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Chapter 11

Structural Insight Into the Viral 3C-Like Protease Inhibitors: Comparative SAR/QSAR Approaches

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1 INTRODUCTION

In early 2003, about 8500 people were diagnosed across the world with severe acute respiratory syndrome (SARS). Among them, almost 800 died due to its first outbreak. The disease was broken out and turned into an epidemic in Guangdong of South China. Two cases of SARS infections were noticed in Taiwan and Singapore due to improper handling of the samples in the research laboratory. During April 2004, a “mini outbreak” of infections took place in a research laboratory of Beijing that, in turn, led to a chain of infections across three generations. Fortunately, the total number of SARS-infected people was only nine that time. This incidence threatens us about the mini outbreaks of SARS globally at any time (Anand et al., 2005). The SARS is caused by the SARS-coronavirus (SARS-CoV) that belongs to the family of Coronaviridae. This family also includes viruses, such as feline infectious peritonitis virus, murine hepatitis virus, bovine coronavirus, transmissible gastroenteritis virus (TGEV), as well as human coronavirus 229E (Kim et al., 2015). The SARS is considered as a global threat to the health (Khan, 2013; Perlman and Netland, 2009). Moreover, water and food-borne viral gastroenteritis may be caused by the noroviruses that belong to the family Caliciviridae (Atmar, 2010; Patel et al., 2009). Therefore, there is an urgent need to develop small molecule antiviral drugs to combat these viruses. The picornavirus belongs to the family of viruses namely Picornaviridae, Caliciviridae, and Coronaviridae (Mandadapu et al., 2013a). A number of pathogeneses in human may occur due to these viruses leading to economic and medical burden. For example, human rhinovirus (HRV) is the major reason...
for upper respiratory tract infection (Ren et al., 2012; Turner and Couch, 2007; Winther, 2011) whereas nonpolio enteroviruses are responsible for symptomatic infections with 10–15 million cases per year in United States (McMinn, 2012; Solomon et al., 2010). Depending on the similarity of the polycistronic organization of the genome, common and posttranscriptional strategies along with the conserved region of domain homology in viral proteins, the virus families are related phylogenetically though these families are not related morphologically (Anand et al., 2005; Cavanagh, 1997; Cowley et al., 2000). Coronavirus is found to be responsible for causing a number of diseases not only in human but also in animals, though the human coronavirus has not been taken into account seriously before the SARS outbreak (Anand et al., 2005). Human coronavirus (HCoV) OC43 and 229E may be responsible for illness in the upper portion of the respiratory tract along with common cold-like conditions (Myint, 1995). The HCoV 229E is the only strain till date that can be cultured in cell culture technique efficiently. The symptoms of SARS include rigor, malaise, high degree of fever, cough, headache, and dyspnoea. The symptoms may also lead to produce interstitial infiltrates in lungs that may be treated through ventilation and intubation (Lee et al., 2003). Not only the lungs but also other organs may be affected by SARS infection (such as liver, kidney, and gastrointestinal tract). Therefore, the SARS infection may be treated as a cause of systemic infection. Face-to-face contacts may be supposed to be the reason for transmission of the pathogen though other routes are also possible. A number of inhibitors against SARS-CoV 3CL\textsuperscript{pro} and HRV 3C\textsuperscript{pro} were reported and the process of development of new antivirals against this class has been continued for a decade. In the present report, quantitative structure–activity relationships (QSARs) techniques have been explored to understand the relation between the SARS-CoV 3CL\textsuperscript{pro} and HRV 3C\textsuperscript{pro} enzyme inhibitory activity with the physicochemical and structural properties of these inhibitors developed till now. This approach may be a useful strategy to design and develop novel and potential SARS-CoV 3CL\textsuperscript{pro} and HRV 3C\textsuperscript{pro} inhibitors to combat the dreadful viral infections.

2 GENOME STRUCTURE OF SARS-CoV AND ITS REPLICATIONS

Among the known RNA viruses, the coronaviruses are enveloped, (+) stranded RNA viruses with the largest single-stranded RNA genome (27–31 kb approximately). The RNAs are polyadenylated and 5’capped. These are translated into large polyproteins following their entry into the host cell. The polyproteins are proteolytically cleaved by viral proteinases resulting in viral gene products. The RNA polymerase (pol) is found to be encoded by the genome of SARS-CoV and four structural proteins that commonly include the spike glycoprotein (S), envelope (E), membrane (M), and nucleocapsid (N) proteins in the order of Pol-S-E-M-N. The spike protein (S) is the antigenic determinant for coronavirus and is found to be involved in receptor binding. The E protein plays a significant role during viral assembly. The M glycoprotein transmembrane envelope is found abundantly
and is responsible for budding of the virus, and the N protein is related to the viral RNA packaging (Holmes, 2003; Shigeta and Yamase, 2005; Zhai et al., 2007).

### 3 STRUCTURE AND FUNCTIONS OF CORONAVIRUS MAIN PROTEASES

Coronavirus contains a positive-stranded RNA with a single-stranded, large size (27–31 kb) RNA genome. Two overlapping polyproteins, that is, pp1a (450 kDa approx.) and pp1ab (750 kDa approx.) are encoded by the replicase gene with more than 20,000 nucleotides (Herold et al., 1993). These two polyproteins regulate the replication, as well as transcription processes in the virus (Thiel et al., 2001). Proteolysis helps to liberate nonstructural proteins (nsp) from these polyproteins. The proteolytic cleavage is mainly controlled by the viral proteinase termed as M\(^{\text{pro}}\) (Anand et al., 2005). The M\(^{\text{pro}}\) is a cysteine proteinase which is synonymous or rather called as 3C-like protease (3CL\(^{\text{pro}}\)) as the substrate specificity resembles picornavirus 3C-protease (3C\(^{\text{pro}}\)), though both of these viruses are structurally less similar (Anand et al., 2002, 2005). The 3CL\(^{\text{pro}}\) is found to cleave the polyprotein at 11 conserved region including Leu-Gln sequences which are initiated by the autolytic cleavage of the enzyme from pp1a and pp1ab (Hegyi and Ziebuhr, 2002b; Ziebuhr et al., 2000). The pp1a and pp1ab polyproteins help to release functional polypeptides by papain-like protease (PL\(^{\text{pro}}\)) and 3CL\(^{\text{pro}}\) is located in the nonstructural protein regions, namely nsp3 and nsp5 (Fig. 11.1) via proteolytic reaction mechanisms (Grum-Tokars et al., 2008).

These PL\(^{\text{pro}}\) and 3CL\(^{\text{pro}}\) are processed by the replicase through autocatalytic mechanisms. The PL\(^{\text{pro}}\) is found to be responsible for cleaving 3 sites, whereas 3CL\(^{\text{pro}}\) cleaves 11 sites in the viral genome (Grum-Tokars et al., 2008). The SARS-3CL\(^{\text{pro}}\) cleavage sites are shown in Table 11.1. This type of cleavage is found to be conserved in the 3CL\(^{\text{pro}}\) as evidenced from the experimental data

![FIGURE 11.1 SARS-CoV genomic RNA encoding viral replicase polyproteins pp1a and pp1ab (3 and 11 sites are recognized and processed by PL\(^{\text{pro}}\) and 3CL\(^{\text{pro}}\), respectively). Hel, Helicase coding regions; Pol, polymerase; TM, transmembrane. (Adapted from Grum-Tokars, V., Ratia, K., Begaye, A., Baker, S.C., Mesecar, A.D., 2008. Evaluating the 3C-like protease activity of SARS-CoV: recommendations for standardized assays for drug discovery, Virus Res. 133, 63–73.)](image-url)
Viral Proteases and Their Inhibitors

(Anand et al., 2003) and the sequence of genomic structure (Marra et al., 2003; Rota et al., 2003).

Three noncanonical M\textsuperscript{pro} cleavage sites are observed in SARS coronavirus polyproteins having Val, Met, or Phe amino acid residues at P2 position whereas the same cleavage site is found dissimilar in other coronaviruses. Therefore, the structural and functional criteria of M\textsuperscript{pro} helps to identify it as an important target for developing anti-SARS drugs or other anticoronaviral drugs (Anand et al., 2005). The structures of HCoV 229E M\textsuperscript{pro}, TGEV M\textsuperscript{pro}, and SARS-CoV M\textsuperscript{pro} demonstrate that these enzymes have three distinct domains. The first two domains (domain I and II) together possess similarity with chymotrypsin whereas the third one consists of an α-helical fold which is unique (Anand et al., 2005). The active site which is situated between the first two domains possesses a Cys-His catalytic site. Antiparallel β-barrels with six strands are composed of the domain I and II (residues 8–99 of I and 100–183 of II, respectively). The domain II is connected to domain III (residues 200–300) through a long loop (residues 184–199) (Anand et al., 2005). The hydrophobic amino acid residues are found to compose the domain I β-barrel. The α-helix (residues 53–58) helps to close the β-barrel like a lid. The domain I is bigger than domain II, as well as the homologous domain II of chymotrypsin and 3C\textsuperscript{pro} of HAV (Allaire et al., 1994; Bergmann et al., 1997; Tsukada and Blow, 1985). Moreover, a number of secondary

| Sl. No. | 3CL\textsuperscript{pro} cleavage sites | P5′ | P4′ | P3′ | P2′ | P1′ | P1 | P2 | P3 | P4 | P5 | P6 |
|--------|-----------------|-----|-----|-----|-----|-----|----|----|----|----|----|----|
| 01     | nsp4/5          | LYS | ARG | PHE | GLY | SER | GLN | LEU | VAL | ALA | SER | THR |
| 02     | nsp5/6          | LYS | LYS | PHE | GLY | GLN | PHE | THR | VAL | GLY | SER |
| 03     | nsp6/7          | ASP | SER | MET | GLY | SER | GLN | VAL | THR | ALA | VAL | LYS |
| 04     | nsp7/8          | GLU | SER | ALA | ILE | ALA | GLN | LEU | THR | ALA | ARG | ASN |
| 05     | nsp8/9          | SER | LEU | GLU | ASN | ALN | GLN | LEU | VAL | ALA | SER |
| 06     | nsp9/10         | THR | ALA | ASN | GLY | ALN | GLN | LEU | ARG | VAL | THR | ALA |
| 07     | nsp10–12        | SER | ALA | ASP | ALA | SER | GLN | MET | LEU | PRO | GLU | ARG |
| 08     | nsp12/13        | CYS | ALA | GLY | VAL | ALA | GLN | LEU | VAL | THR | HIS | PRO |
| 09     | nsp13/14        | THR | VAL | ASN | GLU | ALA | GLN | LEU | THR | ALA | VAL | ASN |
| 10     | nsp14/15        | VAL | ASN | GLU | LEU | SER | GLN | LEU | ARG | THR | PHE | THR |
| 11     | nsp15/16        | TRP | ALA | GLN | SER | ALA | GLN | LEU | LYS | PRO | TYR | PHE |

Source: Adapted from Grum-Tokars, V., Ratia, K., Begaye, A., Baker, S.C., Mesecar, A.D., 2008. Evaluating the 3C-like protease activity of SARS-Coronavirus: recommendations for standardized assays for drug discovery, Virus Res. 133, 63–73.
structural elements are found to be missing in coronavirus M\textsuperscript{pro} compared to HAV 3C\textsuperscript{pro} (such as strands b2\text{II} and c\text{II} along with the linking loop). The Gly135 to Ser146 form a portion of the barrel though domain II possesses maximum consecutive turns and loops. Moreover, the structural alignment of coronavirus M\textsuperscript{pro} domain II with the picornavirus 3C\textsuperscript{pro} domain II is found to be different. Superimposition of domain I of TGEV M\textsuperscript{pro}, with HAV 3C\textsuperscript{pro} domain I results in a root mean square deviation (rmsd) of 1.85 Å whereas superimposition of domain II of both of these enzymes yields a rmsd of 3.25 Å. The overall rmsd for the C\textalpha atoms between their structures is >2 Å for all 300 C\textalpha positions and the three M\textsuperscript{pro} structures possess similarity among themselves (Anand et al., 2005). The helical domain III is the most variable domain that exhibits a better overlapping between HCoV M\textsuperscript{pro} and TGEV M\textsuperscript{pro} compared to the SARS-CoV M\textsuperscript{pro}, with each other. Moreover, TGEV and HCoV 229E (belongs to group I coronavirus) show 61% sequence similarity whereas SARS-CoV (belongs to group II coronavirus) exhibits 40% and 44% sequence similarity with HCoV 229E and TGEV, respectively (Anand et al., 2003). A high degree of conserved region (42%–48%) between the domain I and II is observed while comparing group I coronavirus M\textsuperscript{pro}, and group II SARS-CoV M\textsuperscript{pro}. The domain III comparatively exhibits a lower degree of sequence similarity (36%–40%) between these two groups coronaviral enzymes (Anand et al., 2005). The X-ray crystallography structures of SARS-CoV M\textsuperscript{pro}, TGEV M\textsuperscript{pro}, and HCoV 229E M\textsuperscript{pro} show that these form dimers (Anand et al., 2002, 2003; Yang et al., 2003). Moreover, it was also confirmed that the dimer form is enzymatically active but the monomeric form is not active (Anand et al., 2005; Fan et al., 2004). The dimerization process is found to be mandatory for enzyme activity and this process helps to discriminate the coronavirus M\textsuperscript{pro}, and the picornavirus M\textsuperscript{pro} distinctly.

4 CATALYTIC SITE OF SARS-CoV M\textsuperscript{PRO}

A catalytic dyad is formed by Cys145 and His41 at the SARS-CoV active site, whereas other cysteine and serine protease are found to form a catalytic triad. A water molecule is found to have hydrogen bonding interaction with His41 and Asp187. Moreover, if the cysteine residue is replaced with serine at the enzyme active site, the enzymatic activity of SARS-CoV M\textsuperscript{pro} is decreased. For coronaviral main protease, as well as the picornaviral protease, the cysteine residue is located at the same place of the active site of the His41 imidazole ring plane (distance 3.5–4 Å). For hydrogen bonding interaction between the side chains, the sulfur atom of cysteine residue should be along with the same plane of imidazole function (Anand et al., 2005).

5 SUBSTRATE BINDING SITES OF SARS-CoV M\textsuperscript{PRO}

The substrate binding sites are found to be conserved in all coronavirus main proteases as suggested by the experimental observations (Anand et al., 2003, 2005). The X-ray crystallographic study between the inhibitor-SARS CoV M\textsuperscript{pro} suggests
that the imidazole function of His163 is located at the bottom of the S1 site of M\textsuperscript{pro} to donate hydrogen bond to the backbone carbonyl function of glutamine. For interaction with glutamine at S1 site, the histidine amino acid residue has to be remained unaltered over a broad range of pH. This may be possible through two interactions involved in the imidazole ring. It may either stack to the phenyl ring of Phe140 or may accept a hydrogen bond from the hydroxyl function of Tyr161. Replacement of the His163 is found to abolish the proteolytic activity (Hegyi et al., 2002a; Ziebuhr et al., 2000). All these residues discussed are found to be conserved not only in SARS-CoV M\textsuperscript{pro} but also in all other coronavirus main proteases. Moreover, residues Ile51, Met151, Glu166, and His172 of the S1 pocket take part in the conformation of SARS-CoV M\textsuperscript{pro} (Anand et al., 2005). Regarding the S2 specificity site, all the coronaviruses M\textsuperscript{pro} consists of a leucine residue at the S2 cleavage site. This S2 site is hydrophobic in nature and is composed of side chain amino acid residues, such as His41, Thr47, Met49, Tyr53, and Met165. The longer methionine residue may restrict the S2 pocket and requires slight spatial orientation to accommodate the substrate leucine residue. Due to the presence of Ala46 residue and differences in amino acid sequences, the S2 pocket is bigger in SARS-CoV M\textsuperscript{pro} compared to HCoV 229E M\textsuperscript{pro} and TGEV M\textsuperscript{pro}. In SARS-CoV M\textsuperscript{pro}, a stretch of amino acid sequences is observed in 40–50 residues that help to enlarge the size by forming a helix which is not observed in other coronaviruses. This bigger size may be effective in the substrate binding (Anand et al., 2005). Apart from the S1 and S2 pockets, some other substrate binding pockets should be taken into consideration. At the P4 position, small amino acid residues may be preferable (such as Val, Thr, Ser, and Pro) whereas no specificity at the P3 position is observed for coronavirus M\textsuperscript{pro}. At the P4 position, some amino acid residues are found to be conserved in SARS-CoV M\textsuperscript{pro} (such as Met165 and Thr190). Moreover, P5 amino acid side chains are found to interact with the main chain at Pro168, Thr190, and Gln192 in SARS-CoV M\textsuperscript{pro}, and help like a linker between domain II and III.

6 RNA INTERFERENCE AND VACCINES OF SARS-CoV

Apart from antivirals to fight against these coronaviruses, RNA interference (RNAi) and vaccine development may be a useful strategy though it is a challenging task. The RNAi is an important tool for gene silencing. Apart from the use of RNAi in cancer and genetic disorder (Wang et al., 2004), development of siRNA inhibitors in SARS infection may be a boon for the treatment of the disease (Li et al., 2005). The replication of the SARS may be inhibited effectively through RNAi in vero cells. Therefore, siRNA therapy may be effective to combat SARS infection (Wang et al., 2004). Short hairpin RNA (shRNA) may be useful to target the N gene sequence of SARS coronavirus and to inhibit shRNA of SARS-CoV antigen expression (Tao et al., 2005; Zhai et al., 2007). These results suggest that gene silencing through RNAi may effectively inhibit the SARS-CoV antigen expression, and, therefore, RNAi approach may
be effectively utilized as possible therapy for inhibiting SARS-CoV infection. Moreover, the RNAi is used to target the replicase enzyme of human SARS virus. It not only targets the hSARS gene but also produces inhibitory effects on the SARS RNA virus expression (Zhai et al., 2007). As far as the development of SARS vaccines is concerned, the inactivated SARS-CoV along with the full-length S protein and an attenuated weak virus, and recombinant SARS protein may be used (Jiang et al., 2005; Zhai et al., 2007). The S protein and the inactivated virus were reported to be used to neutralize antibodies. The attenuated or the weak form of the virus might be used to induce immunity, as well as to neutralize antibodies (Finlay et al., 2004). The development of recombinant vaccines may be a useful strategy to prevent SARS infections. It mainly depends on the best antigen identification, as well as the choice of expression system. The S glycoprotein of SARS-CoV along with its truncated form may be targeted for development of recombinant vaccine as the best candidate (Babcock et al., 2004; Bisht et al., 2004; Buchholz et al., 2004; Yang et al., 2004; Zhai et al., 2007). A number of reports were published regarding recombinant S protein vaccine against different SARS-CoV through aryl delivery system (Pogrebnyak et al., 2005; Tuboly et al., 2000).

7 DEVELOPMENT OF QSAR MODELS

QSAR is a useful tool to understand the relation between the structural and physicochemical properties of the drug molecules, and their biological activity which may be useful for predicting the activity or toxicity profile of drugs (Gupta, 2007; Verma and Hansch, 2009). The data required for developing the QSAR models are collected from the literature (see individual QSAR for corresponding references). The IC\textsubscript{50} (molar concentration required to produce 50\% inhibition of the enzyme), EC\textsubscript{50} (effective concentration), or \( K_i \) (binding affinity) data are obviously considered as the biological activity term or dependent variable. The independent variables include physicochemical parameters [such as hydrophobicity, molar refractivity, dipole moment along with different axes, molecular weight (MW), polar surface area (PSA), and polar volume, as well as surface area (SA) and volume] and many topological parameters, such as Kier’s molecular connectivity indices, Balaban indices, etc. Regarding the statistics of QSAR models, \( N \) is used to indicate the number of compounds in the set, \( R \) to indicate the correlation coefficient of the QSAR model obtained, \( R^2 \) refers to the squared correlation coefficient exhibiting the goodness of fit, \( q^2 \) indicates square of the leave-one-out cross-validated correlation coefficient (represents the internal validation of the model), \( R_{\lambda}^2 \) refers to the adjusted \( R^2 \), \( F \) value represents the Fischer statistics (Fischer ratio) that actually means the ratio between the explained and unexplained variance for a particular degree of freedom, \( P \) stands for the probability factor related to \( F \)-ratio, SEE means the standard error of estimate, \( Q \) is the quality factor that can be a measure of chance correlation. A high \( Q \) represents the high predictivity, as well as the lack of over-fitting of the model.
Compounds that misfit in the correlation are considered as outliers and are usually removed from the regression. We discuss here the QSAR models obtained for different categories of SARS-CoV 3CL\(^\text{pro}\) and HRV 3C\(^\text{pro}\) inhibitors.

### 7.1 Coronaviral 3CL\(^\text{pro}\) Inhibitors

#### 7.1.1 Metal-Conjugated SARS-CoV 3CL\(^\text{pro}\) Inhibitors

Hsu et al. (2004) reported some metal-conjugated compounds as promising SARS-CoV 3CL\(^\text{pro}\) inhibitors (Fig. 11.2; Table 11.2). The model obtained was as shown by Eq. (11.1):

\[
pK_i = 4.806 (\pm 0.369) + 0.013 (\pm 0.003) \text{PSA}
\]

\(N = 5\), \(R = 0.910\), \(R^2 = 0.828\), \(R_A^2 = 0.771\), \(F (1, 3) = 14.459\), \(P < 0.03195\), \(\text{SEE} = 0.229\), \(q^2 = 0.643\), \(Q = 3.974\), Outlier = Compounds 1, 3

This model suggested that the increasing value of the PSA may contribute positively to the binding enzyme. Compounds with a higher PSA (Compounds 4–6, Table 11.2) have higher activity than compounds with a lower PSA (Compounds 2, 7, Table 11.2). Compound 1 has a lower PSA but higher activity whereas compound 3 having the higher PSA has lower activity. These molecules are not explained properly by this model. Therefore, these molecules (Compounds 1, 3, Table 11.2) were considered as outliers. They may have different mechanism(s) of action(s).

#### 7.1.2 Some Small Molecule SARS-CoV 3CL\(^\text{pro}\) Inhibitors

Blanchard et al. (2004) reported some SARS-CoV 3CL\(^\text{pro}\) inhibitors (Fig. 11.3; Table 11.3). The QSAR model for these compounds was as shown by Eq. (11.2):

\[
pIC_{50} = 4.845 (\pm 0.064) + 0.002 (\pm 0.000) \text{PSA}
\]
### TABLE 11.2 The Biological Activity and Physicochemical Parameters of Metal-Conjugated SARS-CoV 3CL\textsuperscript{pro} Inhibitors (Fig. 11.2) for QSAR Model [Eq. (11.1)]

| Compound | Obsd\textsuperscript{b} | Calcd\textsuperscript{c} | Res\textsuperscript{d} | Del res\textsuperscript{e} | Pred\textsuperscript{f} | PSA     |
|----------|-------------------------|---------------------------|-----------------------|-------------------------|-------------------------|---------|
| 1\textsuperscript{a} | 6.155                   | 5.625                     | 0.530                 | 0.716                   | 5.439                   | 69.998  |
| 2        | 5.620                   | 5.511                     | 0.109                 | 0.168                   | 5.452                   | 61.487  |
| 3\textsuperscript{a} | 4.863                   | 5.791                     | −0.928                | −1.124                  | 5.987                   | 82.389  |
| 4        | 6.523                   | 6.506                     | 0.017                 | 0.029                   | 6.494                   | 135.592 |
| 5        | 6.770                   | 6.444                     | 0.326                 | 0.514                   | 6.256                   | 130.932 |
| 6        | 6.000                   | 6.213                     | −0.213                | −0.267                  | 6.267                   | 113.794 |
| 7        | 5.854                   | 5.694                     | 0.160                 | 0.204                   | 5.649                   | 75.130  |

\textsuperscript{a}Considered as outliers.
\textsuperscript{b}Observed or experimental activity.
\textsuperscript{c}Calculated activity of compounds according to Eq. (11.1).
\textsuperscript{d}Difference between the observed and calculated activity.
\textsuperscript{e}Difference between the observed and leave-one-out cross-validated activity.
\textsuperscript{f}Leave-one-out cross-validated activity.

### FIGURE 11.3 SARS-CoV 3CL protease inhibitors.
This model also exhibited that the PSA of the molecule might be conducive to the enzyme inhibitory activity of the compounds. As obvious from Table 11.3, compounds 2 and 4 with a higher PSA have higher activity than compounds with the lower PSA. The sulfone and amino functions of compound 2 and the disubstituted amino acid function of compound 4 may produce higher PSA as compared to the trichloro-substituted compound 5 and the monohydroxy trifluoro substituted ester analog (compound 2). It also suggested that the enzyme–drug interaction might be taking place in a nonhydrophobic space at the enzyme active site. Compound 1 has the lower PSA but possesses comparatively higher activity than other compounds. It may be assumed that compound 1 may behave differently. Probably, the ester function and the chloro group may have some electronic interaction with the enzyme responsible for the higher inhibitory activity. Therefore, compound 1 may be considered as an outlier.

7.1.3 Keto-Glutamine SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Jain et al. (2004) synthesized and evaluated some keto-glutamine analogs as potent SARS-CoV 3CL\textsuperscript{pro} inhibitors (Table 11.4). For this series of compounds, the QSAR model obtained was as shown by Eq. (11.3). In this equation, ‘I’ is an indicator parameter that was used with a value of 1 for the presence of the CONMe\textsubscript{2}. For the absence of this group, its value was zero. The negative coefficient of I suggests that compounds with CONMe\textsubscript{2} function (Compounds 1–4, Table 11.4) are less active than compounds with 3-pyrrolidinone function (Compounds 5–8, Table 11.4). Therefore, compounds with 3-pyrrolidinone functions (Compounds 5–8) are preferable for the higher inhibitory activity.

\[ pIC_{50} = 5.699(\pm 0.139) - 1.405(\pm 0.197)I \]  

(11.3)

\[ N = 8, \, R = 0.946, \, R^2 = 0.894, \, R_A^2 = 0.877, \, F (1, 6) = 50.793, \, P < 0.00038, \, SEE = 0.279, \, q^2 = 0.812, \, Q = 3.391 \]
7.1.4 Lopinavir-Like SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Wu et al. (2004) reported some Lopinavir-like inhibitors of SARS-3CL\textsuperscript{pro} (Table 11.5). The model obtained was as by Eq. (11.4), where SA refers to surface area. Eq. (11.4) suggested that the increase in value of the SA may be
Viral Proteases and Their Inhibitors

The compounds 2, 8, and 10 (Table 11.5) may behave in a different fashion and, therefore, they were considered as outliers.

\[ p \text{IC}_{50} = 6.968(\pm0.617) - 0.002(\pm0.001)\text{SA} \quad (11.4) \]

\( N = 8, R = 0.849, R^2 = 0.721, R^2_\Delta = 0.675, F (1, 6) = 15.531, P < 0.00762, \)
\( \text{SEE} = 0.059, q^2 = 0.618, Q = 14.390, \text{Outlier} = \text{Compounds 2, 8, 10} \)
7.1.5 Anilide-Based SARS-CoV 3CL<sub>pro</sub> Inhibitors

Shie et al. (2005a) reported a series of potent anilide inhibitors against SARS-3CL<sub>pro</sub> (Fig. 11.4; Table 11.6), for which the QSAR model obtained was as shown by Eq. (11.5). This model showed the importance of dipole moment along the X-axis ($D_X$), MW, PSA, and volume (Vol) for controlling the enzyme inhibition. The positive coefficient of the dipole moment along X-axis suggested that the bulky substitutions along X-axis may favor the activity. Moreover, the MW was also shown to have a positive impact on the activity, whereas PSA was shown to have the negative effect. Therefore, it may be suggested that molecules with the bigger size along with bulky substituents may be conducive to the inhibition. Moreover, the volume is found to have a parabolic relation with the enzyme inhibition. The optimum value of the volume is 6500. Compounds 1, 7, 9, and 14 were considered as outliers as these molecules may work with a different mechanism(s).

$$pIC_{50} = 13.858 \pm 2.004 + 0.066 \pm 0.022 D_X + 0.011 \pm 0.002 MW - 0.004 \pm 0.001 PSA - 0.013 \pm 0.002 Vol - 0.000001 \pm 0.000 Vol^2$$  \hspace{1cm} (11.5)

$N = 26$, $R = 0.904$, $R^2 = 0.817$, $R_X^2 = 0.771$, $F (5, 20) = 17.862$, $P < 0.00000$, $SEE = 0.185$, $q^2 = 0.680$, $Q = 4.886$, $Vol_{opt} = 6500$, Outlier = Compounds 1, 7, 9, 14

FIGURE 11.4 General structure of anilide-based SARS-CoV 3CL<sub>pro</sub> inhibitors.
| Compound | R     | R′                  | Obsd | Calcd | Res  | Del res | Pred  | DX    | MW       | PSA       | Vol       |
|----------|-------|---------------------|------|-------|------|---------|-------|-------|----------|-----------|-----------|
| 1        | —     | Me₂NC₆H₄            | 7.222| 6.730 | 0.492| 1.161   | 6.061 | −3.032| 466.917  | 132.531   | 1184.630  |
| 2        | —     | C₁₄H₂₉CH(Br)        | 5.523| 5.533 | −0.010| −0.025  | 5.548 | −3.999| 637.048  | 164.054   | 1505.220  |
| 3        | —     | 3,4-(NH₃)₂C₆H₃      | 5.699| 6.054 | −0.355| −0.589  | 6.288 | −2.424| 453.878  | 266.781   | 1142.890  |
| 4        | —     | (Indol-3-yl)-CH═CH  | 5.523| 5.614 | −0.091| −0.109  | 5.632 | −3.716| 488.922  | 177.675   | 1290.600  |
| 5        | —     | (2-NH₂-1,3-thiazol-4-yl)−C(NOCH₃) | 5.155| 4.900 | 0.255 | 0.559 | 4.596 | −4.072| 502.931  | 304.411   | 1273.020  |
| 6        | i-Bu  | Et                  | 5.155| 5.298 | −0.143| −0.155  | 5.310 | 0.087 | 588.095  | 150.968   | 1561.070  |
| 7        | i-Bu  | Ph                  | 5.398| 4.970 | 0.428 | 0.492   | 4.906 | 1.527 | 636.138  | 151.962   | 1742.770  |
| 8        | i-Bu  | Morpholino          | 4.721| 4.791 | −0.070| −0.076  | 4.797 | −0.806| 645.146  | 167.607   | 1715.620  |
| 9        | i-Bu  | Thien-2-yl          | 5.301| 4.887 | 0.414 | 0.457   | 4.844 | 1.890 | 642.165  | 192.606   | 1716.130  |
| 10       | PhCH₂ | 5-Me-isoxazol-3-yl  | 5.155| 5.477 | −0.322| −0.400  | 5.555 | 4.564 | 675.131  | 209.168   | 1697.490  |
| 11       | PhCH₂ | Thien-2-yl          | 5.301| 5.261 | 0.040 | 0.044   | 5.257 | 1.903 | 676.182  | 191.190   | 1708.000  |
| 12       | i-Bu  | Et                  | 5.155| 4.697 | 0.458 | 0.551   | 4.603 | −1.876| 689.199  | 176.439   | 1789.010  |
| 13       | i-Bu  | Morpholino          | 4.796| 4.899 | −0.103| −0.118  | 4.914 | 2.387 | 746.250  | 203.573   | 1980.620  |
| Compound | R | R' | Obsd MW | Calcd MW | Res | Del res | Pred D | MW | PSA Vol |
|----------|---|----|---------|----------|-----|---------|--------|-----|---------|
| 14       | PhCH₂ | t-Bu | 5.699   | 5.095    | 0.604| 0.704   | 4.995 | 1.521 | 751.268 |
| 15       | PhCH₂ | 5-Me-isoxazol-3-yl | 5.301 | 5.347 | 0.046 | 0.050 | 5.351 | 4.917 | 776.235 |
| 16       | PhCH₂ | PhCH₂O | 5.222 | 5.407 | -0.185 | -0.222 | 5.444 | 2.696 | 801.284 |
| 17       | 4-FC₆H₄CH₂ | Et | 5.301 | 5.350 | -0.049 | -0.053 | 5.354 | 2.908 | 741.206 |
| 18       | 4-FC₆H₄CH₂ | Ph | 5.699 | 5.519 | 0.180 | 0.208 | 5.491 | 2.716 | 789.248 |
| 19       | (S)-OH | H | 5.398 | 5.175 | 0.223 | 0.304 | 5.094 | 7.882 | 737.543 |
| 20       | (R)-OH | (R)-OH | 5.301 | 5.261 | 0.040 | 0.067 | 5.234 | 9.257 | 753.542 |
| 21       | H | H | 5.699 | 5.737 | -0.038 | -0.050 | 5.749 | 6.265 | 923.751 |
| 22       | (S)-OH | H | 5.699 | 5.764 | -0.065 | -0.090 | 5.789 | 7.011 | 939.751 |
| 23       | (R)-OH | (R)-OH | 5.699 | 5.846 | -0.147 | -0.216 | 5.915 | 7.863 | 955.750 |
| 24       | t-Bu | Et | 4.569 | 5.055 | -0.486 | -0.537 | 5.106 | -0.653 | 587.107 |
| 25       | t-Bu | Ph | 4.678 | 5.003 | -0.325 | -0.355 | 5.033 | -1.172 | 635.150 |
| 26       | t-Bu | t-BuO | 4.721 | 4.964 | -0.243 | -0.261 | 4.983 | -0.444 | 631.159 |
| 27       | t-Bu | Morpholino | 4.538 | 4.844 | -0.306 | -0.338 | 4.875 | -0.935 | 644.158 |
| 28       | t-Bu | Thien-2-yl | 4.658 | 4.853 | -0.196 | -0.210 | 4.868 | -0.247 | 641.177 |
| 29       | PhCH₂ | 5-Me-isoxazol-3-yl | 5.222 | 5.105 | 0.117 | 0.126 | 5.096 | 1.855 | 674.143 |
| 30       | PhCH₂ | Thien-2-yl | 4.796 | 4.864 | -0.069 | -0.082 | 4.878 | -1.901 | 675.194 |

*Considered as outliers.*
7.1.6 Peptidomimetic $\alpha,\beta$ Unsaturated Esters as SARS-CoV 3CL$^\text{pro}$ Inhibitors

Shie et al. (2005b) reported a series of peptidomimetic $\alpha,\beta$ unsaturated esters as promising SARS-3CL$^\text{pro}$ inhibitors (Table 11.7). The QSAR model obtained for them was as shown by Eq. (11.6).

$$
pIC_{50} = 14.827 (\pm 1.418) - 0.016 (\pm 0.002) MW - 0.006 (\pm 0.001) PSA
$$  \hspace{1cm} (11.6)

$$N = 15, R = 0.906, R^2 = 0.822, R^2_A = 0.792, F (2, 12) = 27.656, P < 0.00003, SEE = 0.227, q^2 = 0.710, Q = 3.991, \text{Outlier} = \text{Compound 8}\n$$

It was observed from Eq. (11.6) that increase in the value of both the MW, as well as the PSA may be detrimental to the activity. Thus, the model suggested that the smaller molecules with less steric bulk might favor the activity. Moreover, the enzyme-drug interaction would be more favored in non-hydrophobic space. It was observed that compounds having unsaturation at the R’ position (Compounds 11–16, Table 11.7) possess lower MW compared to the other molecules in the dataset and possess higher inhibitory activity. In compound 13, both the phenyl rings might be accommodated in the S2 and S3 pockets. Moreover, the (dimethylamino) cinnamyl function adopts a coplanar rigid structure at the end terminal, which may help it in forming hydrogen bonding with amino acids residues Glu166, Glu189, and Glu192 at the enzyme active site. Compound 8 may behave differently and hence, this was considered as an outlier.

7.1.7 Benzotriazole Esters as SARS-CoV 3CL$^\text{pro}$ Inhibitors

Wu et al. (2006) reported some benzotriazole esters as promising SARS-3CL$^\text{pro}$ mechanism-based inhibitors (Table 11.8). The model obtained for this series is as shown by Eq. (11.7).

$$pK_i = 3.814 (\pm 1.495) - 1.405 (\pm 0.115) D_Y + 0.014 (\pm 0.005) MW \hspace{1cm} (11.7)$$

$$N = 11, R = 0.974, R^2 = 0.949, R^2_A = 0.937, F (2, 8) = 75.154, P < 0.00001, SEE = 0.282, q^2 = 0.893, Q = 3.454\n$$

It was observed from Eq. (11.7) that increasing value of the dipole moment along Y-axis ($D_Y$) may lead to a decrease in the activity, whereas increasing value of the MW may be conducive to the activity. It also suggests that compounds with the higher molecular bulk with lower steric effect may be favorable for the higher inhibitory activity. Compounds with ester functions (Compounds 1–8, Table 11.8) is better active than compounds with acetyl function (Compounds 9–11) as these molecules (Compounds 1–8) possess higher bulkiness. Therefore, it may be assumed that the ester analogs impart less steric effect with the enzyme and hence, produce higher activity.
| Compound | R          | R′          | R′′ | X   | Obsd | Calcd | Res   | Del res | Pred | MW     | PSA   |
|----------|------------|-------------|-----|-----|------|-------|-------|---------|------|--------|-------|
| 1        | Ph         | 5-Me-isoxazolyl-3-yl | —   | NH  | 4.097| 4.173 | −0.076| −0.125  | 4.222| 581.660| 233.331|
| 2        | Ph         | PhCH₃O      | —   | NH  | 4.071| 4.195 | −0.124| −0.157  | 4.228| 606.709| 175.330|
| 3        | 4-FPh      | 5-Me-isoxazolyl-3-yl | Ph  | CH₂ | 4.409| 4.563 | −0.154| −0.169  | 4.578| 591.670| 150.782|
| 4        | 4-FPh      | PhCH₃O      | Ph  | CH₂ | 4.509| 4.544 | −0.036| −0.046  | 4.555| 616.719| 99.131 |
| 5        | Ph         | 5-Me-isoxazolyl-3-yl | Ph  | CH₂ | 4.886| 4.815 | 0.072 | 0.077   | 4.809| 573.679| 150.790|
| 6        | Ph         | PhCH₃O      | Ph  | CH₂ | 4.420| 4.796 | −0.376| −0.441  | 4.861| 598.729| 99.149 |
| 7        | 4-FPh      | 5-Me-isoxazolyl-3-yl | Ph  | NH  | 4.678| 4.483 | 0.194 | 0.217   | 4.461| 592.658| 161.032|

(Continued)
| Compound | R  | R’    | R”   | X    | Obsd | Calcd | Res    | Del res | Pred | MW      | PSA    |
|---------|----|-------|------|------|------|-------|--------|---------|------|---------|--------|
| 8       | 4-FPh | PhCH₂O | Ph   | NH   | 4.959 | 4.502 | 0.457  | 0.592   | 4.366 | 617.707 | 103.559 |
| 9       | Ph   | 5-Me-isoxazolyl-3-yl | Ph | NH   | 4.523 | 4.735 | −0.212 | −0.230 | 4.753 | 574.667 | 161.010 |
| 10      | Ph   | PhCH₂O | Ph   | NH   | 4.959 | 4.754 | 0.205  | 0.239   | 4.720 | 599.716 | 103.573 |
| 11      | Ph   | BiPhCH═CH | Ph | NH   | 5.000 | 5.167 | −0.167 | −0.195 | 5.195 | 572.693 | 98.047  |
| 12      | Ph   | 4-NO₂PhCH═CH | Ph | NH   | 5.301 | 5.054 | 0.247  | 0.317   | 4.984 | 541.594 | 183.426 |
| 13      | Ph   | 4-Me₂NPhCH═CH | Ph | NH   | 6.000 | 5.662 | 0.338  | 0.515   | 5.485 | 539.665 | 92.953  |
| 14      | Ph   | 2,4-diOMePhCH═CH | Ph | NH   | 5.000 | 5.278 | −0.278 | −0.326  | 5.326 | 556.649 | 115.705 |
| 15      | Ph   | 3-Benzo[1,3]dioxol-5-yl-CH═CH | Ph | NH   | 5.155 | 5.398 | −0.243 | −0.308  | 5.463 | 540.606 | 131.977 |
| 16      | Ph   | 3-Benzo[1,3]dioxol-5-yl-CH═CH | — | NH   | 5.000 | 4.847 | 0.153  | 0.203   | 4.797 | 547.599 | 202.480 |

*Considered as outliers.*
### TABLE 11.8 Biological Activity and Physicochemical Parameters of Benzotriazole Esters as SARS-CoV 3CL\(^\text{pro}\) Inhibitors for QSAR Model [Eq. (11.7)]

![Chemical Structure](image.png)

| Compound | Ar          | X   | Obsd | Calcd | Res  | Del res | Pred | \(D_Y\) | MW    |
|----------|-------------|-----|------|-------|------|---------|------|--------|-------|
| 1        | 2-NH\(_2\)Ph | O   | 7.710| 7.592 | 0.118| 0.186   | 7.524| −0.218 | 254.244|
| 2        | 4-N(Me)\(_2\)Ph | O   | 7.759| 7.880 | −0.120| −0.138  | 7.897| −0.150 | 282.297|
| 3        | 4-NHMePh     | O   | 7.917| 8.083 | −0.165| −0.211  | 8.129| −0.431 | 268.271|
| 4        | 4-N(Et)\(_2\)Ph | O   | 7.955| 8.311 | −0.356| −0.662  | 8.617| −0.185 | 310.350|
| 5        | 5-Benzimidazolyl | O   | 7.640| 7.690 | −0.050| −0.056  | 7.696| −0.045 | 279.254|
| 6        | 5-Indolyl    | O   | 8.125| 7.611 | 0.514 | 0.577   | 7.548| 0.002  | 278.265|
| 7        | 2-Indolyl    | O   | 7.910| 7.970 | −0.060| −0.070  | 7.980| −0.254 | 278.265|
| 8        | 5-F-2-Indolyl| O   | 7.860| 7.595 | 0.265 | 0.320   | 7.540| 0.188  | 296.256|
| 9        | 4-N(Et)\(_2\)Ph | CH\(_2\) | 6.000| 5.782 | 0.218 | 0.437   | 5.563| 1.597  | 308.378|
| 10       | 4-NHMePh     | CH\(_2\) | 5.347| 5.529 | −0.182| −0.310  | 5.657| 1.368  | 266.298|
| 11       | 4-N(Me)\(_2\)Ph | CH\(_2\) | 5.174| 5.357 | −0.183| −0.295  | 5.469| 1.627  | 280.324|
7.1.8 A Diverse Set of SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Chen et al. (2006a) reported some diverse chemical entities through virtual screening, surface plasmon resonance and fluorescence resonance energy transfer based assays as promising against SARS-CoV 3CL\textsuperscript{pro} (Fig. 11.5; Table 11.9). The QSAR model obtained was as shown by Eq. (11.8):

\[ p\text{IC}_{50} = 2.508(\pm 0.417) - 0.012(\pm 0.003)\text{PSA} \]  

\[ N = 6, R = 0.923, R^2 = 0.851, R_A^2 = 0.814, F (1, 4) = 22.908, P < 0.00874, \]
\[ \text{SEE} = 0.167, q^2 = 0.746, Q = 5.527, \text{Outlier} = \text{Compounds 5, 7} \]

It is observed from Eq. (11.8) that increasing the value of the PSA may be detrimental to the activity. Thus it suggested that less polar molecules may have better inhibitory activity. Due to the presence of electronegative function (such as carboxyl, chloro, etc.), the molecule may have larger PSA. Compounds 5 and 7 (Table 11.9), though possess lower PSA, have higher activity and this could not be explained by this model. Thus these compounds might be supposed to involve the different mechanism of action for producing the higher activity. Therefore, these compounds are considered as outliers.

\[ R_A^2 = 0.814 \]

\[ q^2 = 0.746, Q = 5.527, \text{Outlier} = \text{Compounds 5, 7} \]

\[ F (1, 4) = 22.908, P < 0.00874, \]

\[ \text{SEE} = 0.167, q^2 = 0.746, Q = 5.527, \text{Outlier} = \text{Compounds 5, 7} \]
7.1.9 Isatin Analogs as SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Zhou et al. (2006) reported some isatin analogs as SARS-CoV 3CL\textsuperscript{pro} inhibitors (Table 11.10), for which the correlation obtained was as in Eq. (11.9):

\[ pIC_{50} = -5.298(\pm1.846) + 0.020(\pm0.004)SA \tag{11.9} \]

\[ N = 7, R = 0.929, R^2 = 0.862, R_{A2}^2 = 0.835, F (1, 5) = 31.349, P < 0.00251, \]
\[ SEE = 0.347, q^2 = 0.688, Q = 2.677, \text{Outlier} = \text{Compound 4} \]

It was observed from Eq. (11.9) that increasing the SA of these molecules may impart higher inhibitory activity. Bulky substitution at the R\textsubscript{1} position, such as β-naphthylmethyl (compounds 3 and 8, Table 11.10) may impart higher SA and hence, produce higher activity. Thus substitution with –CONH\textsubscript{2} function at the R\textsubscript{2} position in place of iodo function may have a better effect (compound 8 vs. 3, compound 6 vs. 1, and compound 7 vs. 2, Table 11.10). Similarly, bulky aryl function may be more favorable than the alkyl function. The larger SA may help the molecule to occupy more space in the enzyme active site to have better binding interaction as evidenced by the molecular docking analysis (Zhou et al., 2006). Compound 8 having maximum SA exhibits hydrogen bonding with His41 and Cys145 through the keto functions of the isatin moiety. Moreover, the carboxamide function at the R\textsubscript{2} position makes hydrogen bonding with Phe140 and His163. The β-naphthyl moiety (Compound 8) fits well into the hydrophobic S2 pocket whereas smaller and less bulky substituents, such as methyl (Compound 4), n-propyl (Compound 5), n-butyl (Compound 6), and benzyl (Compound 7) do not accommodate well into the S2 pocket. It is not clear why the compound 4 behaves aberrantly though possessing a comparable good SA. Therefore, compound 4 may be considered as an outlier.

| Compound | Obsd | Calcd | Res  | Del res | Pred  | PSA       |
|----------|------|-------|------|---------|-------|-----------|
| 1        | 4.301| 4.522 | -0.221| -0.258  | 4.559 | 152.625   |
| 2        | 4.094| 4.306 | -0.212| -0.318  | 4.413 | 129.832   |
| 3        | 4.375| 4.610 | -0.235| -0.269  | 4.644 | 161.878   |
| 4        | 5.164| 5.158 | 0.006 | 0.027   | 5.136 | 219.559   |
| 5\textsuperscript{a} | 5.037| 4.709 | 0.328 | 0.383   | 4.653 | 172.296   |
| 6        | 4.668| 4.582 | 0.086 | 0.099   | 4.569 | 158.861   |
| 7\textsuperscript{a} | 5.020| 4.415 | 0.605 | 0.769   | 4.251 | 141.289   |
| 8        | 4.250| 4.607 | -0.357| -0.408  | 4.658 | 161.493   |

\textsuperscript{a}Considered as outliers.
TABLE 11.10 Biological Activity and Physicochemical Parameters of Isatin Analogs as SARS-CoV 3CL\textsuperscript{pro} Inhibitors for QSAR Model [Eq. (11.9)]

![Chemical structure of isatin analogs]

| Compound | R\textsubscript{1} | R\textsubscript{2} | Obsd | Calcd | Res  | Del res | Pred | SA    |
|----------|-----------------|-----------------|-------|-------|------|---------|------|-------|
| 1        | n-Butyl         | I               | 4.180 | 4.665 | −0.485 | −0.564  | 4.745 | 469.003 |
| 2        | Benzyl          | I               | 4.301 | 4.902 | −0.601 | −0.686  | 4.987 | 485.295 |
| 3        | β-Napthylmethyl | I               | 5.959 | 5.730 | 0.228  | 0.329   | 5.630 | 542.453 |
| 4\textsuperscript{a} | Me              | CON\textsubscript{2}H | 4.149 | 3.613 | 0.535  | 1.243   | 2.906 | 396.444 |
| 5        | n-Propyl        | CON\textsubscript{2}H | 4.602 | 4.421 | 0.181  | 0.223   | 4.379 | 452.138 |
| 6        | n-Butyl         | CON\textsubscript{2}H | 4.721 | 4.869 | −0.148 | −0.169  | 4.890 | 483.059 |
| 7        | Benzyl          | CON\textsubscript{2}H | 4.903 | 5.103 | −0.199 | −0.231  | 5.134 | 499.156 |
| 8        | β-Napthylmethyl | CON\textsubscript{2}H | 6.432 | 5.944 | 0.488  | 0.829   | 5.603 | 557.185 |

\textsuperscript{a}Considered as outliers.
7.1.10 A Diverse Set of Potent SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Tsai et al. (2006) reported a series of SARS-CoV 3CL\textsuperscript{pro} inhibitors through pharmacophore mapping and virtual screening approach (Fig. 11.6; Table 11.11). For this, the QSAR model obtained was as shown by Eq. (11.10).

\[ pIC_{50} = 3.050 \pm 0.544 + 1.044 \pm 0.151 \text{CMR} - 0.204 \pm 0.033 \text{D}_\text{Y} - 0.010 \pm 0.001 \text{Vol} \] (11.10)

\text{N} = 24, \ R = 0.915, \ R^2 = 0.836, \ R_\text{adj}^2 = 0.812, \ F (3, 20) = 34.080, \ P < 0.00000, \ SEE = 0.282, \ q^2 = 0.754, \ Q = 3.245, \text{Outlier} = \text{Compounds 9, 13, 24}

It was observed from Eq. (11.10) that increasing the value of the molar refractivity (CMR) and decreasing the value of the dipole moment along \( Y \)-axis (\( D_Y \)), as well as the volume (Vol) may contribute positively to the enzyme inhibitory activity. It was, therefore, suggested that increasing the total molecular bulk may increase the activity whereas bulky substituent along \( Y \)-axis may be detrimental to the activity. Bulky substitution along \( Y \)-axis may produce some unfavorable steric interaction with the enzyme. Therefore, the bulky molecule with less steric effect may be favorable for the activity. Compounds 9, 13, and 24 (Table 11.11) may act through different mechanism(s) of action and hence, they were considered as outliers.
### TABLE 11.11 Biological Activity and Physicochemical Parameters of a Diverse Set of Potent SARS-CoV 3CL\textsuperscript{pro} Inhibitors (Fig. 11.6) for QSAR Model [Eq. (11.10)]

| Compound | Obsd | Calcd | Res | Del res | Pred | CMR  | $D_V$ | Vol    |
|----------|------|-------|-----|---------|------|------|-------|--------|
| 1        | 5.523| 5.092 | 0.431| 0.557   | 4.966| 12.519| −3.187| 1169.180|
| 2        | 5.000| 4.615 | 0.385| 0.484   | 4.516| 12.431| −5.072| 1263.640|
| 3        | 4.959| 5.005 | −0.046| −0.057 | 5.016| 14.035| −2.218| 1326.330|
| 4        | 4.921| 4.902 | 0.019| 0.022   | 4.899| 14.035| −2.750| 1351.480|
| 5        | 4.854| 4.876 | −0.022| −0.026 | 4.880| 12.090| −4.583| 1180.750|
| 6        | 4.824| 4.491 | 0.333| 0.355   | 4.469| 11.433| −3.308| 1132.790|
| 7        | 4.824| 4.455 | 0.369| 0.411   | 4.413| 12.434| −3.499| 1251.610|
| 8        | 4.824| 4.812 | 0.012| 0.014   | 4.810| 11.924| −3.530| 1148.570|
| 9\textsuperscript{a} | 4.523| 3.698 | 0.825| 0.948   | 3.575| 8.952 | −2.453| 948.018 |
| 10       | 4.398| 4.131 | 0.267| 0.283   | 4.114| 11.976| −0.619| 1182.810|
| 11       | 4.398| 4.313 | 0.085| 0.091   | 4.307| 10.628| −3.433| 1070.780|
| 12       | 4.347| 4.220 | 0.127| 0.135   | 4.212| 10.814| −3.237| 1099.490|
| 13\textsuperscript{a} | 4.222| 3.362 | 0.860| 1.193   | 3.029| 11.698| 2.871 | 1180.190|
| 14       | 4.222| 4.050 | 0.172| 0.226   | 3.996| 12.626| 1.981 | 1209.220|
| 15       | 4.000| 4.371 | −0.371| −0.469 | 4.469| 10.749| −0.795| 1019.780|
| 16       | 3.699| 3.794 | −0.095| −0.124 | 3.823| 8.024 | −2.450| 833.212 |
| 17       | 3.699| 4.193 | −0.494| −0.699 | 4.398| 14.036| −1.711| 1424.160|
| 18       | 3.699| 3.986 | −0.287| −0.331 | 4.030| 9.615 | −3.899| 1013.380|
| 19       | 3.699| 3.759 | −0.060| −0.073 | 3.772| 12.531| −0.188| 1284.230|
| 20       | 3.699| 3.998 | −0.299| −0.315 | 4.014| 10.628| −2.143| 1085.260|
| 21       | 3.602| 3.703 | −0.101| −0.112 | 3.714| 9.476 | −2.069| 996.643 |
| 22       | 3.523| 3.808 | −0.285| −0.327 | 3.850| 9.710 | −3.228| 1033.240|
| 23       | 3.523| 3.557 | −0.034| −0.040 | 3.563| 11.346| 1.299 | 1149.300|
| 24\textsuperscript{a} | 3.523| 4.283 | −0.760| −0.871 | 4.394| 11.073| −0.759| 1066.380|
| 25       | 3.456| 4.031 | −0.575| −0.625 | 4.081| 12.067| 0.024 | 1192.450|
| 26       | 3.398| 3.887 | −0.489| −0.539 | 3.937| 11.435| −1.858| 1182.620|
| 27       | 3.301| 3.264 | 0.037| 0.047   | 3.255| 8.397 | −0.405| 901.161  |

\textsuperscript{a}Considered as outliers.
7.1.11 A Series of Nonpeptide SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Lu et al. (2006) reported a series of nonpeptide SARS-CoV M\textsuperscript{pro} inhibitors (Fig. 11.7; Table 11.12) through structure-based drug design approach, for which the QSAR model obtained was as shown by Eq. (11.11). It was observed from this equation that the increase in the value of the SA and the polar volume (Pol Vol) may be conducive to the activity, whereas the increasing in the value of volume and dipole moment along X-axis ($D_X$) might be detrimental to the activity. Thus it could be suggested that bulky substitutions along X-axis might produce unfavorable steric hindrance that may lower the activity. Moreover, this model also revealed that compounds having higher polar volume may favor the activity compared to compounds with lower polar volume. In compound 1 (Table 11.12), one of the nitro groups is closer to the imidazole function of His41 and thus there may be some electrostatic interaction between them leading to better activity. Moreover, the phenyl ring may form π–π interactions with His237 at the enzyme active site leading to potent activity. Compounds 1 and 8 (Table 11.12) might act in a different manner and hence, they were considered as outliers.

\[
pIC_{50} = 2.664 (\pm 0.339) + 0.020 (\pm 0.003) \text{SA} - 0.010 (\pm 0.002) \text{Vol} - 0.075 (\pm 0.015) D_X + 0.003 (\pm 0.001) \text{Pol Vol}
\]  

\begin{align*}
N &= 19, \quad R = 0.911, \quad R^2 = 0.830, \quad R^2_A = 0.781, \quad F (1, 14) = 17.089, \quad P < 0.00003, \\
\text{SEE} &= 0.178, \quad q^2 = 0.605, \quad Q = 5.118, \quad \text{Outlier} = \text{Compounds 1, 8}
\end{align*}
| Compound | Obsd  | Calcd | Res   | Del res | Pred | $D_X$ | Pol Vol | SA   | Vol   |
|----------|-------|-------|-------|---------|------|-------|---------|------|-------|
| 1        | 6.523 | 4.965 | 1.558 | 1.879   | 4.644| −1.109| 177.492 | 547.807| 939.699|
| 2        | 6.046 | 5.466 | 0.579 | 0.931   | 5.115| −1.905| 182.783 | 733.597| 1184.370|
| 3        | 5.222 | 5.057 | 0.165 | 0.212   | 5.010| −0.568| 251.310 | 497.859| 803.261|
| 4        | 4.921 | 5.232 | −0.311| −0.389  | 5.310| −4.454| 158.771 | 509.445| 843.770|
| 5        | 4.886 | 4.955 | −0.069| −0.073  | 4.960| 0.390 | 216.773 | 526.936| 873.061|
| 6        | 4.886 | 5.053 | −0.167| −0.180  | 5.066| −0.772| 211.376 | 534.514| 881.205|
| 7        | 4.824 | 4.559 | 0.265 | 0.366   | 4.458| 7.202 | 245.339 | 483.718| 773.796|
| 8        | 4.796 | 5.293 | −0.497| −0.851  | 5.647| 0.780 | 299.398 | 829.728| 1389.050|
| 9        | 4.796 | 5.013 | −0.217| −0.235  | 5.031| −0.547| 171.214 | 524.341| 865.596|
| 10       | 4.796 | 4.991 | −0.196| −0.242  | 5.038| −1.866| 136.667 | 477.650| 800.051|
| 11       | 4.602 | 4.655 | −0.053| −0.072  | 4.674| 6.493 | 261.992 | 497.278| 787.197|
| 12       | 4.495 | 4.811 | −0.316| −1.040  | 5.534| 2.675 | 283.177 | 773.777| 1382.880|
| 13       | 5.523 | 5.228 | 0.295 | 0.340   | 5.183| −0.933| 175.089 | 612.441| 988.794|
| 14       | 5.301 | 5.179 | 0.122 | 0.141   | 5.160| −1.175| 255.605 | 614.602| 1017.590|
| 15       | 5.000 | 5.216 | −0.216| −0.247  | 5.247| −2.424| 233.334 | 638.284| 1077.980|
| 16       | 4.824 | 5.028 | −0.204| −0.294  | 5.118| −2.348| 289.728 | 543.817| 943.419|
| 17       | 4.796 | 4.945 | −0.149| −0.176  | 4.972| 0.299 | 141.590 | 526.835| 873.189|
| 18       | 4.745 | 4.559 | 0.186 | 0.334   | 4.410| 5.607 | 371.972 | 528.119| 903.617|
| 19       | 4.745 | 4.905 | −0.161| −0.207  | 4.952| 3.748 | 158.165 | 534.331| 834.408|
| 20       | 4.699 | 4.788 | −0.089| −0.111  | 4.810| 4.862 | 190.284 | 564.125| 911.548|
| 21       | 4.398 | 4.921 | −0.523| −0.711  | 5.109| −0.151| 98.696  | 388.069| 601.894|

*Considered as outliers.*
7.1.12 Quercetin-3-β-Galactoside SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Chen et al. (2006b) reported some quercetin-3-β-galactoside and its analogs as promising SARS-CoV 3CL\textsuperscript{pro} inhibitors (Table 11.13), for which the QSAR model obtained was as in Eq. (11.12):

\[
pIC_{50} = 6.112(\pm0.057) - 0.005(\pm0.0002) \text{PSA} \quad (11.12)
\]

\( N = 4, R = 0.999, R^2 = 0.998, R^2_A = 0.996, F (1, 2) = 842.36, P < 0.00119, \)
\( \text{SEE} = 0.008, q^2 = 0.984, Q = 124.875, \text{Outlier} = \text{Compound 4} \)

It was observed from Eq. (11.12) that decreasing the value of the PSA would have the positive effect on the biological activity. It meant that less polar molecules would be preferred to the high polar molecules. Due to the presence of a number of hydroxyl groups, these molecules may interact with the enzyme as hydrogen bond acceptors. The molecular modeling study revealed that the side chain of Gln189 forms four hydrogen bonds with compound 5 (Table 11.13), whereas two hydrogen bonding interactions are observed with the nitrogen atom of Glu166. It was, however, observed that compound 4 having the highest PSA value due to the presence of two galactose rings was less active. Probably, compound 4 might behave in an aberrant fashion and hence, it was considered as an outlier.

7.1.13 Phthalhydrazide Ketones as Potent SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Zhang et al. (2007) synthesized and evaluated some phthalhydrazide ketones (Table 11.14) and heteroatomic ester as potential SARS-3CL\textsuperscript{pro} inhibitors. The QSAR model developed for this set of compounds was as shown by Eq. (11.13):

\[
pIC_{50} = 8.108(\pm0.131) - 0.009(\pm0.001) \text{PolVol} \quad (11.13)
\]

\( N = 6, R = 0.970, R^2 = 0.942, R^2_A = 0.927, F (1, 4) = 64.539, P < 0.00130, \)
\( \text{SEE} = 0.072, q^2 = 0.739, Q = 13.472, \text{Outlier} = \text{Compounds 2, 7} \)

Eq. (11.13) suggested that high polar volume of the compound would not favor the activity. A molecular modeling study had revealed that the halopyridine moiety of the compounds was well accommodated in the S1 binding pocket where it could have van der Waals interactions. Moreover, it was observed that the halogen atom does not interact with the enzyme and is directed toward the solvent exposed area. The furyl group of compound 3 is located near the catalytic Cys145 residue where it can have hydrophobic interaction. Compounds 2 and 7 being a misfit in the correlation were excluded.

7.1.14 Some Peptidomimetic SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Ghosh et al. (2007) reported some peptidomimetic SARS-CoV 3CL\textsuperscript{pro} inhibitors (Table 11.15), for which a QSAR model obtained was as:

\[
pIC_{50} = 5.009(\pm0.174) - 0.504(\pm0.067) D_Z \quad (11.14)
\]
**TABLE 11.13** Biological Activity and Physicochemical Parameters of Quercetin-3-\(\beta\)-Galactoside SARS-CoV 3CL\(^{\text{pro}}\) Inhibitors for QSAR Model [Eq. (11.12)]

| Compound | \(R_1\) | \(R_2\)       | Obsd | Calcd | Res  | Del res | Pred | PSA       |
|----------|---------|---------------|------|-------|------|---------|------|-----------|
| 1        | H       | L-Fucose      | 4.617| 4.568 | 0.049| 0.099   | 4.518| 306.747   |
| 2        | H       | D-Arabinose   | 4.500| 4.486 | 0.014| 0.019   | 4.481| 333.869   |
| 3        | H       | D-Glucose     | 4.311| 4.378 | −0.067| −0.084 | 4.395| 369.951   |
| 4\(^a\)  | D-Galactose | D-Galactose | 4.211| 4.166 | 0.045| 0.236   | 3.975| 440.138   |
| 5        | H       | D-Galactose   | 4.369| 4.410 | −0.041| −0.052 | 4.420| 359.227   |

\(^a\)Considered as outliers.
TABLE 11.14 Biological Activity and Physicochemical Parameters of Phthalhydrazide Ketones as Potent SARS-CoV 3CL\textsuperscript{pro} Inhibitors for QSAR Model [Eq. (11.13)]

| Compound | Ar          | X   | Obsd | Calcd | Res  | Del res | Pred  | Pol Vol |
|----------|-------------|-----|------|-------|------|---------|-------|---------|
| 1        | 2-Furyl     | Cl  | 7.222| 7.134 | 0.088| 0.115   | 7.106 | 93.111  |
| 2\textsuperscript{a} | Benzofuran-2-yl | Cl  | 6.770| 7.086 | −0.317| −0.388 | 7.158 | 99.866  |
| 3        | 2-Furyl     | Br  | 7.301| 7.144 | 0.157| 0.211   | 7.090 | 91.748  |
| 4        | 2-Indolyl   | Cl  | 7.187| 6.993 | 0.194| 0.222   | 6.965 | 113.106 |
| 5        | 2-Benzothiophenyl | Cl  | 7.022| 6.889 | 0.133| 0.157   | 6.866 | 127.948 |
| 6        | Thiazole-4-yl| Cl  | 6.569| 6.562 | 0.006| 0.031   | 6.537 | 174.454 |
| 7\textsuperscript{a} | 3-OMePh | Cl  | 6.469| 6.962 | −0.493| −0.564 | 7.032 | 117.647 |
| 8        | 5-(4-ClPh)-Furan-2-yl | Cl  | 7.201| 6.969 | 0.231| 0.264   | 6.936 | 116.549 |

\textsuperscript{a}Considered as outliers.
### TABLE 11.15 Biological Activity and Physicochemical Parameters of Some Peptidomimetic SARS-CoV 3CL\(^{pro}\) Inhibitors for QSAR Model [Eq. (11.14)]

![Chemical structure](image)

| Compound | R                  | R\(_1\)    | Obsd | Calcd | Res | Del res | Pred  | \(D_Z\) |
|----------|--------------------|------------|------|-------|-----|---------|-------|---------|
| 1        | 5-Me-isoxazolyl-3-yl | Benzyl     | 3.060| 3.334 | -0.273 | -0.359 | 3.419 | 3.323 |
| 2        | 5-Me-isoxazolyl-3-yl | CH\(_2\)\(\text{C}(\text{Me})\)\(_2\) | 3.097| 3.365 | -0.268 | -0.348 | 3.444 | 3.260 |
| 3        | CH(CH\(_2\)OH)NH\text{Boc} | CH\(_2\)\(\text{C}(\text{Me})\)\(_2\) | 4.097| 4.062 | 0.035  | 0.041  | 4.055 | 1.879 |
| 4        | CH(CH\(_2\)OH)NH\text{Boc} | \(i\)-Butyl | 5.000| 5.049 | -0.049 | -0.106 | 5.106 | -0.080 |
| 5        | CH(CH\(_2\)OH)NH\text{Boc} | Benzyl     | 4.824| 4.786 | 0.038  | 0.061  | 4.763 | 0.442 |
| 6        | 5-Me-isoxazolyl-3-yl | Benzyl     | 3.523| 3.334 | 0.189  | 0.249  | 3.274 | 3.323 |
| 7        | 5-Me-isoxazolyl-3-yl | \(i\)-Butyl | 3.699| 3.371 | 0.328  | 0.424  | 3.275 | 3.249 |
\[ N = 7, R = 0.959, R^2 = 0.919, R_A^2 = 0.903, F (1, 5) = 56.603, P < 0.00066, \]
\[ \text{SEE} = 0.243, q^2 = 0.860, Q = 3.947 \]

It was observed from Eq. (11.14) that increasing the value of the dipole moment along Z-axis \( (D_Z) \) will lead to decrease the enzyme inhibitory activity. It thus suggested that the bulky substituent along Z-axis will not be conducive to the activity. The long chain linear aminobutoxy derivatives (Compounds 4 and 5, Table 11.15) are better than the isoxazole analogs (Compounds 1, 2, 6, and 7, Table 11.15) as the isoxazole moiety may produce more bulkiness that may impart unfavorable steric effect with the enzyme.

### 7.1.15 Arylmethylene Ketones and Fluorinated Methylene Ketones as SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Zhang et al. (2008) reported some arylmethylene ketones and fluorinated methylene ketones as SARS-CoV 3CL\textsuperscript{pro} inhibitors (Table 11.16). The QSAR model for them was as shown by Eq. (11.15), where the indicator variable “I” stands for a value of unity for the ester group. A positive coefficient of it suggested that the ester group may be favorable for imparting the higher inhibitory activity. Compounds bearing ester functions (Compounds 2–4, Table 11.16) are highly active compared to the nonester derivatives (Compounds 5–8, Table 11.16). Compounds 5–7 are found to be oriented from S1 to S4 pocket and the furan oxygen atom forms hydrogen bonds with the amino function of Glu166. Moreover, it is observed that compound 1 though having ester function, may behave in an aberrant fashion. Therefore, it was considered as an outlier.

\[
pIC_{50} = 4.452 (\pm 0.133) + 2.789 (\pm 0.203) I \\
(11.15)
\]
\[ N = 7, R = 0.987, R^2 = 0.974, R_A^2 = 0.961, F (1, 5) = 188.18, P < 0.00004, \]
\[ \text{SEE} = 0.266, q^2 = 0.954, Q = 3.711, \text{Outlier} = \text{Compound } 1 \]

### 7.1.16 Chloropyridine Esters as Potent SARS-CoV 3CL\textsuperscript{pro} Inhibitors

The QSAR model obtained for a series of chloropyridine esters reported by Niu et al. (2008) as potent SARS-CoV 3CL\textsuperscript{pro} inhibitors (Table 11.17) was as shown by Eq. (11.16), which suggested that increasing the molar refractivity and decreasing the total dipole moment may favor 3CL protease inhibitory activity

\[
pIC_{50} = 3.460 (\pm 0.429) + 0.470 (\pm 0.063) \text{CMR} - 0.067 (\pm 0.019) D_{\text{Tot}} \\
(11.16)
\]
\[ N = 10, R = 0.945, R^2 = 0.892, R_A^2 = 0.861, F (2, 7) = 29.024, P < 0.0004, \]
\[ \text{SEE} = 0.148, q^2 = 0.778, Q = 6.385, \text{Outlier} = \text{Compound } 5, 6. \]

This also suggested that the smaller molecules with less steric effect may be conducive to the inhibitory activity. The \( \alpha \)-naphthyl (Compound 11, Table 11.17) and the 2-oxochromene function (Compound 12, Table 11.17) at Ar position yield less dipole moment and better molar refractivity compared to the nitrophenyl (Compounds 9 and 10), the chlorophenyl (Compound 8) or the.
TABLE 11.16 Biological Activity and Physicochemical Parameters of Arylmethylene Ketones and Fluorinated Methylene Ketones as SARS-CoV 3CL{\textsubscript{pro}} Inhibitors for QSAR Model [Eq. (11.15)]

![Chemical Structure](image)

| Compound | R     | X     | Y     | Z     | W     | Obsd | Calcd | Res  | Del res | Pred  | I  |
|----------|-------|-------|-------|-------|-------|------|-------|------|---------|-------|----|
| 1\textsuperscript{a} | H     | H     | CH    | O     | —     | 5.102| 6.706 | −1.604| −2.139  | 7.241 | 1  |
| 2        | H     | Br    | CH    | O     | —     | 7.301| 6.706 | 0.595 | 0.793   | 6.508 | 1  |
| 3        | H     | Cl    | CH    | O     | —     | 7.222| 6.706 | 0.515 | 0.687   | 6.535 | 1  |
| 4        | 4-ClPh| Cl    | CH    | O     | —     | 7.201| 6.706 | 0.494 | 0.659   | 6.542 | 1  |
| 5        | 4-ClPh| Br    | CH    | CH\textsubscript{2} | —     | 4.886| 4.452 | 0.434 | 0.579   | 4.307 | 0  |
| 6        | 4-ClPh| Br    | CH    | CH    | F     | 4.553| 4.452 | 0.101 | 0.134   | 4.418 | 0  |
| 7        | 4-ClPh| Br    | CH    | C     | F,F   | 4.244| 4.452 | −0.208| −0.277  | 4.521 | 0  |
| 8        | 4-ClPh| Br    | N     | CH\textsubscript{2} | —     | 4.125| 4.452 | −0.327| −0.436  | 4.561 | 0  |

\textsuperscript{a}Considered as outliers.
### TABLE 11.17 Biological Activity and Physicochemical Parameters of Chloropyridine Esters as Potent SARS-CoV 3CL<sup>pro</sup> Inhibitors for QSAR Model [Eq. (11.16)]

*Considered as outliers.*

| Compound | R       | Ar      | Obsd | Calcd | Res  | Del res | Pred | CMR  | $D_{\text{tot}}$ |  
|----------|---------|---------|------|-------|------|---------|------|------|-----------------|
| 1        | 4-ClPh  | —       | 7.201| 7.087 | 0.114| 0.156   | 7.045| 8.349| 3.682           |
| 2        | 4-NO<sub>2</sub>Ph | —       | 7.222| 7.022 | 0.200| 0.252   | 6.970| 8.469| 5.001           |
| 3        | 2-NO<sub>2</sub>,4-ClPh | —       | 6.914| 6.789 | 0.125| 0.184   | 6.730| 8.961| 10.027          |
| 4        | 2-NO<sub>2</sub>Ph | —       | 6.682| 6.594 | 0.088| 0.130   | 6.552| 8.469| 10.059          |
| 5<sup>a</sup> | 3-NO<sub>2</sub>Ph | —       | 6.301| 6.727 | −0.426| −0.534  | 6.835| 8.469| 8.490           |
| 6<sup>a</sup> | —       | 4-Pyr   | 6.785| 6.378 | 0.407| 0.568   | 6.217| 5.922| 0.861           |
| 7        | —       | 3-Pyr   | 6.157| 6.348 | −0.191| −0.266  | 6.423| 5.922| 1.216           |
| 8        | —       | 4-ClPh  | 6.363| 6.633 | −0.270| −0.331  | 6.693| 6.624| 1.092           |
| 9        | —       | 2-NO<sub>2</sub>Ph | 6.478| 6.260 | 0.217| 0.305   | 6.172| 6.744| 6.047           |
| 10       | —       | 3-NO<sub>2</sub>Ph | 6.165| 6.371 | −0.206| −0.252  | 6.417| 6.744| 4.736           |
| 11       | —       | α-Napthyl | 6.907| 7.022 | −0.115| −0.157  | 7.064| 7.821| 2.014           |
| 12       | —       | 2-Oxo-chromene | 6.967| 6.909 | 0.058| 0.071   | 6.896| 7.607| 2.361           |
Viral Proteases and Their Inhibitors

pyridyl analog (Compound 7) and thus compounds 11 and 12 are more potent than compounds 7–10. Furyl derivatives (Compounds 1–4) are better inhibitors as compared to the other aryl ester analogs (Compounds 7–12) as they have higher molar refractivity despite having comparatively moderate bulky p-chlorophenyl or the p-nitrophenyl groups at R position. A slight reduction in the activity is noticed for the disubstituted aryl function (Compound 3) and the alteration of the nitro function at the 2nd position of the phenyl ring (Compound 4) in contrast to the 4th position (Compound 2), which increases the bulkiness or total bulk, and reduces the activity slightly. It is observed from the molecular modeling study that increasing the length of the side chain may increase the interaction between S2 and S4 pocket and the inhibitor that can be reflected by the QSAR model. Compound 5 possesses the higher molar refractivity while compound 6 possesses the lowest value of total dipole moment but it is not reflected in their activity. Probably, these compounds behave differently from other compounds in the dataset and hence were outliers.

7.1.17 Cinanserin Analogs as Promising SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Yang et al. (2008) reported some cinanserin analogs as SARS-CoV 3CL\textsuperscript{pro} inhibitors (Table 11.18), for which the QSAR model obtained was as shown by Eq. (11.17). This equation clearly exhibited that high molecular volume will not be favorable to the activity. Thus compounds having aryl (Compound 4), the heteroaryl (Compounds 6, 7), or the long chain amide function (Compounds 1, 2) at Y position have the lower activity than compounds having at this position the unsaturation (Compounds 8, 9) or the ester function (Compound 5). Compound 8 enters into the deep S1 pocket and has hydrophobic interactions. However, compound 3 has the lowest volume but it does not show the highest activity. Probably, this compound (Compound 3) may behave in a different manner with the enzyme and hence it is considered as an outlier.

\[
pIC_{50} = 24.586 (\pm 3.262) - 0.020 (\pm 0.003) \text{Vol} \tag{11.17}
\]

\[N = 8, R = 0.931, R^2 = 0.867, R^2_A = 0.845, F (1, 6) = 39.280, P < 0.00077, \]
SEE = 0.347, \[q^2 = 0.686, Q = 2.683, \text{Outlier} = \text{Compound 3}\]

7.1.18 Trifluoromethyl, Benzothiazolyl, and Thiazolyl Ketone Compounds as Promising SARS-CoV 3CL\textsuperscript{pro} Inhibitors

The QSAR model derived for some trifluoromethyl, benzothiazolyl, and thiazolyl ketone compounds with peptide side chain reported by Regnier et al. (2009) as promising SARS-CoV 3CL\textsuperscript{pro} inhibitors (Table 11.19) was as shown by Eq. (11.18)

\[
pK_i = 6.096 (\pm 0.893) - 0.027 (\pm 0.008) \text{PolVol} + 0.0001 (\pm 0.000) \text{PolVol}^2 \tag{11.18}
\]

\[N = 15, R = 0.856, R^2 = 0.732, R^2_A = 0.687, F (2, 12) = 16.394, P < 0.00037, \]
SEE = 0.375, \[q^2 = 0.536, Q = 2.283, \text{Pol Vol}_{\text{opt}} = 135. \]
### TABLE 11.18 Biological Activity and Physicochemical Parameters of Cinanserin Analogs as Promising SARS-CoV 3CL\textsuperscript{pro} Inhibitors for QSAR Model [Eq. (11.17)]

| Compound | X       | Y                  | Obsd | Calcd | Res  | Del res | Pred | Vol      |
|----------|---------|--------------------|------|-------|------|---------|------|----------|
| 1        | H       | (CH\textsubscript{2})\textsubscript{3}N(Me)\textsubscript{2} | 3.491 | 3.964 | −0.473 | −0.542 | 4.033 | 1020.630 |
| 2        | CN      | (CH\textsubscript{2})\textsubscript{3}N(Me)\textsubscript{2} | 3.903 | 3.771 | 0.132  | 0.158  | 3.745 | 1034.690 |
| 3\textsuperscript{a} | H       | CH\textsubscript{2}C═CH | 4.706 | 5.450 | −0.745 | −1.488 | 6.194 | 912.242 |
| 4        | H       | Benzyl             | 3.686 | 3.477 | 0.209  | 0.280  | 3.406 | 1056.120 |
| 5        | H       | (CH\textsubscript{2})\textsubscript{3}COOMe | 4.870 | 4.741 | 0.128  | 0.157  | 4.713 | 963.919 |
| 6        | H       | 2-Pyridylmethyl    | 3.533 | 3.638 | −0.104 | −0.130 | 3.663 | 1044.400 |
| 7        | H       | 3-Pyridylmethyl    | 3.457 | 3.663 | −0.206 | −0.254 | 3.711 | 1042.560 |
| 8        | H       | COCH═CH\textsubscript{Ph} | 5.975 | 5.019 | 0.955  | 1.318  | 4.657 | 943.645 |
| 9        | CN      | COC(CN)═CH\textsubscript{Ph} | 4.360 | 4.257 | 0.103  | 0.116  | 4.244 | 999.248 |

\textsuperscript{a}Considered as outliers.
| Compound | AA      | X          | Y          | Obsd  | Calcd  | Res  | Del res | Pred  | Pol Vol |
|----------|---------|------------|------------|-------|--------|------|---------|-------|---------|
| 1        | Cbz-Val-Leu-NH | OH   | CF$_3$    | 3.936 | 3.959  | −0.023 | −0.026  | 3.961 | 416.522 |
| 2        | Cbz-Ala-Val-Leu-NH | NH$_2$ | CF$_3$    | 3.870 | 3.939  | −0.069 | −0.078  | 3.947 | 415.318 |
| 3        | Cbz-Val-Leu-NH | N(Et)$_2$ | CF$_3$    | 3.440 | 3.882  | −0.442 | −0.499  | 3.939 | 411.755 |
| 4        | Cbz-Val-Leu-NH | Morpholine | CF$_3$    | 4.678 | 4.267  | 0.411 | 0.455  | 4.223 | 434.513 |
| 5        | Cbz-Val-Leu-NH | N(Me)Benzyl | CF$_3$    | 4.467 | 3.779  | 0.688 | 0.795  | 3.672 | 405.044 |
| 6        | Cbz-Ala-Val-Leu-NH | N(Et)$_2$ | CF$_3$    | 3.527 | 3.426  | 0.101 | 0.135  | 3.393 | 379.365 |
| 7        | Cbz-Leu-NH | N(Et)$_2$ | CF$_3$    | 3.234 | 3.469  | −0.235 | −0.324  | 3.558 | 133.810 |
| 8        | Cbz-Val-Leu-NH | Morpholine | Thiazole-2-yl | 3.321 | 3.520  | −0.200 | −0.253  | 3.574 | 386.735 |
| 9        | Cbz-Val-Leu-NH | N(Et)$_2$ | Thiazole-2-yl | 3.951 | 4.131  | −0.180 | −0.199  | 4.150 | 426.813 |
| 10       | Cbz-Val-Leu-NH | 2-Oxo-pyrrolidin-3-yl | Thiazole-2-yl | 5.658 | 5.214  | 0.443 | 0.862  | 4.795 | 480.804 |
| 11       | Cbz-Val-Leu-NH | N(Et)$_2$ | Thiazole-2-yl | 4.345 | 4.787  | −0.442 | −0.576  | 4.921 | 461.239 |
| 12       | Cbz-Leu-NH | N(Et)$_2$ | Thiazole-2-yl | 3.335 | 3.316  | 0.020 | 0.026  | 3.310 | 146.432 |
| 13       | Cbz-Val-NH | N(Et)$_2$ | Thiazole-2-yl | 3.212 | 3.415  | −0.203 | −0.273  | 3.485 | 138.098 |
| 14       | Cbz-Val-Leu-NH | N(Et)$_2$ | Benzohiazole-2-yl | 4.307 | 4.604  | −0.297 | −0.355  | 4.662 | 452.238 |
| 15       | Cbz-Val-NH | N(Et)$_2$ | Benzohiazole-2-yl | 3.799 | 3.370  | 0.429 | 0.567  | 3.232 | 141.781 |
Eq. (11.18) showed that the enzyme inhibitory activity was correlated with the polar volume of the molecules through a parabolic relation. It, therefore, suggests that the activity would decrease up to an optimum value of polar volume (Pol Vol$_{opt}$ = 135) and beyond that will start increasing. Compound with the 2-oxo-pyrrolidin-3-yl function (Compound 10, Table 11.19) possesses the higher polar volume and hence, possess the maximum inhibition. Comparing the activity of this compound with those of compounds 8, 10–13, it may be suggested that the 2-oxo-pyrrolidin-3-yl function in compound 10 is favorable than the diethylamino function in compounds 11–13 and morpholino function in compound 8 at the X position. Moreover, the benzothiazole-2-yl function in compounds 14, 15 is favorable than the thiazole function in compounds 8, 12, 13. The bulky group, such as the morpholino in compound 4 and the benzylmethylamino function in compound 5 are favorable than the smaller substituents, such as the hydroxyl in compound 1, the amino group in compound 2, and the diethylamino group in compounds 3, 6, and 7 at X position. Comparing compound 14 with 15, it may be inferred that the bulky amino acid moiety (compound 14) is favorable than smaller amino acid functions (Compound 15), as bulky functions may produce the higher polar volume. The molecular modeling study revealed that the benzyloxycarbonyl moiety of compound 10 did not make any hydrophobic interaction rather had hydrogen bonding interactions with Glu166 through its adjacent amino function.

7.1.19 Pyrazolone Analogs as Promising SARS-CoV 3CL$^{pro}$ Inhibitors

Ramajayam et al. (2010) reported some pyrazolone analogs as promising SARS-CoV 3CL$^{pro}$ inhibitors (Table 11.20), for which the QSAR model obtained was as:

$$pIC_{50} = 9.292 (\pm 0.347) - 0.281 (\pm 0.074) C \log P$$ (11.19)

$N = 7, R = 0.862, R^2 = 0.744, R^2_A = 0.692, F (1, 5) = 14.512, P < 0.01251, SEE = 0.119, q^2 = 0.529, Q = 7.244, \text{Outlier} = \text{Compounds 1, 5}$

Eq. (11.19) thus suggested that increasing value of the hydrophobicity of these molecules may be detrimental to the activity. Compounds with the smaller halogen substitution, such as fluorine at R position (Compound 8, Table 11.20) are better than compounds with the bigger halogen substituents, such as the chloro (Compounds 2 and 6, Table 11.20). Further, a dihalo substituted compound, such as compound 7 was shown to be less active as compared to mono-halo-substituted analogs (Compounds 2, 6, and 8). The cyano (Compound 4) and the nitro (Compound 9) substitutions also produced the higher activity as compared to the methoxy substitution (Compound 3). The docking study suggested that the N1-phenyl group was located near to the S1’ pocket. One of the oxygen atoms of the nitro group forms a hydrogen bond with Gly143. The keto function of the pyrazolone ring was also found to form another hydrogen bond.
with Glu166. The C-3 phenyl ring was found to be well-accommodated in the S2 pocket. The benzylidene ring without any carboxyl functions lost the activity. Therefore, it may be assumed that hydrogen bonding interaction is more important than the hydrophobic interaction. The oxygen atom of the carboxyl group forms a hydrogen bond with Gln192. Therefore, apart from S2 pocket, none of the aryl functions has exhibited hydrophobic interactions, whereas three hydrogen bonding interactions were observed. Compounds 1 and 5 considered as outliers.

### TABLE 11.20 Biological Activity and Physicochemical Parameters of Pyrazolone Analogs as Promising SARS-CoV 3CLpro Inhibitors for QSAR Model [Eq. (11.19)]

| Compound | R   | Obsd | Calcd | Res  | Del res | Pred | C Log P |
|----------|-----|------|-------|------|---------|------|---------|
| 1         | H   | 7.745| 7.998 | -0.254 | -0.297 | 8.042 | 4.380   |
| 2         | 4-Cl| 7.857| 7.760 | 0.097 | 0.115 | 7.742 | 5.093   |
| 3         | 4-OMe| 7.921| 8.025 | -0.105 | -0.125 | 8.046 | 4.299   |
| 4         | 4-CN| 8.260| 8.188 | 0.072 | 0.113 | 8.147 | 3.813   |
| 5         | 4-OCF3| 7.377| 7.655 | -0.278 | -0.377 | 7.754 | 5.408   |
| 6         | 3-Cl| 7.967| 7.760 | 0.207 | 0.245 | 7.722 | 5.093   |
| 7         | 3,4-diCl| 7.614| 7.562 | 0.052 | 0.089 | 7.526 | 5.686   |
| 8         | 4-F | 8.167| 7.951 | 0.217 | 0.247 | 7.920 | 4.523   |
| 9         | 3-NO2| 8.076| 8.084 | -0.008 | -0.011 | 8.087 | 4.123   |

*Considered as outliers.*
7.1.20 Biflavonoids as Potential SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Ryu et al. (2010) reported a series of biflavonoids (Fig. 11.8; Table 11.21) from Torreya nucifera having potential SARS-CoV 3CL\textsuperscript{pro} inhibitory activity. The QSAR model obtained for them was as shown by Eq. (11.20). It was observed from Eq. (11.20) that the increasing value of the dipole moment along X-axis may be conducive to the activity. Thus, the bulky substitution at X-axis of these molecules may be favorable for activity. Compounds 10–12 (Table 11.21) possess higher dipole moment due to much bulky aryl groups as compared to the compounds 1–2, 4–8 and, therefore, have higher activity. Compounds 3 and 9 exhibited the aberrant behavior and thus were considered as outliers.

\[
p\text{IC}_{50} = 3.833 (\pm 0.037) + 0.212 (\pm 0.026) D_X \tag{11.20}
\]

\(N = 10, R = 0.946, R^2 = 0.895, R_A^2 = 0.882, F (1, 8) = 68.528, P < 0.00003, \)
\(\text{SEE} = 0.114, q^2 = 0.805, Q = 8.298, \text{Outlier} = \text{Compounds 3, 9}\)

7.1.21 A Series of Some Promising SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Nguyen et al. (2011) reported some promising SARS-CoV 3CL\textsuperscript{pro} inhibitors through virtual screening (Fig. 11.9; Table 11.22). The QSAR model obtained for these compounds was as shown by Eq. (11.21), which exhibited that the activity is well correlated with the hydrophobicity of the molecules. The docking
TABLE 11.21 Biological Activity and Physicochemical Parameters of Biflavonoids as Potential SARS-CoV 3CL\textsuperscript{pro} Inhibitors (Fig. 11.8) for QSAR Model [Eq. (11.20)]

| Compound | Obsd | Calcd | Res | Del res | Pred | $D_X$ |
|----------|------|-------|-----|---------|------|-------|
| 1        | 3.656| 3.749 | −0.093 | −0.108 | 3.764 | −0.708 |
| 2        | 3.632| 3.811 | −0.179 | −0.204 | 3.835 | −0.460 |
| 3\textsuperscript{a} | 4.305| 3.843 | 0.461 | 0.518 | 3.786 | −0.333 |
| 4        | 3.787| 3.920 | −0.133 | −0.146 | 3.934 | −0.028 |
| 5        | 3.890| 4.018 | −0.129 | −0.140 | 4.030 | 0.364 |
| 6        | 3.684| 3.498 | 0.187 | 0.261 | 3.423 | −1.708 |
| 7        | 3.547| 3.783 | −0.235 | −0.270 | 3.818 | −0.573 |
| 8        | 3.861| 3.933 | −0.072 | −0.079 | 3.940 | 0.024 |
| 9\textsuperscript{a} | 5.081| 4.462 | 0.619 | 0.777 | 4.303 | 2.129 |
| 10       | 4.141| 4.223 | −0.082 | −0.092 | 4.233 | 1.179 |
| 11       | 4.495| 4.581 | −0.087 | −0.121 | 4.615 | 2.603 |
| 12       | 4.416| 4.672 | −0.257 | −0.398 | 4.814 | 2.965 |

\textsuperscript{a}Considered as outliers.

FIGURE 11.9 General structure of some potent SARS-CoV 3CL\textsuperscript{pro} inhibitors.
study had revealed that compound 7 (Table 11.22) had good hydrophobic interactions with His41, Phe140, Leu141, Cys145, His163, Glu166, Gly170, and His172 apart from a number of hydrogen bonding interactions (the nitro group with Gly143, methacrylamide group with Phe140, one of the oxygen atoms of the nitro group with Cys145). The nitrophenyl group was found to be the most crucial moiety to enter into the S1 pocket for imparting potent inhibition. Compounds 2 and 4 though possessed a higher value of hydrophobicity but less activity than expected, hence, they were considered as outliers.

\[
pIC_{50} = 6.238 (\pm 0.213) + 0.233 (\pm 0.050) \log P \\
N = 5, \ R = 0.937, \ R^2 = 0.878, \ R^2_A = 0.837, \ F (1, 3) = 21.594, \ P < 0.01879, \ SEE = 0.077, \ q^2 = 0.703, \ Q = 12.169, \ Outlier = \text{Compounds 2, 4}
\]

### 7.1.22 Peptidomimetic SARS-CoV 3CL\(^{pro}\) Inhibitors

Some peptidomimetic SARS-CoV 3CL\(^{pro}\) inhibitors (Table 11.23) were synthesized and evaluated by Akaji et al. (2011) and the QSAR model obtained for this [Eq. (11.22)] indicated that the activity is controlled by a single indicator parameter “I” used for an imidazolyl-4-yl methyl substituent at the R\(_1\) position. The positive coefficient of this indicated that such a substituent would conducive to the activity. The reason of this may be that this substituent might have better steric fitting in the S1 pocket of the enzyme formed by Phe140, Leu141, and Glu166. Compounds 4 and 8 (Table 11.23) were considered as outliers.

\[
pIC_{50} = 4.319 (\pm 0.168) + 2.409 (\pm 0.213) I \\
N = 8, \ R = 0.977, \ R^2 = 0.955, \ R^2_A = 0.948, \ F (1, 6) = 128.20, \ P < 0.00003, \ SEE = 0.291, \ q^2 = 0.929, \ Q = 3.397, \ Outlier = \text{Compounds 4, 8}
\]
TABLE 11.23 Biological Activity and Physicochemical Parameters of Peptidomimetic SARS-CoV 3CL\textsuperscript{pro} Inhibitors for QSAR Model [Eq. (11.22)]

| Compound | R         | R\(_1\) | R\(_2\) | Obsd | Calcd | Res    | Del res | Pred | I  |
|----------|-----------|---------|---------|------|-------|--------|---------|------|----|
| 1        | i-Butyl   | (CH\(_2\))\(_2\)CONMe\(_2\) | Me     | 4.432| 4.319| 0.112  | 0.169   | 4.263| 0  |
| 2        | i-Butyl   | c-Hexylmethyl | Me     | 4.208| 4.319| −0.112 | −0.168  | 4.375| 0  |
| 3        | i-Butyl   | 2-Thiophenylmethyl | Me     | 4.319| 4.319| −0.001 | −0.001  | 4.320| 0  |
| 4\(^a\)  | i-Butyl   | Imidazole-4-ylmethyl | Me     | 5.244| 6.127| −0.882 | −1.030  | 6.274| 1  |
| 5        | Benzyl    | Imidazole-4-ylmethyl | Me     | 6.409| 6.127| 0.282  | 0.329   | 6.080| 1  |
| 6        | c-Hexylmethyl | Imidazole-4-ylmethyl | Me     | 7.187| 6.127| 1.061  | 1.237   | 5.950| 1  |
| 7        | c-Hexylmethyl | Imidazole-4-ylmethyl | Me     | 6.569| 6.127| 0.442  | 0.516   | 6.053| 1  |
| 8\(^a\)  | c-Hexylmethyl | Imidazole-4-ylmethyl | CH\(_2\)CONH\(_2\) | 4.000| 6.127| −2.127 | −2.481  | 6.481| 1  |
| 9        | c-Hexylmethyl | Imidazole-4-ylmethyl | CH\(_2\)OH | 6.469| 6.127| 0.342  | 0.399   | 6.070| 1  |
| 10       | c-Hexylmethyl | Imidazole-4-ylmethyl | CH(OH)Me | 7.009| 6.127| 0.882  | 1.029   | 5.980| 1  |

\(^a\)Considered as outliers
7.1.23 Flavonoids as SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Nguyen et al. (2012) reported some flavonoids from \textit{Pichia pastoris} (Fig. 11.10; Table 11.24) having SARS-CoV 3CL\textsuperscript{pro} inhibitory activity. For these compounds, the inhibition activity was shown to be correlated with the PSA of the molecule [Eq. (11.23)], suggesting that highly polar molecules may have better activity. Substituents like hydroxy might give better PSA, leading to better

![General structure of some flavonoids as SARS-CoV 3CL\textsuperscript{pro} inhibitors.](image)

**TABLE 11.24** Biological Activity and Physicochemical Parameters of Flavonoids as SARS-CoV 3CL\textsuperscript{pro} Inhibitors (Fig. 11.10) for QSAR Model [Eq. (11.23)]

| Compound | Obsd | Calcd | Res  | Del res | Pred   | PSA     |
|----------|------|-------|------|---------|--------|---------|
| 1\textsuperscript{a} | 3.439 | 3.873 | −0.435 | −0.525 | 3.964  | 314.921 |
| 2       | 4.137 | 3.794 | 0.343 | 0.412   | 3.725  | 290.968 |
| 3       | 3.419 | 3.644 | −0.225 | −0.291 | 3.710  | 245.862 |
| 4       | 3.455 | 3.320 | 0.134 | 0.392   | 3.062  | 148.364 |
| 5       | 4.137 | 4.052 | 0.085 | 0.117   | 4.020  | 368.594 |
| 6       | 4.328 | 4.230 | 0.097 | 0.195   | 4.133  | 422.452 |

\textsuperscript{a}Considered as outliers.
activity and also such substituents might form the hydrogen bonds. A molecular docking study showed that the galloyl group forms hydrogen bonds with Leu141, Gly143, Ser144, and His163 at the enzyme active site.

\[ pIC_{50} = 2.859( \pm 0.339) + 0.004( \pm 0.001) \text{PSA} \]  

(11.23)

\[ N = 5, \quad R = 0.880, \quad R^2 = 0.774, \quad R^2_\lambda = 0.699, \quad F (1, 3) = 10.292, \quad P < 0.04903, \]
\[ \text{SEE} = 0.233, \quad q^2 = 0.556, \quad Q = 3.777, \quad \text{Outlier} = \text{Compound 1} \]

Compounds without any B ring (Compounds 3 and 4) are less active. Compound 1 with no 2, 3 double bond in the C ring is less active than the compound 2 though possessing the higher PSA. Compound 1 was found to act as an outlier. It was also observed that the rigid aryl substitution with the hydroxyl group (Compound 6) was better than the flexible cycloalkyl substitution with the hydroxyl group (Compound 5).

7.1.24 Dipeptidyl Aldehydes and α-Keto Amides as Promising SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Mandadapu et al. (2013b) reported some dipeptidyl aldehydes and α-keto amides as potent norovirus 3CL\textsuperscript{pro} inhibitors (Table 11.25). The QSAR model obtained for these compounds was as shown by Eq. (11.24) that again exhibited that the hydrophobicity of the compounds may be beneficial to SARS-CoV 3CL\textsuperscript{pro} inhibitory activity of the compounds. Compounds with cyclohexylmethyl group appeared to be more potent than other compounds. This might be due to the bulkiness of this group providing the higher C log \( P \) value and due to its better fitting in the active site of the enzyme. Compounds 1 and 7, however, showed aberrant behaviors and thus were considered as outliers.

\[ pIC_{50} = 4.890( \pm 0.129) + 0.553( \pm 0.085) \text{C log } P \]  

(11.24)

\[ N = 8, \quad R = 0.936, \quad R^2 = 0.876, \quad R^2_\lambda = 0.855, \quad F (1, 6) = 42.329, \quad P < 0.00063, \]
\[ \text{SEE} = 0.164, \quad q^2 = 0.781, \quad Q = 5.707, \quad \text{Outlier} = \text{Compounds 1, 7} \]

7.1.25 A Series of Dipeptide-Type SARS CoV 3CL\textsuperscript{pro} Inhibitors

Thanigaimalai et al. (2013a) reported a series of dipeptide-type SARS-CoV 3CL\textsuperscript{pro} inhibitors (Table 11.26), for which the QSAR model obtained was as shown by Eq. (11.25).

\[ pK_i = -67.682( \pm 23.859) - 0.082( \pm 0.014) \text{SA} + 0.145( \pm 0.034) \text{Vol} - 0.00001( \pm 0.000) \text{Vol}^2 \]  

(11.25)

\[ N = 17, \quad R = 0.865, \quad R^2 = 0.749, \quad R^2_\lambda = 0.691, \quad F (3, 13) = 12.899, \quad P < 0.00034, \]
\[ \text{SEE} = 0.557, \quad q^2 = 0.548, \quad Q = 1.553, \quad \text{Vol}_{opt} = 7250, \quad \text{Outlier} = \text{Compound 14} \]
TABLE 11.25 Biological Activity and Physicochemical Parameters of Dipeptidyl Aldehydes and α-Keto Amides as Promising SARS-CoV 3CL\textsuperscript{pro} Inhibitors for QSAR Model [Eq. (11.24)]

| Compound | R\textsubscript{1} | R\textsubscript{2} | R\textsubscript{3} | Obsd | Calcd | Res | Del res | Pred | C Log P |
|----------|---------------------|---------------------|---------------------|-------|-------|-----|--------|------|--------|
| 1\textsuperscript{a} | Benzyl | i-But | CHO | 6.222 | 5.632 | 0.590 | 0.666 | 5.556 | 1.075 |
| 2 | Benzyl | n-Pr | CHO | 5.215 | 5.435 | -0.221 | -0.278 | 5.493 | 0.676 |
| 3 | Benzyl | i-But | CHO | 5.347 | 5.696 | -0.349 | -0.389 | 5.736 | 1.205 |
| 4 | Benzyl | (c-Hex)methyl | CHO | 6.301 | 6.220 | 0.081 | 0.122 | 6.179 | 2.268 |
| 5 | Benzyl | Benzyl | CHO | 5.292 | 5.613 | -0.320 | -0.364 | 5.657 | 1.036 |
| 6 | 4-FBenzyl | i-But | CHO | 5.745 | 5.703 | 0.042 | 0.047 | 5.698 | 1.218 |
| 7\textsuperscript{a} | m-FBenzyl | i-But | CHO | 6.155 | 5.703 | 0.452 | 0.504 | 5.651 | 1.218 |
| 8 | 2-Phenethyl | i-But | CHO | 5.721 | 5.826 | -0.105 | -0.117 | 5.838 | 1.468 |
| 9 | (2-c-Hex)ethyl | i-But | CHO | 6.222 | 6.359 | -0.137 | -0.274 | 6.496 | 2.550 |
| 10 | Benzyl | i-But | C(OH)(SO\textsubscript{3}Na) CONHc-Pr | 5.276 | 5.309 | -0.033 | -0.047 | 5.323 | 0.419 |

\textsuperscript{a}Considered as outliers.
**TABLE 11.26** Biological Activity and Physicochemical Parameters of a Series of Dipeptide-Type SARS CoV 3CL\textsuperscript{pro} Inhibitors for QSAR Model [Eq. (11.25)]

![Chemical Structure](image_url)

| Compound | R                  | Obsd | Calcd | Res  | Del res | Pred  | SA    | Vol   |
|----------|--------------------|------|-------|------|---------|-------|-------|-------|
| 1        | 5-Oxo-pyrrolidin-2-yl | 5.569| 5.978 | -0.410| -0.712  | 6.280 | 729.379 | 1329.150 |
| 2        | 2-Pyrolyl          | 5.770| 5.306 | 0.464 | 1.066   | 4.704 | 727.381 | 1313.560 |
| Compound                  | Obsd  | Calcd | Res | Del res | Pred | SA   | Vol  |
|---------------------------|-------|-------|-----|---------|------|------|------|
| 2-Indolyl                 | 7.187 | 7.437 | -0.250 | -0.294 | 7.481 | 795.312 | 1463.480 |
| 5-OMe-Indole-2-yl         | 7.174 | 6.483 | 0.691 | 0.761 | 6.413 | 840.460 | 1523.020 |
| 5-OH-Indole-2-yl          | 6.796 | 7.262 | -0.466 | -0.524 | 7.320 | 810.363 | 1486.140 |
| 5-Cl-Indole-2-yl          | 7.553 | 7.276 | 0.277 | 0.310 | 7.243 | 818.124 | 1500.870 |
| 6-OMe-Indole-2-yl         | 6.481 | 6.843 | -0.362 | -0.392 | 6.874 | 836.137 | 1524.160 |
| 4-OMe-Indole-2-yl         | 8.201 | 7.584 | 0.616 | 0.718 | 7.482 | 834.821 | 1541.680 |
| 4-O-i-Pr-Indole-2-yl      | 7.319 | 7.720 | -0.402 | -0.535 | 7.853 | 865.057 | 1612.100 |
| 4-O-i-But-Indole-2-yl     | 7.523 | 7.143 | 0.380 | 0.914 | 6.608 | 901.604 | 1687.260 |
| 4-OH-Indole-2-yl          | 7.585 | 7.337 | 0.248 | 0.284 | 7.302 | 804.247 | 1476.920 |
| 3-Me,5-OMe-Indole-2-yl   | 5.174 | 5.199 | -0.025 | -0.040 | 5.213 | 894.897 | 1601.640 |
| 3-Et,5-OMe-Indole-2-yl    | 5.125 | 5.626 | -0.501 | -0.818 | 5.943 | 913.184 | 1661.880 |
| Benzimidazole-2-yl        | 7.658 | 6.210 | 1.447 | 1.648 | 6.010 | 832.069 | 1499.850 |
| Benzthiazole-2-yl         | 6.097 | 6.343 | -0.246 | -0.275 | 6.372 | 830.805 | 1500.860 |
| 2,3-dihydroindole-2-yl   | 6.921 | 6.510 | 0.410 | 0.451 | 6.470 | 842.313 | 1527.410 |
| Benzofuran-2-yl           | 4.854 | 5.812 | -0.958 | -1.187 | 6.041 | 834.923 | 1495.060 |
| Indole-3-yl               | 6.167 | 7.082 | -0.915 | -1.012 | 7.180 | 811.144 | 1483.120 |

*aConsidered as outlier.*
It was suggested from Eq. (11.25) that decreasing value of the SA may be conducive to the enzyme inhibition. However, the volume of the molecules was found to exhibit a parabolic relation with the enzyme inhibitory activity. It, therefore, suggested that increase in volume may be responsible for enhancing the activity only up to an optimum value of 7250. Beyond this value, the activity would decrease. Thus it indicated that molecules with limited bulk or with substituents with limited bulk might be favorable to the activity. Thus indole derivatives with less bulky substitution (Compounds 3–11, Table 11.26) resulted in higher activity than those with a greater bulk (Compounds 12, 13). Compared to the indole analogs, the oxopyrrolidine (Compound 1), the pyrrole (Compound 2), the benzothiazole (Compound 15), and the benzofuran (Compound 17) analogs were comparatively less active. However, it could not be explained by the model why benzimidazole analog (Compound 14) had higher activity as compared to the benzothiazole (Compound 15) and benzofuran analogs (Compound 17). Probably, this compound may behave differently as compared to the other compounds in the dataset. Therefore, this compound is considered as an outlier.

7.1.26 A Series of Novel Dipeptide-Type SARS-CoV 3CL<sub>pro</sub> Inhibitors

In the subsequent study, Thanigaimalai et al. (2013b) reported a series of dipeptide-type SARS-CoV 3CL protease inhibitors (Table 11.27) whose activity was shown to be controlled by the molar refractivity (CMR) and the polar volume (Pol Vol) of the compounds [Eq. (11.26)]. Since the correlation was quadratic with respect to both CMR and Pol Vol, it suggested that compounds with limited bulk and polarity may have a better binding affinity. Several compounds, however, were treated as outliers.

\[
pK_i = -177.032 (\pm 33.763) + 18.238 (\pm 3.699) \text{CMR} - 0.598 (\pm 0.124) \text{CMR}^2 + 0.334 (\pm 0.077) \text{Pol Vol} - 0.001 (\pm 0.000) \text{Pol Vol}^2
\]

\[N = 19, R = 0.874, R^2 = 0.764, R_A^2 = 0.697, F (4, 14) = 11.331, P < 0.00026,\]
\[\text{SEE} = 0.275, q^2 = 0.577, Q = 3.178, \text{CMR}_{\text{opt}} = 15.249, \text{Pol Vol}_{\text{opt}} = 167, \text{Outlier} = \text{Compounds 1, 6, 7, 15, 21, 24, 25}\]

7.1.27 A Series of N-(Benzo [1,2,3]Triazol-1-yl)-N-(Benzyl) Acetamido) Phenyl) Carboxamides as SARS-CoV 3CL<sub>pro</sub> Inhibitors

Turlington et al. (2013) reported a series of N-(benzo [1,2,3]triazol-1-yl)-N-(benzyl)acetamido) phenyl) carboxamides as promising SARS-CoV 3CL<sub>pro</sub> inhibitors (Table 11.28). The QSAR model obtained for these compounds [Eq. (11.27)] suggested that highly hydrophobic (\(C \log P > 4.1\)) molecule with high molar refractivity but the less MW will be conducive to the activity. With the
### TABLE 11.27 Biological Activity and Physicochemical Parameters of a Series of Novel Dipeptide-Type SARS-CoV 3CL\textsuperscript{pro} Inhibitors for QSAR Model [Eq. (11.26)]

| Compound | R     | R\textsubscript{1} | Obsd | Calcd | Res  | Del res | Pred | CMR  | Pol Vol |
|----------|-------|---------------------|------|-------|------|---------|------|------|---------|
| 1\textsuperscript{a} | \textit{i}-But | \textit{i}-But | 5.229 | 4.658 | 0.571 | 1.189 | 4.040 | 13.395 | 246.218 |
| 2        | O-t-But | \textit{i}-But | 4.638 | 4.998 | −0.359 | −0.645 | 5.284 | 13.548 | 277.670 |
| 3        | OBnz   | \textit{i}-But | 6.337 | 5.834 | 0.503 | 0.559 | 5.778 | 14.667 | 249.660 |
| 4        | OBnz   | \textit{n}-But | 5.796 | 5.921 | −0.125 | −0.147 | 5.943 | 14.667 | 283.458 |
| 5        | OBnz   | \textit{i}-Pr  | 5.767 | 5.501 | 0.266 | 0.308 | 5.459 | 14.204 | 242.641 |
| 6\textsuperscript{b} | OBnz   | Sec-But | 4.538 | 5.851 | −1.313 | −1.454 | 5.992 | 14.667 | 251.687 |
| 7\textsuperscript{a} | OBnz   | (CH\textsubscript{2})\textsubscript{2}SMe | 5.027 | 5.035 | −0.008 | −0.058 | 5.085 | 15.010 | 348.627 |

(Continued)
### TABLE 11.27 Biological Activity and Physicochemical Parameters of a Series of Novel Dipeptide-Type SARS-CoV 3CL<sub>pro</sub> Inhibitors for QSAR Model [Eq. (11.26)] (cont.)

| Compound          | R       | R<sub>1</sub> | Obsd | Calcd | Res  | Del res | Pred  | CMR   | Pol Vol |
|-------------------|---------|---------------|------|-------|------|---------|-------|-------|---------|
| 8                 | OBnz    | Bnz           | 5.921| 5.826 | 0.095| 0.104   | 5.817 | 15.787| 260.830 |
| 9                 | Bnz     | i-But         | 5.495| 5.688 | −0.193| −0.223  | 5.717 | 14.514| 241.735 |
| 10                | 4-OMe-Bnz | i-But      | 6.377| 6.019 | 0.358| 0.397   | 5.980 | 15.131| 266.950 |
| 11                | 4-OMe-Phenethyl | i-But  | 6.215| 5.928 | 0.287| 0.312   | 5.903 | 15.595| 282.725 |
| 12                | 3-Pyridylethyl | i-But    | 5.131| 5.657 | −0.527| −0.726  | 5.857 | 14.767| 231.621 |
| 13                | PhCH═CH | i-But         | 6.161| 5.743 | 0.418| 0.575   | 5.587 | 15.257| 234.084 |
| 14                | 4-OMe-PhCH═CH | i-But  | 6.155| 5.774 | 0.380| 0.418   | 5.737 | 15.874| 260.311 |
| 15<sup>a</sup>    | 3,4-diOMe-PhCH═CH | i-But | 5.886| 5.205 | 0.681| 0.951   | 4.935 | 16.491| 294.794 |
| 16                | Phenoxymethyl | i-But    | 6.252| 5.930 | 0.322| 0.364   | 5.888 | 14.667| 267.498 |
| 17                | 4-OMe-Phenoxymethyl | i-But | 5.807| 5.881 | −0.074| −0.084  | 5.891 | 15.284| 301.759 |
| 18                | 4-OH-Phenoxymethyl | i-But  | 5.076| 5.790 | −0.715| −0.853  | 5.929 | 14.821| 307.175 |
| 19                | 3-NMe<sub>2</sub>-Phenoxymethyl | i-But | 6.076| 5.739 | 0.337| 0.366   | 5.709 | 15.964| 281.487 |
| 20                | 4-OMe-PHCH<sub>2</sub> | i-But | 5.495| 5.822 | −0.327| −0.365  | 5.859 | 15.500| 303.153 |
| 21<sup>a</sup>    | 3-OMe-PHCH<sub>2</sub> | i-But | 6.409| 5.779 | 0.630| 0.708   | 5.701 | 15.500| 307.108 |
| 22                | 2-OMe-PHCH<sub>2</sub> | i-But | 6.481| 5.918 | 0.564| 0.621   | 5.860 | 15.500| 291.600 |
| 23                | OBnz    | i-But         | 6.180| 5.874 | 0.307| 0.330   | 5.850 | 15.745| 269.597 |
| 24<sup>a</sup>    | OBnz    | i-But         | 4.432| 5.560 | −1.128| −1.299  | 5.731 | 16.209| 275.135 |
| 25<sup>a</sup>    | OBnz    | i-But         | 4.284| 5.416 | −1.132| −1.405  | 5.689 | 16.362| 276.355 |
| 26                | OBnz    | i-But         | 5.602| 5.417 | 0.185| 0.230   | 5.372 | 16.362| 274.643 |

<sup>a</sup>Considered as outlier.
TABLE 11.28 Biological Activity and Physicochemical Parameters of a Series of \( N^-\)-(benzo[1,2,3]triazol-1-yl)-\( N^-\)-(benzyl) acetamido) phenyl) carboxamides as SARS-CoV 3CL\textsuperscript{pro} Inhibitors for QSAR Model [Eq. (11.27)]

![Structural Insight Into the Viral 3C-Like Protease Inhibitors | Chapter 11](image)

| Compound | R       | R\(_1\)          | Obsd | Calcd | Res  | Del res | Pred | C Log \( P \) | CMR | MW   |
|----------|---------|------------------|------|-------|------|---------|------|--------------|-----|------|
| 1        | NHCOMe  | CONH-t-But       | 5.112| 5.374 | -0.262| -0.326  | 5.439| 3.135        | 14.067| 504.604|
| 2        | NHSO\(_2\)Me | CONH-t-But     | 4.597| 4.665 | -0.068| -0.117  | 4.714| 2.925        | 14.440| 540.658|
| 3        | NHCOEt  | CONH-t-But       | 5.161| 5.034 | 0.127 | 0.142   | 5.019| 3.664        | 14.530| 518.630|
| 4        | NHCO-i-Pr | CONH-t-But     | 5.387| 5.030 | 0.357 | 0.421   | 4.966| 3.973        | 14.994| 532.657|
| 5\(^a\) | NHCO-t-But | CONH-t-But   | 4.648| 5.151 | -0.504| -0.641  | 5.289| 4.372        | 15.458| 546.684|
| 6        | NHCO-c-Pr | CONH-t-But      | 5.041| 4.993 | 0.048 | 0.055   | 4.986| 3.719        | 14.857| 530.641|
| 7        | NHCO-c-But | CONH-t-But    | 5.420| 4.943 | 0.477 | 0.575   | 4.845| 4.048        | 15.281| 544.668|
| 8        | NHCO-5-(Isoxazole) | CONH-t-But | 4.585| 4.440 | 0.145 | 0.190   | 4.395| 3.410        | 15.117| 557.624|
| 9        | NHCOEt  | H                | 5.538| 5.400 | 0.138 | 0.163   | 5.374| 3.267        | 11.807| 419.499|

(Continued)
| Compound | R       | R<sub>1</sub> | Obsd | Calcd | Res | Del res | Pred  | C Log P | CMR  | MW     |
|----------|---------|--------------|------|-------|-----|---------|-------|---------|-------|--------|
| 10       | NHCO-<i>-i</i>-Pr | H             | 5.444 | 5.256 | 0.188 | 0.212   | 5.231 | 3.576   | 12.271 | 433.526 |
| 11       | NHCO-<i>-t</i>-But | H             | 4.876 | 5.198 | −0.322 | −0.364  | 5.240 | 3.975   | 12.735 | 447.553 |
| 12       | NHCO(CH<sub>2</sub>)<sub>2</sub>OMe | H             | 5.469 | 5.563 | −0.094 | −0.133  | 5.602 | 2.862   | 12.424 | 449.525 |
| 13       | NHCO-c-Pr    | H             | 5.387 | 5.334 | 0.053  | 0.061   | 5.326 | 3.322   | 12.133 | 431.510 |
| 14       | NHCO-c-But   | H             | 5.092 | 5.136 | −0.044 | −0.050  | 5.141 | 3.651   | 12.557 | 445.537 |
| 15<sup>a</sup> | NHCO-c-Hex       | H             | 4.656 | 5.432 | −0.776 | −0.857  | 5.512 | 4.769   | 13.485 | 473.590 |
| 16       | NHCOO-<i>-i</i>-but | H             | 4.987 | 4.862 | 0.125  | 0.179   | 4.808 | 4.645   | 12.888 | 463.552 |
| 17       | NHMe         | H             | 5.678 | 5.770 | −0.093 | −0.131  | 5.809 | 3.218   | 10.844 | 377.463 |
| 18       | NHNbz        | H             | 5.824 | 6.029 | −0.205 | −0.277  | 6.101 | 4.666   | 13.355 | 453.559 |
| 19       | Ph           | H             | 7.292 | 7.037 | 0.255  | 0.595   | 6.697 | 5.607   | 12.522 | 424.517 |
| 20       | 3-Pyridyl    | H             | 6.013 | 5.549 | 0.465  | 0.527   | 5.486 | 4.672   | 12.680 | 440.520 |
| 21       | 2-OMe-3-Pyridyl | H             | 6.155 | 6.115 | 0.040  | 0.066   | 6.089 | 5.520   | 13.297 | 470.546 |
| 22       | 4-Pyridyl    | H             | 5.699 | 5.549 | 0.150  | 0.171   | 5.528 | 4.672   | 12.680 | 440.520 |
| 23       | 2-OMe-Pyrimidin-5-yl | H         | 4.903 | 5.104 | −0.201 | −0.296  | 5.199 | 5.011   | 13.086 | 471.534 |

<sup>a</sup> Considered as outlier.

**TABLE 11.28** Biological Activity and Physicochemical Parameters of a Series of N-(benzo[1,2,3]triazol-1-yl)-N-(benzyl) acetamido) phenyl) carboxamides as SARS-CoV 3CL<sup>pro</sup> Inhibitors for QSAR Model [Eq. (11.27)] (cont.)
adjustment of such parameters, compounds 19–22 of Table 11.28 were found to have higher activity.

\[
pIC_{50} = 12.976(\pm 1.456) - 4.268(\pm 0.773)C\text{Log}P + 0.520(\pm 0.089)C\text{Log }P^2 + 1.681(\pm 0.279)CMR - 0.045(\pm 0.007)MW
\]

(11.27)

\[N = 21, R = 0.941, R^2 = 0.885, R^2_\text{A} = 0.857, F(4, 16) = 30.898, P < 0.00000, \text{SEE} = 0.228, q^2 = 0.799, Q = 4.127, \text{C log } P_{\text{Opt}} = 4.104, \text{Outlier = Compounds 5, 15}\]

### 7.1.28 Tripeptidyl Transition State Norwalk Virus 3C-Like Protease Inhibitors

A QSAR model obtained [Eq. (11.28)] for some tripeptidyl transition state Norwalk virus 3C-like protease inhibitors (Table 11.29) reported by Prior et al. (2013) suggested that the PSA of the molecules will control their activity and that a \(-\text{CHO}\) group at their X-position, for which an indicator parameter “I” was used, will have an added advantage. While the PSA may affect the activity due to a polar interaction of the molecule, the \(-\text{CHO}\) group might be involved in some hydrogen bond interactions with some residue of the active site.

\[
pIC_{50} = 1.825(\pm 0.582) + 0.023(\pm 0.003)\text{PSA} + 1.614(\pm 0.189)I
\]

(11.28)

\[N = 8, R = 0.972, R^2 = 0.944, R^2_\text{A} = 0.921, F(2, 5) = 42.078, P < 0.00074, \text{SEE} = 0.236, q^2 = 0.742, Q = 4.119\]

### 7.1.29 5-Sulfonyl Isatin Derivatives as Promising SARS-CoV 3CLpro Inhibitors

Liu et al. (2014) reported a series of 5-sulfonyl isatin derivatives as potent SARS-CoV 3CL protease inhibitors (Table 11.30), for which the QSAR model was as shown by Eq. (11.29).

\[
pIC_{50} = 9.333(\pm 1.030) + 0.376(\pm 0.079)C\text{Log }P - 3.002(\pm 0.537)D_{\text{Tot}} + 0.379(\pm 0.064)D_{\text{Tot}}^2 - 1.047(\pm 0.244)I
\]

(11.29)

\[N = 21, R = 0.894, R^2 = 0.800, R^2_\text{A} = 0.750, F(4, 16) = 15.999, P < 0.00002, \text{SEE} = 0.307, q^2 = 0.655, Q = 2.912, D_{\text{Tot (opt)}} = 3.960, \text{Outlier = Compounds 5, 8, 16, 18}\]

It was observed from Eq. (11.29) that increasing value of hydrophobicity may be favorable for the activity and that the moderate dipole moment of the compound will also be conducive to the inhibition of the enzyme. However, a negative value of the indicator variable “I”, which was used with a value of 1 for compounds having a \(\beta\)-napthylmethyl function at R1-position, indicated
TABLE 11.29 Biological Activity and Physicochemical Parameters of Tripeptidyl Transition State Norwalk Virus 3C-like Protease Inhibitors for QSAR Model [Eq. (11.28)]

| Compound | R        | X            | Obsd | Calcd | Res  | Del res | Pred     | PSA       | I  |
|----------|----------|--------------|------|-------|------|---------|----------|-----------|----|
| 1        | Ph       | CHO          | 6.678| 6.898 | −0.220| −0.284  | 6.962    | 153.457   | 1  |
| 2        | (S)-α-Napthyl | CHO         | 6.854| 6.789 | 0.065| 0.082  | 6.772    | 148.629   | 1  |
| 3        | (R)-α-Napthyl | CHO          | 6.155| 5.822 | 0.333| 0.647  | 5.508    | 105.728   | 1  |
| 4        | (S)-β-Napthyl | CHO          | 6.824| 6.898 | −0.074| −0.096 | 6.920    | 153.477   | 1  |
| 5        | (S)-Biph   | CHO          | 6.745| 6.848 | −0.103| −0.131 | 6.876    | 151.233   | 1  |
| 6        | (S)-α-Napthyl | COONH-i-Pr  | 5.585| 5.656 | −0.071| −0.107 | 5.692    | 169.965   | 0  |
| 7        | (S)-α-Napthyl | CH(OH)SO₃Na | 6.620| 6.372 | 0.248| 0.641  | 5.979    | 201.709   | 0  |
| 8        | (S)-α-Napthyl | CH(OH)P(OiOEt)₂ | 4.450| 4.627 | −0.177| −0.569 | 5.019    | 124.302   | 0  |
### TABLE 11.30 Biological Activity and Physicochemical Parameters of 5-Sulfonyl Isatin Derivatives as Promising SARS-CoV 3CLpro Inhibitors for QSAR Model [Eq. (11.29)]

![Chemical Structure of 5-Sulfonyl Isatin Derivatives](image)

| Compound | R<sub>1</sub> | R<sub>2</sub>                              | Obsd   | Calcd  | Res    | Del res | Pred   | C Log P | D<sub>Tot</sub> | I  |
|----------|-------------|------------------------------------------|--------|--------|--------|---------|--------|---------|---------------|----|
| 1        | H           | 4-Me-Piperazine                           | 4.115  | 4.836  | -0.721 | -0.829  | 4.944  | 0.530   | 5.641         | 0  |
| 2        | H           | 3-ClBnz-Piperazine                        | 4.499  | 4.860  | -0.361 | -0.402  | 4.901  | 2.252   | 2.880         | 0  |
| 3        | H           | 3,4,5-triOMeBnz-Piperazine                | 4.494  | 4.836  | -0.342 | -0.380  | 4.874  | 1.552   | 5.150         | 0  |
| 4        | H           | 4-Phenethyl-piperazine                    | 4.457  | 4.917  | -0.460 | -0.519  | 4.976  | 2.508   | 2.909         | 0  |
| 5<sup>a</sup> | H            | (Furan-2-carbonyl)-piperazine             | 4.997  | 5.301  | -0.304 | -0.982  | 5.979  | 0.311   | 1.277         | 0  |
| 6        | H           | 2-Pyridyl-(4-piperazine)                  | 4.290  | 4.445  | -0.156 | -0.182  | 4.472  | 1.013   | 3.230         | 0  |
| 7        | H           | Piperidine                                | 5.352  | 5.164  | 0.187  | 0.217   | 5.135  | 1.216   | 5.866         | 0  |
| 8<sup>a</sup> | H            | Morpholine                               | 4.898  | 4.519  | 0.379  | 0.463   | 4.435  | -0.031  | 5.346         | 0  |
| 9        | H           | 4-Me-Piperidine                           | 5.928  | 5.282  | 0.646  | 0.752   | 5.176  | 1.735   | 5.839         | 0  |
| 10       | H           | 2-Me-Piperidine                           | 5.648  | 5.294  | 0.354  | 0.413   | 5.235  | 1.735   | 5.857         | 0  |

(Continued)
### TABLE 11.30 Biological Activity and Physicochemical Parameters of 5-Sulfonyl Isatin Derivatives as Promising SARS-CoV 3CL\textsuperscript{pro} Inhibitors for QSAR Model [Eq. (11.29)] (cont.)

| Compound | R\textsubscript{1} | R\textsubscript{2} | Obsd  | Calcd | Res   | Del res | Pred   | C Log P | \(D_{\text{tot}}\) | I |
|----------|------------------|------------------|-------|-------|-------|---------|--------|---------|-----------------|---|
| 11       | H                | 3,5-diMe-Piperidine | 5.367 | 5.409 | −0.042 | −0.051  | 5.417  | 2.254  | 5.827           | 0 |
| 12       | Me               | 4-Me-Piperazine   | 4.927 | 4.724 | 0.203  | 0.251   | 4.676  | 0.585  | 2.191           | 0 |
| 13       | Bnz              | 4-Me-Piperazine   | 4.173 | 4.768 | −0.595 | −0.690  | 4.862  | 2.353  | 3.395           | 0 |
| 14       | β-NapthylCH\textsubscript{2} | 4-Me-Piperazine | 4.081 | 4.758 | −0.677 | −0.834  | 4.915  | 3.527  | 5.326           | 1 |
| 15       | β-NapthylCH\textsubscript{2} | 4-Phenethyl-piperazine | 4.858 | 4.922 | −0.064 | −0.084  | 4.942  | 5.505  | 3.322           | 1 |
| 16\textsuperscript{a} | β-NapthylCH\textsubscript{2} | 2-Pyridyl-(4-piperazine) | 5.258 | 4.520 | 0.738  | 0.933   | 4.325  | 4.010  | 3.398           | 1 |
| 17       | β-NapthylCH\textsubscript{2} | Piperidine | 4.854 | 4.929 | −0.075 | −0.095  | 4.949  | 4.213  | 2.309           | 1 |
| 18\textsuperscript{a} | Me               | Morpholine       | 5.004 | 4.147 | 0.857  | 1.167   | 3.837  | 0.024  | 3.492           | 0 |
| 19       | Bnz              | Morpholine       | 4.858 | 4.989 | −0.131 | −0.145  | 5.004  | 1.792  | 5.334           | 0 |
| 20       | β-NapthylCH\textsubscript{2} | Morpholine | 4.399 | 4.617 | −0.218 | −0.282  | 4.681  | 2.966  | 5.337           | 1 |
| 21       | Bnz              | 4-Me-Piperazine   | 5.983 | 5.392 | 0.591  | 0.752   | 5.231  | 3.558  | 2.403           | 0 |
| 22       | β-NapthylCH\textsubscript{2} | 4-Me-Piperazine | 5.772 | 5.660 | 0.112  | 0.181   | 5.592  | 4.732  | 6.204           | 1 |
| 23       | Me               | 4-Me-Piperazine   | 4.749 | 4.900 | −0.151 | −0.167  | 4.916  | 1.790  | 2.466           | 0 |
| 24       | Bnz              | 3,5-diMe-Piperidine | 5.550 | 5.504 | 0.046  | 0.064   | 5.485  | 4.077  | 2.452           | 0 |
| 25       | β-NapthylCH\textsubscript{2} | 3,5-diMe-Piperidine | 5.328 | 5.144 | 0.184  | 0.234   | 5.094  | 5.251  | 2.424           | 1 |

\textsuperscript{a}Considered as outlier.
that such a substituent would not be preferred, probably such a substituent might create steric hindrance in the interaction of the compounds with the receptor.

### 7.1.30 Some Substituted Pyrazoles and Substituted Pyrimidines as SARS-CoV 3CL\textsuperscript{pro} Inhibitors

Mohamed et al. (2015) recently reported some substituted pyrazoles and substituted pyrimidines as promising SARS-CoV 3CL\textsuperscript{pro} inhibitors (Fig. 11.11; Table 11.31). The QSAR model [Eq. (11.30)] obtained for these compounds simply suggested that highly polar fraction of the molecule with the high value of its $X$-component of dipole moment ($D_X$) will not be conducive to the activity.

\[
\text{pIC}_{50} = 6.437 (\pm 0.052) - 0.162 (\pm 0.036) D_X
\]  

(11.30)

$N = 8$, $R = 0.881$, $R^2 = 0.776$, $R^2_A = 0.739$, $F (1, 6) = 20.776$, $P < 0.00386$, $\text{SEE} = 0.139$, $q^2 = 0.657$, $Q = 6.338$, Outlier = Compounds 1, 2, 5, 12

### 7.1.31 Dipeptidyl Norovirus 3CL\textsuperscript{pro} Inhibitors

Galasiti et al. (2015) recently reported a series of dipeptidyl norovirus 3CL\textsuperscript{pro} inhibitors having potent inhibitory activity (Table 11.32). The QSAR model obtained for these inhibitors was as shown by Eq. (11.31). This equation simply suggested that while the $z$-component of the dipole moment will be favorable to the activity, its moderate PSA will have an adverse effect.

\[
\text{pIC}_{50} = 6.437 (\pm 0.052) - 0.162 (\pm 0.036) D_X
\]  

R $A^2 = 0.739$

\[
\text{FIGURE 11.11} \quad \text{General structure of substituted pyrazoles and substituted pyrimidines.}
\]
**TABLE 11.31 Biological Activity and Physicochemical Parameters of Some Substituted Pyrazoles and Substituted Pyrimidines as SARS-CoV 3CL<sub>pro</sub> Inhibitors (Fig. 11.8) for QSAR Model [Eq. (11.30)]**

| Compound | Obsd | Calcd | Res | Del res | Pred | $D_X$
|----------|------|-------|-----|---------|------|--------|
| 1<sup>a</sup> | 6.009 | 6.357 | −0.348 | −0.382 | 6.391 | 0.582 |
| 2<sup>a</sup> | 6.745 | 6.320 | 0.425 | 0.475 | 6.269 | 0.928 |
| 3 | 6.229 | 6.232 | −0.003 | −0.004 | 6.233 | 1.757 |
| 4 | 6.155 | 6.344 | −0.189 | −0.208 | 6.363 | 0.704 |
| 5<sup>a</sup> | 6.161 | 6.628 | −0.467 | −0.672 | 6.833 | −1.977 |
| 6 | 6.244 | 6.365 | −0.121 | −0.132 | 6.376 | 0.504 |
| 7 | 6.420 | 6.468 | −0.048 | −0.054 | 6.474 | −0.470 |
| 8 | 6.347 | 6.383 | −0.036 | −0.040 | 6.386 | 0.333 |
| 9 | 6.018 | 6.120 | −0.103 | −0.169 | 6.187 | 2.811 |
| 10 | 6.854 | 6.650 | 0.203 | 0.313 | 6.541 | −2.190 |
| 11 | 6.638 | 6.398 | 0.240 | 0.262 | 6.376 | 0.189 |
| 12<sup>a</sup> | 6.921 | 6.475 | 0.446 | 0.501 | 6.420 | −0.533 |

N<sup>a</sup>Considered as outliers.

\[
pIC_{50} = 19.197 (±2.508) + 0.105 (±0.036) D_Z + 0.002 (±0.001) D^2_Z - 0.165 (±0.032) PSA + 0.001 (±0.000) PSA^2
\]  

(11.31)

\[N = 23, \ R = 0.870, \ R^2 = 0.757, \ R^2_\lambda = 0.703, \ F (4, 18) = 14.036, \ P < 0.00002, \ SEE = 0.269, \ q^2 = 0.636, \ Q = 3.234, \ D_{\text{Zopt}} = -26.25, \ PSA_{\text{opt}} = 82.5, \text{ Outlier } = \text{ Compounds 3, 5, 14} \]

7.1.32 Peptidomimetic Bat Coronavirus HKU4 3CL<sub>pro</sub> Inhibitors

St. John et al. (2015) reported a series of peptidomimetic bat coronavirus HKU4 3CL<sub>pro</sub> inhibitors (Table 11.33), for which the QSAR model obtained [Eq. (11.32)] suggested that molecules should have an optimum lipophilicity value for imparting the higher activity.

\[
pIC_{50} = 3.401 (±0.540) + 1.030 (±0.290) C \ Log P - 0.108 (±0.037) C \ Log P^2 + 0.074 (±0.012) D_X + 0.014 (±0.002) PSA - 0.009 (±0.002) PolVol
\]  

(11.32)

\[N = 38, \ R = 0.907, \ R^2 = 0.822, \ R^2_\lambda = 0.795, \ F (5, 32) = 29.620, \ P < 0.00000, \ SEE = 0.238, \ q^2 = 0.745, \ Q = 3.811, \ C \ Log P_{\text{opt}} = 4.769, \text{ Outlier } = \text{ Compounds 20–22, 25, 35.} \]

The activity may be further supported by the $X$-component of the dipole moment and the PSA of the molecule. Notwithstanding, the high polar volume of the molecule will be delirious to the activity.
### TABLE 11.32 Biological Activity and Physicochemical Parameters of Dipeptidyl Norovirus 3CL\(_{pro}\) Inhibitors for QSAR Model [Eq. (11.31)]

![Chemical structure](image)

| Compound | \(R_1\)     | \(R_2\)     | \(X\)     | Obsd | Calcd | Res   | Del res | Pred | \(D_Z\) | PSA  |
|----------|-------------|-------------|-----------|------|-------|-------|---------|------|---------|------|
| 1        | (c-Hex)\(\text{CH}_2\) | \(\alpha\)-Cl | CHO       | 6.097| 6.381 | −0.284| −0.326 | 6.423| −1.786  | 121.901|
| 2        | (c-Hex)\(\text{CH}_2\) | \(\alpha\)-Cl | \(\text{CH(OH)}\text{SO}_3\text{Na}\) | 6.155| 6.524 | −0.369| −0.449 | 6.604| −64.476 | 152.366|
| 3\(^a\)  | (c-Hex)\(\text{CH}_2\) | \(m\)-Cl      | CHO       | 7.000| 6.260 | 0.740 | 0.834  | 6.166| −2.721  | 121.894|
| 4        | (c-Hex)\(\text{CH}_2\) | \(m\)-Cl      | \(\text{CH(OH)}\text{SO}_3\text{Na}\) | 7.000| 6.678 | 0.322 | 0.401  | 6.599| −65.412 | 152.335|
| 5\(^a\)  | (c-Hex)\(\text{CH}_2\) | \(m\)-Cl      | COCONH-c-Pr| 6.602| 5.767 | 0.835 | 1.068  | 5.534| −1.938  | 184.498|
| 6        | c-Hex       | \(m\)-Cl      | CHO       | 5.292| 5.547 | −0.255| −0.289 | 5.582| −2.687  | 144.957|
| 7        | \(i\)-Butyl | \(m\)-Cl      | CHO       | 6.046| 5.995 | 0.050 | 0.061  | 5.985| 0.903   | 147.129|
| 8        | \(i\)-Butyl | \(m\)-Cl      | COCONH-c-Pr| 5.260| 5.496 | −0.237| −0.275 | 5.534| −2.592  | 148.775|
| 9        | (c-Hex)\(\text{CH}_2\) | \(p\)-Cl      | CHO       | 6.149| 6.122 | 0.027 | 0.030  | 6.119| −3.833  | 121.895|

*(Continued)*
### TABLE 11.32 Biological Activity and Physicochemical Parameters of Dipeptidyl Norovirus 3CL<sup>pro</sup> Inhibitors for QSAR Model

[Eq. (11.31)] (cont.)

| Compound | R<sub>1</sub> | R<sub>2</sub> | X            | Obsd  | Calcd | Res   | Del res | Pred | D<sub>Z</sub> | PSA    |
|----------|-------------|-------------|--------------|-------|-------|-------|---------|------|-------------|--------|
| 10       | (c-Hex)CH₂  | o-F         | CHO          | 6.046 | 6.474 | −0.428| −0.509  | 6.554| −1.085     | 121.894|
| 11       | (c-Hex)CH₂  | m-F         | CHO          | 5.921 | 6.277 | −0.356| −0.402  | 6.323| −2.592     | 121.894|
| 12       | (c-Hex)CH₂  | m-F         | COCONH-c-Pr  | 5.456 | 5.635 | −0.179| −0.198  | 5.654| −2.663     | 140.867|
| 13       | (c-Hex)CH₂  | m-Br        | CHO          | 6.523 | 6.258 | 0.265 | 0.299   | 6.224| −2.739     | 121.893|
| 14<sup>a</sup> | (c-Hex)CH₂ | m-Br        | CH(OH)(O)(OEt)₂ | 5.187 | 5.648 | −0.461| −0.556  | 5.743| −5.135     | 130.026|
| 15       | (c-Hex)CH₂  | m-Br        | CH(OH)SO₃Na  | 6.824 | 6.681 | 0.143 | 0.178   | 6.646| −65.428    | 152.344|
| 16       | (c-Hex)CH₂  | m-Br        | COCONH-c-Pr  | 5.824 | 5.616 | 0.208 | 0.231   | 5.592| −2.809     | 140.890|
| 17       | (c-Hex)CH₂  | m-I         | CHO          | 6.456 | 6.258 | 0.198 | 0.223   | 6.233| −2.740     | 121.891|
| 18       | (c-Hex)CH₂  | m-I         | CH(OH)SO₃Na  | 6.824 | 6.681 | 0.143 | 0.178   | 6.645| −65.428    | 152.355|
| 19       | (c-Hex)CH₂  | m-OMe       | CHO          | 5.854 | 5.560 | 0.294 | 0.343   | 5.511| −4.235     | 136.191|
| 20       | (c-Hex)CH₂  | m-NHBOc     | CHO          | 5.347 | 5.720 | −0.373| −0.457  | 5.803| −0.205     | 161.925|
| 21       | (c-Hex)CH₂  | m-NO₂       | CHO          | 6.222 | 6.569 | −0.347| −1.243  | 7.465| −4.328     | 212.100|
| 22       | i-Butyl     | H           | CHO          | 6.222 | 6.125 | 0.097 | 0.129   | 6.093| 1.790      | 147.121|
| 23       | i-Butyl     | H           | CH(OH)SO₃Na  | 6.097 | 6.023 | 0.073 | 0.190   | 5.907| −55.699    | 199.888|
| 24       | i-Butyl     | H           | COCONH-c-Pr  | 5.469 | 5.552 | −0.083| −0.095  | 5.564| −2.016     | 150.177|
| 25       | (c-Hex)CH₂  | H           | CHO          | 6.523 | 6.245 | 0.278 | 0.314   | 6.209| −2.848     | 121.888|
| 26       | (c-Hex)CH₂  | H           | CH(OH)SO₃Na  | 6.398 | 6.698 | −0.300| −0.376  | 6.774| −65.535    | 152.353|

<sup>a</sup> Considered as outliers.
| Compound | R₁ | R₂ | R₃ | R₄ | Obsd | Calcd | Res | Del res | Pred | C Log P | Dₓ | PSA | Pol Vol |
|----------|----|----|----|----|------|-------|-----|---------|------|---------|----|-----|--------|
| 1        | 3-Thienyl | NHCO-(3-thienyl) | (2-Benzotriazolyl)methyl | —   | 6.481 | 6.327 | 0.154 | 0.195   | 6.286 | 4.065   | 6.553 | 237.419 | 302.836 |
| 2        | 3-Thienyl | NHCOPh | (2-Benzotriazolyl)methyl | —   | 6.387 | 5.987 | 0.400 | 0.451   | 5.936 | 4.227   | 6.409 | 194.671 | 291.571 |
| 3        | 3-Thienyl | NHCO-c-but | (2-Benzotriazolyl)methyl | —   | 5.921 | 5.657 | 0.264 | 0.280   | 5.641 | 3.651   | 3.217 | 187.416 | 288.775 |
| 4        | 3-Thienyl | NHCO-c-Pent | (2-Benzotriazolyl)methyl | —   | 5.921 | 6.005 | −0.084 | −0.097  | 6.018 | 4.769   | 6.487 | 179.306 | 266.098 |
| 5        | 3-Thienyl | 4-Pyr | (2-Benzotriazolyl)methyl | —   | 5.824 | 5.854 | −0.030 | −0.034  | 5.857 | 3.474   | 4.957 | 220.355 | 317.406 |
| 6        | 3-Thienyl | NHCO-ᵢ-Pr | (2-Benzotriazolyl)methyl | —   | 5.796 | 5.580 | 0.216 | 0.232   | 5.564 | 3.576   | −1.272 | 184.840 | 252.498 |

(Continued)
| Compound | R<sub>1</sub> | R<sub>2</sub> | R<sub>3</sub> | R<sub>4</sub> | Obsd | Calcd | Res | Del res | Pred | C Log P | DX | PSA | Pol Vol |
|----------|--------------|--------------|--------------|------------|------|-------|-----|--------|------|--------|-----|------|-------|
| 7        | 3-Thienyl    | (2-OMe-Pyr)-3-yl | (2-Benzotriazolyl)methyl | —          | 5.770 | 6.032 | −0.263 | −0.303 | 6.073 | 4.210 | 7.061 | 211.031 | 316.028 |
| 8        | 3-Thienyl    | NHCO-c-Pr    | (2-Benzotriazolyl)methyl | —          | 5.721 | 5.432 | 0.289  | 0.304  | 5.417 | 3.322 | −1.281 | 191.518 | 274.817 |
| 9        | 3-Thienyl    | (2-OMe-Pyr)-5-yl | (2-Benzotriazolyl)methyl | —          | 5.699 | 5.698 | 0.001  | 0.001  | 5.698 | 3.624 | 4.380  | 233.228 | 364.577 |
| 10       | 3-Thienyl    | NHCOCF<sub>3</sub> | (2-Benzotriazolyl)methyl | —          | 5.658 | 5.718 | −0.060 | −0.077 | 5.734 | 3.847 | −3.437 | 195.593 | 237.299 |
| 11       | 3-Thienyl    | 3-Pyr        | (2-Benzotriazolyl)methyl | —          | 5.620 | 5.885 | −0.265 | −0.298 | 5.918 | 3.474 | 5.735  | 220.889 | 320.479 |
| 12       | 3-Thienyl    | NHCOO-i-butyl | (2-Benzotriazolyl)methyl | —          | 5.553 | 5.581 | −0.028 | −0.032 | 5.585 | 4.645 | −2.550 | 186.127 | 263.229 |
| 13       | 3-Thienyl    | NHCOEt       | (2-Benzotriazolyl)methyl | —          | 5.509 | 5.467 | 0.041  | 0.044  | 5.465 | 3.267 | −1.133 | 185.781 | 256.440 |
| 14       | 3-Thienyl    | NHCOCH<sub>2</sub>OMe | (2-Benzotriazolyl)methyl | —          | 5.428 | 5.243 | 0.189  | 0.206  | 5.226 | 2.862 | −2.343 | 196.610 | 274.182 |
| 15       | 3-Thienyl    | NHMe         | (2-Benzotriazolyl)methyl | —          | 5.319 | 5.329 | −0.011 | −0.011 | 5.330 | 3.218 | −2.694 | 156.296 | 216.523 |
| 16       | 3-Thienyl    | NHCH<sub>2</sub>Ph | (2-Benzotriazolyl)methyl | —          | 5.276 | 5.440 | −0.165 | −0.181 | 5.457 | 4.666 | −2.698 | 155.649 | 236.128 |
| 17       | 3-Thienyl    | NHCH<sub>2</sub>F | (2-Benzotriazolyl)methyl | —          | 5.564 | 5.180 | −0.124 | −0.135 | 5.190 | 3.975 | −3.963 | 155.121 | 259.023 |
| 18       | 3-Thienyl    | NHCO-t-butyl | (2-Benzotriazolyl)methyl | —          | 5.056 | 5.151 | 0.097  | 0.110  | 5.167 | 3.250 | −4.660 | 165.375 | 263.429 |
| 19       | 3-Thienyl    | NHCO-i-Pr    | (1,2,3-Triazole)1-yl | —          | 4.796 | 4.709 | 0.087  | 0.130  | 4.666 | 1.982 | −1.272 | 165.375 | 238.400 |
| 20<sup>a</sup> | t-Butyl | t-Butyl     | (1-Me-imidazole)-4-yl | 3-Pyr | 5.886 | 4.965 | 0.921  | 1.120  | 4.766 | 3.604 | −0.676 | 71.112 | 178.341 |
| 21<sup>a</sup> | Benzyl | NHCO-i-Pr | (2-Benzotriazolyl)methyl | 3-FPh | 5.824 | 5.112 | 0.712  | 0.818  | 5.006 | 5.114 | −3.858 | 123.131 | 220.187 |
| 22<sup>a</sup> | t-Butyl | NHCOMe     | (2-Benzotriazolyl)methyl | 3-Thienyl | 5.745 | 4.926 | 0.819  | 0.913  | 4.832 | 3.135 | −4.596 | 175.901 | 290.678 |
| 23<sup>a</sup> | t-Butyl | 2-CNPh     | 2-Furyl | 3-Pyr | 5.658 | 5.407 | 0.251  | 0.281  | 5.377 | 4.147 | −1.284 | 93.556 | 152.746 |
|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 24 | t-Butyl | t-Butyl | (2-Indolyl)methyl | 3-Pyr | 5.658 | 5.256 | 0.402 | 0.488 | 5.169 | 5.466 | −0.015 | 67.832 | 132.826 |
| 25a | t-Butyl | NHCO-c-Pr | (2-Benzotriazolyl)methyl | 3-Thienyl | 5.569 | 5.142 | 0.427 | 0.486 | 5.082 | 3.719 | −1.920 | 189.368 | 330.556 |
| 26 | Benzyl | NHCO-c-butyl | (2-Benzotriazolyl)methyl | 3-FPh | 5.469 | 5.463 | 0.005 | 0.007 | 5.461 | 5.189 | 6.476 | 138.478 | 281.050 |
| 27 | t-Butyl | OCH$_2$F | (2-Indolyl)methyl | 3-Pyr | 5.409 | 5.452 | −0.043 | −0.050 | 5.459 | 3.732 | 0.712 | 84.008 | 137.546 |
| 28 | t-Butyl | NHCOPh | (2-Benzotriazolyl)methyl | 3-Thienyl | 5.377 | 5.268 | 0.108 | 0.138 | 5.239 | 4.624 | 2.529 | 170.484 | 336.095 |
| 29 | t-Butyl | i-Pr | (2-Benzotriazolyl)methyl | 3-Pyr | 5.161 | 5.406 | −0.245 | −0.286 | 5.447 | 5.067 | −0.043 | 67.838 | 120.946 |
| 30 | Benzyl | NHCO-c-Pr | (2-Benzotriazolyl)methyl | 3-FPh | 5.155 | 5.449 | −0.294 | −0.318 | 5.473 | 4.860 | −1.115 | 156.448 | 248.714 |
| 31 | t-Butyl | t-butyl | (2-Oxazo-5-yl)methyl | 3-Pyr | 5.066 | 5.048 | 0.018 | 0.020 | 5.045 | 3.155 | −0.616 | 83.224 | 161.469 |
| 32 | t-Butyl | t-butyl | (2-Imidazo-4-yl)methyl | 3-Pyr | 5.032 | 5.386 | −0.354 | −0.393 | 5.424 | 3.305 | 1.332 | 110.996 | 177.477 |
| 33 | t-Butyl | Me | 2-Furyl | 3-Pyr | 5.022 | 5.203 | −0.181 | −0.227 | 5.249 | 3.949 | 0.627 | 47.293 | 125.546 |
| 34 | t-Butyl | t-Butyl | (2-Imidazo-4-yl)methyl | 3-Pyr | 4.955 | 5.192 | −0.238 | −0.262 | 5.217 | 3.305 | −1.670 | 99.248 | 162.438 |
| 35a | t-Butyl | NHCO(2-benzotri) | (2-Benzotriazolyl)methyl | 3-Thienyl | 4.833 | 5.512 | −0.680 | −0.751 | 5.584 | 3.410 | 1.015 | 237.356 | 360.408 |
| 36 | t-Butyl | t-Butyl | (2-Imidazo-4-yl)methyl | 2-Pyrim-5-y | 4.812 | 4.817 | −0.004 | −0.005 | 4.817 | 2.348 | −2.326 | 122.867 | 182.158 |
| 37 | t-Butyl | NHCO-i-Pr | (2-Benzotriazolyl)methyl | 3-Thienyl | 4.764 | 5.072 | −0.307 | −0.345 | 5.110 | 3.973 | −4.585 | 159.577 | 277.847 |
| 38 | t-Butyl | NHCOEt | (2-Benzotriazolyl)methyl | 3-Thienyl | 4.728 | 4.634 | −0.379 | −0.497 | 5.075 | 2.198 | −3.235 | 194.693 | 295.576 |
| 39 | t-Butyl | NHCOMe | 2-Furyl | 3-Pyr | 4.449 | 4.699 | −0.251 | −0.524 | 4.972 | 6.149 | −1.580 | 35.972 | 119.956 |
| 40 | t-Butyl | NH$_2$ | (2-Benzotriazolyl)methyl | 3-FPh | 4.281 | 4.940 | −0.658 | −0.770 | 5.052 | 4.161 | −3.325 | 125.993 | 261.488 |
| 41 | t-Butyl | t-butyl | 2-Furyl | 3-Pyr | 4.255 | 4.634 | −0.379 | −0.497 | 4.752 | 2.198 | −1.272 | 106.846 | 180.953 |

*aConsidered as outliers.*
7.1.33 Substituted Furan Analogs as Promising SARS CoV 3C\textsuperscript{pro} Inhibitors

Kumar et al. (2016) recently reported a series of substituted furan analogs as promising SARS-CoV 3C\textsuperscript{pro} inhibitors (Table 11.34). The QSAR model obtained for these compounds was as shown by Eq. (11.33)

\[
pIC_{50} = 4.555 (\pm 0.067) + 0.522 (\pm 0.141) I_1 + 0.597 (\pm 0.141) I_2 \tag{11.33}
\]

\(N = 11, \ R = 0.874, \ R^2 = 0.763, \ R^2_\Delta = 0.704, \ F (2, 8) = 12.907, \ P < 0.00313, \ SEE = 0.176, \ q^2 = 0.536, \ Q = 4.966, \) Outlier = Compound 6.

**TABLE 11.34 Biological Activity and Physicochemical Parameters of Substituted Furan Analogs as Promising SARS CoV 3C\textsuperscript{pro} Inhibitors for QSAR Model [Eq. (11.33)]**

| Compound | R\textsubscript{1} | R\textsubscript{2} | R\textsubscript{3} | Obsd | Calcd | Res | Del res | Pred | I\textsubscript{1} | I\textsubscript{2} |
|----------|----------------|----------------|----------------|------|------|-----|--------|------|------|------|
| 1        | COOH | Cl | 3-COOH | 4.350 | 4.634 | −0.285 | −0.325 | 4.675 | 0 | 0 |
| 2        | COOH | Cl | H | 4.785 | 4.634 | 0.151 | 0.172 | 4.613 | 0 | 0 |
| 3        | COOH | Cl | 4-F | 4.695 | 4.634 | 0.060 | 0.069 | 4.626 | 0 | 0 |
| 4        | COOH | Cl | 4-i-Pr | 5.222 | 5.077 | 0.145 | 0.290 | 4.932 | 1 | 0 |
| 5        | COOH | Cl | 4-t-But | 5.237 | 5.151 | 0.086 | 0.171 | 5.066 | 0 | 1 |
| 6\textsuperscript{a} | H | H | 3-COOH | 5.194 | 4.634 | 0.559 | 0.639 | 4.555 | 0 | 0 |
| 7        | COOH | H | H | 4.385 | 4.634 | −0.249 | −0.285 | 4.670 | 0 | 0 |
| 8        | COOH | H | 4-F | 4.426 | 4.634 | −0.208 | −0.238 | 4.664 | 0 | 0 |
| 9        | COOH | H | 4-i-Pr | 4.932 | 5.077 | −0.145 | −0.290 | 5.222 | 1 | 0 |
| 10       | COOH | H | 4-t-But | 5.066 | 5.151 | −0.086 | −0.171 | 5.237 | 0 | 1 |
| 11       | COOH | H | 4-CN | 4.728 | 4.634 | 0.094 | 0.107 | 4.621 | 0 | 0 |
| 12       | COOH | H | 4-OMe | 4.513 | 4.634 | −0.122 | −0.139 | 4.652 | 0 | 0 |

\textsuperscript{a}Considered as outlier.
Where the activity is shown to be correlated with two indicator variables, $I_1$ and $I_2$. $I_1$ and $I_2$, with a value of 1 each, indicate the presence of the $i$-propyl and the $t$-butyl moiety at $R_3$-position, respectively. The positive coefficients of both these parameters suggested that the $i$-propyl and the $t$-butyl functions at $R_3$-position will be favorable for inhibitory activity. Compound 6 behaved aberrantly and therefore it was considered as an outlier. It may be observed that the $t$-butyl substitution at $R_3$-position in compounds 5 and 10 gave better activity than the $i$-butyl substitution at the same position in compounds 4 and 9.

7.2 QSAR Model Development on Human Rhinovirus 3C\textsuperscript{pro} Inhibitors

7.2.1 A Series of Michael Acceptor Type HRV 3C\textsuperscript{pro} Inhibitors

Dragovich et al. (1998a) reported a series of Michael acceptor type potent HRV 3C\textsuperscript{pro} inhibitors (Fig. 11.12; Table 11.35), for which the QSAR model [Eq. (11.34)] exhibited that the positive effect on the activity of the compounds will be produced by the $Z$-component of the dipole moment and the SA of the compounds till it attains an optimum value. These two properties indicate the same kind of electronic interactions of the molecule with the receptor.

\[
pEC_{50} = -56.622 (\pm 19.902) + 0.423 (\pm 0.117) D_Z + 0.102 (\pm 0.021) D_Z^2 + 0.134 (\pm 0.041) SA - 0.0001 (\pm 0.00002) SA^2 - 0.018 (\pm 0.004) PolVol
\]

\[\text{Eq. (11.34)}\]

\[
N = 33, R = 0.841, R^2 = 0.708, R^2_x = 0.654, F (5, 27) = 13.087, P < 0.00000, \quad \text{SEE} = 0.411, \quad q^2 = 0.584, \quad Q = 2.046, \quad D_{Z\text{opt}} = -2.074, \quad SA_{\text{opt}} = 670, \quad \text{Outlier} = \text{Compounds 4, 9, 11, 15, 16, 18, 21, 23, 30, 34}
\]

**Figure 11.12** General structure of Michael acceptor type HRV 3C\textsuperscript{pro} inhibitors.
| Compound | X      | Y  | X | Y | Z | n | R   | Obsd | Calcd | Res  | Del res | Pred  | $D_Z$ | SA   | Pol Vol |
|----------|--------|----|---|---|---|---|-----|------|-------|------|---------|-------|-------|------|---------|
| 1        | COOMe  | H  | — | — | — | — | —   | 5.886| 5.268 | 0.618| 0.699   | 5.187 | 0.447 | 892.098 | 240.514 |
| 2        | H      | COOMe| — | — | — | — | —   | 5.495| 5.269 | 0.226| 0.258   | 5.237 | 0.501 | 889.632 | 239.189 |
| 3        | COOEt  | H  | — | — | — | — | —   | 6.268| 5.819 | 0.449| 0.599   | 5.668 | 1.733 | 919.558 | 252.873 |
| 4        | COOEt  | Me | — | — | — | — | —   | 5.523| 5.922 | −0.399| −0.523  | 6.046 | 1.697 | 925.084 | 241.339 |
| 5        | COO-c-Pent | H | — | — | — | — | —   | 6.252| 5.258 | 0.994| 1.075   | 5.177 | −0.640| 1019.220 | 263.005 |
| 6        | COO-c-Hex | H | — | — | — | — | —   | 5.495| 5.206 | 0.288| 0.313   | 5.182 | −0.667| 1004.590 | 259.677 |
| 7        | COOBnz  | H  | — | — | — | — | —   | 5.444| 5.322 | 0.122| 0.136   | 5.308 | −0.610| 1025.570 | 240.828 |
| 8        | COOCH$_2$-t-But | H | — | — | — | — | —   | 6.301| 5.633 | 0.668| 0.757   | 5.544 | 0.277 | 972.403 | 237.458 |
| 9        | CONMe$_2$ | H | — | — | — | — | —   | 4.252| 5.764 | −1.512| −1.750  | 6.002 | 0.314 | 932.597 | 206.888 |
| 10       | COPyrrolidine | H | — | — | — | — | —   | 4.658| 5.090 | −0.432| −0.457  | 5.114 | −2.650| 983.638 | 266.905 |
| 11       | CON(Me)Ph | H | — | — | — | — | —   | 3.801| 4.981 | −1.180| −1.258  | 5.059 | −2.564| 1025.570 | 263.713 |
| 12       | CO(Tetrahydroquinoline) | H | — | — | — | — | —   | 3.900| 4.573 | −0.673| −0.749  | 4.649 | −2.685| 1058.120 | 288.062 |
| 13       | CO(Indoline) | H | — | — | — | — | —   | 4.796| 4.564 | 0.232| 0.255   | 4.541 | −2.671| 1048.840 | 299.918 |
| 14       | CON(Me)OMe | H | — | — | — | — | —   | 5.398| 5.246 | 0.152| 0.160   | 5.238 | −1.033| 944.039 | 248.567 |
| 15       | CON(Me)OH | H | — | — | — | — | —   | 4.377| 5.268 | −0.892| −0.980  | 5.357 | 0.311 | 915.220 | 260.579 |
| 16       | C(O)oxazolidine | H | — | — | — | — | —   | 4.347| 5.246 | −0.899| −1.000  | 5.346 | −4.621| 971.546 | 280.447 |
| 17       | CO(1,2)Oxazinan | H | — | — | — | — | —   | 4.796| 4.997 | −0.201| −0.213  | 5.009 | −4.087| 989.697 | 298.674 |
| 18       | COPyrrole | H | — | — | — | — | —   | 5.854| 4.952 | 0.901| 0.964   | 4.890 | −2.527| 967.760 | 284.960 |
| 19       | COIndole | H | — | — | — | — | —   | 5.745| 4.837 | 0.907| 0.959   | 4.786 | −2.454| 1032.130 | 277.918 |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 20\textsuperscript{a} | COMe | H   | —   | —   | —   | —   | —   | —   | —   | —   | 5.699 | 5.118 | 0.581 | 0.773 | 4.926 | 0.619 | 870.192 | 236.384 |
| 21  | CO-\texttt{t}-Butyl | H   | —   | —   | —   | —   | —   | —   | —   | —   | 5.770 | 5.811 | -0.042 | -0.049 | 5.819 | 0.326 | 945.814 | 208.111 |
| 22  | COPh | H   | —   | —   | —   | —   | —   | —   | —   | —   | 5.398 | 5.160 | 0.238 | 0.255 | 5.143 | -2.434 | 985.661 | 256.507 |
| 23  | 4-OMeCOPh | H   | —   | —   | —   | —   | —   | —   | —   | —   | 4.658 | 5.147 | -0.489 | -0.582 | 5.240 | -2.980 | 1030.290 | 240.131 |
| 24  | 4-NO\textsubscript{2}COPh | H   | —   | —   | —   | —   | —   | —   | —   | —   | 4.495 | 4.660 | -0.165 | -0.183 | 4.678 | -4.312 | 1025.260 | 333.702 |
| 25\textsuperscript{a} | 4-CNCOPh | H   | —   | —   | —   | —   | —   | —   | —   | —   | 4.301 | 4.714 | -0.413 | -0.457 | 4.758 | -2.116 | 1021.670 | 302.664 |
| 26\textsuperscript{a} | CO-2-(1,3-Benzodioxole) | H   | —   | —   | —   | —   | —   | —   | —   | —   | 5.495 | 4.830 | 0.665 | 0.706 | 4.926 | 0.619 | 870.192 | 236.384 |
| 27  | CO-2-Furyl | H   | —   | —   | —   | —   | —   | —   | —   | —   | 5.620 | 5.317 | 0.303 | 0.320 | 5.300 | -0.875 | 962.609 | 248.127 |
| 28  | SO\textsubscript{2}Ph | H   | —   | —   | —   | —   | —   | —   | —   | —   | 3.699 | 4.439 | -0.740 | -1.075 | 4.774 | -3.287 | 1005.240 | 355.178 |
| 29  | CN  | H   | —   | —   | —   | —   | —   | —   | —   | —   | 4.745 | 4.971 | -0.161 | -0.183 | 4.678 | -4.312 | 1025.260 | 276.486 |
| 30  | 2-Oxopyrrolidine | H   | —   | —   | —   | —   | —   | —   | —   | —   | 6.051 | 5.354 | 0.697 | 0.799 | 5.252 | -5.150 | 982.770 | 283.742 |
| 31  | 2-Oxooxazolidine | H   | —   | —   | —   | —   | —   | —   | —   | —   | 5.796 | 5.369 | 0.427 | 0.514 | 5.282 | -6.068 | 968.853 | 321.802 |
| 32  | 3-Me-2-oxo-imidazolidine | H   | —   | —   | —   | —   | —   | —   | —   | —   | 5.301 | 4.939 | 0.362 | 0.410 | 4.891 | -5.335 | 1007.300 | 340.586 |
| 33  | —   | —   | —   | —   | —   | —   | —   | —   | —   | —   | 4.770 | 5.228 | -0.458 | -1.727 | 6.496 | -8.144 | 1088.210 | 380.953 |
| 34  | —   | —   | —   | —   | —   | —   | —   | —   | —   | —   | 4.959 | 4.645 | 0.314 | 0.347 | 4.612 | -3.694 | 1058.160 | 289.980 |
| 35  | —   | —   | H   | F   | —   | —   | —   | —   | —   | —   | 4.252 | 4.490 | -0.238 | -0.266 | 4.518 | -3.307 | 1060.860 | 301.647 |
| 36  | —   | —   | Cl  | H   | —   | —   | —   | —   | —   | —   | 5.252 | 4.531 | 0.721 | 0.859 | 4.393 | -3.370 | 1071.540 | 282.633 |
| 37  | —   | —   | H   | Cl  | —   | —   | —   | —   | —   | —   | 4.328 | 4.455 | -0.127 | -0.159 | 4.486 | -3.179 | 1077.580 | 281.707 |
| 38  | —   | —   | H   | Br  | —   | —   | —   | —   | —   | —   | 5.796 | 5.369 | 0.427 | 0.514 | 5.282 | -6.068 | 968.853 | 321.802 |
| 39  | —   | —   | —   | —   | O 1 | —   | —   | —   | —   | —   | 5.284 | 4.876 | 0.408 | 0.509 | 4.775 | -4.057 | 907.495 | 280.430 |
| 40\textsuperscript{a} | —   | —   | —   | —   | O 2 | —   | —   | —   | —   | —   | 4.796 | 5.025 | -0.229 | -0.260 | 5.056 | -3.775 | 930.567 | 273.891 |
| 41  | —   | —   | —   | N 1 | COMe | 6.149 | 5.364 | 0.785 | 0.912 | 5.236 | -5.619 | 969.035 | 301.375 |
| 42\textsuperscript{a} | —   | —   | —   | N 1 | COOMe | 4.553 | 4.683 | -0.132 | -0.156 | 4.709 | -3.719 | 990.921 | 333.132 |
| 43  | —   | —   | —   | N 1 | OMe | 4.745 | 5.195 | -0.450 | -0.506 | 5.250 | -5.047 | 954.961 | 298.399 |  \\

\textsuperscript{a} Considered as outlier.
7.2.2 A Series of Peptide-Derived HRV 3C\textsuperscript{pro} Inhibitors

Dragovich et al. (1998b) reported a series of peptide-derived potent HRV 3C\textsuperscript{pro} inhibitors (Table 11.36), the QSAR model [Eq. (11.35)] suggested that the activity would be primarily controlled by the hydrophobicity of the molecule. The polar volume and the total dipole moment of the compounds would also help to increase the activity of the compounds. “I” is an indicator parameter indicating the presence of \textit{i}-butyl moiety at R\textsubscript{3} position. Its negative coefficient suggested that \textit{i}-butyl function is not favorable at R\textsubscript{3}-position. This might be creating some steric problem.

\[
P_{\text{EC}_{50}} = 5.030 (\pm 0.717) + 0.549 (\pm 0.060) C \text{ Log } P - 0.076 (\pm 0.032) D_{T} \\
+ 0.160 (\pm 0.042) D_{\text{Tot}} - 0.007 (\pm 0.001) MW \\
+ 0.008 (\pm 0.001) \text{ PolVol} - 0.869 (\pm 0.109) I
\]  

\(N = 64, R = 0.858, R^2 = 0.736, R_A^2 = 0.708, F(6, 57) = 26.421, P < 0.00000,\) \(\text{SEE} = 0.361, q^2 = 0.648, Q = 2.377, \) Outlier = Compounds 5, 9, 11, 20, 25, 26, 40, 42, 51, 60, 69, 71, 73, 77

7.2.3 Ketomethylene Containing Peptide-Based HRV 3C\textsuperscript{pro} Inhibitors

Dragovich et al. (1999a) reported some ketomethylene group containing peptide-based HRV 3C\textsuperscript{pro} inhibitors (Table 11.37). The QSAR model obtained for them was as shown by Eq. (11.36):

\[
P_{\text{EC}_{50}} = 6.795 (\pm 0.154) - 0.154 (\pm 0.036) D_{T} - 0.434 (\pm 0.190) I_1 \\
+ 0.601 (\pm 0.196) I_2
\]  

\(N = 14, R = 0.927, R^2 = 0.859, R_A^2 = 0.816, F(3, 10) = 20.273, P < 0.00014,\) \(\text{SEE} = 0.266, q^2 = 0.727, Q = 3.485\)

It is observed from Eq. (11.36) that decreasing value of the dipole moment along \(Y\)-axis may increase the activity. This model also showed the importance of two indicator variables, \(I_1\) and \(I_2\), each of which was used with a value of unity \(i\)-butyl and the \(i\)-propyl substituent at R\textsubscript{2} position, respectively. The negative coefficient of \(I_1\) suggested that \(i\)-butyl group will not be conducive to the activity, while the positive coefficient of \(I_2\) suggested that \(i\)-propyl group would be favorable to the activity. These facts are observed from the \(i\)-butyl substituted compounds \textit{1–3} and \textit{5–7} and the \(i\)-propyl substituted compounds \textit{4, 8–11}.

7.2.4 Peptide-Based HRV 3C\textsuperscript{pro} Inhibitors

Dragovich et al. (1999b) reported some HRV 3C\textsuperscript{pro} inhibitors (Table 11.38). The QSAR model is shown in Eq. (11.37) obtained for them suggested that the high polarity of the compound in the \(X\)-direction will be detrimental to the inhibition potency of the compound. The simple structure–activity relationship study of
TABLE 11.36 Biological Activity and Physicochemical Parameters of a Series of Peptide-Derived HRV 3C<sup>pro</sup> Inhibitors for QSAR Model [Eq. (11.35)]

| Compound | R<sub>1</sub> | R<sub>2</sub> | R<sub>3</sub> | R<sub>4</sub> | Obsd | Calcd | Res | Del res | Pred | C Log P | D<sub>y</sub> | D<sub>tot</sub> | MW   | Pol Vol | I |
|----------|-------------|--------------|--------------|--------------|------|-------|-----|---------|------|---------|-------|-----------|------|--------|---|
| 1        | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | Bnz | i-But | Cbz | 6.268 | 5.643 | 0.625 | 0.644 | 5.623 | 4.402 | −0.526 | 2.710 | 594.698 | 413.706 | 1 |
| 2        | (CH<sub>2</sub>)<sub>2</sub>CONHTr | Bnz | i-But | Cbz | 4.000 | 4.542 | −0.542 | −1.136 | 5.136 | 6.581 | −1.113 | 1.932 | 825.002 | 330.906 | 1 |
| 3        | (CH<sub>2</sub>)<sub>2</sub>CONHMe | Bnz | i-But | Cbz | 5.252 | 5.273 | −0.021 | −0.023 | 5.275 | 4.582 | 2.135 | 2.543 | 608.725 | 398.617 | 1 |
| 4        | (CH<sub>2</sub>)<sub>2</sub>CONMe<sub>2</sub> | Bnz | i-But | Cbz | 5.398 | 5.323 | 0.075 | 0.083 | 5.315 | 4.954 | 2.531 | 3.027 | 622.752 | 389.226 | 1 |
| 5<sup>a</sup> | (CH<sub>2</sub>)<sub>2</sub>COOH | Bnz | i-But | Cbz | 4.854 | 5.724 | −0.870 | −0.933 | 5.787 | 5.138 | −2.225 | 2.775 | 595.683 | 337.877 | 1 |
| 6        | (CH<sub>2</sub>)<sub>2</sub>COMe | Bnz | i-But | Cbz | 5.796 | 5.550 | 0.246 | 0.266 | 5.530 | 5.278 | −0.507 | 2.894 | 593.710 | 318.394 | 1 |
| 7        | (CH<sub>2</sub>)<sub>2</sub>SOMe | Bnz | i-But | Cbz | 5.796 | 5.602 | 0.194 | 0.204 | 5.592 | 4.342 | −2.187 | 3.447 | 613.765 | 387.787 | 1 |
| 8        | CH<sub>2</sub>NHCOMe | Bnz | i-But | Cbz | 5.658 | 5.155 | 0.502 | 0.564 | 5.094 | 4.379 | 5.417 | 7.240 | 594.698 | 313.448 | 1 |
| 9<sup>a</sup> | CH<sub>2</sub>NHCONH<sub>2</sub> | Bnz | i-But | Cbz | 4.495 | 5.681 | −1.186 | −1.274 | 5.769 | 4.015 | −0.559 | 2.258 | 595.687 | 465.089 | 1 |
| 10       | CH<sub>2</sub>OCONH<sub>2</sub> | Bnz | i-But | Cbz | 5.796 | 5.587 | 0.209 | 0.229 | 5.567 | 4.459 | −0.530 | 0.909 | 596.671 | 446.942 | 1 |
| 11<sup>a</sup> | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | H | i-But | Cbz | 3.851 | 5.073 | −1.222 | −1.323 | 5.174 | 2.675 | 2.269 | 5.487 | 504.576 | 315.571 | 1 |
| 12       | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | Me | i-But | Cbz | 4.699 | 5.020 | −0.321 | −0.357 | 5.056 | 2.984 | −0.004 | 4.193 | 518.602 | 291.439 | 1 |

(Continued)
| Compound | R_1      | R_2 | R_3 | R_4 | Obsd | Calcd | Res  | Del res | Pred  | C Log P | D_Y  | D_tot | MW     | Pol Vol | I   |
|----------|----------|-----|-----|-----|------|-------|------|---------|-------|---------|------|-------|--------|---------|----|
| 13       | (CH_2)_2CONH_2 | Et  | i-But | Cbz | 5.222 | 5.181 | 0.041 | 0.044 | 5.178 | 3.513 | 0.010 | 4.173 | 532.629 | 295.871 | 1  |
| 14       | (CH_2)_2CONH_2 | n-Pr | i-But | Cbz | 5.301 | 5.517 | −0.216 | −0.233 | 5.534 | 4.042 | 2.612 | 3.991 | 546.656 | 381.286 | 1  |
| 15       | (CH_2)_2CONH_2 | i-But | i-But | Cbz | 5.268 | 5.452 | −0.184 | −0.199 | 5.467 | 4.441 | −0.030 | 4.239 | 560.682 | 301.966 | 1  |
| 16       | (CH_2)_2CONH_2 | CH_2Me | i-But | Cbz | 5.051 | 5.422 | −0.371 | −0.399 | 5.449 | 3.513 | −0.768 | 5.152 | 564.694 | 342.413 | 1  |
| 17       | (CH_2)_2CONH_2 | CH_2Se | i-But | Cbz | 5.000 | 5.654 | −0.564 | −0.606 | 5.606 | 4.042 | −0.744 | 5.171 | 578.721 | 342.413 | 1  |
| 18       | (CH_2)_2CONH_2 | CH_2C-Hex | i-But | Cbz | 5.721 | 5.933 | −0.212 | −0.230 | 5.951 | 5.634 | 0.021 | 2.242 | 600.746 | 394.126 | 1  |
| 19       | (CH_2)_2CONH_2 | 4-FBnz | i-But | Cbz | 5.745 | 5.543 | 0.201 | 0.209 | 5.536 | 4.545 | −2.108 | 2.393 | 612.689 | 386.902 | 1  |
| 20       | (CH_2)_2CONH_2 | 4-MeBnz | i-But | Cbz | 6.745 | 5.717 | 1.028 | 1.071 | 5.673 | 4.901 | −2.119 | 2.623 | 608.725 | 378.323 | 1  |
| 21       | (CH_2)_2CONH_2 | 4-OHBnz | i-But | Cbz | 5.276 | 5.308 | −0.032 | −0.033 | 5.309 | 3.735 | −1.100 | 2.275 | 610.698 | 428.516 | 1  |
| 22       | (CH_2)_2CONH_2 | 4-OAcBnz | i-But | Cbz | 4.959 | 4.819 | 0.139 | 0.153 | 4.806 | 3.751 | 4.402 | 6.233 | 652.735 | 384.882 | 1  |
| 23       | (CH_2)_2CONH_2 | 4-OMeBnz | i-But | Cbz | 5.770 | 5.303 | 0.467 | 0.545 | 5.224 | 4.321 | 6.526 | 8.296 | 624.725 | 375.690 | 1  |
| 24       | (CH_2)_2CONH_2 | 4-OPO_3H_2Bnz | i-But | Cbz | 4.854 | 4.636 | 0.218 | 0.322 | 4.532 | 2.397 | 6.797 | 9.078 | 691.686 | 481.642 | 1  |
| 25       | (CH_2)_2CONH_2 | 4-CH_2OHBnz | i-But | Cbz | 6.260 | 5.157 | 1.103 | 1.197 | 5.062 | 3.364 | −2.137 | 3.570 | 624.725 | 398.350 | 1  |
| 26       | (CH_2)_2CONH_2 | 4-CH_2OMeBnz | i-But | Cbz | 4.409 | 5.260 | −0.851 | −0.882 | 5.291 | 4.200 | 0.299 | 3.968 | 638.751 | 397.994 | 1  |
| 27       | (CH_2)_2CONH_2 | 4-(CH_2)_3OHBnz | i-But | Cbz | 5.456 | 5.026 | 0.430 | 0.463 | 4.993 | 3.593 | −2.114 | 2.115 | 638.751 | 410.287 | 1  |
| 28       | (CH_2)_2CONH_2 | 4-CNBNz | i-But | Cbz | 5.252 | 5.483 | −0.232 | −0.244 | 5.496 | 3.835 | −2.202 | 2.611 | 619.708 | 436.415 | 1  |
| 29       | (CH_2)_2CONH_2 | CH_2-2-Imidazol | i-But | Cbz | 4.569 | 4.524 | 0.045 | 0.049 | 4.519 | 2.001 | 5.302 | 7.567 | 584.664 | 371.088 | 1  |
| 30 | (CH$_2$)$_2$CONH$_2$ | CH$_2$-2-(N-Melmid) | i-But | Cbz | 5.000 | 4.958 | 0.042 | 0.047 | 4.953 | 2.017 | −0.320 | 3.569 | 598.691 | 471.960 | 1 |
| 31 | (CH$_2$)$_2$CONH$_2$ | CH$_2$-2-Thienyl | i-But | Cbz | 6.252 | 5.770 | 0.481 | 0.542 | 5.710 | 4.048 | −0.074 | 2.329 | 600.726 | 491.708 | 1 |
| 32 | (CH$_2$)$_2$CONH$_2$ | CH(R-OH)Me | i-But | Cbz | 4.252 | 4.698 | −0.446 | −0.499 | 4.750 | 2.437 | −0.602 | 3.575 | 548.629 | 320.804 | 1 |
| 33 | (CH$_2$)$_2$CONH$_2$ | Bnz | H | Cbz | 5.252 | 5.644 | −0.392 | −0.451 | 5.703 | 2.636 | 6.383 | 7.818 | 538.592 | 342.483 | 0 |
| 34 | (CH$_2$)$_2$CONH$_2$ | Bnz | Me | Cbz | 5.699 | 5.673 | 0.026 | 0.030 | 5.669 | 2.945 | 6.386 | 7.863 | 552.619 | 338.858 | 0 |
| 35 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-Pr | Cbz | 6.420 | 6.292 | 0.128 | 0.137 | 6.283 | 3.873 | −0.517 | 2.730 | 580.672 | 422.592 | 0 |
| 36 | (CH$_2$)$_2$CONH$_2$ | Bnz | CH(S-Me)Et | Cbz | 6.102 | 6.405 | −0.303 | −0.326 | 6.429 | 4.402 | −0.561 | 2.688 | 594.698 | 417.655 | 0 |
| 37 | (CH$_2$)$_2$CONH$_2$ | Bnz | t-But | Cbz | 6.495 | 6.325 | 0.170 | 0.182 | 6.313 | 4.272 | −0.577 | 2.633 | 594.698 | 414.693 | 0 |
| 38 | (CH$_2$)$_2$CONH$_2$ | Bnz | (CH$_2$)$_2$SMe | Cbz | 5.854 | 6.212 | −0.358 | −0.401 | 6.255 | 3.093 | −0.565 | 3.842 | 612.737 | 483.809 | 0 |
| 39 | (CH$_2$)$_2$CONH$_2$ | Bnz | CH$_2$SMe | Cbz | 6.745 | 6.005 | 0.740 | 0.798 | 5.946 | 3.329 | −0.522 | 1.569 | 598.710 | 467.024 | 0 |
| 40 | (CH$_2$)$_2$CONH$_2$ | Bnz | CH(R-Me)S-i-Pr | Cbz | 5.000 | 5.942 | −0.942 | −1.017 | 6.017 | 4.476 | −1.336 | 1.448 | 640.790 | 402.437 | 0 |
| 41 | (CH$_2$)$_2$CONH$_2$ | Bnz | c-Hex | Cbz | 6.000 | 6.254 | −0.254 | −0.277 | 6.277 | 5.066 | 0.233 | 2.017 | 620.736 | 398.422 | 0 |
| 42 | (CH$_2$)$_2$CONH$_2$ | Bnz | CH$_3$-c-Hex | Cbz | 5.921 | 6.531 | −0.610 | −0.681 | 6.602 | 5.595 | 0.242 | 2.071 | 634.762 | 422.208 | 0 |
| 43 | (CH$_2$)$_2$CONH$_2$ | Bnz | Bnz | Cbz | 6.252 | 6.009 | 0.243 | 0.256 | 5.996 | 4.363 | 0.637 | 2.656 | 628.715 | 412.373 | 0 |
| 44 | (CH$_2$)$_2$CONH$_2$ | Bnz | CH$_2$SPh | Cbz | 6.921 | 5.975 | 0.946 | 1.048 | 5.873 | 4.975 | 0.134 | 0.894 | 660.780 | 432.119 | 0 |
| 45 | (CH$_2$)$_2$CONH$_2$ | Bnz | CH$_2$SBnz | Cbz | 6.699 | 6.057 | 0.642 | 0.711 | 5.988 | 5.252 | 0.595 | 1.560 | 674.806 | 432.894 | 0 |
| 46 | (CH$_2$)$_2$CONH$_2$ | Bnz | Phenethyl | Cbz | 6.602 | 6.088 | 0.514 | 0.552 | 6.050 | 4.892 | 0.147 | 2.107 | 642.741 | 406.351 | 0 |
| 47 | (CH$_2$)$_2$CONH$_2$ | Bnz | CH$_2$OH | Cbz | 5.745 | 5.409 | 0.336 | 0.373 | 5.371 | 1.944 | 5.520 | 7.889 | 568.618 | 377.703 | 0 |
| 48 | (CH$_2$)$_2$CONH$_2$ | Bnz | CH(R-OH)Me | Cbz | 5.745 | 5.382 | 0.363 | 0.393 | 5.352 | 2.253 | 5.016 | 6.785 | 582.645 | 384.249 | 0 |
| 49 | (CH$_2$)$_2$CONH$_2$ | Bnz | CMe$_2$OH | Cbz | 6.180 | 5.584 | 0.596 | 0.631 | 5.550 | 2.652 | 0.924 | 3.276 | 596.671 | 424.567 | 0 |
| 50 | (CH$_2$)$_2$CONH$_2$ | Bnz | CMe$_2$CH$_2$OH | Cbz | 5.886 | 5.452 | 0.434 | 0.468 | 5.418 | 2.285 | 0.346 | 3.352 | 610.698 | 436.415 | 0 |

(Continued)
### TABLE 11.36 Biological Activity and Physicochemical Parameters of a Series of Peptide-Derived HRV 3C\textsuperscript{pro} Inhibitors for QSAR Model [Eq. (11.35)] (cont.)

| Compound | R\textsubscript{1} | R\textsubscript{2} | R\textsubscript{3} | R\textsubscript{4} | Obsd | Calcd | Res | Del res | Pred | C Log P | D\textsubscript{Y} | D\textsubscript{tot} | MW | Pol Vol | I |
|----------|----------------|----------------|----------------|----------------|------|-------|-----|--------|------|--------|-----|----------|-----|--------|---|
| 51\textsuperscript{a} | (CH\textsubscript{2})\textsubscript{2}CONH\textsubscript{2} | Bnz | (CH\textsubscript{2})\textsubscript{4}NH\textsubscript{2} | Cbz | 3.688 | 5.803 | −2.115 | −2.293 | 5.981 | 2.645 | −0.448 | 2.678 | 609.713 | 473.406 | 0 |
| 52 | (CH\textsubscript{2})\textsubscript{2}CONH\textsubscript{2} | Bnz | (CH\textsubscript{2})\textsubscript{2}Morphol | Cbz | 5.292 | 5.349 | −0.056 | −0.063 | 5.356 | 2.418 | −0.519 | 2.657 | 651.750 | 460.861 | 0 |
| 53 | (CH\textsubscript{2})\textsubscript{2}CONH\textsubscript{2} | Bnz | (CH\textsubscript{2})\textsubscript{3}Morphol | Cbz | 5.149 | 5.564 | −0.415 | −0.465 | 5.613 | 2.947 | −1.018 | 2.732 | 665.776 | 463.920 | 0 |
| 54 | (CH\textsubscript{2})\textsubscript{2}CONH\textsubscript{2} | Bnz | CH\textsubscript{2}COOH | Cbz | 5.620 | 5.486 | 0.134 | 0.153 | 5.467 | 2.366 | 4.934 | 8.528 | 596.628 | 365.901 | 0 |
| 55 | (CH\textsubscript{2})\textsubscript{2}CONH\textsubscript{2} | Bnz | (CH\textsubscript{2})\textsubscript{2}COOH | Cbz | 5.260 | 5.101 | 0.158 | 0.199 | 5.061 | 2.057 | 8.211 | 10.633 | 610.655 | 341.532 | 0 |
| 56 | (CH\textsubscript{2})\textsubscript{2}CONH\textsubscript{2} | Bnz | CH\textsubscript{2}CONMe\textsubscript{2} | Cbz | 5.229 | 5.213 | 0.016 | 0.018 | 5.211 | 2.309 | −0.516 | 0.519 | 623.697 | 464.062 | 0 |
| 57 | (CH\textsubscript{2})\textsubscript{2}CONH\textsubscript{2} | Bnz | i-But | 2-MeCbz | 6.000 | 5.732 | 0.268 | 0.279 | 5.721 | 5.049 | 0.227 | 3.329 | 608.725 | 391.567 | 1 |
| 58 | (CH\textsubscript{2})\textsubscript{2}CONH\textsubscript{2} | Bnz | i-But | 2-ClCbz | 6.201 | 5.874 | 0.327 | 0.345 | 5.855 | 5.313 | −1.058 | 3.636 | 629.144 | 391.664 | 1 |
| 59 | (CH\textsubscript{2})\textsubscript{2}CONH\textsubscript{2} | Bnz | i-But | COOCH\textsubscript{2}(4-Pyr) | 4.252 | 4.818 | −0.566 | −0.614 | 4.866 | 3.103 | 0.604 | 2.039 | 595.687 | 407.187 | 1 |
| 60\textsuperscript{b} | (CH\textsubscript{2})\textsubscript{2}CONH\textsubscript{2} | Bnz | i-But | COOMe | 5.886 | 5.071 | 0.815 | 0.881 | 5.006 | 2.243 | −1.063 | 3.298 | 518.602 | 366.847 | 1 |
| 61 | (CH\textsubscript{2})\textsubscript{2}CONH\textsubscript{2} | Bnz | i-But | COO-c-Hex | 5.119 | 5.702 | −0.583 | −0.601 | 5.720 | 4.274 | −0.617 | 3.216 | 586.720 | 410.790 | 1 |
| 62 | (CH\textsubscript{2})\textsubscript{2}CONH\textsubscript{2} | Bnz | i-But | COO-t-But | 5.347 | 5.683 | −0.336 | −0.359 | 5.706 | 3.480 | −0.904 | 4.859 | 560.682 | 393.366 | 1 |
| 63 | (CH\textsubscript{2})\textsubscript{2}CONH\textsubscript{2} | Bnz | i-But | COSMe | 5.959 | 5.787 | 0.172 | 0.188 | 5.770 | 3.236 | −1.830 | 4.270 | 534.668 | 398.801 | 1 |
|   | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | COSEt | Obsd | Calcd | Res | Del res | Pred | MW | Pol Vol | I |
|---|---------------------|-----|-------|-------|------|-------|-----|--------|------|-----|---------|---|
| 64 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | 6.337 | 6.099 | 0.328 | 0.364 | 5.974 | 3.765 | -1.847 | 4.246 | 548.695 | 414.000 | 1 |
| 65 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | 6.745 | 6.060 | 0.685 | 0.737 | 6.007 | 4.708 | -1.713 | 3.770 | 588.759 | 410.214 | 1 |
| 66 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | 6.569 | 5.908 | 0.661 | 0.693 | 5.876 | 4.940 | -1.782 | 2.960 | 610.764 | 410.261 | 1 |
| 67 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | 6.000 | 5.632 | 0.368 | 0.410 | 5.590 | 4.898 | -3.035 | 3.347 | 614.731 | 336.399 | 1 |
| 68 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | 5.284 | 5.551 | -0.267 | -0.275 | 5.559 | 3.724 | -1.847 | 3.364 | 564.673 | 401.162 | 1 |
| 69 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | 6.351 | 6.060 | -1.067 | -1.295 | 6.079 | 4.902 | -0.349 | 3.770 | 656.768 | 452.361 | 1 |
| 70 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | 4.854 | 4.855 | -0.001 | -0.001 | 4.855 | 2.073 | 0.390 | 3.347 | 502.603 | 342.891 | 1 |
| 71 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | 6.000 | 5.185 | 0.815 | 0.854 | 5.146 | 2.911 | 0.267 | 3.332 | 502.603 | 342.891 | 1 |
| 72 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | 5.284 | 5.551 | -0.267 | -0.275 | 5.559 | 3.724 | -1.847 | 3.364 | 564.673 | 401.162 | 1 |
| 73 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | 5.185 | 5.312 | 0.815 | 0.854 | 5.146 | 2.911 | 0.267 | 3.332 | 502.603 | 342.891 | 1 |
| 74 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | 4.523 | 4.666 | -0.143 | -0.164 | 4.687 | 1.913 | 1.111 | 2.402 | 518.602 | 379.856 | 1 |
| 75 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | 4.721 | 4.816 | -0.095 | -0.102 | 4.824 | 1.746 | 1.759 | 4.449 | 532.629 | 398.315 | 1 |
| 76 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | 5.252 | 5.496 | -0.244 | -0.254 | 5.506 | 4.072 | 0.071 | 2.815 | 607.740 | 438.202 | 1 |
| 77 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | 4.201 | 5.106 | -0.906 | -0.998 | 5.198 | 3.802 | 4.372 | 4.664 | 574.709 | 374.435 | 1 |
| 78 | (CH$_2$)$_2$CONH$_2$ | Bnz | i-But | 4.699 | 5.077 | -0.378 | -0.397 | 5.096 | 2.874 | 2.249 | 4.207 | 546.656 | 385.237 | 1 |

*Considered as outlier.*
### TABLE 11.37 Biological Activity and Physicochemical Parameters of Ktomethylene Containing Peptide-Based HRV 3C<sub>pro</sub> Inhibitors for QSAR Model [Eq. (11.36)]

![Chemical structure](image_url)

| Compound | Ar   | Y   | X   | R<sub>1</sub> | R<sub>2</sub> | Obsd | Calcd | Res  | Del res | Pred | D<sub>Y</sub> | I<sub>1</sub> | I<sub>2</sub> |
|----------|------|-----|-----|-------------|-------------|------|-------|------|---------|------|-----------|----------|----------|
| 1        | Bnz  | O   | NH  | Bnz         | i-But       | 6.268| 6.245 | 0.023| 0.029   | 6.238| 0.755     | 1         | 0        |
| 2        | Bnz  | O   | CH₂ | Bnz         | i-But       | 6.444| 6.207 | 0.237| 0.307   | 6.137| 1.002     | 1         | 0        |
| 3        | Bnz  | S   | CH₂ | Bnz         | i-But       | 6.167| 6.284 | −0.117| −0.146  | 6.313| 0.498     | 1         | 0        |
| Compound | Ar | Y | X | R | Obsd | Calcd | Res | Del res | Pred | D |
|---------|----|---|---|---|------|-------|-----|---------|------|---|
| 4       | Bnz | S | CH₂ | Bnz | i-Pr | 6.721 | 7.317 | −0.596 | −0.778 | 7.499 | 0.508 | 0 | 1 |
| 5       | c-Pent | S | CH₂ | Bnz | i-But | 6.721 | 6.827 | −0.106 | −0.141 | 6.863 | −3.025 | 1 | 0 |
| 6       | c-Pent | S | CH₂ | 4F-Bnz | i-But | 6.553 | 6.536 | 0.016 | 0.020 | 6.533 | −1.139 | 1 | 0 |
| 7       | c-Pent | S | CH₂ | 4-MeBnz | i-But | 6.796 | 6.850 | −0.054 | −0.073 | 6.869 | −3.172 | 1 | 0 |
| 8       | c-Pent | S | CH₂ | Bnz | i-Pr | 7.699 | 7.861 | −0.162 | −0.226 | 7.925 | −3.021 | 0 | 1 |
| 9       | c-Pent | S | CH₂ | 4F-Bnz | i-Pr | 7.699 | 7.570 | 0.129 | 0.162 | 7.537 | −1.130 | 0 | 1 |
| 10      | c-Pent | S | CH₂ | 4-MeBnz | i-Pr | 8.222 | 7.883 | 0.338 | 0.480 | 7.742 | −3.168 | 0 | 1 |
| 11      | c-Pent | S | CH₂ | 4-CF₃Bnz | i-Pr | 7.301 | 7.011 | 0.290 | 0.485 | 6.816 | 2.495 | 0 | 1 |
| 12      | c-Pent | S | CH₂ | 4F-Bnz | Bnz | 6.319 | 6.445 | −0.126 | −0.227 | 6.545 | 2.268 | 0 | 0 |
| 13      | c-Pent | S | CH₂ | 4-MeBnz | Bnz | 6.854 | 6.759 | 0.095 | 0.143 | 6.710 | 0.233 | 0 | 0 |
| 14      | c-Pent | S | CH₂ | Bnz | t-But | 7.301 | 7.270 | 0.031 | 0.060 | 7.241 | −3.084 | 0 | 0 |
**TABLE 11.38** Biological Activity and Physicochemical Parameters of Peptide-Based HRV 3C\(^{pro}\) Inhibitors for QSAR Model [Eq. (11.37)]

| Compound | Ar   | \(\text{Ar}_1\) | R    | \(\text{R}_1\) | \(\text{R}_2\) | n  | X   | Y     | Obsd | Calcd | Res  | Del res | Pred | \(D_X\) |
|----------|------|----------------|------|--------------|-------------|----|-----|-------|------|-------|------|---------|------|---------|
| 1 \(^a\) | Cbz  | Cbz           | i-But| H            | H           | —  | —   | —     | 6.268| 4.694 | 1.573| 2.178   | 4.090| 2.748   |
| 2        | Cbz  | Cbz           | i-But| Me           | H           | —  | —   | —     | 3.125| 4.926 | −1.801| −2.359  | 5.484| 2.545   |
| 3        | Cbz  | Cbz           | i-But| Me           | Me          | —  | —   | —     | 4.222| 4.419 | −0.197| −0.296  | 4.517| 2.988   |
| 4        | Cbz  | Cbz           | i-But| —            | 1           | (S)-CH| NH   | 7.000| 7.112 | −0.112| −0.122| 7.122| 0.640   |
| 5        | Cbz  | Cbz           | i-But| —            | 2           | (S)-CH| NH   | 7.523| 8.286 | −0.763| −0.922| 8.445| −0.383  |
| 6        | Cbz  | Cbz           | i-But| —            | 1           | (R)-CH| NH   | 5.796| 7.112 | −1.316| −1.432| 7.228| 0.640   |
| 7        | Cbz  | Cbz           | i-But| —            | 1           | N    | NH   | 6.222| 6.177 | 0.045 | 0.050  | 6.172| 1.456   |
| 8        | Cbz  | Cbz           | i-Pr | —            | 1           | (S)-CH| NH   | 7.523| 7.128 | 0.395 | 0.430  | 7.093| 0.627   |
| 9        | 5-Me-isoxazole-3-CO | 4F-Bnz | i-Pr | —            | 1           | (S)-CH| NH   | 8.000| 7.938 | 0.062 | 0.071  | 7.929| −0.079  |
| 10       | 5-Me-isoxazole-3-CO | 4F-Bnz | i-Pr | —            | 2           | (S)-CH| NH   | 7.699| 6.937 | 0.762 | 0.826  | 6.873| 0.793   |
| 11       | 5-Me-isoxazole-3-CO | 4F-Bnz | i-Pr | —            | 1           | (S)-CH| CH\(_2\) | 8.301| 8.522 | −0.221| −0.278| 8.579| −0.589  |
| 12       | 5-Me-isoxazole-3-CO | 4F-Bnz | i-Pr | —            | 2           | (S)-CH| CH\(_2\) | 9.000| 7.510 | 1.490 | 1.651  | 7.349| 0.293   |
| 13       | 5-Me-isoxazole-3-CO | 4F-Bnz | t-But | —            | 1           | (S)-CH| NH   | 8.000| 7.915 | 0.085 | 0.098  | 7.902| −0.059  |

\(^a\)Considered as outlier.
these compounds had suggested that (S)-conformation of the compound had better activity than (R)-conformation.

\[
pEC_{50} = 7.890 (\pm 0.309) - 1.383 (\pm 0.239) D_X \tag{11.37}
\]

\[
N = 12, R = 0.877, R^2 = 0.769, R^2_A = 0.746, F (1, 10) = 33.377, P < 0.00018, \\
SEE = 0.876, q^2 = 0.652, Q = 1.001, \text{Outlier = Compound 1}
\]

Dragovich et al. (1999c) had also reported some tripeptidyl N-methyl amino acids as HRV 3C\textsuperscript{pro} inhibitors (Table 11.39), for which the QSAR model obtained [Eq. (11.38)] had suggested that the activity will be totally governed by the total dipole moment of the compound. This indicated the strong electronic interaction between the molecule and the receptor.

\[
pEC_{50} = 6.094 (\pm 0.122) + 0.075 (\pm 0.019) D_{Tot} \tag{11.38}
\]

\[
N = 8, R = 0.852, R^2 = 0.726, R^2_A = 0.680, F (1, 6) = 15.869, P < 0.00725, \\
SEE = 0.173, q^2 = 0.537, Q = 4.925, \text{Outlier = Compounds 7, 10}
\]

However, for some ketone containing tripeptidyl HRV 3C\textsuperscript{pro} inhibitors (Table 11.40) reported by Dragovich et al. (2000), the QSAR model [Eq. (11.39)] exhibited the importance of only Z-component of the dipole moment of the compound. In the Z-direction, the polarity of the compound may be more favorable for electronic interaction with the receptor.

\[
pK_i = 3.662 (\pm 0.583) + 2.862 (\pm 0.713) D_Z \tag{11.39}
\]

\[
N = 6, R = 0.895, R^2 = 0.801, R^2_A = 0.751, F (1, 4) = 16.096, P < 0.01597, \\
SEE = 0.490, q^2 = 0.594, Q = 1.827, \text{Outlier = Compounds 5, 7}
\]

7.2.5 Depsipeptidyl HRV 3C\textsuperscript{pro} Inhibitors

Webber et al. (2001) reported some depsipeptidyl HRV 3C\textsuperscript{pro} inhibitors (Table 11.41), for which the QSAR model obtained was as is shown by Eq. (11.40). This model suggested that in this case, the polar volume of the molecule will not be conducive to the activity.

\[
pEC_{50} = 18.601 (\pm 2.905) - 0.029 (\pm 0.008) PolVol \tag{11.40}
\]

\[
N = 7, R = 0.866, R^2 = 0.750, R^2_A = 0.700, F (1, 5) = 15.030, P < 0.01168, \\
SEE = 0.499, q^2 = 0.533, Q = 1.735, \text{Outlier = Compounds 2, 6}
\]

7.2.6 2-Pyridone Containing Peptidomimetics as HRV 3C\textsuperscript{pro} Inhibitors

For some 2-pyridone containing peptidomimetics as promising HRV 3C\textsuperscript{pro} inhibitors (Table 11.42) reported by Dragovich et al. (2002), the QSAR model [Eq. (11.41)] had, however, suggested that the SA of the molecule will be favorable to the activity, probably because of dispersion interaction between the active surface of the molecule and that of the receptor. However, a very high
**TABLE 11.39** Biological Activity and Physicochemical Parameters of Some Tripeptidyl N-methyl Amino Acids for QSAR Model [Eq. (11.38)]

| Compound | R          | R₁    | R₂    | Ar     | Obsd | Calcd | Res  | Del res | Pred    | Dₜot |
|----------|------------|-------|-------|--------|------|-------|------|---------|---------|-------|
| 1        | NHCBz      | H     | i-But | Bnz    | 6.268| 6.165 | 0.103| 0.222   | 6.108   | 1.102 |
| 2        | NHCBz      | Me    | i-But | Bnz    | 6.000| 6.187 | −0.187| −0.272  | 6.272   | 1.542 |
| 3        | CO-S-c-Pent| Me    | i-But | Bnz    | 6.495| 6.351 | 0.144| 0.163   | 6.331   | 4.724 |
| 4        | CO-S-c-Pent| Me    | i-Pr  | Bnz    | 6.721| 6.353 | 0.368| 0.418   | 6.303   | 4.759 |
| 5        | CO-S-c-Pent| Me    | CH₂SPh| Bnz    | 6.268| 6.331 | −0.064| −0.073  | 6.341   | 4.336 |
| 6        | 5-Methyl-isoxazole-3-carbonyl | Me | i-But | 4-FBnz | 6.854| 6.547 | 0.307| 0.364   | 6.490   | 8.521 |
| 7         | 5-Methyl-isoxazole-3-carbonyl | Me | i-But | 4-FBnz | 6.398| 6.594 | −0.197| −0.249  | 6.647   | 9.449 |
| 8        | 5-Methyl-isoxazole-3-carbonyl | Me | CH₂(1-Napthyl)| 4-FBnz | 6.699| 6.592 | 0.107| 0.135   | 6.564   | 9.400 |
| 9        | 5-Methyl-isoxazole-3-carbonyl | Me | CH₂(2-Napthyl)| 4-FBnz | 6.796| 6.641 | 0.155| 0.214   | 6.581   | 10.349 |
| 10        | 5-Methyl-isoxazole-3-carbonyl | Me | CH₂(4-Imidazole) | 4-FBnz | 5.745| 6.482 | −0.737| −0.831  | 6.575   | 7.262 |

*Considered as outlier.*


| Compound | R           | R₁            | R₂         | R₃         | Obsd | Calcd | Res  | Del res | Pred  | Dₓ             |
|----------|-------------|---------------|------------|------------|------|-------|------|---------|-------|----------------|
| 1        | Benzothiazol-2-yl | NHCOMe |           |            | 5.770 | 5.512 | 0.257 | 0.321   | 5.449 | 0.645         |
| 2        | Benzothiazol-2-yl | CH₂CONH₂   |           |            | 5.456 | 5.458 | −0.002 | −0.003  | 5.459 | 0.596         |
| 3        | Benzothiazol-2-yl | 2-Oxo-pyrrolidin-3-yl |          |           | 7.187 | 6.227 | 0.960 | 1.266 | 5.921 | 1.287         |
| 4        | Benzothiazol-2-yl | 2-Oxo-pyrrolidin-3-yl | OH |            | 4.469 | 5.225 | −0.756 | −1.245 | 5.714 | 0.386         |
| 5ᵃ        | Thiazol-2-yl | 2-Oxo-pyrrolidin-3-yl |           |            | 6.155 | 6.350 | −0.195 | −0.290 | 6.445 | 1.399         |
| 6        | 2-Pyridyl     | 2-Oxo-pyrrolidin-3-yl |         |            | 6.770 | 5.742 | 1.028 | 1.182 | 5.588 | 0.851         |
| 7ᵃ        | Benzothiophen-2-yl | 2-Oxo-pyrrolidin-3-yl |          |            | 5.328 | 6.387 | −1.059 | −1.639 | 6.966 | 1.431         |
| 8        | Ph           | 2-Oxo-pyrrolidin-3-yl |          |            | 5.495 | 5.727 | −0.232 | −0.268 | 5.763 | 0.838         |

ᵃConsidered as outlier.
**TABLE 11.41** Biological Activity and Physicochemical Parameters of Depsipeptidyl HRV 3C<sup>Pro</sup> Inhibitors for QSAR Model [Eq. (11.40)]

| Compound | R               | R<sub>1</sub>            | X     | Obsd | Calcd | Res  | Del res | Pred  | Pol Vol |
|----------|-----------------|--------------------------|-------|------|-------|------|---------|-------|---------|
| 1        | S-c-pent        | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | O     | 6.000| 6.466 | −0.466| −0.692  | 6.692 | 426.668 |
| 2<sup>a</sup> | S-c-pent        | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | NH    | 6.721| 6.244 | 0.477 | 0.894   | 5.827 | 438.416 |
| 3        | S-c-pent        | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | CH<sub>2</sub> | 7.699| 7.329 | 0.370 | 0.418   | 7.281 | 380.864 |
| 4        | 5-Methyl-isoxazole | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | O     | 7.000| 7.360 | −0.360| −0.407  | 7.407 | 379.172 |
| 5        | 5-Methyl-isoxazole | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | NH    | 6.377| 7.042 | −0.665| −0.762  | 7.138 | 396.070 |
| 6<sup>a</sup> | 5-Methyl-isoxazole | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | CH<sub>2</sub> | 7.000| 7.773 | −0.773| −0.974  | 7.974 | 357.284 |
| 7        | 5-Methyl-isoxazole | 5-(2-Oxo-pyrrolidin-3-yl) | O     | 8.155| 7.516 | 0.639 | 0.739   | 7.416 | 370.905 |
| 8        | 5-Methyl-isoxazole | 5-(2-Oxo-pyrrolidin-3-yl) | NH    | 8.000| 7.379 | 0.621 | 0.703   | 7.297 | 378.176 |
| 9        | 5-Methyl-isoxazole | 5-(2-Oxo-pyrrolidin-3-yl) | CH<sub>2</sub> | 8.301| 8.144 | 0.157 | 0.258   | 8.043 | 337.594 |

<sup>a</sup>Considered as outlier.
### TABLE 11.42 Biological Activity and Physicochemical Parameters of 2-Pyridone Containing Peptidomimetics as HRV 3C<sup>pro</sup> Inhibitors for QSAR Model [Eq. (11.41)]

| Compound | R<sub>1</sub>          | R<sub>2</sub> | R<sub>3</sub> | Obsd | Calcd | Res  | Del res | Pred  | SA    |
|----------|----------------------|--------------|--------------|------|-------|------|---------|-------|-------|
| 1        | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | Bnz          | OBnz         | 7.481 | 7.493 | −0.012 | −0.013  | 7.495 | 882.377|
| 2        | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | 4-FBnz       | OBnz         | 7.854 | 7.492 | 0.362  | 0.410   | 7.444 | 883.062|
| 3        | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | 3,4-diFBnz   | OBnz         | 8.523 | 7.492 | 1.031  | 1.165   | 7.358 | 882.859|
| 4        | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | CH$_2$-c-Hex | OBnz         | 6.750 | 7.368 | −0.618 | −0.850  | 7.600 | 906.641|
| 5<sup>a</sup> | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | Bnz          | Me           | 6.052 | 5.531 | 0.520  | 9.821   | −3.770| 749.850|
| 6        | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | Bnz          | c-Pent       | 7.469 | 7.194 | 0.275  | 0.325   | 7.144 | 825.095|
| 7        | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | Bnz          | [1,3]Dithiolane-2-yl | 6.983 | 7.190 | −0.207 | −0.245  | 7.228 | 824.774|
| 8        | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | Bnz          | Tetrahydrofuran-2-yl | 5.750 | 7.049 | −1.299 | −1.550  | 7.299 | 814.614|
| 9        | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | Bnz          | t-Butyl      | 6.286 | 7.120 | −0.835 | −0.991  | 7.277 | 819.529|
| 10       | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | Bnz          | 5-Me-Benzoxazol-3-yl | 7.796 | 7.394 | 0.402  | 0.466   | 7.330 | 845.229|
| 11       | (CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub> | Bnz          | 5-Cl-Benzoxazol-3-yl | 7.620 | 7.315 | 0.305  | 0.357   | 7.263 | 836.004|
| 12       | (R)-2-Oxopryrodine-3-yl | Bnz          | OBnz         | 8.523 | 7.476 | 1.047  | 1.204   | 7.319 | 888.453|
| 13       | (S)-2-Oxopryrodine-3-yl | Bnz          | OBnz         | 6.329 | 7.300 | −0.971 | −1.592  | 7.921 | 914.072|

<sup>a</sup>Considered as outlier.
SA was shown to be detrimental to the activity, probably because of the steric problem.

\[ p\text{EC}_{50} = -670.463(\pm 111.246) + 1.568(\pm 0.259)\text{SA} - 0.001(\pm 0.0001)\text{SA}^2 \]  

(11.41)

\[ N = 12, \: R = 0.905, \: R^2 = 0.819, \: R^2_A = 0.779, \: F (2, 9) = 20.403, \: P < 0.00045, \]
\[ \text{SEE} = 0.413, \: q^2 = 0.715, \: Q = 2.191, \: \text{SA}_{\text{opt}} = 784, \: \text{Outlier = Compound 5} \]

7.2.7 Michael Acceptor Containing Irreversible HRV 3C\text{pro} Inhibitors

Johnson et al. (2002) reported some Michael acceptor containing irreversible HRV 3C\text{pro} inhibitors (Table 11.43). For these inhibitors, the QSAR model [Eq. (11.42)] indicated that the activity of compounds will simply depend upon the presence or absence of \( \beta \)-naphthyl group or chromene ring at the R-position of the compound. Of the two indicator variables, \( I_1 \) and \( I_2 \), the former with a value of 1 indicated the presence of \( \beta \)-naphthyl group and the latter with a value of unity indicated the presence of chromene ring at the R-position. The positive coefficients of both the variables indicated the favorable contribution of either of the substituent. Both might have steric interactions with the active site of the enzyme.

\[ p\text{EC}_{50} = 5.951(\pm 0.086) + 0.833(\pm 0.172)I_1 + 0.819(\pm 0.172)I_2 \]  

(11.42)

\[ N = 10, \: R = 0.917, \: R^2 = 0.841, \: R^2_A = 0.796, \: F (2, 7) = 18.528, \: P < 0.00160, \]
\[ \text{SEE} = 0.210, \: q^2 = 0.765, \: Q = 4.367, \: \text{Outlier = Compounds 7, 11} \]

7.2.8 2-Pyridone Containing Peptidomimetics as HRV 3C\text{pro} Inhibitors

Dragovich et al. (2003) reported a series of 2-pyridone containing peptidomimetics as HRV 3C\text{pro} inhibitors (Table 11.44). The QSAR model obtained for these compounds was as shown by Eq. (11.43). This model suggested that have less bulky molecules with small X-component of their dipole moment will be favored. Simultaneously, the high value of the PSA of these molecules may be conducive to activity. Further, the positive coefficient of the indicator variable “I” that was defined with a value of unity for a benzyl substituent at \( R_1 \)-position indicated that such a substituent should be desired for the better activity of the compound. This benzyl group might have steric interaction with the receptor.

\[ p\text{EC}_{50} = 7.013(\pm 2.741) - 0.471(\pm 0.091)\text{CMR} - 0.329(\pm 0.042)D_X + 0.032(\pm 0.009)\text{PSA} + 0.675(\pm 0.165)I \]  

(11.43)

\[ N = 18, \: R = 0.947, \: R^2 = 0.897, \: R^2_A = 0.865, \: F (4, 13) = 28.323, \: P < 0.00000, \]
\[ \text{SEE} = 0.175, \: q^2 = 0.737, \: Q = 5.411 \]
### TABLE 11.43 Biological Activity and Physicochemical Parameters of Michael Acceptor Containing Irreversible HRV 3C\textsuperscript{pro} Inhibitors for QSAR Model [Eq. (11.42)]

![Chemical Structure](attachment:image1.png)

| Compound | R          | Obsd | Calcd | Res  | Del res | Pred  | $I_1$ | $I_2$ |
|----------|------------|------|-------|------|---------|-------|-------|-------|
| 1        | 3-BrPhCH═CH | 5.854| 5.951 | −0.098| −0.117  | 5.971 | 0     | 0     |
| 2        | 3-Br,4-MePhCH═CH | 5.889| 5.951 | −0.062| −0.074  | 5.964 | 0     | 0     |
| 3        | 3-Br,4-FPhCH═CH | 6.201| 5.951 | 0.249 | 0.299   | 5.902 | 0     | 0     |
| 4        | Benzo[1,3]dioxole | 5.742| 5.951 | 0.209 | 0.251   | 5.993 | 0     | 0     |
| 5        | 5-Bromo-benzo[1,3]dioxole | 6.310| 5.951 | 0.358 | 0.430   | 5.880 | 0     | 0     |
| 6        | 2-Methyl-5-phenyl-furan | 5.712| 5.951 | 0.239 | 0.287   | 5.999 | 0     | 0     |
| 7\(^a\)  | 2H-Chromene-3-yl | 5.924| 6.488 | −0.564| −0.846  | 6.770 | 0     | 1     |
| 8        | 6-Chloro-2H-chromene-3-yl | 6.796| 6.488 | 0.308 | 0.461   | 6.335 | 0     | 1     |
| 9        | 6-Bromo-2H-chromene-3-yl | 6.745| 6.488 | 0.256 | 0.385   | 6.360 | 0     | 1     |
| 10       | Napthaleny-2-yl | 6.824| 6.541 | 0.283 | 0.424   | 6.400 | 1     | 0     |
| 11\(^a\) | 6-Methyl-napthaleny-2-yl | 6.056| 6.541 | −0.486| −0.729  | 6.784 | 1     | 0     |
| 12       | 7-Bromo-napthaleny-2-yl | 6.745| 6.541 | 0.203 | 0.305   | 6.440 | 1     | 0     |

\(^a\)Considered as outlier.
**TABLE 11.44** Biological Activity and Physicochemical Parameters of 2-Pyridone Containing Peptidomimetics as HRV 3C<sup>pro</sup> Inhibitors for QSAR Model [Eq. (11.43)]

| Compound | $R_1$ | $R_2$ | Obsd  | Calcd | Res  | Del res | Pred  | CMR  | $D_X$ | PSA  | $I$  |
|----------|-------|-------|-------|-------|------|--------|-------|------|-------|------|------|
| 1        | Et    | CH$_2$(3,4-F)Ph | 7.959 | 7.724 | 0.234 | 0.463  | 7.495 | 15.443 | -2.386 | 226.148 | 0    |
| 2        | $i$-Pr | CH$_2$(3,4-F)Ph | 7.108 | 7.394 | -0.286 | -0.507 | 7.615 | 15.907 | -2.400 | 222.485 | 0    |
| 3        | Et    | CH$_3$CCH    | 7.237 | 7.243 | -0.006 | -0.008 | 7.245 | 13.625 | 1.971  | 229.100 | 0    |
| 4        | $i$-Pr | CH$_3$CCH    | 6.759 | 6.808 | -0.049 | -0.054 | 6.814 | 14.089 | 1.926  | 221.859 | 0    |
| Compound       | R                | Obsd | Calcd | Res | Del res | Pred | CMR  | PSA | I  |
|----------------|------------------|------|-------|-----|---------|------|------|-----|----|
| 6              | CH$_2$-t-But     | CH$_2$CCH | 6.559 | 6.345 | 0.214 | 0.312 | 6.247 | 15.017 | 2.128 | 223.123 | 0 |
| 7              | c-But            | CH$_2$CCH | 7.046 | 6.959 | 0.087 | 0.110 | 6.936 | 14.376 | 0.459 | 215.681 | 0 |
| 8              | c-Pent           | CH$_2$CCH | 6.759 | 6.756 | 0.003 | 0.003 | 6.756 | 14.839 | 0.494 | 216.549 | 0 |
| 9              | c-Hex            | CH$_2$CCH | 6.391 | 6.438 | −0.047 | −0.056 | 6.447 | 15.303 | 0.536 | 213.857 | 0 |
| 10             | c-Hept           | CH$_2$CCH | 6.090 | 6.234 | −0.143 | −0.200 | 6.291 | 15.767 | 0.581 | 214.763 | 0 |
| 11             | Bnz              | CH$_2$CCH | 7.444 | 7.298 | 0.145 | 0.292 | 7.152 | 15.673 | 0.533 | 225.091 | 1 |
| 12             | Et               | Et    | 7.328 | 7.356 | −0.028 | −0.047 | 7.375 | 13.364 | 2.199 | 231.167 | 0 |
| 13             | i-Pr             | Et    | 6.492 | 6.808 | −0.316 | −0.371 | 6.863 | 13.828 | 2.155 | 220.347 | 0 |
| 14             | t-But            | Et    | 6.393 | 6.402 | −0.009 | −0.011 | 6.404 | 14.292 | 2.297 | 215.939 | 0 |
| 15             | CH$_2$-t-But     | Et    | 6.509 | 6.460 | 0.049 | 0.071 | 6.437 | 14.756 | 2.353 | 225.186 | 0 |
| 16             | c-But            | Et    | 7.119 | 6.943 | 0.176 | 0.260 | 6.859 | 14.115 | 0.733 | 214.152 | 0 |
| 17             | c-Hex            | Et    | 6.504 | 6.424 | 0.080 | 0.098 | 6.407 | 15.042 | 0.807 | 212.348 | 0 |
| 18             | Bnz              | Et    | 7.194 | 7.339 | −0.145 | −0.292 | 7.486 | 15.412 | 0.797 | 225.237 | 1 |


8 OVERVIEW AND CONCLUSIONS

A total of 43 QSAR models (33 for SARS-CoV 3CL\textsuperscript{pro} inhibitors and 10 for HRV 3C\textsuperscript{pro} inhibitors) have been reported here to get an insight into the relation between the enzyme inhibitory activities of the antiviral compounds and their physicochemical and structural properties. QSAR models exhibited that the physicochemical parameters, such as dipole moment, PSA, polar volume, hydrophobicity, molar refractivity, SA, and molecular volume of the compounds play a crucial role in controlling both SARS-CoV 3CL\textsuperscript{pro} and HRV 3C\textsuperscript{pro} inhibitory activities. Moreover, some structural indicator variables were found to play an important role for inhibition of these enzymes. In many cases, the dipole moment and the PSA were found to be dominant factors. The bulk of the inhibitors and their flexibility and polarity also appeared to play crucial roles in the inhibition of the enzyme. Most of the QSAR models exhibited a direct correlation of dipole moment with the 3CL\textsuperscript{pro} or 3C\textsuperscript{pro} inhibitory activity, where a majority of them showed the positive effect of dipole moment on activity but few showed the negative effect, too. These positive and negative effects may be attributed to the orientation of the inhibitor molecules in the active site of the enzyme.

The PSA and the polarity of the inhibitors were some other important factors that were found in some cases to influence the activity. With their positive coefficients in the correlation, they indicated the attractive electronic interactions of the molecules with the enzyme, and with negative coefficient, they indicated the repulsive interaction. In many cases, the polar volume was found to govern the activity. The polar volume also indicated the attractive or repulsive dispersion interaction between the molecule and the receptor.

Among all, the hydrophobicity of the molecules had its own role. In any drug-receptor interaction, hydrophobicity is found to play an important role because in most of the enzymes the active site has a hydrophobic pocket which plays an important role in the activity of the site. In most of the cases, the bulky portion of the molecule tries to occupy this hydrophobic pocket where it may have hydrophobic interaction. The molecular volume, MW, or molar refractivity all sometimes become synonymous to the hydrophobic property of the molecules. If they are not found related to hydrophobicity and are crucial for the activity, then it means that the inhibitor-enzyme interaction involves dispersion interaction. The QSAR models discussed here may be a great help to design some new, more potent compounds in any given category of SARS-CoV 3CL\textsuperscript{pro} or HRV 3C\textsuperscript{pro} inhibitors.

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Structural Insight Into the Viral 3C-Like Protease Inhibitors  Chapter | 11  407

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