High Resolution X-ray Diffraction Analysis of CB1 Receptor Antagonists as a Means to Explore Binding Affinity

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High Resolution X-ray Diffraction Analysis of CB1 Receptor Antagonists as a Means to Explore Binding Affinity

A Dissertation

Submitted to the Graduate Faculty of the University of New Orleans in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry Physical

by

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B.S. University of New Orleans, 2007
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Abstract

Charge density studies have been conducted on ten CB₁ cannabinoid receptor antagonists via high resolution x-ray crystallography. The experimental electron density distributions were determined from multiple redundant high-resolution diffraction measurements at reduced temperatures. Topological analysis of the experimental densities was performed using the Quantum Theory of Atoms in Molecules (QTAIM) approach. Bond critical point values and various other properties derived from the charge density, including various statistical measures of the electrostatic potential, were analyzed in correlation to the affinity (Kᵢ) of each compound with the CB₁ receptor. The data was also interpreted by principal component analysis with three principal components accounting for 80.14% of the data variation. Exploratory factor analysis was limited due to the low sample count and the requirements set for the inclusion of correlated/anti-correlated variables left fewer variables to analyze. Correlation/anti-correlation was found between several properties and Kᵢ. Of these correlations, the most well-established of these properties by this data were the charges on the ortho-chlorines (correlated) of the first ring system (in this papers organizational scheme), the charge of both oxygens of the ester group of each compound (correlated), average charge of the triazole nitrogens (anti-correlated), and the total volume and substituent volume of each compound (anti-correlated).
Introduction

Part 1: The Cannabinoid System

Marijuana, which contains the psychoactive cannabinoid Δ⁹-THC (Δ⁹-tetrahydrocannabinol), has been used for thousands of years for both its recreational effects and its medicinal benefits.¹ It was not until 1964 that the compound was isolated and identified as the component responsible for the effects of cannabis by Gaoni and Mechoulam.² At the time it was believed that Δ⁹-THC and its analogues produced their pharmacological actions through membrane disruption effects and not through ligand-receptor interactions.³ After high-affinity ligands were synthesized, making it easier to discover the associated target, the first cannabinoid receptor was discovered.⁴ It was termed cannabinoid type 1 receptor (CB₁). This established the ligand-receptor mechanism of cannabinoids’ actions. Shortly thereafter the receptor was cloned, first in rats (1990), then in humans (1991).⁵ ⁶ This led to the discovery of yet a second cannabinoid receptor (CB₂) in 1993 by sequence homology analysis.⁷ Both of these receptors are A-Class (rhodopsin like) G-coupled-protein receptors (GPCR) and share their typical attributes. The CB₁ and CB₂ receptors are concentrated in different areas throughout the body. The CB₁ has been found primarily in the central nervous system in high concentration in the substantia nigra (largely responsible for the production of dopamine), globus pallidus, putamen, hippocampus, and cerebellum tissue.⁸ ⁹ It is thought that this receptor subtype is primarily responsible for the psychoactive effects of cannabinoid ligands as the CB₁ receptor is involved in memory, cognition, and the mediation of transmitter release through its coupling to ion channels in the brain.¹⁰ The CB₂ receptor however is found primarily in peripheral tissues such as in the tonsils and spleen, adipose tissue, and throughout the immune system.¹¹ The CB₂ receptor is targeted by the drug industry primarily for therapeutic immune treatment as it is involved in
signal transduction in the immune system. The CB$_1$ receptor, the receptor target of this study, however is targeted for a host of neuronal disorders such as obesity (in the case of overeating), nicotine and cocaine dependence, in the case of its antagonists, and stoke, multiple sclerosis, and Parkinson’s disease, in the case of its agonists.

At the outset of drug development for the cannabinoid system there was very little knowledge of the endocannabinoid system. Efforts were typically focused on modifying the structure of $\Delta^9$-THC, a tricyclic structured cannabinoid, in a manner that would inhibit the activation of the CB receptors without reducing its affinity for the receptor. This would effectively turn $\Delta^9$-THC, an agonist to CB receptors, into an antagonist. These compounds are termed classical cannabinoids. Though there are some good candidates from this research it has by enlarge been abandoned. In the early nineties while investigating non-steroidal anti-inflammatory drugs, the company Sterling serendipitously discovered aminoalkylindole derived cannabinoid agonists. These drugs were related to the anti-inflammatory pravadoline. The most notable of these drugs is WIN-55,212, which has a notably higher binding affinity than $\Delta^9$-THC. These compounds were discovered to bind to a different region of the CB$_1$ receptor than classical cannabinoids or anandamide (an endocannabinoid) which was verified by mutagenic studies. It has also been discovered that this region is the same region that binds rimonabant, which acts as a mild inverse agonist as opposed to an agonist. Other novel CB$_1$ antagonists and inverse agonists have been discovered. Azetidine (Aventis), Aryl-Imidazolidine-2,4-Dione (Didier Lamert team), Diarylimidazole (Merck), and 3,4-Diaryl-Pyrazolin (Solvay) derivatives have been reported to be antagonists or inverse agonists. None of these compounds have gained as much attention as rimonabant.
In more recent years a large portion of the drug development effort has been directed towards creating drugs that have a similar scaffold to rimonabant (often referred to in the literature as SR141716A), including the compounds in this study. Rimonabant was formerly prescribed in Europe for the treatment of obesity. It is a lead compound of the diarylpyrazole derived class of cannabinoids introduced by Sanofi in 1994. Rimonabant is highly selective for the CB₁ over the CB₂ receptor, having a Kᵢ value of 5.6 nM and over 1000 nM, respectively. It is the first antagonist/inverse agonists to do so. Evidence also suggests that rimonabant binds to other receptors potentially causing some of its in-vivo effects. Its intended goal of development was as an anti-obesity agent targeting CB₁ receptors in the central nervous system to reduce food intake. It has been found that CB₁ knockout mice are also leaner and resist diet-induced obesity. This suggests that the mechanism includes more than just feeding behavior. It follows that if the activity of these receptors are blocked a similar result will occur. In the United States over 100,000 deaths are estimated to be associated with obesity and its complications. It is a major public health concern.

In the clinical study, Rimonabant in Obesity (RIO), a program conducted in various clinical centers globally, rimonabant was shown to be effective against placebos in double blind trials in reducing different quantifiers of obesity. In an overview of the research in 2008, which assessed cardiometabolic risk factors, Van Gaal sums up its findings. Subjects in the study were given a placebo, 5 mg, or 20 mg of rimonabant daily. They were also given a restricted calorie diet and an increased physical activity regime. The side effects of the drug were analyzed using the Hospital Anxiety and Depression Scale to evaluate the psychological effects, if any, on the subjects. It was found that for those taking a daily dose of 20 mg of rimonabant there was a reduction in weight by 6.3 kg to 6.6 kg versus a loss of 1.6 kg to 1.8 kg for those taking a
placebo over six months. Also an average of 3.6 cm of waist circumference reduction, 13.2% triglycerides reduction, 7.2% increase in HDL cholesterol, and a decrease in blood pressure were observed. Due to such positive initial results with the drug, despite having been taken off of the market for safety concerns, studies continue on rimonabant to assess tolerability.

CB₁ antagonists and inverse agonist, like rimonabant, have also shown promise in dealing with drug addiction. It has been reported that Δ⁹-THC, a CB₁ agonist, causes a “high” or a euphoric experience in humans and primates. This is assumed to be the cause of the wide spread abuse of marijuana. The administration of rimonabant (90 mg) has been shown to reduce the effects of smoking marijuana without reducing Δ⁹-THC blood plasma concentration. This suggests the effects are due to the blockade of the CB₁ receptor, and not an alteration in the pharmacokinetics of Δ⁹-THC. Rimonabant has been shown to be effective in attenuating nicotine self-administration in rats and reduces the anxiety reducing effects of nicotine on mice that were pre-exposed to nicotine. There have been somewhat mixed results favoring rimonabant as an aid in the cessation of smoking in preclinical trials in humans under the program “Studies with Rimonabant and Tobacco Use” (STRATUS), with the STRATUS-US (United States) study showing a doubled rate of abstinence 42 weeks after a 10 week regime of 20 mg of rimonabant compared to placebo. The study also notes a reduction in weight of test subjects. CB₁ agonists on the other hand, such as WIN 55,212-2, have been shown to increase nicotine self-administration. Rimonabant also has a positive effect on opiate self-administration in rats and may have therapeutic usages in opiate addiction. Unfortunately studies on alcoholism are currently inconclusive. Results from animal studies suggest a decline in self-administration. However, Human trials are too small and short in duration to be conclusive. Methamphetamine self-administration in rats is attenuated by rimonabant as
well. Although rimonabant has shown to be effective or partially effective in the treatment of the aforementioned substance addictions it has shown to be less effective in treating ongoing stimulant addictions.42-45

In spite of the beneficial therapeutic effects CB₁ inverse agonists and antagonists have had in numerous studies, their potential as safe and effective drugs are not so clear cut. Rimonabant and other CB₁ antagonist/inverse agonist treatment has side-effects and can adversely affect patients taking these drugs. In the RIO studies of rimonabant, many adverse psychological effects of the drug were observed in substantial percentages, though they were generally mild. These side effects usually occurred within the first few months of treatment.46 They include psychiatric side effects such as anxiety, depression, irritability, and insomnia as well as physical side effects such as nausea, vomiting, and diarrhea. In RIO studies twenty six percent of patients experienced psychiatric symptoms while only fourteen percent of patients receiving a placebo experienced psychiatric symptoms. Nine percent was due to depression.47 This is especially significant because people that are obese are already at a higher risk for depression. The study excluded people with preexisting psychiatric disorders at the outset. Of the patients taking 20 mg doses, 13-16% discontinued treatment because of side effects.47-50

Due to adverse effects, rimonabant was withdrawn from the market and several other CB₁ receptor antagonist/inverse agonists were withdrawn from clinical studies in 2008 for similar reasons. Other CB₁ ligands include tatanabant (Merck), otenabant (Pfizer), ibipinabant (Solvay/Bistol-Myers Squibb), and surinabant (Sanofi-Aventis).51,52 With so many CB₁ receptor antagonists/inverse agonists withdrawn from the market for psychiatric side effects, alternative approaches are beginning to be utilized:
1) Develop drugs that do not cross the blood brain barrier and rely entirely on peripheral effects to reduce weight.

2) Select out patients that simply don’t respond adversely.

3) Develop neutral antagonists instead of inverse agonists so that the drugs only competitively inhibit the CB₁ receptor instead of deactivating it (In order for a CB₁ antagonist to be effective in treating addictive disorders, the drug must cross the blood brain barrier).

The first approach relies on the fact that a significant percent of side effects are due to direct interactions with the central nervous system (CNS) as previously noted. While CB₁ receptors have an effect on food intake when in the CNS, they also play a role in the hormonal signaling to the brain that food is required, causing the experience of hunger. The experience of hunger is complex and involves interactions between adipocytes, the mesolimbic system, the hypothalamus and the gastrointestinal tract as well as the production of the hormones ghrelin and leptin.⁵³ Along with the ability of the endocannabinoid system to regulate these interactions, it has also been shown in rat studies to increase adiponectin (when deactivated), an adipose tissue protein that increases fatty acid oxidation.⁵⁴-⁵⁶ This tactic focuses on the peripheral effects a CB₁ antagonist can have on the onset of hunger. The second approach deals with the filtering out of potential patients based on their prior mental health and family history of mental health. Some have suggested attempting to identify genes responsible for the depressive and anxiolytic symptoms, as it is known that CB₁ receptors are present on both GABA and serotonin neurons, both of which are involved in anxiety and depression, and interact with the serotonin transporter, to select candidates for CB₁ antagonist therapy.⁵⁴,⁵⁷-⁵⁹ The third approach focuses on the idea
that the negative side effects of the compounds, as well as rimonabant, are due to these ligands being inverse agonists, and as such produce effects opposite of agonists (which are euphoric). A neutral antagonist would, in theory, be able to block the receptor site without causing negative emotional side effects. This would allow drugs that have both central activity (due to crossing the blood brain barrier), and peripheral activity, allowing for a greater variety of treatment uses. However there is debate as to whether this is possible in a system with endogenous ligands.\textsuperscript{60,61}

Currently there are a host of drugs that target the endocannabinoid system that are offered on the market. \textit{Nonselective} cannabinoid receptor \textit{agonists} are currently used as appetite stimulants, anti-emetics, tumor growth inhibitors, anti-glaucoma agents and for the treatment of multiple sclerosis.\textsuperscript{62-65} Synthetic $\Delta^9$-THC is currently sold as dronabinol.\textsuperscript{22} There are no CB\textsubscript{1} antagonists for the treatment of drug addiction or obesity. And with the other drugs for obesity being suspended (dexitfanfluramine, sibutramine), interest in CB\textsubscript{1} antagonists has been rekindled despite past failings.\textsuperscript{57}

The action of a CB\textsubscript{1} ligand at the CB\textsubscript{1} receptor depends on whether it is an agonist, antagonist, or inverse-agonist. These three terms are all relative to the unperturbed equilibrium of active (R\*\textsuperscript{\textdagger}) and inactive (R) states of the CB\textsubscript{1} receptor. That is to say, the CB\textsubscript{1} receptor produces signal transduction in the absence of a ligand. It has basal activity. This activity is referred to as constitutive activity. This is explained using a hypothetical thermodynamic process.\textsuperscript{66} If binding of a ligand pushes the equilibrium in the direction of the active confirmation (R\*\textsuperscript{\textdagger}), it is considered to be an agonist. If it causes the equilibrium to favor the inactive confirmation (R), it is considered to be an inverse agonist. If the ligand competitively binds but shows no efficacy, that is, it stabilizes both the active and inactive confirmations in a way that does not disrupt their natural ratio, it is termed an antagonist. This model of a two state
system shared by all GPCRs is considered useful but rudimentary.\textsuperscript{67-69} It provides a template for understanding why inverse agonists produce the reverse effect of agonists (they reduce signal transduction) and why neutral antagonists are sought (they would inhibit both agonists and inverse agonists while not reducing basal signal transduction). CB\textsubscript{1} receptors follow the same receptor-ligand interactions as other GPCR. The basic equation used to quantify their interactions is:

\[ K_i = \frac{[P][L]}{[PL]} \]

where \( K_i \) is the value at which 50\% of the receptor sites are binded to by a ligand. \([P]\) and \([L]\) are the unbound protein and ligand concentrations respectively. Though the kinetics of \([PL]\) are the same as for agonist, inverse agonist, and antagonist as far as setting the 50\% occupancy as \( K_i \), \([PL]\) may represent an agonist-receptor complex, inverse agonist-receptor complex, or antagonist-receptor complex, in binding scheme.

Figure 1.1.1 illustrates the dynamic between \( K_i \) and efficacy in the cannabinoid system.
Though the CB₁ receptor does express signaling without ligand binding, there are two known lipid-like ligands (agonist) that are endogenously produced. These are called the endocannabinoids. The two endocannabinoids to have been discovered are anandamide and 2-arachidonoyl glycerol (2-AG). In in-vivo assays used to characterize the form of activity a ligand produces, agonist of the CB₁ receptor induce analgesia, catalepsia, hypomotility, and hypothermia (in rats). Antagonist blockade the action of agonist. And inverse-agonist produce effects opposite of those produce by agonist. In in-vitro assays commonly cAMP quantification is used based on the cannabinoid receptors negative coupling to adenylyl cyclase. A decrease in cAMP production is measurable with the administration of a CB₁ agonist. $[^{35}\text{S}]$-GTPγS, due to a dual-coupling effect for the CB₁ receptor, can also be used as an assay as it shares the commonality with the CB₁ as among all GPCRs in that it binds to a GTP molecule when activated by an agonist. So an agonist will increase the binding to $[^{35}\text{S}]$-GTPγS, a radiolabelled analogue of GTP. This assay allows for the identification of full agonists, partial agonists,
neutral antagonist, and inverse agonist. Based on these two assays rimonabant is considered to be a mild inverse agonist.\textsuperscript{76,77}

Though the CB\textsubscript{1} receptor has not been crystalized and no definite x-ray structure obtained, the potential binding site of CB\textsubscript{1} agonist/inverse agonist has been explored computationally and experimentally by the use of homology and mutagenic studies. 3D homology models are frequently based on bovine rhodopsin, a GPCR, which has been structurally determined by x-ray crystallography at 2.8 Å resolution. And the resulting predictions are tested by mutating specific amino acids in the presumed binding pocket to determine if binding has increased or decreased by the aforementioned bioassays.\textsuperscript{23,78,79} From these studies, specific amino acid residues have been identified as being directly involved in the binding of antagonist and inverse agonist to specific binding regions of the CB\textsubscript{1} receptor.

The CB\textsubscript{1} receptor consists of seven hydrophobic alpha helix transmembrane segments (TMH), an intracellular C terminus, and a 116 residue long extracellular N terminus tail, which seems to have no relevance in receptor recognition.\textsuperscript{80} It consists of 472 total residues.\textsuperscript{70,81} There is evidence that not all CB\textsubscript{1} ligands bind to the same receptor site. Aminoalkylinodoles, such as WIN 55,212-2, have been shown not to bind to the same location of the receptor as anandamide or classical cannabinoids (THC analogues), but bind to the same region as rimonabant. This has been confirmed by mutation studies.\textsuperscript{17,18,82} This also points to the potential of there being multiple activation confirmations. The binding site that has received the most attention is that of WIN 55,212-2 and rimonabant. Figure 1.1.2 is an illustration of the hCB\textsubscript{1}. 
Several key areas of the receptor have been explored with modeling and mutation studies. K3.28 (Lys192) located in the third transmembrane domain (TMH3) of the human CB₁ receptor (hCB₁) was shown to be key in the inverse agonist action of rimonabant in mutation studies by substitution with K3.28A, the non-polar residue alanine. This was verified when molecular modeling techniques showed that the Lys192 residue interacts directly via hydrogen bonding with the C₃ substituent (carbonyl group) of rimonabant. This substitution does not stop rimonabant from binding to the mutant receptor as it will still antagonize WIN 55,212-2, but instead prevents it from acting as an inverse agonist/antagonist. When hydrogen bonding occurs between the Lys192 residue and the C3 substituent (carbonyl oxygen), a salt bridge with
D6.58 (Asp366) is stabilized. This stabilization of the Lys192-Asp366 salt bridge is thought to be responsible for inverse agonism/antagonism as it has been shown by modeling mutagenic studies to contribute to stabilizing the inactive state of the receptor (R). Studies of the binding domain at the CB₁ receptor revealed that rimonabant binds within the TMH3-4-5-6 aromatic microdomain by aromatic stacking interactions with the F3.36 (Phe200), W6.48 (Try356), W5.43 (Try279), and the dichlorophenyl ring system of Rimonabant, and W4.64 (Trp255), Y5.39 (Tyr275), F5.42 (Phe278), and the monochlorophenyl ring system of Rimonabant. Also, hydrophobic interactions occur between the piperidinyl moiety, V3.32 (Val196), F2.57 (Phe170), Leu387, and Met384. These studies also reconfirmed the Lys192 hydrogen bonding interactions with rimonabant. WIN 55, 212-2 was shown to bind in the same domain but with aromatic stacking occurring with the Phe200, Try279, and Try356 residues. It does not stabilize the Lys192-Asp366 salt bridge. This causes it to acts as an agonist as it stabilizes the active confirmation. Within this domain only the F3.25A (alanine) mutation had an effect on anandamide (which binds in the TMH2-3-6-7 region) binding, illustrating a separate binding location for anandamide from rimonabant.

From these binding cues, rational drug designers can begin to make sense of binding affinity and efficacy data, and attempt to design drugs that mimic specific effects of a set of ligands based on their structure. After key binding positions based on hydrogen bonding, steric, electrostatics, and aromatic stacking (other properties may also be included) have been identified, a pharmacophore may be developed to represent a particular class of compounds, i.e. rimonabant-like inverse agonist. Figures 1.1.3 and 1.1.4 are a basic illustration of a rimonabant-like inverse agonist pharmacophore (above), compared to rimonabant, and its presumed binding interactions within the CB₁ receptor and a 3D pharmacophore.
Figure 1.1.3. A 3D pharmacophore mapped onto rimonabant: A) Cyan spheres represent hydrophobic features. B) Beige sphere represent aromatic features. C) Green spheres represent hydrogen bonding features (small: hydrogen bond acceptor, large: hydrogen bond donor).
The CB₁ ligands in this study are rimonabant-like compounds and follow this basic pharmacophore model. However they are triazole-centered, as opposed to pyrazole-centered compounds. They have been analyzed using high resolution x-ray crystallographic data, providing a more detailed look at their surface electrostatics (as binding is achieved by complementary surface properties), atomic basins, and bond ellipticities in an attempt to qualitatively correlate their affinity and efficacy to this data.

In principle, all of the physical and chemical properties of a molecule are the result of its distribution of electrons, the electron density distribution, \( \rho(r) \), and the distribution of nuclear charges. From a knowledge of the electron density, it should be possible to obtain data useful for drug design such as atomic charges, molecular electrostatic potentials, and intermolecular interaction energies.\(^87\) This information can be gained in several fashions. It can be computed theoretically using density functional theory or by a more traditional quantum mechanical approach (molecular orbital calculations), and empirically by direct measurement of the electron density via diffraction. This study utilizes the direct measurement of the electron density distribution by high resolution x-ray diffraction intensity measurements at low temperature. A high resolution description of the ED is necessary for an accurate determination of electrostatic moments as the features in the ED responsible for the above molecular properties occur due to slight alterations in the ED, caused by chemical bonding, at subatomic resolutions.\(^87\)

In crystallography resolution can be quantified in terms of inverse angstroms (\( \text{Å}^{-1} \)) as 
\[ 2 \sin(\theta) / \lambda \]
where \( \lambda \) is the wavelength of the x-ray radiation (0.71073 Å from a Molybdenum source, as used in this experimental setup) and \( \theta \) is half the angle at which the x-rays diffract relative to the incident beam. This formalism can be derived from the basic Bragg diffraction equation \[ \left( \frac{2 \sin(\theta)}{\lambda} = \frac{1}{d} \right) \].\(^88\) High resolution data is collected out to approximately 1.0 Å\(^{-1} \) or greater. The use of this data not only allows for a better determination of positional and thermal displacement parameters associated with individual atoms in the molecule, but also yields a better deconvolution of the static electron density from the positional and thermal parameters.\(^89\)

In order to benefit from this, the static electron density must be modeled not on spherical...
scattering factors, but on aspherical scattering factors. This is what makes high resolution x-ray
crystallography special in regards to a more accurate determination of the ED. What follows is a
basic description of this technique.\(^{87}\)

The most fundamental equation in crystallography is:

\[
\rho(r) = \frac{1}{V} \sum_{H} F_H e^{-2\pi i H \cdot r} \tag{Equation 2.1}
\]

where \(\rho(r)\) is the electron distribution within the unit cell, \(\frac{1}{V}\) is the reciprocatal volume of the unit
cell, \(F_H\) is the structure factor, \(H\) is the scattering vector (in terms of \(h,k,l\)), \(r\) is the position vector
in fractional coordinates \((x,y,z)\) of the unit cell, and the \(e^{-2\pi i H \cdot r}\) are terms of the Fourier series
expansion. The volume of the unit cell can be determined by geometric analysis and will not be
discussed here. The determination of \(F_H\), where the differences in the conventional independent
atom model (IAM) and high resolution x-ray crystallography are present, is more complicated.

The structure factor, a complex variable, is mathematically represented by this equation:

\[
F_H = \sum_{j=1}^{N} f_j(H) t_j(H) e^{(2\pi i H \cdot r)} \tag{Equation 2.2}
\]

where \(t_j(H)\) is the temperature factor of atom \((j)\), a dynamic parameter, and \(f_j(H)\), a static
parameter, is the scattering power of atom \((j)\) at position \((r)\) within the unit cell and in the
direction of \(H\), the scattering vector. Both of these variables decrease with an increase in
\(\sin(\theta)/\lambda\).\(^{88}\) For anisotropic-harmonic temperature factors, the expression is as follows:

\[
t_j(H) = e^{-(2\pi^2 r' \cdot U \cdot r)}
\]

where \(U\) is the mean-square displacement amplitude matrix. This equation is the result of the
Fourier transform of the probability distribution function (pdf or \(P(u)\)) as a function of the
nuclear displacement vector \(u\) in the harmonic approximation of the nuclear displacement due to
vibration about the equilibrium position of atom \(j\) which follows a normal distribution. Higher order treatments of thermal motion (anisotropic-anharmonic motion) may be treated with the Gram-Charlier expansion.\(^9^0\) The expression for aspherical scattering is:

\[
f_j(H) = \int \rho_j(r)e^{2\pi iHr}dr
\]

where \(\rho_j(r)\) is the electron density of atom \(j\) at position \(r\). \(\rho_j(r)\) is represented using the Hansen-Coppens formalism\(^9^1\):

\[
\rho_j(r) = \rho_c(r) + P_v\rho_v(kr) + \rho_d(k'r)
\]

\(\rho_c(r)\) is the core electron density expressed as a spherical function. \(\rho_v(kr)\) is the valence shell electron density (expressed by a spherical harmonic monopole), normalized to one electron, with an expansion-contraction parameter \(k\) that allows the monopole to scale in size. \(P_v\) is the population parameter used to adjust the value of the monopole. \(\rho_d(k'r)\) is an expansion of spherical harmonic multipoles that takes into account aspherical valence shell electron deformations due to chemical bonding. It has its own expansion-contraction parameter \(k'\).\(^9^2\) Its expression is:

\[
\rho_d(k'r) = \sum_l R_l(k'r) \sum_{m=-l}^l P_{lm} y_{lm}\left(\frac{r}{r}\right)
\]

The radial functions \(R_l(r)\) are normalized Slater functions:

\[
R_l(k'r) = \frac{k'^{n(l)+3}}{(n(l) + 2)!} r^{n(l)} e^{-(k'r)}
\]

\(y_{lm}\left(\frac{r}{r}\right)\) are normalized spherical harmonics that are multiplied by a population parameter in order to attenuate the amount of electron density relocated. The \(\rho_d(k'r)\) do not alter the total charge, as their integrals over all space are equal to zero. They merely reallocate electron density
to another part of the atomic environment they describe. All of these parameters are centered about the nucleus of the atom who’s ED they describe.\(^9\)

Thermal parameters are more accurately determined using higher resolution data. This is based on the principle that the core electrons are relatively unaffected by chemical bonding. As a result, near the core of each atom there is a sharp peak in electron density that is relatively unaffected by bonding as in the case of valence electrons. At high angle diffraction, or high resolution data \(\left(\frac{\sin \theta}{\lambda} \geq 0.75 \ \text{Å}^{-1}\right)\), the valence or bond density contribution to the Bragg reflections is greatly reduced due to limitations of the x-ray wavelength and electron density falling out of phase.\(^8\) Due to this phenomenon, it is approximated that all of the electron density contributing to the high angle Bragg reflections are from each atom’s core. As core electrons occupy space near the nucleus and as mentioned earlier are not affected by chemical bonding, and therefore of spherical geometry, the nuclear probability distribution functions are refined using ED modeled on spherical scattering factors including this high resolution data. In an attempt to limit the effect that temperature has on x-ray diffraction, as higher thermal parameters result in lower diffraction at higher angles and to ensure better signal to noise ratios at higher angles, data sets are collected on crystals that are cooled using a cryostream of nitrogen gas. In this experimental setup data were collected at 120 K. The result is better position and thermal parameters due to lower temperatures increasing the angle which x-ray intensities may be observed, and thus the inclusion of data at higher angles in the least-squares refinement.

As the actual data collected, \(|F_H|^2\) (observed as the intensity of reflection H), contains information on both the static scattering factor and the dynamic temperature factor, the two must be separated in order to obtain the static ED.\(^9\) This process is called deconvolution and relies on the Fourier convolution theorem which states that the Fourier transform of a convolution is the
product of the Fourier transforms of the individual functions \( \hat{F}(f * g) = \hat{F}(f) \cdot \hat{F}(g) \).\(^{94}\) As the dynamic electron density of an atom is a convolution of static electron density with the probability density function \( [\rho_j(r) = \rho_j(r)_{\text{static}} * P(u)] \) and the scattering factor is the Fourier transform of the static electron density \( f_j(H) = \int \rho_j(r) e^{2\pi i H \cdot r} \, dr \) or \( f_j(H) = \hat{F}\{\rho_j(r)\} \) and the temperature factor is the Fourier transform of the probability distribution, \( t_j(H) = \int P(u) e^{2\pi i H \cdot u} \, du \) or \( t_j(H) = \hat{F}\{P(u)\} \), then the Fourier transform of the convolution of \( \rho_j(r)_{\text{static}} \) with \( P(u) \) is the dynamic scattering factor which includes both the static aspherical scattering factor and the temperature factors. That is:

\[
\hat{F}\{\rho_j(r) * P(u)\} = \hat{F}\{\rho_j(r)\} \cdot \hat{F}\{P(u)\} = f_j(H) \cdot t_j(H) \tag{Equation 2.7}
\]

Once refined and deconvoluted the thermal parameters are subjected to a Hirshfeld test\(^{95}\) to ensure their reasonability. In the Hirshfeld test, the mean square amplitudes of displacement due to thermal motion for bonded atoms are compared along the bond direction.

Accurate determination of \( t_j(H) \) from refinement of high resolution data at low temperature and \( f_j(H) \) with the use of the Hansen-Coppens formalism for asymmetric scattering factors, which introduces more refinable parameters, ultimately leads to a better model of the ED.\(^{91}\) The model parameters are refined using a least-squares method where the difference between observed and calculated structure factors is minimized by setting the derivative of the difference equal to 0,

\[
0 = \sum w_i(|F_o| - k|F_c|) \frac{\partial |kF_c|}{\partial x_j} \tag{Equation 2.8}
\]

where \(|F_o|\) and \(|F_c|\) are the magnitudes of the observed and calculated structure factors respectively. Here \( k \) is a scale factor used to bring the observed structure factors to the same
scale as the calculated structure factors. The validity of the model may be tested by computing an R-factor which is the fraction of disagreement between $|F_o|$ and $|F_c|$ in terms of $|F_o|$. 

$$R_1 = \left( \frac{\sum |F_o| - |F_c|}{\sum |F_o|} \right)$$

Equation 2.9

Major improvements are noticed in this value after refinement with aspherical scattering factors compared to independent atom model (IAM), a rudimentary refinement in which scattering factors are approximated by spherical functions. It can also be visualized in order to assess the fit of the aspherical scattering factors to individual atoms or group of atoms using a Fourier difference map. This is called the residual density.

$$\Delta \rho_{res} = \left( \frac{1}{V} \right) \sum_H \left[ |F_o| - |F_c| \right] e^{i\alpha e^{-2\pi i(H \cdot r)}}$$

Equation 2.10

Since the phase factor $\alpha$ cannot be measured experimentally, both the observed and calculated structure factors use the calculated phase information. This is referred to as the model biasing problem as the model is biased towards the calculated phases. In Figure 1.2.1 the improvements to the fit of the model for one of the aromatic rings in the compound AVG-229Ph can be seen due to the employment of aspherical scattering factors and high resolution x-ray crystallography (left) compared to the fit with a spherical atom model (right).
Figure 1.2.1: An illustration of the difference density with spherical scattering factors (right) and aspherical scattering factors (left). The lower R-factor and lower peaks in the residual density map indicate a substantial improvement in the aspherical model compared to the spherical IAM model for the ED. Contours are in $0.1 \cdot \text{Å}^{-3}$ increments. Blue solid lines are positive increments. Grey dashed lines are negative. Dotted red lines hold a value of zero. To the left is a residual map in the plane of C(10), C(12), and C(14), part of a ring system in AVG-229Ph, at an approximate resolution of $\sin(\theta)/\lambda = 1.1 \text{ Å}^{-1}$. The final refinement on F of the complete structure is $R_I = 0.0248$. To the right is the same ring system refined with spherical scattering factors. The final refinement on F of the complete structure is $R_I = 0.0462$.

When a difference density is calculated by subtracting the density corresponding to neutral spherical atoms from the electron density of the crystal, it is called an electron deformation density (EDD), because it reveals how atoms are deformed due to chemical bonding and their crystal environment.

$$\Delta \rho(r)_{\text{EDD}} = \rho(r)_{\text{multi}} - \rho(r)_{\text{promolecule}}$$  \hspace{1cm} \text{Equation 2.11}

If $\rho_f(r)_{\text{crystal}}$ is calculated by Fourier transformation of the experimental structure factors, $F_o$, the deformation density is called an ‘experimental dynamic deformation density’ (as seen in the right side of Figure 1.2.1). This density will include the smearing due to thermal motion of the atoms, and will suffer from noise due to errors in the x-ray intensity measurements and series termination errors due to the finite resolution of the experiment.

If, however, $\rho_f(r)_{\text{crystal}}$ is calculated by direct evaluation of the multipole functions used in the Hansen-Coppens multipole model refinement, then the resulting difference density
is called the ‘model electron deformation density’, and can be either a ‘dynamic’ density if the thermal motion is included, or a ‘static’ density if the thermal motion is omitted from the calculation.\cite{96,97} Below is the (static) deformation density of the same ring system as in Figure 1.2.2.

![Deformation density map of the same ring system as in Figure 1.2.1. Contours are in 0.1 e Å⁻³ increments. Blue solid lines are positive increments. Grey dashed lines are negative. Dotted red lines hold a value of zero.](image)

It is clear that electron density has moved into regions between atoms to create chemical bonds. This density may be analyzed to determine any one electron property such as atomic charge, bond order, and aromatic bonding character (ellipticity). Once all qualifying measures of the model’s fit to the data have been checked and reviewed for error and “chemical sense” (if the results seem chemically reasonable), the molecular properties and moments of interest that are available to be calculated may be derived.\cite{87}
Part 3: Useful Molecular Properties Determined From the Electron Density Distribution

For drug design, the principle molecular properties of interest include the electrostatic potential, $V(r)$, net atomic charges, $q(\Omega)$, and magnitude and ellipticity of the density in the bonding region between atoms.\(^{98}\) $\pi$-stacking is considered to be a major interaction with the CB\(_1\) receptor binding site of the ligands tested. Each property of an individual molecule is derived from the total electronic distribution and quantitatively analyzed relative to the rest of the molecule set in an attempt to correlate molecular features with pharmacological affinity in ($K_i$). Atomic charges are calculated by integrating the atomic basins of each nuclei in accord with Bader’s quantum theory of atoms in molecules (QTAIM).\(^{99}\)

A. Atomic Charges and QTAIM

The assignment of net charges has a long history in chemistry, and has proven to be a useful method of prediction of electrostatic interactions between molecules. Atomic charge is also an indicator of an atom’s capacity for hydrogen bonding. For instance if an oxygen or nitrogen is highly negative, it may act as a hydrogen bond acceptor. If in the right orientation, hydrogen bonds will contribute to the stabilizing of the ligand-receptor complex. In addition to molecular shape, a complimentary distribution of atomic charges may stabilize the complex through electrostatic interactions.\(^{100}\) This gain in stability may also be true of other supramolecular interactions that rely on similar mechanisms. For this reason atomic charges are tabulated and analyzed. In order to compute the atomic charges of an atom in a molecule, one must partition the molecular density among the atoms of the molecule. In most schemes for obtaining atomic charges the partitioning is arbitrary.
In QTAIM, defining where one atom ends and where another begins in a molecule is not arbitrary. In order to properly understand the concept of an atom in a molecule, we must first provide a basic background on QTAIM topological analysis of the electron density. This is not a comprehensive review of the topic and is only intended to provide a meaningful understanding of atomic basins and their charges.

Most attempts to obtain atomic charges and understand chemical bonding have been based on molecular wavefunctions which are solutions to Schrödinger’s equation. Although widely used, these methods are highly dependent on the approximations used, such as basis set size, and suffer from the arbitrary nature of the partitioning method. Schrödinger himself warned against attaching physical significance to wavefunctions. However, the properties of chemistry and physics are based on phenomenon in real space. QTAIM was developed as a real space description of the charge density distributions. Its topological features serve as the carrier of physical information regarding the concepts of atoms, bonds, structure, and structural stability.

Topological features of $\rho(r)$ are associated with “critical points” (cp’s), locations in the electron density where the first derivative of $\rho(r)$ is equal to zero ($\nabla \rho(\mathbf{r}_c) = 0$). They are defined by the behavior of the ED surrounding them. The second derivative matrix, the Hessian matrix, of $\rho(r)$ determines whether a cp is of a topology of (3,-3) [local maximum at $r_c$ typically at a nuclear attractor], (3,-1) [local maximum at $r_c$ in the plane defined by two axes and a minimum in the third, typically at the center of a bond], (3,+1) [local minimum at $r_c$ in two axes and a maximum in the third, typically occurs at the interior of a ring system], or (3,+3) [local minimum at $r_c$ typically at the interior of a cage system]. When taking the gradient field vector (gradient path) starting from an arbitrary point and stepwise progressing to $\nabla \rho(\mathbf{r}_c) = 0$, all paths terminate at one of the cps, a nuclear attractor, a bonding cp, or ring cp. The nuclei serve as
attractors to ED, which makes sense. A ridge line of density connects bonded atoms, with a (3,-
1) cp at the minimum (saddle point) along the ridge. Topologically an interatomic surface can be
deefined as the set of trajectories that terminate at a (3,-1) cp. This results in a partitioning of the
ED in a molecule into individual point attractors centered at “atoms in the molecule” and the
surrounding “atomic basin”. Where one atomic partition ends and the other begins is considered
an interatomic surface \((S_{AB})\) of each respective domain. It can be very elegantly expressed as:
\[
\nabla \rho(r) \cdot \mathbf{n}(r) = 0 \text{ for each point on the surface } S(r) \quad \text{Equation 3.1}
\]
where \(\mathbf{n}(r)\) is the unit vector normal to the surface being evaluated at \(r\). This is called the zero-
flux surface and it defines the atomic basin, and contains the nucleus and volume of the electron
density associated with it. From this definition of an atom in a molecule, the atomic charge can
be determined by taking the integral of the difference between the nuclear and electronic charges
over the atomic basin within the zero-flux surface.
\[
q(\Omega) = Z_\Omega - N(\Omega) \quad \text{Equation 3.2}
\]
\(Z_\Omega\) is the electronic charge and \(N(\Omega)\) is the nuclear charge. The result is a definition of atomic
charge and atomic volume based only on the electron density distribution which is independent
of the basis set, or the method used for obtaining the density. Below is a graph of the path
trajectories in the plane of ring system from Part: 2 of this intro to illustrate in 2D how these
surfaces appear.\textsuperscript{99}
B. The Electrostatic Potential and Binding

The electrostatic potential (ESP) is considered to be a molecular property which is highly predictive of noncovalent interactions. This includes hydrogen bonding and interactions that occur at the “surface” of a molecule and thus is expected to play a major role in initial phases of ligand recognition by a receptor site. Therefore we consider the computation of the ESP at the molecular surface of these compounds to hold useful information about the activity of each molecule. This is because a ligand’s surface will be attracted to its negative compliment within the receptor site causing it to approach and begin to orient. Along with complementary surface attraction, it may also help in understanding lipophilic/hydrophobic interactions, as the more
neutral the ESP is at a molecule’s surface, the less polar it may appear to surrounding molecules.\textsuperscript{103} This is far from the only factor involved in ligand-receptor binding. It does not include entropy factors such as changes in the degrees of freedom of both the ligand or of the surrounding environment. It also does not account directly for changes in molecular conformation as the molecules are not rigid. But it is necessary at the outset of ligand recognition.\textsuperscript{104}

Before calculating the ESP, the value of an isodensity surface must be determined. This is done by calculation of the ED at a particular isodensity value. It should also be taken into consideration the effects that a perturbing field, such as that induced by an approaching molecule, will have on the ESP at that density level. The nearer the ESP is to the “inside” of a molecule, the greater the density and the less effected it is by outside forces. The isodensity value commonly used as a molecular envelope in the experimental determination of ESP is 0.007 $e \cdot \text{Å}^{-3}$ (approximately 0.001 au in e/bohr$^3$) as proposed separately by Bader, and Politzer and Murray.\textsuperscript{100,105} Other low values are valid. At this isodensity surface, features such as the lone pairs and π electronic charge are still apparent. Below is a visualization of a typical isodensity surface.
If one has both the electron distribution and the charge and location of the nuclei in the molecule, calculating the ESP is relatively straightforward. The ESP is calculated as:

\[ V(r) = \sum \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')dr'}{|r' - r|} \]  

Equation 3.3

\( Z_A \) is the atomic charge of atom A at the position of \( R_A \). \( |R_A - r| \) is the distance from the nuclei to point \( r \), which will be calculated on the isodensity surface. And the integral is the electronic charge produced by the ED at a distance of \( |r' - r| \) to point \( r' \). The total integral of the ED is a positive value and is then subtracted from the sum of the effects of all \( Z_A \) to account for the negative charge of the electron.100 The data on which the ESP is based are obtained in the crystalline environment, and the forces between the individual molecules in the crystal are electrostatic and therefore are complimentary to each other. Thus, this ESP calculation may be more representative of a ligand in solution or in the binding pocket than an ESP calculated from
wavefunctions for a molecule in a vacuum.\textsuperscript{104} The ESP is not to be calculated at every point, but only at points where $\rho(r) = 0.007 \, e \cdot \textnormal{Å}^{-3}$. The resulting ESP is the surface electrostatic potential and is denoted as $V_s$.\textsuperscript{106} When projected with a color gradient it may be analyzed visually to determine whether it is positive or negative as well as the strength of the potential. In this fashion one may compare multiple molecules against one another and compare the ESP with other data such as each molecule’s affinity, to identify any regions whose ESP may play an important role in binding. Figure 1.3.3 shows the ESP projected on to the molecular surface from Figure 1.3.2. A similar type of analysis has been performed previously by Politzer and Murray on a series of compounds to assess the toxicity of ligands (dibenzo-p-dioxins) that bind to a porphine like receptor, the cytosolic receptor. It was found in that study, and later verified by modeling studies, that two compounds exhibited very different toxicities due to an accumulation of or lack of negative ESP in the center ring system. This feature of negative ESP in dibenzo-p-dioxin, centered around oxygen groups, prevented it from binding due to interactions with nitrogen lone pairs within the receptor site. The added chloro-groups in 2,3,7,8-tetrachlorodibenso-p-dioxin, which is structurally similar otherwise, provided enough electronegativity to prevent this accumulation of negative ESP on the oxygen groups of the molecule. This change in ESP (observed in other compounds as well) increased binding to the receptor causing greater toxicity. Other compounds similar in structure with the added chloro-groups that were able to maintain the negative ESP showed reduced toxicity as well.\textsuperscript{100} Efforts to experimentally determine the affinity of compounds from experimental electron distributions has also been conducted by A. Pinkerton on estrogen molecules.\textsuperscript{104}
Though very local alterations in the ESP may change binding affinity, it is also recognized that more global parameters may be predictive of binding as well.\textsuperscript{100} This is because not all ligand-receptor binding occurs in the same fashion. Some ligands-receptor interactions are due to broader contacts. To assess this, it is possible to calculate several globally defined statistics of the ESP to analyze the general interaction properties functions (GIPF). These are properties introduced by Politzer and Murray.\textsuperscript{107,108} Of interest are the average deviation ($\Pi$), total variance ($\sigma_{tot}$), balance parameter ($\nu$), and maximum and minimum values of the ESP.

$$\Pi = \frac{1}{n} \sum_{i=1}^{n} |V_s(r_i) - \bar{V}_s|$$  \hspace{2cm} \text{Equation 3.4}$$

$$\sigma_{tot} = \sigma^2_+ + \sigma^2_- = \frac{1}{\alpha} \sum_{j=1}^{\alpha} [V^+_s(r_j) - \bar{V}^+_s]^2 + \frac{1}{\beta} \sum_{k=1}^{\beta} [V^-_s(r_j) - \bar{V}^-_s]^2$$  \hspace{2cm} \text{Equation 3.5}$$
Another property of the ED of interest is the bond ellipticity, as π-stacking is considered to be a significant factor in the binding of CB₁ ligands. σ-bonds are cylindrically symmetric while π-bonds are elongated perpendicular to the molecular plane. For single or double bonds, the amount of π character a bond has can be quantified by its ellipticity. Single bonds display an ellipticity of close to zero while double bonds are near 0.2 among C-C interactions.\textsuperscript{109} In QTAIM, bond ellipticity is calculated as:

$$\epsilon = \frac{\lambda_1}{\lambda_2} - 1$$ \hspace{1cm} \text{Equation 3.7}

where $\lambda_1$ and $\lambda_2$ are the principle curvatures perpendicular to the bond path (the two negative eigenvalues of the Hessian matrix). $\lambda_1$ is the component that undergoes contraction (thus $\lambda_1 < \lambda_2$). It will be analyzed to see if molecules with higher ellipticity in their aromatic ring systems have a greater affinity for receptor binding.
**Methods**

Part 1: Crystallization

Each crystal in this study was obtained by slow solvent evaporation from a solution contained in a scintillation vial. By covering the vial with parafilm with small needle sized holes poked in it, solvent was allowed to slowly evaporate at ambient temperature and pressure. Many different solvents and mixed solvents with varying ratios of solvents were used until adequate resulting crystals were grown. Frequently crystals took several weeks or months to form, if at all, as the compounds are prone to retain non-polar solvents. Non-polar solvents generated the best results. Compounds rarely dissolved in polar solvents. And attempts to “crash” crystals out of solution via polar solvent dilution or by increasing the temperature to increase solubility, then reducing the temperature to bring the saturated solution beyond its saturation point, resulted in unsuitable crystals due to small size or disorder within the crystal on a molecular level. Diffusion methods were also explored but generally failed to generate usable crystals within the time invested. After evaporation of solvent, the vials were examined under a stereoscopic microscope with light polarizing capabilities to determine if potential crystalline samples had formed. Only crystals that appeared under polarized light to be single, non-twinned crystals without satellite crystals were considered as candidates for data collection. If crystals were too large in any dimension to remain within the diameter of the x-ray beam during the experiment, a razor blade was used alter their shape. This was frequently problematic as many compounds formed brittle crystals that shattered under the pressure of the blade. Table 1 contains details on solvents used to obtain the crystals used for successful data collection, and the morphology of each crystal.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Mol. Formula</th>
<th>Solvent</th>
<th>Crystal Dimensions (in mm)</th>
<th>Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVG-229Ph</td>
<td>C21 N2 O2 Cl2 F1 H13</td>
<td>DCM</td>
<td>0.4 x 0.5 x 0.5</td>
<td>Block</td>
</tr>
<tr>
<td>HS-P183</td>
<td>C17 N3 O2 Cl3 H12</td>
<td>1 THF : 1 EtOH</td>
<td>0.15 x 0.3 x 0.5</td>
<td>Plate</td>
</tr>
<tr>
<td>HS-P226</td>
<td>C17 N3 O2 Cl3 H12</td>
<td>THF</td>
<td>0.5 x 0.5 x 0.6</td>
<td>Block</td>
</tr>
<tr>
<td>HS-P53-1</td>
<td>C16 N3 O2 Cl2 H11</td>
<td>1 THF : 2 EtOH</td>
<td>0.17 x 0.2 x 0.4</td>
<td>Needle</td>
</tr>
<tr>
<td>HS-P53-2</td>
<td>C14 N1 Cl2 H9</td>
<td>1 THF : 1 EtOH : 1 CHCl3</td>
<td>0.1 x 0.5 x 0.5</td>
<td>Plate</td>
</tr>
<tr>
<td>HS-P57-2</td>
<td>C14 N3 Cl3 H8</td>
<td>CHCl3</td>
<td>0.25 x 0.5 x 0.6</td>
<td>Plate</td>
</tr>
<tr>
<td>HS-P57-3</td>
<td>C17 N3 O2 Cl3 H12</td>
<td>1 THF : 1 Acetone</td>
<td>0.2 x 0.5 x 0.5</td>
<td>Plate</td>
</tr>
<tr>
<td>HS-P57-4</td>
<td>C18 N3 O2 Cl3 H14</td>
<td>EtOH</td>
<td>0.25 x 0.5 x 0.5</td>
<td>Plate</td>
</tr>
<tr>
<td>HS-P57-7</td>
<td>C21 N3 O2 Cl3 H18</td>
<td>1 THF : 3 Acetone</td>
<td>0.07 x 0.2 x 0.5</td>
<td>Needle</td>
</tr>
<tr>
<td>HS-P69</td>
<td>C20 N5 O1 Cl3 H18</td>
<td>1 DCM : 3EtOAc</td>
<td>0.15 x 0.25 x 0.5</td>
<td>Plate</td>
</tr>
</tbody>
</table>

Table 2.1.1: Basic compound and crystal information.

Part 2: Crystal Mounting and Data Collection

Once crystals were grown, selected, and trimmed, they were glued to a glass needle under the microscope with an amorphous epoxy resin. Each needle was then individually placed at the end of a goniometer head and fitted on to the goniometer of the x-ray diffractometer. Each crystal was centered in the x-ray beam path and the cooling nozzle lowered into place. After mounting, cooling to the final temperature, and centering the crystal, collecting data was begun.

Data were collected on a Bruker Kappa Apex II 4-circle diffractometer with each sample cooled to 120(2) K via a gaseous N₂ stream generated by an Oxford Cryostream 700 low temperature device. A Molybdenum target x-ray source and graphite monochromator was used producing x-rays with a wavelength of 0.71073 Å. An Apex II CCD detector was placed 40.00 mm or 60.00 mm away from the sample, depending on the size of the unit cell. Compounds with larger unit cell dimensions were collected at 60.00 mm to avoid reflection overlap as larger direct space cell dimensions result in contracted reciprocal space cell dimensions, the space data is collected in. The length of x-ray exposure per frame varied from 20 to 300 seconds depending on the 2θ angle range being observed (higher angles require longer exposures), crystal size, and individual diffraction capacity of each compound. The x-ray beam
was defined by a 0.6 mm collimator which limited the size of the uniform region of the x-ray beam, and thus the size of the crystal sample that could be used. Scans were conducted varying either omega or phi angles with the other axes remaining fixed per scan. That is, for an omega scan over 115 degrees, phi, chi, and 20 angles were set at fixed values while omega was varied. Each frame was collected over a 0.5 degree sweep for the 20 to 300 seconds allotted for that collection. The number of reflections, redundancy, and peak resolution differed from compound to compound. The consistency/internal agreement of the data was verified against itself and quantified in $R_{(int)}$:  

$$R_{(int)} = \sum \frac{|I_H - \langle I_H \rangle|}{I_H}$$  

Equation 2.2

Table 2.2.2 is a basic description of each data set after data processing.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Unique Reflections</th>
<th>Avg. Redundancy</th>
<th>Peak Resolution (Å)</th>
<th>R(int) x 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVG-229Ph</td>
<td>15,821</td>
<td>12.86</td>
<td>0.48</td>
<td>1.83</td>
</tr>
<tr>
<td>HS-P183</td>
<td>18,220</td>
<td>6.37</td>
<td>0.45</td>
<td>2.28</td>
</tr>
<tr>
<td>HS-P226</td>
<td>14,985</td>
<td>7.17</td>
<td>0.456</td>
<td>1.51</td>
</tr>
<tr>
<td>HS-P53-1</td>
<td>11,923</td>
<td>8.74</td>
<td>0.5</td>
<td>2.41</td>
</tr>
<tr>
<td>HS-P53-2</td>
<td>9,174</td>
<td>9.71</td>
<td>0.47</td>
<td>2.47</td>
</tr>
<tr>
<td>HS-P57-2</td>
<td>10,494</td>
<td>8.24</td>
<td>0.47</td>
<td>2.24</td>
</tr>
<tr>
<td>HS-P57-3</td>
<td>12,952</td>
<td>4.4</td>
<td>0.47</td>
<td>1.53</td>
</tr>
<tr>
<td>HS-P57-4</td>
<td>42,192</td>
<td>15.7</td>
<td>0.55</td>
<td>2.53</td>
</tr>
<tr>
<td>HS-P57-7</td>
<td>10,740</td>
<td>7.51</td>
<td>0.45</td>
<td>2.39</td>
</tr>
<tr>
<td>HS-P69</td>
<td>15,848</td>
<td>9.43</td>
<td>0.52</td>
<td>2.00</td>
</tr>
</tbody>
</table>

Table 2.2.2: An overview of crystal data quality.

Part 3: Independent Atom Model Refinement Using Apex2/Shelx

After data were collected for a crystal, they were was processed and refined using the Apex2/Shelx software package. Initially, a small set of reflections were indexed and used to determine the unit cell of each compound, and the Bravais lattice was determined using geometric analysis. This unit cell was then used to predict the locations of all reflections to be integrated for total intensity. The integration program “searches” for a reflection in the predicted location with an initial box around the reflection. The box size is refined so that it includes the
entire reflection and subtracts out the background noise by measuring the intensity surrounding each reflection. Reflections typically span several frames and it is the total intensity count across these frames that yield the integrated intensity value. Also, using lower angle data, where the signal to noise ratio is higher, a reflection’s 3D profile is computed to help box size optimization and noise subtraction of weaker reflections and reflections that occur at greater 2θ values. This is done because the signal to noise ratio at higher angles or higher resolution is much lower. During this process, cell dimensions are further refined using a larger set of reflections. Once reflection intensities have been determined, the data are corrected for absorption in the subroutine Scale, formerly known as SADABS. This corrects for absorption of x-rays that have to pass through a greater or lesser distance through the crystal, as the crystals are not spherical. This is done by comparing differences in multiple measurements of the intensities that should be equivalent due to Friedel’s Law or symmetry. The shape of the crystal’s absorption correction surface is defined by refining coefficients of a spherical harmonic expansion, which is used to calculate corrections for the remaining reflections. From this, each reflection’s intensity is adjusted for absorption. The corrected file of intensities is analyzed using Xprep. Xprep determines the space group of a crystal by looking for systematic absences or “holes” in an x-ray pattern that are caused by the presence of specific symmetry elements. Along with the Bravais lattice, this information is used to assign a space group may. Xprep outputs an intensity data file (.hkl) for Shelx which is used to refine the parameters based on the independent atom model (IAM). Also, for future use in the refinement strategy, a merged HKL file is generated for use by the program XD2006 in which all duplicate data is averaged with the data spread present as a standard deviation for each observation. Structure solution was performed by direct methods within Shelx. Initial phasing using the direct methods solution with
the best figure of merit was used to calculate an approximate electron density (e-map). The XP module with Shelx was used to assign atoms to peaks in the electron density, referred to as Q-peaks, which also assigns the spherical scattering factor associated with that atom in the position of the Q-peak. These are tabulated within Shelx. XP produces an instructions file (.ins). This file, with its new scattering factors, in turn was used to refine thermal parameters and atomic positions via least squares with the XL module. XL produces a results file (.res) that was used by XP for further manipulation of atom assignment. This process of refining positional and thermal parameters with least squares in XL (which also generates new Q-peaks) and assigning atoms was performed repeatedly until no further improvements could be made. On all occasions for the final data sets used in the study, after adding anisotropic thermal parameters, and peaks corresponding to hydrogen atoms were clearly present in the difference map generated by XL, and hydrogen atoms were added to the least squares refinement model. All final data sets were absent of disorder and had reasonable thermal parameters, a prerequisite for high resolution analysis of the ED. Once satisfactory results were achieved at this stage, the resulting .ins file and merged .hkl file were exported to XD2006 for further refinement. Varying R-factors were recorded for each compound and are tabulated in the results section.

Part 4: XD2006 and the Hansen-Coppens Formalism with Aspherical Scattering Factors

The computer program XD2006 was used for the refinement of high resolution data with aspherical scattering factors using the Hansen-Coppens multipole formalism. The Windows interface for XD2006 is shown in Figure 2.4.1 where graphics are displayed and text notifications of refinements in process appear. In this case a simple stick model of AVG-229Ph is displayed.
Once a refinement has been completed in APEX2\textsuperscript{112} and the instructions and HKL files copied to a working directory in the XD2006 file system, the XDINI module is executed. This produces files usable to XD2006, namely the input file (.inp), a XD2006 compatible HKL file, and a master file (.mas). The input file is where the parameters (temperature parameters, positions, multipoles, kappa values) of the molecule are written. This file is ultimately the description of the electron density of the asymmetric unit and is used to calculate all properties derived from it by all modules with XD2006. The HKL file is relatively unaltered and contains the intensities.
and standard deviations of each reflection. The master file contains all basic information about the cell (dimensions, symmetry operations, etc.) and instructions for each individual module. The primary modules of XD2006 involved in this study are XDLSM, XDFOUR, XDPROP and TOPXD. To illustrate how a refinement is performed in XD2006 and how these modules are utilized, the refinement of AVG-229Ph will be detailed. All other compounds are refined in the same basic fashion.

After usable files for XD2006 have been created, a local coordinate system must be assigned to each atom in the asymmetric unit. This must be done keeping in mind the shape of spherical harmonic functions that will be used to refine the ED and their orientation to each axis. Shown below is a segment of the XDLSM module portion of the master file which contains a list of atoms in the first column (ATOM) that corresponds to the molecule in the graphical display above. This is the atom for which the local coordinate system will be centered. In the second column (ATOM0) is the atom whose position will serve as the direction of a vector for which an axis will be assigned. This axis assignment is in the third column (AX1). The fourth (ATOM1), fifth (ATOM2), and sixth (AX2) columns function in the same fashion except that the only the components perpendicular to the previous vector are used. This resulting vector is also centered at the atom in the first column. The third axis (the only unlabeled axis left) is generated normal to the plane defined by the first two vectors. The seventh column (R/L) defines the handedness of the axis system and therefore the direction of the remaining axis. This means that for local coordinates of O(2), the vector from O(2) to C(7) is defined as the x-axis. The component of the vector from C(8) to O(1) that is perpendicular to the previous axis is defined as the y-axis. And the normal vector to the resulting plane is the z-axis in the direction that creates a right handed axis system.
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Figure 2.4.2: Atom list, local coordinate setup, chemical constraint, and refinement options layout of an XD2006 master file.

Also present in this section is the level of treatment for thermal parameters designated in column 8 (TP). A value of 1 designates the use of isotropic thermal parameters (scalar), 2 designates
anisotropic harmonic thermal parameters, and 3 and 4 designate anisotropic-anharmonic thermal parameters. In most cases anisotropic-harmonic thermal parameters are sufficient. But in this model Cl(1) refined better with anharmonic anisotropic thermal parameters.\textsuperscript{117,118} This was evident in an improvement in the residual map of both atoms. Column 9 (TBL) defines which core and valence scattering factor tables are used for each atom. Column 10 (KAP) specifies which set of kappa values will be refined with that particular atom. Several atoms that are of a similar environment will usually use the same kappa set. When XDLSM performs a least squares refinement on a set of kappas it considers all atoms associated with that set. Column 11 (LMX) designates the level of the \textit{spherical harmonic multipoles} whose \textit{populations} may be refined for that atom.\textsuperscript{91} Designations of these spherical harmonics are as follows: 0–monopole, 1–dipole, 2–quadrapole, 3–octapole, and 4–hexadecapole. If 2 is selected as in the case of the hydrogen atoms monopole, dipole, and quadrapole spherical harmonic functions may be used to refine the atoms ED but not octapole and hexadecapole functions. All other atoms in this study that are not hydrogen use up to the hexadecapolar level of refinement. Column 12 (SITESYM) was not used for any compounds as no atoms were located on special symmetry sites. The last column (CHEMCON) is used to apply chemical constraints to the multipole parameters of the atom in that row to be identical to those of the labeled atom. In this case Cl(2)’s multipoles are constrained to be the same as Cl(1)’s. The least-squares process is modified so that the resulting parameters are those that provide the best overall fit at both atoms.\textsuperscript{119} Typically all aliphatic hydrogens are constrained to be equal as well as all aromatic hydrogens. The benefit of these constraints is that there is a reduction in the number of refined parameters. For the optimization problem to be over determined, for every parameter to be refined there must be more than one experimental observation, a reflection. The more reflection there are per parameter, the more
over determined the system is. In analysis of x-ray data, over determination by a factor of 10 observations per parameter is considered desirable. Since the number of observable reflections is often limited by the details of the experiment, the model should be as efficient as possible by reducing the number of parameters as much as possible.

With local coordinates set up for each atom, expansion contraction parameters\(^{92}\) (kappa values) are assigned, and the multipoles of chemically independent atoms are selected to be refined.

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<tr>
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<td>111111</td>
<td>0000000000000000</td>
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<td>100</td>
<td>10010</td>
<td>100010</td>
<td>100100011</td>
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<tr>
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<td>111</td>
<td>111111</td>
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<td>10</td>
<td>000</td>
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<td>0000000000000000</td>
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<td></td>
</tr>
</tbody>
</table>

Figure 2.4.3.: Example of thermal parameter and multipole refinement setup within the master file LSM module in XD2006.

Shown above is a list of parameters to be refined for the first 10 atoms in AVG-229Ph for illustration. All of the digits in this caption are potential parameters to refine (0 – do not refine, 1 – refine). After the atom names the next there columns are position parameters. These are refined on every least squares cycle except for hydrogens. The following three sets of columns (U2, U3, and U4) define what level of thermal motions refinement will be used. Typically U2 (anisotropic-harmonic) is refined for all atoms except for hydrogens. In this case Cl(1) refined better with anisotropic-anharmonic thermal parameters. As seen for these atoms, the entire column U3 has ‘1’ designations for these parameters. All of the anharmonic parameters are refined based on the Gram-Charlier temperature factor formalism.\(^{90}\) The multipole section works differently. Each digit stands for a different multipole deformation parameter. In column
-D- there are three digits. The first dipole is anti-symmetric about the x-axis (negative in the negative range of x and positive in the positive range of x), the second about the y-axis, and the third about the z-axis. But each is also symmetric in the other two unmentioned axes. All of the multipoles are either symmetric or anti-symmetric about a particular axis or axes. When setting up the local coordinates, the symmetry of the local environment was taken into account to exploit these symmetry properties of the spherical harmonics functions.\textsuperscript{119} This attention to symmetry allows for a further reduction in the number of refined parameters. As is shown in Figure 2.4.3, Cl(1) only has one dipole being refined, the dipole anti-symmetric about the z-axis. This is because its z-axis is aligned along the bond path, and it is expected that electron density from Cl(1) will be moved into the bonding region. As electron density in the Cl-C bonds is expected to be cylindrically symmetric, the populations of the x-dipoles and y-dipoles are not refined, but are fixed at zero. This same logic is applied to the remaining spherical harmonic multipoles. This is done for every single independently refined atom in the asymmetric unit. Figure 2.4.4 shows the spherical harmonics with a radial function applied up to the octapolar level.

![Spherical Harmonics](image)

Figure 2.4.4: Examples of spherical harmonic functions.
During a multipole refinement, all of the potential multipole populations may not be refined at once. Usually the monopole populations are refined first. Next monopole and octapole populations are refined. Then monopole, octapole, and quadrapole populations are refined. And finally all potential multipole populations are refined at once. The monopole kappa is refined at every step of this refinement process as well. This strategy is followed because there is a correlation between the multipole populations. The multipoles that are typically the most populated are refined first. Once the monopole kappa and multipole for every atom has been refined to convergence, the monopole kappa and the kappa for the multipoles (which are constrained to be equal across all multipole kappas per kappa set) is refined. Then it is cycled back through the monopole kappas and multipole population refinement again. These two refinements are cycled till convergence. Once converged and the R(F) has reached its minimum, the modeling of the ED has been completed. Residual maps generated by difference Fourier transforms within the XDLSM module are then produced. Using the XDFOUR module these maps are plotted and analyzed for quality. The less residual density, or unmodeled density, the better the refinement is. Once satisfied with the refinement, molecular properties based on the ED and nuclear positions may be derived. This is performed by the XDPROP and TOPXD modules. Properties that were computed are the ESP, bond critical points, and bond ellipticity using XDPROP, and atomic charges using TOPXD. The ESPs were projected onto the ED at a density isosurface value of $0.007 \text{e} \cdot \text{Å}^{-3}$ using the computer program MolIso.

Part 5: Data Analysis and Principal Component Analysis

All data analysis was conducted using R (programming language) within RStudio (integrated development environment). Before a covariance matrix was generated, to
determine correlation, each data set was mean centered by subtracting the mean of each property from each value and scaled by dividing by that set’s standard deviation to account for unit variance. The covariance matrix of each property with $K_i$ was solved. This entire process was repeated three more consecutive times, each time leaving out the most extreme data point. Correlation was then determined by observing which variables maintained correlation with $K_i$ throughout all covariance matrices. Principal component analysis$^{123,124}$ was performed only on the correlated parameters. This was performed by singular value decomposition.$^{125}$ The data was projected onto the first three principal components (PC) using the ‘rgl’, ‘scatterplot3D’, and ‘BPCA’ packages for R.$^{126-128}$ For the purpose of this document to substitute for a three dimensional rendering of the data, two biplots were provided of the data projected onto the first and second principal components, and the second and third principal components.
Results

This section contains data on ten separate molecules provided by Professor Mark Trudell, and his collaborators Dr. Hong Shu, and Dr. Aba Verma of the University of New Orleans. Each molecule has been structurally determined via high resolution x-ray crystallography at low temperature (120 K). A charge density study using the Hansen-Coppens multipole formalism\(^9\) has been conducted on each molecule to generate atomic position and thermal parameters as well as the charge/electron distribution. ORTEP\(^{129}\) (Oakridge thermal ellipsoid plot) diagrams at 50% occupancy are presented. An analysis of the electronic distribution of \(\rho(r)\) has yielded the topological parameters \(\rho(BCP)\) (charge density at the bond critical point), \(\nabla^2 \rho(BCP)\) (Laplacian of the charge density at the bond critical point), \(\varepsilon\) (bond ellipticity), \(q(\Omega)\) (charge of the atomic basin), and \(V(\Omega)\) (volume of the atomic basin). Furthermore, an ESP (electrostatic potential) map has been graphed on to an isodensity surface (at a value of \(\rho(r) = 0.007 \; e \cdot \AA^{-3}\)) for each molecule.

The molecules have been arranged by decreasing \(K_i\) (affinity). Relevant information about the molecule, crystal system, and x-ray data has been tabulated for each molecule. Experimental details considered important or unusual have been brought to attention. Finally a table of Politzer’s and Murray’s global parameter analysis\(^{100}\) of the ESP is given. A discussion of these results follows.

**Note:** All Ki values produced by Professor Sari Izenwasser, Department of Psychiatry and Behavioral Science, University of Miami, Miller School of Medicine.
**Compound 1**

**Name:**

HS-P53-2

1,5-bis(4-chlorophenyl)-1H-1,2,3-triazole

**Affinity:**

\[ K_i = 6,931 \text{ nM} \pm 1305 \]

**ORTEP:**

![ORTEP diagram](image-url)

*Moliso (c) 2009 Christian B. Hübschle*

**Figure 3.1.1**

**ESP Maps:**
Refinement Note:

A broad peak shows a maximum at 3 contours (0.30 e·Å⁻³) about Cl(2) in the plane of C(9), C(11), and C(13). All other residuals are relatively flat. The R(F) value of the overall refinement is low.

Crystal Data Table:

<table>
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<tr>
<th>General Sample Information</th>
<th></th>
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<tbody>
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<td>Formula weight</td>
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<td>120(2)</td>
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<tr>
<td>Wavelength (Å)</td>
<td>0.71073</td>
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<td>Crystal System</td>
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</tr>
<tr>
<td>Space Group</td>
<td>Pc</td>
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<tr>
<td>Cell Dimensions</td>
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<td>----------------</td>
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<td>c (Å)</td>
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<td>Unique reflections</td>
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<tr>
<td>Average redundancy</td>
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<tr>
<td>Completeness to (sinθ/λ)max</td>
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<tr>
<td>Absorption correction</td>
<td>Empirical (t_min = 0.756, t_max = 0.952)</td>
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**Spherical Atom Refinement**

- Refinement method: Full-matrix least-squares on F²
- Data(l>2σ(I))/restraints/parameters: 8709 / 2 / 208
- Goodness-of-fit on F²: 1.079
- Final R indices [l>2σ(I)]: R₁ = 0.0286
- R indices (all data): R₁ = 0.0310, wR₂ = 0.0752
- Largest difference peak and trough: 0.719 and -0.216 e · Å⁻³
- N_ref/N_v: 41.87

**Multipole Atom Refinement**

- Refinement method: Full-matrix least-squares on F
- Data(l>2σ(I))/restraints/parameters: 4791 / 0 / 416
- Goodness-of-fit (GoF) on F: 2.580
- Final R indices [l>2σ(I)]: R₁ = 0.0184, wR₂ = 0.0175
- R indices (all data): R₁ = 0.0247
- Largest difference peak and trough: 0.409 and -0.296 e · Å⁻³
- N_ref/N_v: 11.5446

**Atomic Basin Calculations Table:**

<table>
<thead>
<tr>
<th>Atom</th>
<th>e⁻ Population in Basin</th>
<th>q(Ω) (e⁻)</th>
<th>V(Ω) (Å³)</th>
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<tbody>
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<td>Cl(1)</td>
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<td>1.3928E-01</td>
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<tr>
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\[
R_1 = \sum \frac{|F_o| - |F_c|}{|F_o|}, \quad wR_F = \left[ \frac{\sum w(|F_o|^2 - |F_c|^2)^2}{\sum w|F_o|^2} \right]^{1/2}, \quad GoF = \left[ \frac{\sum w(|F_o|^2 - |F_c|^2)^2}{(N_{ref} - N_v)} \right]^{1/2}
\]
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<tr>
<td>Inner Carbon Bonds</td>
<td></td>
<td></td>
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<td></td>
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<td><strong>Outer Atom – Inner Carbon Bonds</strong></td>
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<tr>
<td>H(11) - C(11)</td>
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<tr>
<td>Inner Carbon Bonds</td>
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<tr>
<td></td>
<td></td>
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<tr>
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Table 3.1.2

Topological Parameters Table:
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<td>C(2) - C(3)</td>
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</tr>
<tr>
<td>C(4) - C(5)</td>
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<td>2.072</td>
</tr>
<tr>
<td>C(5) - C(6)</td>
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<td>2.109</td>
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</table>

Outer Atom – Inner Carbon Bonds

<table>
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<th>Length</th>
<th>Energy</th>
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</thead>
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<td>H(2) - C(2)</td>
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<tr>
<td>Cl(1) - C(3)</td>
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<td>H(4) - C(4)</td>
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<td>H(5) - C(5)</td>
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Triazole Ring

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<td>N(2) - N(3)</td>
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<td>N(3) - C(7)</td>
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<td>2.197</td>
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<td>C(7) - C(8)</td>
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<tr>
<td>C(8) - N(1)</td>
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Outer Atom – Inner Carbon Bonds

<table>
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<tr>
<th>Bond</th>
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<th>Energy</th>
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</thead>
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<tr>
<td>H(8) - C(8)</td>
<td>0.06</td>
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</table>

Table 3.1.3
Compound 2

Name:

HS-P53-1

methyl 1,5-bis(4-chlorophenyl)-1H-1,2,3-triazole-4-carboxylate

Affinity:

$K_i = 4,400 \pm 764$ nM

ORTEP:

Figure 3.1.4
ESP Maps:

Moliso (c) 2009 Christian B. Hübschle

Figure 3.1.5
Figure 3.1.6

**Refinement Note:**

Residual maps are flat throughout the model.

**Crystal Data Table:**

<table>
<thead>
<tr>
<th>General Sample Information</th>
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<tr>
<td>Molecular formula</td>
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<td>Formula weight</td>
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<td>Wavelength (Å)</td>
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<tr>
<td>b (Å)</td>
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<td>β</td>
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</tr>
</tbody>
</table>
\[
R_1 = \sum \frac{|F_o| - |F_c|}{|F_o|}, \quad wR_F = \left( \sum \frac{w(|F_o| - |F_c|)^2}{w|F_o|^2} \right)^{1/2}, \quad GoF = \left( \frac{\sum w(|F_o|^2 - |F_c|^2)^2}{(N_{\text{ref}} - N_v)} \right)^{1/2}
\]

**Atomic Basin Calculations Table:**

<table>
<thead>
<tr>
<th>Atom</th>
<th>e Population in Basin</th>
<th>(q(\Omega)) (e)</th>
<th>(V(\Omega)) (Å(^3))</th>
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<td>N(2)</td>
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<td>-1.3137E-01</td>
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<tr>
<td>N(3)</td>
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<td>2.3940E-01</td>
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<tr>
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Table 3.1.5
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Monochlorophenyl Ring [C(4) connectivity]
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<th>Energy</th>
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<td></td>
</tr>
<tr>
<td>C(4) - C(5)</td>
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<td>1.903</td>
<td>-17.673</td>
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<tr>
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Table 3.1.6
**Compound 3**

**Name:**

HS-P57-2

5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole

**Affinity:**

$K_i = 1,400 \pm 266 \text{ nM}$

**ORTEP:**

![ORTEP Diagram](image)

*Moliso (c) 2009 Christian B. Hübschle*

*Figure 3.1.7*
ESP Maps:

Figure 3.1.8

Moliso (c) 2009 Christian B. Hübschle
Refinement Note:

A peak of 4 contours (0.40 e · Å\(^{-3}\)) about Cl(3) in the C(3), C(5), and C(7) plane is present. Residuals elsewhere are a slightly bumpy though not severe.

Crystal Data Table:

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<th>General Sample Information</th>
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<td>C14 N3 Cl3 H8</td>
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<tr>
<td>Formula weight</td>
<td>324.59</td>
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<tr>
<td>Temperature (K)</td>
<td>120(2)</td>
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<tr>
<td>Wavelength (Å)</td>
<td>0.71073</td>
</tr>
<tr>
<td>Crystal System</td>
<td>Monoclinic P</td>
</tr>
<tr>
<td>Space Group</td>
<td>P2(1)/c</td>
</tr>
<tr>
<td>Cell Dimensions</td>
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</tr>
<tr>
<td>Parameter</td>
<td>Value</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------</td>
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<td>a (Å)</td>
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<td>b (Å)</td>
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</tr>
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<td>c (Å)</td>
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<tr>
<td>Density</td>
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<td>Absorption coefficient</td>
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<td>Crystal size (mm)</td>
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<td>(sinθ/λ)max (Å⁻¹)</td>
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<tr>
<td>Unique reflections</td>
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<td>Average redundancy</td>
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<td>Completeness to (sinθ/λ)max</td>
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<tr>
<td>Absorption correction</td>
<td>Empirical (t_min = 0.668, t_max = 0.849)</td>
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**Spherical Atom Refinement**

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<th>Refinement method</th>
<th>Full-matrix least-squares on F²</th>
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<td>9051 / 0 / 213</td>
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<td>Goodness-of-fit on F²</td>
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<tr>
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<tr>
<td>Largest difference peak and trough</td>
<td>0.769 and -0.439 e · Å⁻³</td>
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<td>N_v/N_v</td>
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</table>

**Multipole Atom Refinement**

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<tr>
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<td>N_v/N_v</td>
<td>20.63</td>
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</table>

Table 3.1.7

\[
R₁ = \sum \left| \frac{F_o - |F_c|}{|F_o|} \right| w_{RF} = \left[ \sum \frac{w(|F_o - |F_c|)^2}{w|F_o|^2} \right]^{1/2}; GoF = \left[ \sum \frac{w(|F_o|^2 - |F_c|^2)^2}{(N_v - N_v)^2} \right]^{1/2}
\]

**Atomic Basin Calculations Table:**

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<th>e Population in Basin</th>
<th>q(Ω) (e⁻)</th>
<th>V(Ω) (Å³)</th>
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<td>Cl(2)</td>
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<td>29.2742</td>
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<td>28.2134</td>
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<tr>
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<td>9.6717</td>
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Table 3.1.8
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<th>Distance (Å)</th>
<th>Angle (°)</th>
<th>Energy (kJ/mol)</th>
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<td>C(7) - C(8)</td>
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<td>H(8) - C(8)</td>
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### Outer Atom – Inner Carbon Bonds

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### Triazole Ring

#### Inner Atom Bonds

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<tr>
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<th>Angle (°)</th>
<th>Energy (kJ/mol)</th>
</tr>
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### Outer Atom – Inner Carbon Bonds

Table 3.1.9
**Compound 4**

**Name:**

HS-P226

methyl 2-[(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2H-1,2,3-triazol-2-yl]acetate

**Affinity:**

$K_i = 885 \pm 370 \text{ nM}$
Figure 3.1.10
ESP Maps:

Figure 3.1.11
Refinement Note:

A very compact peak of 6 contours (0.60 e·Å\(^{-3}\)) about the Cl(1) in the C(6), C(8), and C(10) plane is present. Large residuals around Cl(2) and Cl(3) in the C(12), C(14), and C(16) plane that are of 8 contours (0.80 e·Å\(^{-3}\)) are present. No refinement tactic has resolved this issue though the final R(F) value is moderately low.

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<td>β</td>
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<td>γ</td>
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<td>(sinθ/λ)max (Å⁻¹)</td>
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<td>Completeness to (sinθ/λ)max</td>
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Spherical Atom Refinement

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<tr>
<td>Largest difference peak and trough</td>
<td>1.545 and -0.696 e · Å⁻³</td>
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| Nₘᵣᵣ/Nᵥ | 50.60 |

Multipole Atom Refinement

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| Nₘᵣᵣ/Nᵥ | 27.24 |

Atomic Basin Calculations Table:

\[ R₁ = \sum \frac{|F_{o}|-|F_{c}|}{|F_{o}|}, wR_F = \left( \sum \frac{w(|F_{o}|-|F_{c}|)^2}{w|F_{o}|^2} \right)^{1/2} \; GoF = \left( \sum \frac{w(|F_{o}|^2-|F_{c}|^2)^2}{(N_{ref}-N_{v})} \right)^{1/2} \]
### Table 3.1.11

#### Topological Parameters Table:

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<th>Bond</th>
<th>Ellipticity</th>
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<th>$q(\Omega)$ (e')</th>
<th>$V(\Omega)$ (Å³)</th>
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Table 3.1.12
**Compound 5**

**Name:**

HS-P69

5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-1,2,3-triazole-4-carboxamide

**Affinity:**

$K_i = 590 \pm 173$ nM

**ORTEP:**

*Figure 3.1.13*
ESP Maps:

Figure 3.1.14
Refinement Note:

Thermal ellipsoids on the aliphatic ring system are slightly larger than normal but are not extreme.

Residuals peak about Cl(3) with a sharp 3 contour (0.30 $e \cdot \AA^{-3}$) peak in the C(3), C(5), and C(7) plane.

All other residual peaks are relatively flat.

Crystal Data Table:

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<th>General Sample Information</th>
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<td>Wavelength (Å)</td>
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<td>Cell Dimensions</td>
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<td>b (Å)</td>
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### Table 3.1.13

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**Atomic Basin Calculations Table:**

\[
R_1 = \frac{\sum |F_o| - |F_c|}{|F_o|}, \quad wR_F = \left[ \frac{\sum w(|F_o| - |F_c|)^2}{\sum w|F_o|^2} \right]^{1/2}; \quad GoF = \left[ \frac{\sum w(|F_o|^2 - |F_c|^2)^2}{N_{ref} - N_v} \right]^{1/2}
\]
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### Outer Atom – Inner Carbon Bonds

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### Monochlorophenyl Ring

#### Inner Carbon Bonds

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### Outer Atom – Inner Carbon Bonds

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### Aliphatic Ring

#### Inner Atom Bonds

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### Outer Atom – Inner Carbon Bonds

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Table 3.1.15
**Compound 6**

**Name:**

HS-P183

methyl 2-[(5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-1H-1,2,3-triazol-1-yl)acetate

**Affinity:**

\[ K_i = 250 \pm 86 \text{ nM} \]

**ORTEP:**

---

**ESP Maps:**

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Figure 3.1.16
Figure 3.1.17
Figure 3.1.18

**Refinement Note:**

Residual density peaks at 5 contours (0.50 e·Å\(^{-3}\)) about Cl(3) in the plane of C(4), Cl(3), and Cl(2). All other residual density is flat.

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**Outer Atom – Inner Carbon Bonds**

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**Dichlorophenyl Ring**

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**Outer Atom – Inner Carbon Bonds**

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**Triazole Ring**

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Table 3.1.18
**Compound 7**

**Name:**

HS-P57-7
cyclohexyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole-4-carboxylate

**Affinity:**

\[ K_i = 240 \text{ nM} \pm 83.5 \]

**ORTEP:**

![ORTEP Image]

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Figure 3.1.19

**ESP Maps:**
Figure 3.1.20

Figure 3.1.21

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Refinement Note:

The refinement of this molecule has left clean residuals, with a sharp peak of just barely 3 contours (0.30 e · Å⁻³) about Cl(1), and a low R(F) value.

Crystal Data Table:

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<td>Density</td>
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<tr>
<td>Unique reflections</td>
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<td>Full-matrix least-squares on F</td>
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Data(I>2σ(I))/restraints/parameters 14504 / 0 / 666
Goodness-of-fit (GoF) on F 2.595
Final R indices [I>2σ(I)] R₁ = 0.0237, wR₁ = 0.0207
R indices (all data) R₁ = 0.0588
Largest difference peak and trough 0.756 and -0.575 e·Å⁻³
Nref/Nv 21.8105

R₁ = \frac{\sum \left| \frac{F_{ol}}{F_{ol}} - \frac{F_{el}}{F_{el}} \right| \cdot w}{\sum \left( \frac{w(F_{el}^2 - F_{ol}^2)^2}{(N_{ref} - N_{v})} \right)}^{1/2}
GoF = \left( \sum \frac{w(F_{el}^2 - F_{ol}^2)^2}{(N_{ref} - N_{v})} \right)^{1/2}

Table 3.1.19

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<td>C(4)</td>
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<td>C(5)</td>
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### Table 3.1.20

Topological Parameters Table:

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### Aliphatic Ring

#### Inner Carbon Bonds

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#### Outer Atom – Inner Carbon Bonds

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### Ester Linker

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### Triazole Ring

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Table 3.1.21
Compound 8

Name:

HS-P57-3
ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole-4-carboxylate

Affinity:

\[ K_i = 180 \text{ nM} \pm 26.7 \]

ORKEP:

Moliso (c) 2009 Christian B. Hübschle
Figure 3.1.22
Refinement Note:

The kappa assignments for this molecule are very unconventional. The final R(F) is very low and residual peak are minimal except about CL(1) which are very sharp and max out at 8 contours (0.80 \( e \cdot \text{Å}^{-3} \)). Deformation densities look normal. And other properties are regular.

Crystal Data Table:

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<td>b (Å)</td>
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Table 3.1.22

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<td>-15.106</td>
</tr>
<tr>
<td>H(14) - C(14)</td>
<td>0.05</td>
<td>1.792</td>
<td>-16.596</td>
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</table>

Table 3.1.23

**Topological Parameters Table:**
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<th>Bond</th>
<th>Distance (Å)</th>
<th>Angle (°)</th>
<th>Torsion (°)</th>
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<tbody>
<tr>
<td>Cl(3) - C(15)</td>
<td>0.00</td>
<td>1.347</td>
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<td>H(16) - C(16)</td>
<td>0.05</td>
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<td>-0.732</td>
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<tr>
<td>H(16) - C(16)</td>
<td>0.05</td>
<td>1.799</td>
<td>-17.031</td>
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<tr>
<td>Cl(2) - C(17)</td>
<td>0.01</td>
<td>1.358</td>
<td>-0.732</td>
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### Monochlorophenyl Ring
#### Inner Carbon Bonds
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<th>Distance (Å)</th>
<th>Angle (°)</th>
<th>Torsion (°)</th>
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<tbody>
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<td>C(6) - C(7)</td>
<td>0.10</td>
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<tr>
<td>C(7) - C(8)</td>
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<td>-21.391</td>
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<td>-21.247</td>
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<td>C(9) - C(10)</td>
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<td>-23.883</td>
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<td>C(10) - C(11)</td>
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<td>-21.095</td>
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<td>C(11) - C(6)</td>
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<td>-17.251</td>
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#### Outer Atom – Inner Carbon Bonds
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<th>Torsion (°)</th>
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</thead>
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<td>0.04</td>
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<tr>
<td>H(7) - C(7)</td>
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<td>H(8) - C(8)</td>
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### Ester Side Chain
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<tbody>
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<td>C(3) - C(4)</td>
<td>0.21</td>
<td>1.886</td>
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<tr>
<td>O(2) - C(3)</td>
<td>0.07</td>
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<td>O(1) - C(3)</td>
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<tr>
<td>H(2B) - C(2)</td>
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<td>H(1C) - C(1)</td>
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### Triazole Ring
<table>
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<th>Torsion (°)</th>
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</thead>
<tbody>
<tr>
<td>N(1) - N(2)</td>
<td>0.17</td>
<td>2.873</td>
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<tr>
<td>N(2) - N(3)</td>
<td>0.13</td>
<td>2.574</td>
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<tr>
<td>N(3) - C(5)</td>
<td>0.12</td>
<td>2.273</td>
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<tr>
<td>C(5) - C(4)</td>
<td>0.15</td>
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<tr>
<td>C(4) - N(1)</td>
<td>0.09</td>
<td>2.256</td>
<td>-19.016</td>
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</table>

Table 3.1.24
**Compound 9**

**Name:**

AVG-229Ph

phenyl 1-(2,4-dichlorophenyl)-5-(4-fluorophenyl)-1H-1,2,3-triazole-4-carboxylate

**Affinity:**

\[ K_i = 170 \text{ nM} \]

**ORTEP:**

![ORTEP diagram](image)

*Moliso (c) 2009 Christian B. Hübschle*

Figure 3.1.25

**ESP Maps:**
Refinement Note:
Residual density is large about Cl(1) and medium about Cl(2). To reduce these residual peaks anisotropic-anharmonic temperature factors were applied to Cl(1). This method was ineffective for Cl(2).

Crystal Data Table:

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<tr>
<th>General Sample Information</th>
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<tr>
<td>Molecular formula</td>
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<td>Formula weight</td>
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<tr>
<td>Temperature (K)</td>
</tr>
<tr>
<td>Wavelength (Å)</td>
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<td>Crystal System</td>
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<td>Space Group</td>
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<tr>
<td>Cell Dimensions</td>
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<tr>
<td>b (Å)</td>
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<tr>
<td>c (Å)</td>
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<td>γ</td>
</tr>
<tr>
<td>Volume</td>
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<td>Density</td>
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<tr>
<td>Absorption coefficient</td>
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<tr>
<td>Crystal size (mm)</td>
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<tr>
<td>(sinθ/λ)$_{\text{max}}$</td>
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<tr>
<td>Unique reflections</td>
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<tr>
<td>Average redundancy</td>
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<tr>
<td>Completens to (sinθ/λ)$_{\text{max}}$</td>
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<tr>
<td>Absorption correction</td>
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</table>

Spherical Atom Refinement

<table>
<thead>
<tr>
<th>Refinement method</th>
<th>Full-matrix least-squares on F$^2$</th>
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<tbody>
<tr>
<td>Data(I$&gt;2σ$(I))/restraints/parameters</td>
<td>15821 / 0 / 310</td>
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<tr>
<td>Goodness-of-fit on F$^2$</td>
<td>0.839</td>
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<tr>
<td>Final R indices [I$&gt;2σ$(I)]</td>
<td>R$_1$ = 0.0398</td>
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<tr>
<td>R indices (all data)</td>
<td>R$_1$ = 0.0460, wR$_2$ = 0.1046</td>
</tr>
<tr>
<td>Largest difference peak and trough</td>
<td>1.125 and -0.924 e · Å$^{-3}$</td>
</tr>
<tr>
<td>N$<em>\text{ref}$/N$</em>\nu$</td>
<td>51.04</td>
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</table>

Multipole Atom Refinement

<table>
<thead>
<tr>
<th>Refinement method</th>
<th>Full-matrix least-squares on F</th>
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</thead>
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<tr>
<td>Data(I$&gt;2σ$(I))/restraints/parameters</td>
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<tr>
<td>Goodness-of-fit (GoF) on F</td>
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<tr>
<td>R indices (all data)</td>
<td>R$_1$ = 0.0428</td>
</tr>
<tr>
<td>Largest difference peak and trough</td>
<td>1.586 and -1.328</td>
</tr>
</tbody>
</table>
\[
R_1 = \sum \left| \frac{F_{o1} - |F_{c1}|}{|F_{o1}|} \right| wF_o = \left[ \sum \frac{w(|F_{o1} - |F_{c1}||^2)}{w|F_{o1}|^2} \right]^{1/2}; \quad GOF = \left[ \sum \frac{w(|F_{o1}|^2 - |F_{c1}|^2)}{(N_{ref} - N_v)^2} \right]^{1/2}
\]

**Atomic Basin Calculations Table:**

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<thead>
<tr>
<th>Atom</th>
<th>e⁻ Population in Basin</th>
<th>q(Ω) (e Å⁻¹)</th>
<th>V(Ω) (Å³)</th>
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<tbody>
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<td>Cl(2)</td>
<td>1.7083E+01</td>
<td>-8.3443E-02</td>
<td>29.2362</td>
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<tr>
<td>F(1)</td>
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<td>-7.1410E-01</td>
<td>15.9952</td>
</tr>
<tr>
<td>O(1)</td>
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<tr>
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<td>Inner Carbon Bonds</td>
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</tr>
<tr>
<td>C(16) - C(17)</td>
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<tr>
<td>C(17) - C(18)</td>
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<tr>
<td>C(18) - C(19)</td>
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<td>C(19) - C(20)</td>
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<td>-19.937</td>
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<tr>
<td>Outer Atom – Inner Carbon Bonds</td>
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<td>N(3) - C(16)</td>
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<tr>
<td><strong>Monofluorophenyl Ring</strong></td>
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<tr>
<td>Inner Bonds</td>
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<td></td>
</tr>
<tr>
<td>C(10) - C(11)</td>
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<td>H(12) - C(12)</td>
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<tr>
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<td><strong>Phenyl Ring</strong></td>
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<tr>
<td>Inner Carbon Bonds</td>
<td></td>
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</tr>
<tr>
<td>C(6) - C(1)</td>
<td>0.23</td>
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<td>-21.059</td>
</tr>
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<td>C(1) - C(2)</td>
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<td>-20.322</td>
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<td>90° Value</td>
<td>180° Value</td>
</tr>
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<td>-----------</td>
<td>------------</td>
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<tr>
<td>Outer Atom – Inner Carbon Bonds</td>
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</tr>
<tr>
<td>C(4) - C(5)</td>
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<td>C(5) - C(6)</td>
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<td>O(1) - C(6)</td>
<td>0.03</td>
<td>1.923</td>
<td>-12.248</td>
</tr>
<tr>
<td>H(1) - C(1)</td>
<td>0.05</td>
<td>1.818</td>
<td>-19.063</td>
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<td>H(4) - C(4)</td>
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<td>H(5) - C(5)</td>
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<td>1.818</td>
<td>-19.084</td>
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<td>Ester Linker</td>
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<td>C(7) - C(8)</td>
<td>0.14</td>
<td>1.925</td>
<td>-14.387</td>
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<tr>
<td>O(1) - C(6)</td>
<td>0.03</td>
<td>1.923</td>
<td>-12.248</td>
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<tr>
<td>O(2) - C(7)</td>
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<td>Triazole Ring</td>
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<tr>
<td>N(1) - N(2)</td>
<td>0.10</td>
<td>2.928</td>
<td>-16.522</td>
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<tr>
<td>N(2) - N(3)</td>
<td>0.20</td>
<td>2.451</td>
<td>-5.615</td>
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<tr>
<td>N(3) - C(9)</td>
<td>0.18</td>
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<td>-20.969</td>
</tr>
<tr>
<td>C(9) - C(8)</td>
<td>0.26</td>
<td>2.215</td>
<td>-19.325</td>
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<td>C(8) - N(1)</td>
<td>0.16</td>
<td>2.374</td>
<td>-21.671</td>
</tr>
</tbody>
</table>

Table 3.1.27
**Compound 10**

**Name:**

HS-P57-4 Molecule A

propyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole-4-carboxylate

**Affinity:**

\[ K_i = 4.6 \text{ nM} \pm 0.012 \]

**ORTEP:**

![ORTEP Diagram]

*MolINS (c) 2009 Christian B. Hülschle
Figure 3.1.28*

**ESP Maps:**
Refinement Note:

Despite being the most active compound in this set the refinement of HS-P57-4 has several problems. The Moliso program used to perform the global parameter analysis produces errors when attempting to calculate the global parameters on this compound. And no global parameter analysis has been performed on HS-P57-4. Residual maps are flat. Contours peak at 2 (0.20) about Cl(1A) in the C(8A), C(10A), and C(12A) plane.

Crystal Data Table:

<table>
<thead>
<tr>
<th>General Sample Information</th>
</tr>
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<tbody>
<tr>
<td>Molecular formula</td>
</tr>
<tr>
<td>Formula weight</td>
</tr>
<tr>
<td>Temperature (K)</td>
</tr>
<tr>
<td>Wavelength (Å)</td>
</tr>
<tr>
<td>Crystal System</td>
</tr>
<tr>
<td>Space Group</td>
</tr>
<tr>
<td>Cell Dimensions</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>a (Å)</td>
</tr>
<tr>
<td>b (Å)</td>
</tr>
<tr>
<td>c (Å)</td>
</tr>
<tr>
<td>α</td>
</tr>
<tr>
<td>β</td>
</tr>
<tr>
<td>γ</td>
</tr>
<tr>
<td>Volume</td>
</tr>
</tbody>
</table>

Density 1.457 Mg/m³
Absorption coefficient 0.507 mm⁻¹
Crystal size (mm) 0.25 x 0.5 x 0.5

$$(\sin \theta/\lambda)_{\text{max}} = 0.88$$

Unique reflections 42,192 [R(int) = 0.0253]
Average redundancy 15.7
Completeness to $(\sin \theta/\lambda)_{\text{max}}$ 98.7%
Absorption correction Empirical ($t_{\text{min}}$ = 0.786, $t_{\text{max}}$ = 0.884)

**Spherical Atom Refinement**

<table>
<thead>
<tr>
<th>Refinement method</th>
<th>Full-matrix least-squares on F²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data(I&gt;2σ(I))/restraints/parameters</td>
<td>42,192 / 0 / 1161</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.106</td>
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<tr>
<td>Final R indices [I&gt;2σ(I)]</td>
<td>$R_1 = 0.0391$</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>$R_1 = 0.0542$, $wR_2 = 0.1206$</td>
</tr>
<tr>
<td>Largest difference peak and trough</td>
<td>1.725 and -1.135 e · Å⁻³</td>
</tr>
<tr>
<td>$N_{\text{ref}}/N_v$</td>
<td>36.34</td>
</tr>
</tbody>
</table>

**Multipole Atom Refinement**

<table>
<thead>
<tr>
<th>Refinement method</th>
<th>Full-matrix least-squares on F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data(I&gt;2σ(I))/restraints/parameters</td>
<td>43072 / 0 / 1344</td>
</tr>
<tr>
<td>Goodness-of-fit (GoF) on F</td>
<td>3.606</td>
</tr>
<tr>
<td>Final R indices [I&gt;2σ(I)]</td>
<td>$R_1 = 0.0283$, $wR_2 = 0.0185$</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>$R_1 = 0.0591$</td>
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<tr>
<td>Largest difference peak and trough</td>
<td>1.094 and -0.893 e · Å⁻³</td>
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<tr>
<td>$N_{\text{ref}}/N_v$</td>
<td>26.02</td>
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</tbody>
</table>

Table 3.1.28

$$R_1 = \sum \frac{|F_o|-|F_c|}{|F_o|} w R_F = \left[ \sum \frac{w(|F_o|-|F_c|)^2}{w|F_o|^2} \right]^{1/2}$$

$$GoF = \left[ \sum \frac{w(F_o^2-F_c^2)^2}{(N_{\text{ref}}-N_v)} \right]^{1/2}$$

**Atomic Basin Calculations Table:**

<table>
<thead>
<tr>
<th>Atom</th>
<th>$e^-$ Population in Basin</th>
<th>$q(\Omega)$ ($e^-$)</th>
<th>$V(\Omega)$ (Å³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl(1A)</td>
<td>1.7068E+01</td>
<td>-6.8143E-02</td>
<td>29.9723</td>
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<tr>
<td>Cl(2A)</td>
<td>1.7300E+01</td>
<td>-3.0060E-01</td>
<td>30.6826</td>
</tr>
<tr>
<td>Cl(3A)</td>
<td>1.7359E+01</td>
<td>-3.5960E-01</td>
<td>28.7268</td>
</tr>
<tr>
<td>O(1A)</td>
<td>9.0944E+00</td>
<td>-1.0944E+00</td>
<td>12.4969</td>
</tr>
<tr>
<td>O(2A)</td>
<td>9.1560E+00</td>
<td>-1.1560E+00</td>
<td>16.2483</td>
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<tr>
<td>N(1A)</td>
<td>7.7494E+00</td>
<td>-7.4948E-01</td>
<td>9.1810</td>
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</table>
### Table 3.1.29

<table>
<thead>
<tr>
<th>Bond</th>
<th>Ellipticity</th>
<th>$\rho(r)$</th>
<th>$\nabla^2 \rho(r)$</th>
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<tr>
<td><strong>Dichlorophenyl Ring</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Inner Carbon Bonds</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(13A) - C(14A)</td>
<td>0.18</td>
<td>2.214</td>
<td>-21.270</td>
</tr>
<tr>
<td>C(14A) - C(15A)</td>
<td>0.11</td>
<td>2.124</td>
<td>-18.074</td>
</tr>
<tr>
<td>C(15A) - C(16A)</td>
<td>0.14</td>
<td>2.222</td>
<td>-20.429</td>
</tr>
<tr>
<td>C(16A) - C(17A)</td>
<td>0.20</td>
<td>2.182</td>
<td>-19.406</td>
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<tr>
<td>C(17A) - C(18A)</td>
<td>0.15</td>
<td>2.251</td>
<td>-22.203</td>
</tr>
<tr>
<td>C(18A) - C(13A)</td>
<td>0.20</td>
<td>2.219</td>
<td>-21.137</td>
</tr>
<tr>
<td>Outer Atom – Inner Carbon Bonds</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>------</td>
<td>------</td>
<td>------</td>
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<tr>
<td>N(1A) - C(13A)</td>
<td>0.04</td>
<td>1.948</td>
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<td>H(14A) - C(14A)</td>
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<td>1.839</td>
<td>-18.253</td>
</tr>
<tr>
<td>H(15A) - C(15A)</td>
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<tr>
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<td>1.410</td>
<td>-3.612</td>
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<table>
<thead>
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<td>Inner Carbon Bonds</td>
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<tr>
<td>C(7A) - C(8A)</td>
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<td>-17.231</td>
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<td>-18.743</td>
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<td>C(9A) - C(10A)</td>
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<td>-21.296</td>
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<td>C(10A) - C(11A)</td>
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<td>C(11A) - C(12A)</td>
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<td>2.064</td>
<td>-16.552</td>
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<tr>
<td>C(12A) - C(7A)</td>
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<td>2.162</td>
<td>-19.266</td>
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</table>

<table>
<thead>
<tr>
<th>Outer Atom – Inner Carbon Bonds</th>
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</thead>
<tbody>
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<td>C(6A) - C(7A)</td>
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<td>1.770</td>
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<td>H(12A) - C(12A)</td>
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<td>1.818</td>
<td>-18.628</td>
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<table>
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<th>Ester Side Chain</th>
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<td>C(4A) - C(5A)</td>
<td>0.15</td>
<td>1.886</td>
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<tr>
<td>O(2A) - C(4A)</td>
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<td>2.283</td>
<td>-27.110</td>
</tr>
<tr>
<td>O(1A) - C(4A)</td>
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<td>2.283</td>
<td>-27.110</td>
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<td>C(3A) - O(1A)</td>
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<td>H(3A1) - C(3A)</td>
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<td>1.897</td>
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<td>H(3A2) - C(3A)</td>
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<td>H(2A1) - C(2A)</td>
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<td>H(1A2) - C(1A)</td>
<td>0.23</td>
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<tr>
<td>H(1A3) - C(1A)</td>
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<table>
<thead>
<tr>
<th>Triazole Ring</th>
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<tbody>
<tr>
<td>N(3A) - N(2A)</td>
<td>0.14</td>
<td>2.805</td>
<td>-8.063</td>
</tr>
<tr>
<td>N(2A) - N(1A)</td>
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<tr>
<td>C(6A) - C(5A)</td>
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<td>C(5A) - N(3A)</td>
<td>0.16</td>
<td>2.448</td>
<td>-21.285</td>
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</table>

Table 3.1.30

**Global Parameter Analysis**

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<thead>
<tr>
<th>Molecule</th>
<th>K_i (nm)</th>
<th>Average</th>
<th>Tot Variance</th>
<th>Balance</th>
<th>V(max)</th>
<th>V(min)</th>
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</thead>
</table>

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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Deviation (e/A)</th>
<th>(e/A)^2</th>
<th>Parameter</th>
<th>(e/A)^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HS-P53-2</td>
<td>6900</td>
<td>0.0835</td>
<td>0.0218</td>
<td>0.2191</td>
</tr>
<tr>
<td>HS-P53-1</td>
<td>4400</td>
<td>0.1011</td>
<td>0.0287</td>
<td>0.2450</td>
</tr>
<tr>
<td>HS-P57-2</td>
<td>1400</td>
<td>0.1063</td>
<td>0.0338</td>
<td>0.2487</td>
</tr>
<tr>
<td>HS-P226</td>
<td>860</td>
<td>0.1110</td>
<td>0.0333</td>
<td>0.2411</td>
</tr>
<tr>
<td>HS-P69</td>
<td>590</td>
<td>0.1421</td>
<td>0.0713</td>
<td>0.2095</td>
</tr>
<tr>
<td>HS-P183</td>
<td>250</td>
<td>0.0712</td>
<td>0.0173</td>
<td>0.2493</td>
</tr>
<tr>
<td>HS-P57-7</td>
<td>240</td>
<td>0.1022</td>
<td>0.0343</td>
<td>0.2181</td>
</tr>
<tr>
<td>HS-P57-3</td>
<td>180</td>
<td>0.1403</td>
<td>0.0656</td>
<td>0.2489</td>
</tr>
<tr>
<td>AVG-229Ph</td>
<td>170</td>
<td>0.0753</td>
<td>0.0162</td>
<td>0.2324</td>
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<tr>
<td>HS-P57-4</td>
<td>4.6</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
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</table>

Table 3.1.31: Global parameter analysis as performed by MolIso. Data for HS-P57-4 was not obtainable due to an unresolved program error.
Discussion

Part 1: Refinement Quality

The final multipole refinement for each molecule varied in quality though there were trends in maximum peak and trough residual density values due to similarities in atomic makeup. All multipole refinements were much improved over IAM refinements. On several occasions the largest residual peak and trough for the multipole refinement were greater than that of the corresponding IAM refinement for that molecule, as determined by the XDFFT module (by performing a fast Fourier transform on the residuals) in XD2006, despite having a much lower overall R-factor. This may be due to the difficulties in modeling the electron density of the chlorine atoms in each molecule. The residual density was minimal everywhere except around chlorine atoms where peaks varied from 1 contour \((0.10 \, e \cdot \AA^{-3})\) to the extreme of 8 contours \((0.80 \, e \cdot \AA^{-3})\) in compounds 4 and 8. On some occasions, the introduction of anisotropic-anharmonic temperature factors substantially reduced these residuals. Chlorine is greater in total electron density and thus may be expected to have larger residuals. Goodness of fit (GoF) values for the multipole refinements are increased (of poorer quality) over that of the IAM as no steps were taken during weighting to maximize GoF quality as they were with the IAM refinement. All final multipole refinements are considered of suitable quality for this study.

Bond critical point values and atomic basin charge calculations were reasonable with the exception of a few values. Compound 1 showed low bond ellipticity in between the carbon bonds of nitrogen attached phenyl ring system where high ellipticity is expected.\(^{109}\) Values of the Laplacian of five “covalent” bonds are positive (signifying closed shell interactions) where they are expected to be negative.\(^{99}\) In all instances these bonds were between carbon and a highly electronegative atom. These instances occurred in compound 3 \([\text{Cl}(2) - \text{C}(12)]\), compound 4 \([\text{C}(1) - \text{O}(1)]\), compound 6 \([\text{Cl}(1) - \text{C}(14)]\), and
C(12)], and compound 7 [Cl(2) - C(17)], [Cl(1) - C(13)]. Of note is the existence of both slight positively and negatively charged chlorine atoms as integrated over their atomic basins. This occurs on molecules with well refined chlorines (low residual density) and does not appear to be an artifact of poor refinement. Otherwise the refined multipole parameters were chemically reasonable.

Part 2: Analysis of ESP and QTAIM

Qualitative and Quantitative analysis of the global surface electrostatic properties of each compound ultimately failed show correlation with affinity and statistical parameters of the ESP. Due to a program error, compound 10 (HS-P57-4) could not be analyzed in terms of the surface ESP. No correlation was found between the ESP and $K_i$ of the remaining data. Furthermore, there were no apparent features of the ESP upon visual inspection that indicated greater or lesser $K_i$ values. No local (by atom or ring system) ESP analysis was conducted.

Using the R programing language, principal component analysis (PCA) was performed to identify variables or combinations of variables that correlate with pharmacological affinity and thus could be used to design more potent drugs.\(^{121,125-127}\) The inspected variables consisted of the average aromatic ring ellipticity, average aromatic ring carbon bond critical point rho and Laplacian values, position specific chlorine charge values, average atomic charge deviation, triazole nitrogen charges, average triazole ring charge, carbonyl oxygen and ester oxygen charge, substituent volume, total molecular volume, ring specific and total molecular charge standard deviation (total charge of each molecule is zero), average substituent charge, and substituent charge standard deviation. These variables were chosen based on the rimonabant pharmacophore\(^{85,86}\) despite this molecular set having a slightly different central ring connectivity. Correlation was found between the ortho-chlorine charge (ring 1), both oxygen sites, substituent volume, total volume, triazole nitrogen, ring 2 rho critical point value, and triazol ellipticity (Note: As the two phenyl ring systems on each compound are attached to the central
triazole ring, for cross reference purposes ‘ring 1’ refers to the nitrogen attached phenyl ring system in
the ‘1’ position in compound 1 and ‘ring 2’ refers to the carbon attached phenyl ring system in the 5
position in compound 1). Several notes of importance are that for compounds 6 and 4 an extra carbon
is present before the carbonyl carbon setting it slightly further away from the triazole ring, compound 5
has a nitrogen in place of the ester oxygen making it a carboxamide, and compound 4 has an alternate
relative connectivity of the side chain. An ester functional group and attached substituent are absent in
compounds 1 and 3. As they are absent the values (charge and volume) associated with them are set to
zero. Due to the range of affinity ($K_i = 4.6$ nm to 6900 nm) and lack of concentrated data points at the
far end of the data spectrum (low affinity), only variables that showed a continual trend in correlation or
anti-correlation when leaving out the most extreme data point for three consecutive data points ($K_i =
6900$ nm, 4400 nm, 1400 nm) were considered as correlated or anti-correlated, to ensure correlations
were not a result of a single extreme data point. This left seven data points from $K_i = 4.6$ nm to 860 nm.
Below are tables of the raw data (Table 4.2.1) and scaled for unit variation and centered data (Table
4.2.2) for the correlated and anti-correlated data.

<table>
<thead>
<tr>
<th>Comp.</th>
<th>$K_i$</th>
<th>Ring 1 Ortho Chlorine</th>
<th>Ring 2 Rho</th>
<th>Carbonyl Oxygen</th>
<th>Ester Oxygen</th>
<th>Substituent Volume</th>
<th>Average Triazole Nitrogen</th>
<th>Total Volume</th>
<th>Triazole Ellipticity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6900</td>
<td>0.0819</td>
<td>2.147</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-0.559</td>
<td>299.3423</td>
<td>0.186</td>
</tr>
<tr>
<td>2</td>
<td>4400</td>
<td>0.10925</td>
<td>2.120</td>
<td>-1.1861</td>
<td>-1.0878</td>
<td>28.2821</td>
<td>-0.442</td>
<td>361.4843</td>
<td>0.132</td>
</tr>
<tr>
<td>3</td>
<td>1400</td>
<td>-0.2317</td>
<td>2.198</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-0.422</td>
<td>315.8081</td>
<td>0.132</td>
</tr>
<tr>
<td>4</td>
<td>860</td>
<td>0.0787</td>
<td>2.122</td>
<td>-0.9519</td>
<td>-1.1945</td>
<td>43.6581</td>
<td>-0.427</td>
<td>399.2907</td>
<td>0.154</td>
</tr>
<tr>
<td>5</td>
<td>590</td>
<td>-0.1076</td>
<td>2.220</td>
<td>-1.267</td>
<td>-0.7591</td>
<td>132.4619</td>
<td>-0.557</td>
<td>481.4913</td>
<td>0.138</td>
</tr>
<tr>
<td>6</td>
<td>250</td>
<td>-0.0988</td>
<td>2.203</td>
<td>-1.0191</td>
<td>-1.135</td>
<td>44.9406</td>
<td>-0.458</td>
<td>399.3423</td>
<td>0.210</td>
</tr>
<tr>
<td>7</td>
<td>240</td>
<td>0.1071</td>
<td>2.232</td>
<td>-1.1217</td>
<td>-1.1572</td>
<td>124.4466</td>
<td>-0.461</td>
<td>476.3942</td>
<td>0.252</td>
</tr>
<tr>
<td>8</td>
<td>180</td>
<td>-0.304</td>
<td>2.220</td>
<td>-1.4109</td>
<td>-1.0661</td>
<td>43.8547</td>
<td>-0.493</td>
<td>389.9076</td>
<td>0.132</td>
</tr>
<tr>
<td>9</td>
<td>170</td>
<td>-0.0916</td>
<td>2.216</td>
<td>-1.0414</td>
<td>-1.0632</td>
<td>102.1995</td>
<td>-0.337</td>
<td>447.8958</td>
<td>0.180</td>
</tr>
<tr>
<td>10</td>
<td>4.6</td>
<td>-0.3596</td>
<td>2.139</td>
<td>-1.156</td>
<td>-1.0944</td>
<td>68.7358</td>
<td>-0.407</td>
<td>414.9075</td>
<td>0.174</td>
</tr>
</tbody>
</table>

Table 4.2.1: Raw data. Maroon variables are correlated. The more negative the values the greater the affinity. Dark blue variables are anti-
correlated. A larger value contributes to greater affinity. The lone green variable is also anti-correlated. A less negative value increases
affinity.
Table 4.2.2: Centered and scaled data. Maroon variables are correlated. The more negative the values the greater the affinity. Dark blue variables are anti-correlated. A larger value contributes to greater affinity. The lone green variable is also anti-correlated. A less negative value increases affinity.

Below are the correlations of each variable with affinity ($K_i$) from the covariance matrix of the scaled and centered data.

<table>
<thead>
<tr>
<th>Property</th>
<th>Correlation with $K_i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ring 1 Ortho Chlorine</td>
<td>0.5188</td>
</tr>
<tr>
<td>Ring 2 Rho</td>
<td>-0.5290</td>
</tr>
<tr>
<td>Carbonyl Oxygen</td>
<td>0.5776</td>
</tr>
<tr>
<td>Ester Oxygen</td>
<td>0.5829</td>
</tr>
<tr>
<td>Substituent Volume</td>
<td>-0.5863</td>
</tr>
<tr>
<td>Average Triazole Charge</td>
<td>-0.4432</td>
</tr>
<tr>
<td>Triazole N1 Charge</td>
<td>-0.5706</td>
</tr>
<tr>
<td>Total Molecular Volume</td>
<td>-0.6700</td>
</tr>
<tr>
<td>Triazole Ellipticity*</td>
<td>-0.1248</td>
</tr>
</tbody>
</table>

Table 4.2.2: Property correlation with $K_i$.

Not all reasons for these property correlations can be clearly understood. Others, without a crystal structure of the binding pocket with an attached ligand, can only be inferred. Triazole ellipticity has been included in this list, although with the most extreme data point from compound 1, the anti-correlation is approximately a quarter of its anti-correlation if left out. This persists for leaving out the next three most extreme data points and so it has been included (as is the case with all data points included). The more negative the ortho-position chlorine on ring 1 is, the more it contributes to increased affinity (lower $K_i$). As it is assumed to bind in a similar fashion as rimonabant, this feature of
the compound would come in close contact with a phenylalanine residue of the receptor. It can be speculated that attractive interactions occur with other surrounding residues or positive amine groups. Both oxygen sites are in proximity to features suspected of stabilizing an Asp366-Lys192 salt bridge via hydrogen bonding. More negative oxygens are shown to increase affinity. The ester substituent, according to the rimonabant pharmacophore, is positioned to interact with hydrophobic segments of the binding pocket. Larger ester substituents, assuming hydrophobicity of the substituent, contributes to an increase in affinity made possible by providing more hydrophobic interactions. The same argument can be made for the total molecular volume which has a slightly greater correlation than the substituent volume. There is a general negative correlation of the average charge of the triazole nitrogens charge with affinity at -0.44. The most exposed nitrogen (in the 3 position in compound 1 referred to as N1) had an even more negative correlation at -0.57. This may indicate that it is better for a compound to be charge neutral.

Plots of the scaled and centered data are in the figures below.
Figure 4.2.1.: Ortho-Chlorine charge on ring 1 vs $K_i$. Fit: slope = 0.5188, $R^2 = 0.2690$. 

Figure 4.2.2.: Ring 2 Average Rho BCP vs $K_i$. 

Figure 4.2.3.: Ring 2 Average Rho BCP vs Ring 1 Ortho Chlorine.
Figure 4.2.2.: Ring 2 average carbon-carbon rho bond critical point vs $K_i$. Fit: slope = -0.5300, $R^2 = 0.2798$.

Figure 4.2.3.: Substituent carbonyl oxygen charge vs $K_i$. Fit: slope = 0.5776, $R^2 = 0.3337$.

Figure 4.2.4.: Substituent ester oxygen charge vs $K_i$. Fit: slope = 0.5829, $R^2 = 0.3398$. 
Figure 4.2.5.: Substituent volume vs $K_i$. Fit: slope = -0.5863, $R^2 = 0.3437$.

Figure 4.2.6.: Triazole N1 charge vs $K_i$. Fit: slope = -0.4432, $R^2 = 0.2000$. 
Figure 4.2.6.: Triazole N1 charge vs $K_i$. Fit: slope = -0.5706, $R^2 = 0.3255$.

Figure 4.2.7.: Molecular volume vs $K_i$. Fit: slope = -0.6999, $R^2 = 0.4899$. 

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R-squared values are relatively high, as there are multiple contributing factors to affinity, and R-squared is an indicator of variance in the data unaccounted for by the linear fit.\textsuperscript{130} Outliers that are in extreme with or against the trend in one graph often can be explained by data in others. Correlations were not weighted and a scored model was not generated. In order to reduce the dimensionality of the data, principal component analysis was conducted.\textsuperscript{125} The biplots (a plot that includes both the parameters and measurements) in figures 4.2.8 and 4.2.9 show a graphic representation of correlation and molecular similarity. An attempt was made to interpret the data including only the first three principal components (PC1 [43.66\%], PC2 [22.58\%], PC3 [13.19\%]) which accounts for a total of 80.14\% of the variation in the data. The principal components are the Eigen vectors of the covariance matrix. The three principal components that account for the greatest amount of variation were chosen. This is determined by solving for the Eigen values by singular value decomposition.\textsuperscript{125} The total variance of the data is the sum of all Eigen values. And the percent of variation taken into account by a single principal component is its associated Eigen value divided by the sum of all Eigen values times one hundred. The analysis reconfirms what is expressed in the correlation matrices. In the future data mining techniques that explore in greater detail correlation and co-correlation may be applied to the model generated. The model’s effectiveness may be increased by adding observed variables that were not correlated with $K_i$ but would have to be scrutinized in the same fashion as the included data. This would offer the advantage of obtaining information on how to alter features about the molecule that would affect other features correlated strongly with $K_i$ but not necessarily as correlated with $K_i$ themselves. Below are projections of the data onto the first and second principal components, and the second and third principal components.
Figure 4.2.8.: Biplot of data onto principal components 1 & 2 with percentages of variation accounted for by each axis. The red vectors represent variable. Those vectors that point in the same direction are correlated. Those that point way from each other are anti-correlated. Where each molecule is labeled on the plot shows its similarity or dissimilarity with the rest. The closer a molecules point is to a vector, the greater its value of the associated variable is.
Figure 4.2.9.: Biplot of data onto principal components 2 & 3 with percentages of variation accounted for by each axis. The red vectors represent variable. Those vectors that point in the same direction are correlated. Those that point way from each other are anti-correlated. Where each molecule is labeled on the plot shows its similarity or dissimilarity with the rest. The closer a molecules point is to a vector, the greater its value of the associated variable is.
Conclusion

In conclusion, ten x-ray charge density studies were performed on CB₁ receptor antagonist of similar structure. Properties derived from the study were analyzed in an attempt to correlate them with measured CB₁ binding affinity. These properties included: the magnitude of the electron density at the bond critical points deemed relevant, the magnitude of the Laplacian of the electron density at the bond critical points deemed relevant, average bond ellipticity of moieties of each molecule, the molecular volume, the charge of atoms of functional groups, the average charge of the triazole ring, the volume of specific moieties, and the electrostatic potential (global statistical analysis).

Correlations/anti-correlations were found between affinity and the triazole nitrogen charges, oxygen charges of the ester functional groups, substituent volumes, molecular volumes, ring 1 ortho-chlorine charges, and ring 2 rho bond critical point values. Using principal component analysis, the first three principal components were found to account for 83.9% of the variance in the values. It has been determined that more negative oxygen charges as well as ortho-chlorine charges, and larger substituent and molecular volumes increases affinity. While increased nitrogen charges reduces affinity. With this information it may be possible to further refine CB₁ antagonist affinity. Negatively charged nitrogen atoms may be substituted with carbon atoms, and less negatively charged atoms may be placed where specified chlorines are, etc.

In the future it may be a better approach to use invarioms\textsuperscript{131,132}, an approach that models computed electron density out the next nearest neighbor with the Hansen-Coppens multipole formalism and superimposes the resulting multipoles onto equivalent atoms, to estimate electron densities as this would allow for a larger sample of molecules to be used in the analysis. This would also decrease the resolution needed to perform the analysis and limit the amount of effort required to obtain adequate resolution of data. Also generating a weighting scheme and scoring the model produced is preferable, though it was not performed here.
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multivariate data based on principal components analysis and diagnostic tools of the quality of the reduction.


Vita:

Steven Paul Fournet, author of this thesis was born in New Orleans, Louisiana. He received his bachelor degree in Chemistry from the University of New Orleans in 2007. After which he joined the University of New Orleans graduate school of chemistry in pursuit of a Philosophy Doctorates in the field of physical chemistry under the guidance of Professor Edwin D. Stevens.