry coupled to Raman spectroscopy. *Anal. Chem*. **75**: 2177–2180

Schmidt, A. G., Wartewig, S., Picker, K. M. (2003) Potential of carrageenans to protect drugs from polymorphic transformation. *Eur. J. Pharm. Biopharm*. **56**: 101–110

Silva, C., Leopoldino, A. M., Silva, E. H. T., Espinoza, V. A. A., Taft, C. A. (2005) Computer-aided design of a novel ligand for retinoic acid receptor in cancer chemotherapy. *Int. J. Quantum Chem*. **102**: 1131–1135

Strachan, C. J., Howell, S. L., Rades, T., Gordon, K. C. (2004a) A theoretical and spectroscopic study of carbamazepine polymorphs. *J. Raman Spectrosc*. **35**: 401–408

Strachan, C. J., Rades, T., Newnham, D. A., Gordon, K. C., Pepper, M., Taday, P. F. (2004b) Using terahertz pulsed spectroscopy to study crystallinity of pharmaceutical materials. *Chem. Phys. Lett*. **390**: 20–24

Strachan, C. J., Taday, P. F., Newnham, D. A., Gordon, K. C., Zeitler, J. A., Pepper, M., Rades, T. (2005) Using terahertz pulsed spectroscopy to quantify pharmaceutical polymorphism and crystallinity. *J. Pharm. Sci*. **94**: 837–846

Taday, P. F., Bradley, I. V., Arnone, D. D., Pepper, M. (2003) Using Terahertz pulse spectroscopy to study the crystalline structure of a drug: a case study of the polymorphs of ranitidine hydrochloride. *J. Pharm. Sci*. **92**: 831–838

Taskinen, J., Yliruusi, J. (2003) Prediction of physicochemical properties based on neural network modelling. *Adv. Drug Deliv. Rev*. **55**: 1163–1183

Tasso, S. M., Bruno-Blanch, L. E., Moon, S. C., Estiu, G. L. (2000) Pharmacophore searching and QSAR analysis in the design of anticonvulsant drugs. *Theochem* **504**: 229–240

Taylor, L. S., Zografi, G. (1997) Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm. Res*. **14**: 1691–1698

Taylor, L. S., Zografi, G. (1998) The quantitative analysis of crystallinity using FT-Raman spectroscopy. *Pharm. Res*. **15**: 755–761

Tomlinson, R. V., Ringold, N. J., Qureshi, M. C., Forchielli, E. (1972) Relationship between inhibition of prostaglandin synthesis and drug efficacy: support for current theory on mode of action of aspirin-like drugs. *Biochem. Biophys. Res*. **46**: 552–559

Torimoto, N., Ishii, I., Hata, M., Nakamura, H., Imada, H., Ariyoshi, N., Ohmori, S., Igarashi, T., Kitada, M. (2003) Direct interaction between substrates and endogenous steroids in the active site may change the activity of cytochrome P450 3A4. *Biochemistry* **42**: 15068–15077

Williams, P. A. M., Molinuevo, M. S., Okulik, N., Jubert, A. H., Etcheverry, S. B. (2005) Synthesis, characterization and biological properties of vanadyl(IV) complexes of diclofenac and indomethacin: An experimental and theoretical study. *Appl. Organometallic Chem*. **19**: 711–718

Young, D. C. (2001) *Computational chemistry*. 1st edn, Wiley-Interscience, New York

Zeitler, J. A., Newnham, D. A., Taday, P. F., Strachan, C. J., Pepper, M., Gordon, K. C., Rades, T. (2005) Temperature dependent terahertz pulsed spectroscopy of carbamazepine. *Thermochim. Acta* **436**: 70–76