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Chapter 4

Imidazole derivatives: Impact and prospects in antiviral drug discovery

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Abbreviations

AIDS  acquired immune deficiency syndrome
BKPyV  BK human polyomavirus type 1
BMZ  benzimidazole
BVDV  bovine viral diarrhea virus
CC₅₀  50% cytotoxic concentration
CMV  cytomegalovirus
CV  coxsackie virus
CVB  coxsackievirus B
DENV  dengue virus
EC₅₀  half maximal effective concentration
FHV  flock house virus
FIPV  feline infectious peritonitis virus
HAART  highly active antiretroviral therapy
HBV  hepatitis B virus
HCV  hepatitis C virus
HIV  human immune deficiency virus
HPV  human papilloma virus
HSV  herpes simplex virus
IAV  influenza A virus
IC₅₀  half maximal inhibitory concentration
IMPDH  inosine-5′-monophosphate dehydrogenase
MDBK cells  Madin-Darby bovine kidney cells
MDCK cells  Madin-Darby canine kidney cells
MERS HCoV  Middle-East respiratory syndrome human coronavirus
MPA  mycophenolate acid
Mpro  main protease
NNRTI  nonnucleoside reverse transcriptase inhibitors
PI-3V  parainfluenza-3 virus
Microbes, invisible to the human eye, tend to threaten humans, not only in medical terms but also in terms of disrupting the social and economic aspects of life as depicted by the present-day COVID-19 pandemic. This pandemic has proven how these small viruses can harm the very existence of humans. It has shaken the social, economic, and medical backbone of every nation all around the world [1]. Viruses cause several epidemic diseases and generate havoc for the entire world (Table 4.1). They enter human bodies via various paths, like oral paths, the nasal tract, through the skin, or via any external wound [2].

Data analysis has shown that viral infections alone cause mortality of around 2 million globally [3, 4]. The virulent behavior does not stop here; viruses tend to change their genomic structure and become resistant to the drugs used to stop their multiplication and infection rate [5, 6]. Various viruses are present in our surroundings, yet only a handful are recognized and characterized. Human immune deficiency virus (HIV), hepatitis virus, influenza virus, human papilloma virus (HPV), herpes simplex virus (HSV), and coronavirus are some of the pathogenic viruses that have caused large-scale mortality (Table 4.1). Thus, the identification and generation of antiviral drugs are essential to human well-being.

Antiviral drugs can be either natural or chemically synthesized. Curcumin extracted from turmeric is a trending natural antiviral drug that shows its potent antiviral property upon various viruses including parainfluenza virus type 3 (PIV-3), feline infectious peritonitis virus (FIPV), vesicular stomatitis virus (VSV), herpes simplex virus (HSV), flock house virus (FHV), and respiratory syncytial virus (RSV) [7]. Enfuvirtide, maraviroc, indinavir, acyclovir, foscarinet, abacavir, lamivudine, tenofovir, adeovir, entecavir, telbivudine, tenofovir,
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Camptothecin, ribavirin, and interferons (siRNA) are examples of synthetic antiviral drugs [8]. For the management of morbidities and mortalities incurred by viruses, pharmaceutical departments are in a constant race to develop new bioactive moieties out of which heterocyclic compounds are in the limelight [9].

Nitrogen-based heterocycles are readily available in nature with diverse biological activities and similarities with various bioactive drugs [10]. Some nitrogen-based heterocycles, e.g., imidazoles, are often considered potent drugs in clinical practices. They have been in long run due to their amphoteric nature, i.e., they can act as an acid and base at the same time and further increase their potency [11–13]. Imidazoles and their fused derivatives are five-membered cyclic structures and their structure gives them a unique identity in the field of antiviral drugs [13–16]. Special structural features of imidazole and benzimidazole ring with their desirable electron-rich characters help them to bind with various targets and give them an advantage over other known moieties [17, 18].

| TABLE 4.1 Major epidemics caused by virus strains. |
|-----------------------------------------------|
| **Name** | **Time period** | **Death toll** | **Type/prehuman host** |
| Japanese smallpox epidemic | 735–737 | 1 million | Variola major virus |
| New World smallpox outbreak | 1520 onwards | 56 million | Variola major virus |
| Yellow fever | Late 1800s | 100,000–150,000 (US) | Virus/mosquitoes |
| Russian flu | 1889–90 | 1 million | Believed to be H2N2 (avian origin) |
| Spanish flu | 1918–19 | 40–50 million | H1N1 virus/pigs |
| Asian flu | 1957–58 | 1.1 million | H2N2 virus |
| Hong Kong flu | 1968–70 | 1 million | H3N2 virus |
| HIV/AIDS | 1981–present | 25–35 million | Virus/chimpanzees |
| SARS | 2002–03 | 770 | Coronavirus/bats, civets |
| Swine flu | 2009–10 | 200,000 | H1N1 virus/pigs |
| Ebola | 2014–16 | 11,000 | Ebolavirus/wild animals |
| MERS | 2015–present | 850 | Coronavirus/bats, camels |
| COVID-19 | 2019–present | 2.7 million (Johns Hopkins University estimate as of March 16, 2021) | Coronavirus—unknown (possibly pangolins) |
Imidazole-based drug discovery

These moieties are not specifically antiviral but also possess therapeutic action regarding various other diseases. Extensive research has been carried out to find other imidazole derivatives or imidazole-containing moieties to aid the medical department [19–22]. Some imidazole-based antiviral drugs are depicted in Fig. 4.1. This chapter illustrates recent attempts regarding the antiviral activity of imidazole-based moieties. Furthermore, the structure–activity relationships of various imidazole derivatives against different virus strains are reported for the development of significant antivirals.

2. **Imidazole derivatives and their action against different viruses**

Different potent and drug-like imidazole derivatives have been depicted against several virus strains like ZIKV, HIV, HPC, SARS CoV-2, influenza, dengue, etc. (Fig. 4.2).

2.1 **Zika virus**

Zika virus (ZIKV) belongs to the *Flaviviridae* family and causes congenital abnormalities in fetuses and newborns and upregulated a number of microcephaly cases [23, 24]. Worldwide, more than 2 billion people are at risk of ZIKV and the WHO declared ZIKV a public health emergency in 2016. Moreover, ZIKV is responsible for ophthalmological complications in adults and neural-inflammatory diseases such as Guillain-Barré syndrome [25]. Current data show that it can be sexually transmitted without any signs in tests over a long period [26]. Currently there are no virus-specific drugs or medications available
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to medicate ZIKV-infected patients. Several of the imidazole derivatives have been examined for effective treatment against ZIKV.

A library of 50 structurally diverse benzimidazole derivatives were synthesized by a one-pot condensation of 1,2-phenylenediamines with several aromatic aldehydes using sodium metabisulfite as a catalyst under mild conditions (Scheme 4.1) and assessed for their inhibitory activity against Zika virus. Compound 1 was found to be the most promising ($EC_{50}$ value = $1.9 \pm 1.0 \mu M$) against the African ZIKV strain in Huh-7 (SI > 37) and neural stem cells (SI = 12). The SAR studies demonstrated that the heteroaromatic ring at the C-2 position and 4-OCH$_3$-benzyl, 3-pyridinylmethyl or 2-Cl-benzyl at the N-1 position with the presence of CF$_3$ group at the C-5 position of the benzimidazole ring showed immense pharmacological profile against ZIKA virus viz. compound 1b ($EC_{50}$ value = $24.7 \pm 2.0 \mu M$), 1c ($EC_{50}$ value = $13.3 \pm 1.1 \mu M$), 1d ($EC_{50}$ value = $7.5 \pm 1.1 \mu M$), 1e ($EC_{50}$ value = $18.5 \pm 1.1 \mu M$), 1f ($EC_{50}$ value = $48.3 \pm 1.3 \mu M$), and 1g ($EC_{50}$ value = $6.1 \pm 1.2 \mu M$). Moreover, naphthalene conjugated to benzimidazole with Cl at N-1 and CF$_3$ at the C-5 position exhibited the highest antiviral activity toward ZIKA strains with SI values less than 37 in Huh-7 that are more comparable to the reference, mycophenolate acid (MPA) [27] (Scheme 4.1, Fig. 4.3).

A novel series of 34 compounds of 1H-benzo[d]imidazole-5-carboxamide derivatives was drafted, synthesized, and screened to investigate their anti-yellow fever virus (YFV) and anti-ZIKA virus activity. Compounds 2a–g were found to be efficient against YFV in low micromolar range using human Vero cells and hepatoma Huh-7 cells. The SAR study was explored and it was found that alteration of the carboxylic acid groups and 5-carboxylate ester into amide group enhanced the inhibitory action against YFV. Among all

![FIG. 4.2 Imidazole derivatives against various strains of viruses.](image)

![SCHEME 4.1 Synthesis of benzimidazole derivatives.](image)
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the synthesized compounds, compound 2a proved to be effective against YFV (EC_{50} = 1.7 ± 0.8 μM on Huh-7 cells, EC_{50} = 1.2 ± 0.02 μM on Vero cells), as well as ZIKA virus (EC_{50} = 4.5 ± 2.1 μM) [28] (Fig. 4.4).

2.2 Influenza

Influenza continues to be a highly contagious and barely inhibited human infection. Worldwide, 500 million people suffer every year from the flu with about 2 million fatalities [29, 30]. The influenza A virus is responsible for the two of the four reported rare pandemics and is the cause of recurring epidemic outbreaks, remaining a continuous risk to socioeconomic development and public health.

Available medications for the treatment of influenza mainly focus on some influenza protein targets such as antivirals for M2 ion channels (rimantadine and amantadine) and neuraminidase (peramivir, oseltamivir, laninamivir, and zanamivir) and the vaccines for hemagglutinin [31]. Currently most of the influenza A virus strains have shown strong resistance to these drugs [32–36]. Therefore, there is a crucial demand for novel antiinfluenza agents, particularly after the 2009 H1N1 (swine flu) and 2013 H7N9 outbreaks [37, 38].

A series of novel 2-substituted 7,8-dihydro-6H-imidazo[2,1-b][1,3]benzothiazol-5-ones (3a–k) were synthesized by cyclohexane-1,3-diones and assessed for their cytotoxicity and antiviral activity against influenza virus A/Puerto Rico/8/34 (H1N1) in MDCK cells. The three compounds 3i–k,
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containing a thiophene ring, presented the most promising virus-inhibiting activity and low toxicity profile. The analog 3j demonstrated the highest antiviral activity against influenza virus with CC$_{50}$: > 1000 μM, SI = 77 [39] (Scheme 4.2, Fig. 4.5).

A series of compounds was developed by the conjugation of imidazole moiety with pinanamine derivatives and evaluated for their antiinfluenza activity against the amantadine-sensitive virus A/M2 wild-type virus A/HK/68 and amantadine-resistant strain A/WSN/33. Most of the compounds exhibited inhibitory activity against the amantadine-sensitive virus at a very low concentration by blocking the A/M2-WT ion channel. Compound 4 afforded the inhibition of A/M2 wild-type virus A/HK/68 as well as the amantadine-resistant strain A/WSN/33, with IC$_{50}$ values of 2.5 mM and 3.4 mM, respectively [40] (Scheme 4.3).

A total of 250,000 pure chemicals and semipurified fractions from natural extracts were evaluated by throughput screening for antiviral activity against

FIG. 4.4 Active anti-ZIKV benzimidazole derivatives.
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Twenty-one compounds were found to be active, viz. amantadine, rimantadine, 13 related adamantanes, and six nonadamantanes. Two imidazole-based compounds, 5a and 5b, also exhibited antiviral activity against influenza A virus with EC_{50} values of 0.3 and 0.4 μM, respectively [41] (Fig. 4.6).

Five imidazole alkaloids were extracted from the marine sponge Pericharax heteroraphis and evaluated for their antiviral activity against H1N1 influenza
A virus (IAV) [42]. All the alkaloids have a central 2-aminoimidazole ring substituted at the C-4 and C-5 positions by one or two functionalized benzyl groups. Only alkaloid leucettamine C exhibited weak inhibitory activity against the H1N1 virus with an inhibition rate of 33% while the positive control drug, ribavirin, showed an inhibition rate of 65% (Fig. 4.7).

2.3 SARS-COVID

The first coronavirus (SARS-CoV-2) infection was reported in Wuhan (China) in December 2019, and spread all over the world [43–47]. SARS-CoV-2 belongs to the Betacoronaviruses family like Middle-East Respiratory Syndrome Human Coronavirus (MERS HCoV) and Severe Acute Respiratory Syndrome Human Coronavirus (SARS-CoV-1) [48]. Current studies on SARS-CoV-2 have demonstrated that the chymotrypsin-like protease, 3CL hydrolase, or main protease (Mpro) of SARS-CoV-2 play a crucial role in the life cycle of coronavirus and hence the inhibition of Mpro can provide significant therapeutic treatment against COVID-19 infection [49, 50].
A docking study was performed on 18 imidazole analogs attached with 7-chloro-4-aminoquinoline against coronavirus (SARS-CoV-2) via binding to the active site of SARS-CoV-2 main protease. The study showed that the compounds 6a, 6b, and 6c have greater binding energy with SARS-CoV-2 main protease than other imidazole derivatives, and the two drugs, hydroxychloroquine and chloroquine, caused potent antiviral activity against COVID-19. Furthermore, the study indicated that the molecules with electronegative atoms and more than three cycles have high affinity toward binding site of the protease due to halogen interaction, formation of π-bonds, and hydrogen bonding [51] (Fig. 4.8).

Four new azo imidazole derivatives 7a–d were synthesized by the condensation reaction of amino functionalized imidazole compounds with azo-coupled ortho-vaniline precursor and the molecular docking studies of these ligands were carried out against the main protease (6LU7) of novel coronavirus (COVID-19). The results displayed good binding energies for derivatives 7a–d (−7.7 kcal/mol for 7a, −7.0 kcal/mol for 7b, −7.9 kcal/mol for 7c, and −7.9 kcal/mol for 7d) and promising inhibitory activity of all ligands against the main protease (M pro) of SARS-CoV-2 [52] (Scheme 4.4).

**FIG. 4.8** Active imidazole analogs against coronavirus.

**SCHEME 4.4** Synthesis of azo imidazole derivatives.
2.4 Dengue

Dengue is the most prevalent arthropod-borne viral infection in the world, especially in tropical and subtropical areas, and is estimated to infect 96 million people annually [53]. The genome of DENV is composed of 10.7 kb, positive, single-stranded RNA with four different stereotypes (DENV-1 to DENV-4) [54]. The RNA-dependent RNA polymerase plays a pivotal role in the synthesis of viral genome, and it is thus determined as an effective drug target [55]. Immense efforts have been made to find the potent antiviral chemotherapeutics or vaccine against DENV, but without success as yet, and disease treatment is therefore restricted to supportive care. Further, more biologically active molecules have been explored for the treatment of DENV. In this search, a series of imidazole 4,5-dicarboxamide derivatives has been synthesized (Scheme 4.5) and evaluated for their inhibitory action against dengue virus using high-throughput screening assay of dengue virus-2 replicon. Some of these derivatives have a tendency to inhibit dengue virus (DENV) and yellow fever virus (YFV) in the micromolar range. In particular, compound 8b showed the highest antiviral activity against YFV (EC_{50} ± 1.85 μM) while compound 8c showed the most potent inhibitory activity against DENV in Vero cells (EC_{50} ± 1.93 μM) [56] (Fig. 4.9).

![Scheme 4.5 Synthesis of imidazole 4,5-dicarboxamide derivatives.](image)

![Fig. 4.9 Active imidazole 4,5-dicarboxamide derivatives against dengue virus.](image)
A nucleoside series has been evaluated to detect the effective antiviral compounds that inhibited the replication of DENV. Compound 5-ethynyl-(1-β-D-ribofuranosyl)imidazole-4-carboxamide (9a) and its 4-carbonitrile derivative (9b) were found to be lead compounds against DENV, but due to cytotoxicity, more derivatives were developed. As a result, 4′-thio and 4′-seleno derivatives of 9a and 9b, i.e., 9c–9f, were prepared. These derivatives presented a positive regulation on DENV replication inhibition without any sign of toxicity [57] (Fig. 4.10).

The antiviral activity of the metal complex [Cu(2,4,5-triphenyl-1H-imidazole)$_2$(H$_2$O)$_2$].Cl$_2$ was investigated through inhibition of replication of DENV-2 in Vero cells. The complex was found to be significant in inhibiting the growth of DENV-2 with an IC$_{50}$ value of 98.62 μg/mL and exhibited a low cytotoxicity value (CC$_{50}$ = 300.36 μg/mL) against Vero cells [58].

2.5 Hepatitis

Hepatitis C (HCV) is associated with both mild and acute liver disease and may lead to chronic states like cirrhosis, hepatocellular carcinoma, and liver failure [59, 60]. Globally, approximately 150 million people have been infected by HCV with an estimated 3–4 million new cases occurring annually [61]. The conventional treatment of HCV infection by pegylated interferon and ribavirin also possesses toxicity [62, 63] and in 2011, boceprevir and telaprevir were accepted for the medication of chronic hepatitis C genotype 1 infection [64, 65]. Moreover, due to the drug-resistant nature of HCV, there is an urgent need to discover novel drugs for treatment.

A library of novel 2-aminoalkylsubstituted 6-chloro- or 5,6-dichloro-1H-imidazo[4,5-b]pyridines has been developed and assessed for their anti-HBV activity in an efficient infectious environment. Compounds 10d, 11a, 12a, 12b, and 12d showed promising activity against HBV. The monochloro diethylaminoethyl-substituted derivative 12d was found to be the most active.
to show anti-HBV effect to pegylated interferon α2b while compounds 13a–d did not show significant activity. All the compounds were capable of reducing HBV rcDNA, cccDNA, and pgRNA levels, and possessed significant anti-HBV activity [66] (Scheme 4.6).

A series of imidazole analogs was investigated for their significant HCV NS5B polymerase inhibition activity through their binding at the active site of PDB ID: 2DXS. Some compounds exhibited good binding scores; in particular, compounds 14a (−84.12 kJ mol−1) and 14b (−65.47 kJ mol−1) showed high interaction with promising inhibitory activity toward HCV polymerase [67] (Fig. 4.11).

Twenty imidazole-coumarin conjugates were synthesized by linking imidazole with coumarin derivatives by −SCH2− moiety (Scheme 4.7) and screened for their antiviral activity against HCV. Among all the synthesized compounds,
three derivatives (15b, 15d, and 15e) showed immense anti-HCV activity with EC50 values of 7.2, 5.1, and 8.4 μM combined with SI values of 12, 15, and 21, respectively. Furthermore, the SAR study was explored and it was established that the parent imidazole analog with an N–H proton afforded a larger SI value, and inclusion of different groups into the coumarin ring enhanced selectivity as well as potency of the conjugates [68].

Novel 1H-1,2,4-triazole and imidazole L-ascorbic acid and imino-ascorbic acid derivatives were synthesized (Scheme 4.8) and their antiviral activity was evaluated against HCV through their inhibitory activity on a Huh 5.2 replicon. Compound 16a was established as the most promising agent (EC50 value = 36.6 μg/mL and CC50 value more than 100 μg/mL) against replication of the HCV virus by inhibiting IMPDH, a major target for antiviral activity [69].

Twenty-five new imidazole NH-substituted daclatasvir-modified conjugates were synthesized in order to enhance pharmacokinetic properties and potency against HCV and assessed in a HCV genotype 1b replicon. Among all the synthesized compounds, 2-oxoethyl acetate substituted compound 17 (Fig. 4.12) demonstrated comparable anti-HCV potency (EC50 = 0.08 nM) with respect to the lead drug daclatasvir. Prodrug 17 showed similar exposure to the lead compound in vivo and also behaved as an ideal candidate for a gradual and continuous release of daclatasvir [70]. The entire structure of HCV p7 protein was described and the allosteric site on the channel periphery for the specific drug–protein interactions was determined. Furthermore, the structure guided diverse inhibitory small molecules with high activity and selectivity against HCV was examined. Compound 18 (Fig. 4.12) was found to be effective against HCV by forming two H-bonding interactions with backbone carbonyl of Gly46 and the

**Scheme 4.8** Synthesis of imidazole L-ascorbic acid derivatives.

Reagents and conditions: (i) HMDS/(NH4)2SO4/argon/reflux, 12 h, TMS-triflate/dry acetonitrile/ 55-70 °C
(ii) NH3/MeOH-dioxane/ref 24 h (ii) BCl3/CH2Cl2/-78°C/2 h.
hydroxyl group of Tyr45, and depressed the rimantadine resistance polymorphism at submicromolar concentrations [71].

2.6 HIV

Human immunodeficiency virus (HIV) was discovered in the mid-1980s as a responsible agent for acquired immune deficiency syndrome (AIDS) [72]. Highly active antiretroviral therapy (HAART) was employed in 1995 as a treatment for HIV/AIDS. The main component of HAART is Efavirenz, which has a tendency to inhibit the HIV-1 reverse transcriptase (RT), the enzyme responsible for interchange of viral RNA into double-stranded DNA [73]. However, HAART could not eradicate the virus. Viral resistance emerged toward this mechanistic class of inhibitors [74–76], and urged the demand of new drugs with unique resistance profiles for complete care of patients with the virus.

A series of new 1-substituted-5-aryl-1H-imidazole was synthesized by cycloaddition of para toluenesulfonylmethyl isocyanide with imines and aldehydes using microwave irradiation and all the synthesized compounds were screened for their anti-HIV activity via Alpha Screen HIV-1 IN-LEDGF/p75 inhibition assay. Six imidazole-based derivatives (21c, 21f, 22c, 22f, 25a, and 25b) showed promising inhibitory activity, i.e., more than 50% inhibition at 10μM against the HIV strain. Furthermore, the SAR study indicated that the two aromatic rings and N-heterocyclic moiety played crucial roles in inhibition and directed the HIV-1 IN and LEDGF/p75 protein–protein interaction [77] (Scheme 4.9).

A library of novel nonnucleoside reverse transcriptase inhibitors related to imidazole-amide conjugates was described and evaluated for their antiviral activity toward HIV-1, along with the resilient Y188L-mutated virus. The ligand-protein interaction was optimized for key H-bonding motif using X-ray crystallography and compound 26 (Fig. 4.13) demonstrated enormous antiviral
One novel imidazole sulfate \((27a)\) and three known derivatives \((27b–d)\) were isolated from the sponge *Dercitus (Halinastra) japonensis* and evaluated for their antiviral activity against HIV. Among all compounds, only 27b was found to be active against HIV with an IC\(_{50}\) value of 109 μM and a CC\(_{50}\) value of more than \(2.84 \times 10^2\) μM [79] (Fig. 4.14).

Through the high-throughput screening program, 4-(phenylcarbamoyl)-1H-imidazole-5-carboxylic acid \((28)\) was chosen as a selective and significant inhibitor of the interaction between LEDGF/p75 and HIV-1 IN (IC\(_{50}\) value = 6 ± 4 μM). Furthermore, the SAR study explored active groups in the...
synthesized compounds and a library of nontoxic 5-carbonyl-1H-imidazole-4-carboxamide inhibitors of LEDGF/p75 and HIV-1 IN interaction was synthesized. Compound 28 showed good interactions with protein by forming two H-bonds and inhibited the replication of HIV-1 by depressing the interaction of HIV1 IN to LEDGF/p75 [80] (Fig. 4.15).

A series of imidazole thioacetanilide derivatives was synthesized and screened for their anti-HIV activity. Among all derivatives, compounds 29e (EC<sub>50</sub>=0.18 μM), and 29b (EC<sub>50</sub>=0.20 μM) presented the most potent inhibition of HIV-1 compared to the reference drugs, nevirapine and delavirdine. Moreover, the SAR study demonstrated that the aryl ring attached to imidazole moiety and the hydrophobicity of the aryl group played a crucial role for binding affinity between active binding site and the inhibitors, and thus modified the biological potency [81] (Scheme 4.10) (Fig. 4.16).

### 2.7 Miscellaneous

A library of various imidazo[1,2-a]pyrrolo[3,2-c]pyridines was synthesized and assessed for their anti-BVDV activities in MDBK cells. Furthermore, modification in structure at positions 2, 3, 7, and 8 were performed to enhance the
potency against BVDV. The SAR study concluded that substitution on the pyrrole ring did not affect the activity while modification at position C-3 reduced the antiviral activity. Among all the synthesized compounds, compounds 30a–f demonstrated potent anti-BVDV activity [82] (Fig. 4.17).

A library of 2-oxoimidazolidines derivatives was synthesized and their antiviral activities were assessed against BK human polyomavirus type 1 (BKPyV) in vitro. The bioassay study identified that derivatives 31b and 31a demonstrated moderate antiviral potency against BKPyV with EC\(_{50}\) values of 5.4 and 5.5 μM, respectively, that were comparable to those of the standard drug cidofovir. Compound 31b showed the same selective index and cytotoxicity to cidofovir while compound 31a has high toxicity and a less selective index than the reference drug [83] (Fig. 4.18).

The antiviral activity of 7-(6-(2-methyl-imidazole))-coumarin (32) was examined against spring viremia of carp virus (SVCV) in zebra fish. The data indicated that compound 32 was able to inhibit the half-life in the early stage of viral infection (1–4 days) and reduced the viral titer in fish body by suppressing the SVCV glycoprotein gene expression. Moreover, compound 32 enhanced the expression of interferon genes (IFN\(\gamma\), IFNφ1, IFNφ2, and RIG-1) in nonviral infected zebra fish and strengthened the immune response. Compound 32 also displayed antioxidant protection on fish by raising the levels of antioxidant-related enzyme activities and gene transcription in SVCV-infected zebra fish [84] (Scheme 4.11).

**FIG. 4.17** Biologically active imidazo[1,2-\(a\)]pyrrolo[3,2-\(c\)]pyridines against BVDV.

**FIG. 4.18** 2-oxoimidazolidines derivatives with anti-BK human polyomavirus.
A series of 1-hydroxyimidazole derivatives was synthesized by the condensation of oximes with salicylaldehyde derivatives and ammonium acetate in glacial acetic acid and evaluated for their antiviral activity against vaccinia virus in Vero cell culture. The synthesized compounds presented good inhibitory activity and compound 33c showed the most promising activity (IC$_{50}$ = 1.29 ± 0.09 μg/mL) against the vaccinia virus. Furthermore, the SAR study showed that modification at the 2-hydroxyphenyl moiety of 1-hydroxyimidazoles led to enhanced cytotoxicity while the N-phenylcarbamoyl substituent in position 5 caused cytotoxicity and loss of inhibitory activity. The N-hydroxy group proved crucial for antiviral activity against the vaccinia virus [85] (Scheme 4.12).

An effective method was introduced for the synthesis of different chalcone derivatives and their antiviral activity was screened against TMV and CMV. The assay study illustrated that various compounds showed potential anti-CMV and anti-TMV activities in vivo. Specifically, compound 34 presented the most promising inactivating activity against TMV (EC$_{50}$ value of 51.65 μg/mL), which was more than the reference drug ribavirin; it also behaved as an excellent protective and curative agent against CMV. Moreover, the molecular docking study was performed and four hydrogen bonds were found between
TMV coat protein and compound 34, which confirmed the strong binding capacity to TMV-CP. The SAR study demonstrated that the substitution of an electron-releasing group at the 2-position of benzenesulfonamide aromatic cycles with less steric hindrance enhanced the antiviral activity [86] (Fig. 4.19). A series of 2-(substituted phenyl)-1H-imidazole and (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-methanone derivatives was synthesized and evaluated for their antiviral activity against various virus strains such as vaccinia virus (VV), herpes simplex virus-1 (KOS) (HSV-1 KOS), herpes simplex virus-2 (G) (HSV-2G), Coxsackie virus B4 (CV-B4), vesicular stomatitis virus (VSV), respiratory syncytial virus (RSV), reovirus-1 (RV-1), Sindbis virus (SV), parainfluenza-3 virus (PI-3V), and Punta Toro virus (PTV). Among all the compounds, compounds 35a and 35b were found to be the most prominent antiviral agents against VV with EC<sub>50</sub> values of 2 and 4 mg/mL, respectively. Moreover, compound 35b showed good antiviral activity against HSV-1 KOS (EC<sub>50</sub> = 59 mg/mL) and HSV-2G (EC<sub>50</sub> = 50 mg/mL) [87] (Fig. 4.19).

Seventy-six 2-phenylbenzimidazole analogs were synthesized and screened for the cytotoxicity and antiviral activity toward a group of 10 RNA and DNA viruses. The compounds showed good antiviral activity against CVB-2, BVDV, Sb-1, HSV-1, and YFV. Among these compounds, compound 36a exhibited an immense antiviral profile against VV (EC<sub>50</sub> = 0.1 μM) and compounds 36b, 36c, and 36d showed promising inhibitory activity against BVDV with EC<sub>50</sub> values of 1.5, 0.8, and 1.0 μM, respectively [88] (Fig. 4.20).

The repurposing-based design of drugs was performed for the evaluation of antiviral activity of the imidazole molecules at sublethal doses to reduce Newcastle disease virus replication in vivo, in ovo, and in vitro. Chickens treated with the repurposed drug of imidazole developed antiviral type I interferon and exhibited absence of the virus [89]. In addition, the N-methylpyrrole–imidazole polyamides exhibited significant antiviral activity against three different genotypes of HPV: HPV16 (in W12 cells), HPV18 (in Ker4–18 cells), and HPV31 (in HPV31 maintaining cells) [90].

FIG. 4.19  Active antiviral agents containing imidazole moiety.
3. Conclusion

The present era is full of stressful life and poor eating habits and has decreased immunity, making our bodies optimum place for food and shelter for many pathogens, including viruses. Viruses not only disrupt daily life but also are contagious, and their genomic structure is constantly mutating. Many antiviral drugs are present to curb viral infections, but there are problems associated with available antiviral drugs including limited efficiency, toxicity, low bioavailability, and complex synthesis. Therefore, discovery of a new generation of active antiviral drugs with better drug activity and a good pharmacological profile seems to be challenging in pharmaceutical sciences and antiviral research.

Imidazoles have emerged as appealing scaffolds with exceptional structural features and noteworthy biological properties. The present chapter is focused on providing insights for the synthesis of novel imidazole-based antiviral agents. For some decades, numerous studies have been dedicated to the advancement of antiviral imidazoles. Several natural, semisynthetic, and synthetic imidazole derivatives have been described as potential antiviral agents against a wide range of viruses. This chapter systematically describes the mode of action of imidazoles on various viruses including novel coronavirus, Zika virus, HIV, hepatitis, dengue, etc. Subsections of this chapter also discussed synthesis, SAR, molecular docking, and biological profile of imidazoles and their derivatives, opening a new platform for easier understanding of readers, and motivating researchers to create new imidazole drug templates with ease. The chapter also provides abundant knowledge, ample information, and prospects about imidazoles with updated literature. Regardless of extensive work and promising outcomes on imidazole moiety as significant antiviral drugs, a few challenges and opportunities remain for researchers that need to be discussed:

- evaluation of the antiviral activity of numerous imidazole-based chemical derivatives and exploration of novel methodologies, biomarkers for determining the most relevant molecular targets, and appropriate mechanism of action of active analogs;
● promotion of more rational design of antivirals by determining X-ray crystallography of target-ligand complexes; and
● more efficient and effective methods such as computer-aided drug design, structure-based drug design, fragment-based drug design, etc. should be used for designing new antiviral molecules.

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Conflict of interest
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