ORIGINAL PAPER

BENZIMIDAZOLE AS A PROMISING ANTIVIRAL HETEROCYCLIC SCAFFOLD: A REVIEW

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Abstract. *Heterocyclic derivatives are unavoidable in many fields of natural disciplines. These derivatives play numerous significant roles in research, medication, and nature. Nitrogenous heterocyclic derivatives extremely are the main target of concern in synthetic chemistry to ensue active natural products with pharmaceuticals and agrochemicals interest. Benzimidazole skeleton is another example of some active heterocyclic moiety that significantly contributes in the numerous bioactive of essential compounds. Benzimidazole skeleton is studied as a prominent moiety of biologically active compounds with various activities including antimicrobial, antiprotozoal, anticancer, antiviral, acetylcholinesterase, antihistaminic, anti-inflammatory, antimalarial, analgesic, anti-HIV and antitubercular. Therefore, in this review we summarize the various antiviral activities of several benzimidazole derivatives and outline the correlation among the structures of different benzimidazoles scaffold with their therapeutic significance.*

Keywords: *antiviral activity; benzimidazole; heterocyclic system; scaffold; IC_{50} values.*

1. INTRODUCTION

Benzimidazole skeleton is most common in heterocyclic as well as in medicinal chemistry. Due to their regular use in the field of pharmaceutical, bioinformatics, and drug design, these scaffolds are also known as privileged [1]. It is also playing an valuable pharmacophore role and also a privileged substructure in drug discovery which provides a significant portion for various natural activities [2].

At the 4 and 5 positions of the imidazole ring system, the fusion of benzene and imidazole ring produce benzimidazole moiety. Benzimidazole is amphoteric because it possesses assets of both acids as well as bases in the presence of the NH group. An additional aspect of the benzimidazole ring is to quickly form salts. Therefore, the benzimidazole scaffold is valuable to produce a new drug applicant [3].

2. BENZIMIDAZOLE DERIVATIVES AS A SIGNIFICANT PHARMACOLOGICAL SCAFFOLD

Many biological activities of benzimidazole scaffolds are previously reported including antimicrobial [4], antiprotozoal [5], anticancer [6], antiviral [7], acetylcholinesterase

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[8], antihistaminic [9], anti-inflammatory [10], antimalarial [11], analgesic [12], anti-HIV [13] and antitubercular [14]. Discovery of effective and new antimicrobial agents signifies one of the most vital improvements in therapeutics to control the severe infections as well as in the inhibition and treatment of specific infectious difficulties of other medicinal modalities including chemotherapy and surgery [15-17]. But previously, considerable interest has been dedicated to delivering the challenge of Multidrug resistant (MDR) bacteria and fungi subsequent from the extensive consumption and exploitation of traditional anti-microbial drugs [18].

Current research recommended that substituted benzimidazoles, benzoxazoles, and associated heterocycles (isosteres of nucleotides), simply interact with biopolymers and have probable activity with inferior noxiousness in the chemotherapeutic method [19]. Benzimidazole scaffolds display their activities against helminths, bacteria, and fungi by blocking microtubule in numerous nematodes, trematodes, and cystode. Global infective disease statistics have displayed shocking data in the spread of Gram-positive and Gram-negative bacteria with MDR varieties [20]. Liberal non-observance and the incidence of MDR pathogens frequently inhibit modern infection treatments based on a persistent Multidrug targets. Reasonable drug design has been proven to be incredibly advantageous in this regard, while the biological origin of innate and developed resistance methods is mostly known [21]. Through modifying the substitutions on the benzimidazole scaffold, their numerous biological activities are achieved. Several marketed drugs possess benzimidazole skeleton are displayed in Fig. 1.

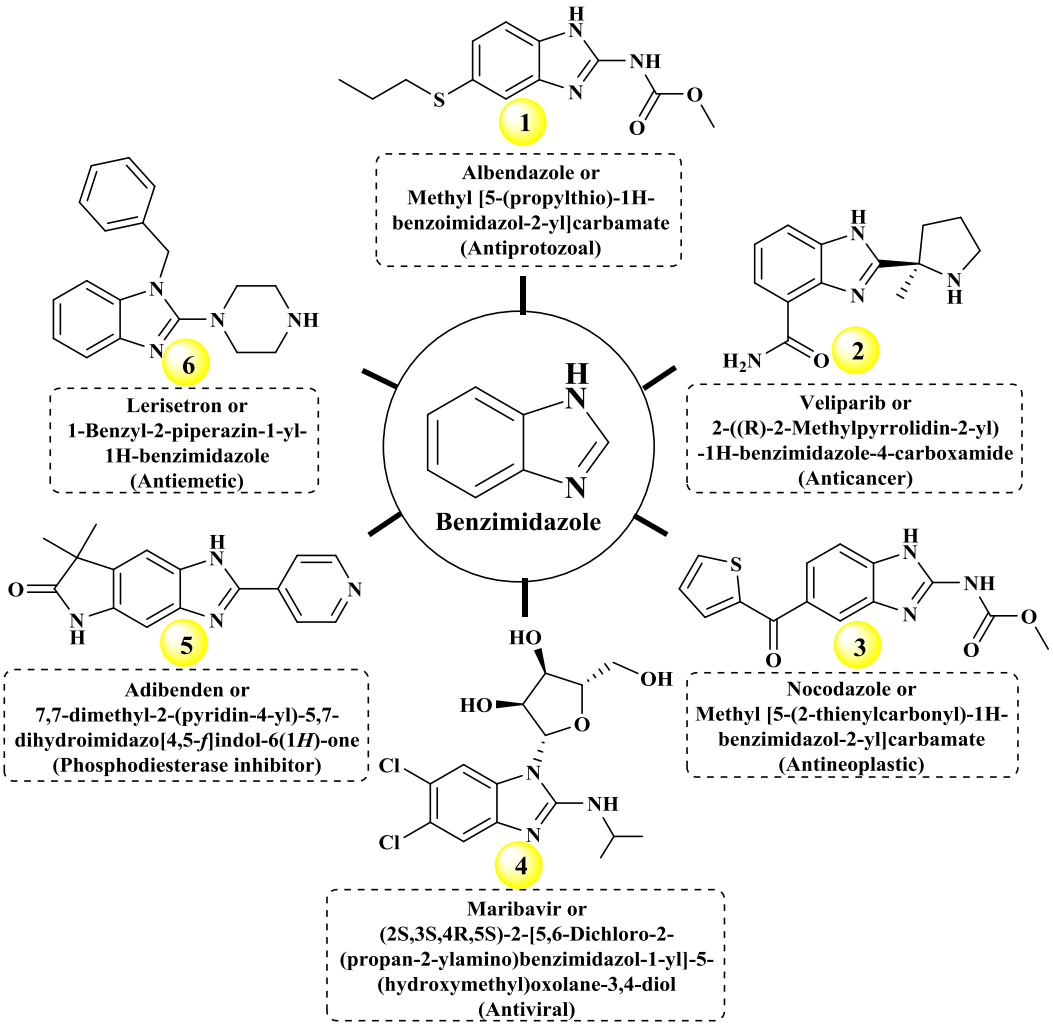

Figure 1. Marketed drugs having benzimidazole scaffold.

Albendazole **1** is the most common benzimidazole drug and used as antiprotozoal (such as neurocysticercosis and hydatid disease) [19]. Veliparib **2** is another potential benzimidazole anti-cancer drug appearing as a poly(ADP-ribose) polymerase (PARP) inhibitor and widely used in the curing of ovarian cancer, cell lung cancer and BRCA breast cancer [22]. Nocodazole **3** is an antineoplastic benzimidazole drug. Its action mechanism includes the prevention of mitosis and produces apoptosis in tumor cells [23]. Maribavir **4** is an effective benzimidazole antiviral drug and display their activity against cytomegalovirus (CMV) [24]. Adibenden **5** is also an example of a benzimidazole drug, it shows potential phosphodiesterase inhibitor activity. Lerisetron **6** acts as an antihistaminic agent. It also shows effective antiemetic and clinical studies against nausea related to cancer chemotherapy [25].

Parasitic illnesses are still worldwide problems that severely affect common health. Infections fetched about by protozoa, such as *Plasmodium falciparum*, *Trypanosoma cruzi*, *Trichomonas vaginalis*, *Giardia intestinalis*, *Leishmania Mexicana* and *Entamoeba histolytica* [26]. Some helminth also involves causing infections, including *Trichinella spiralis* or *Taenia solium*, has globally distributed associated ailments that impact largely undeveloped territories, where model temperatures occur, still in adding terrible unpolluted and hygiene environments are usual [27].

Viral fever is a illness exposed by large vascular damage and depleting diathesis, fever, and several organ insertions. Several diseases can affect this illness, each with its extremely specific individual origin, procedure of spread, death rate, and medical consequence in individuals [28]. World Health Organization (WHO) has been distinguished Tuberculosis (TB) is the prominent cause of death from an uncontrollable illness, which is generally produced by *Mycobacterium tuberculosis* (Mtb) [27]. In the world, mosquitoes are one of the lethal *Creepy crawlies* which produce biting irritation and transfer dangerous diseases such as yellow fever, intestinal sickness, encephalitis chikungunya, dengue, and filariasis. In the class mosquitoes, Aedes (*Aedes aegypti*) is responsible for the spread of dengue, chikungunya, yellow fever as well as other pathogenic arbo-infections. Similarly, the main trajectory for lymphatic filariasis is *Culex quinquefasciatus* also known as southern house mosquito. it normally stays nearby human lodging and on growing comparable to morsel individuals than diverse warm-blooded mortals. Abdominal infection is a mosquito-borne infective illness that is mainly spread by a diseased female *Anopheles mosquito* [29].

3. REPORTED ANTIVIRAL ACTIVITIES OF BENZIMIDAZOLE DERIVATIVES

In 2004, Fonseca et al. were described the synthesis of numerous benzimidazole derivatives, introduce into naphthalene as well as hydrophenanthrene scaffolds. All the prepared compounds were also exposed to the investigation of their in vitro antiviral activity versus some RNA and DNA viruses [30]. Out of all the synthesized compounds **10**, **12** and **13** benzimidazole derivatives exhibited highest activity against CMV (*cyto-megalo virus*) with antiviral potency IC_{50} >0.2, 1.1–3.2 and 1.0–1.2 μg/mL, respectively and against VZV (*varicella-zoster virus*) with antiviral potency IC_{50} 0.2–0.5, 0.6–2.8 and 0.8–1.4 μg/mL, respectively. All the obtained results were also compared with standard drugs such as Acyclovir and Ganciclovir (Fig. 2).

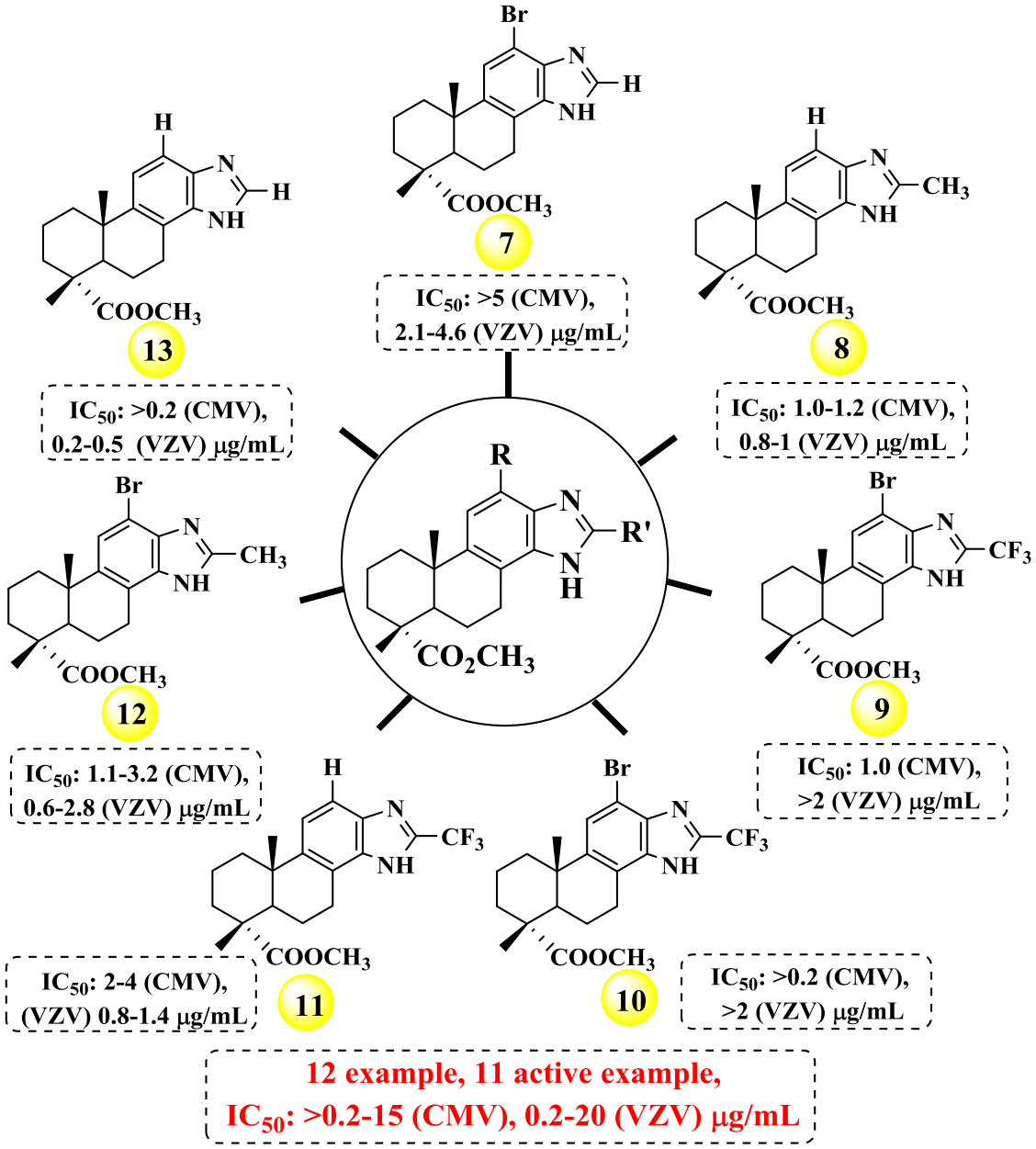

Figure 2. Some benzimidazole derivatives with activity against VZV (varicella-zoster virus).

Similarly, in 2005 Cheng et al. were described the synthesis of various novel benzimidazoles derivatives and further subjected for the evaluation of their antiviral activity *versus* CVB3 (*Coxsackie virus B3)* in Vero cells, well-known as African green monkey kidney (GMK) cells [31]. The benzimidazoles derivatives **21, 22,** and **25** were showing the highest potential with IC_{50} values 1.43, 0.54, and 1.17 μg/mL obtained results were also compared with the standard drug Ribavirin (RVB) displayed (Fig. 3).

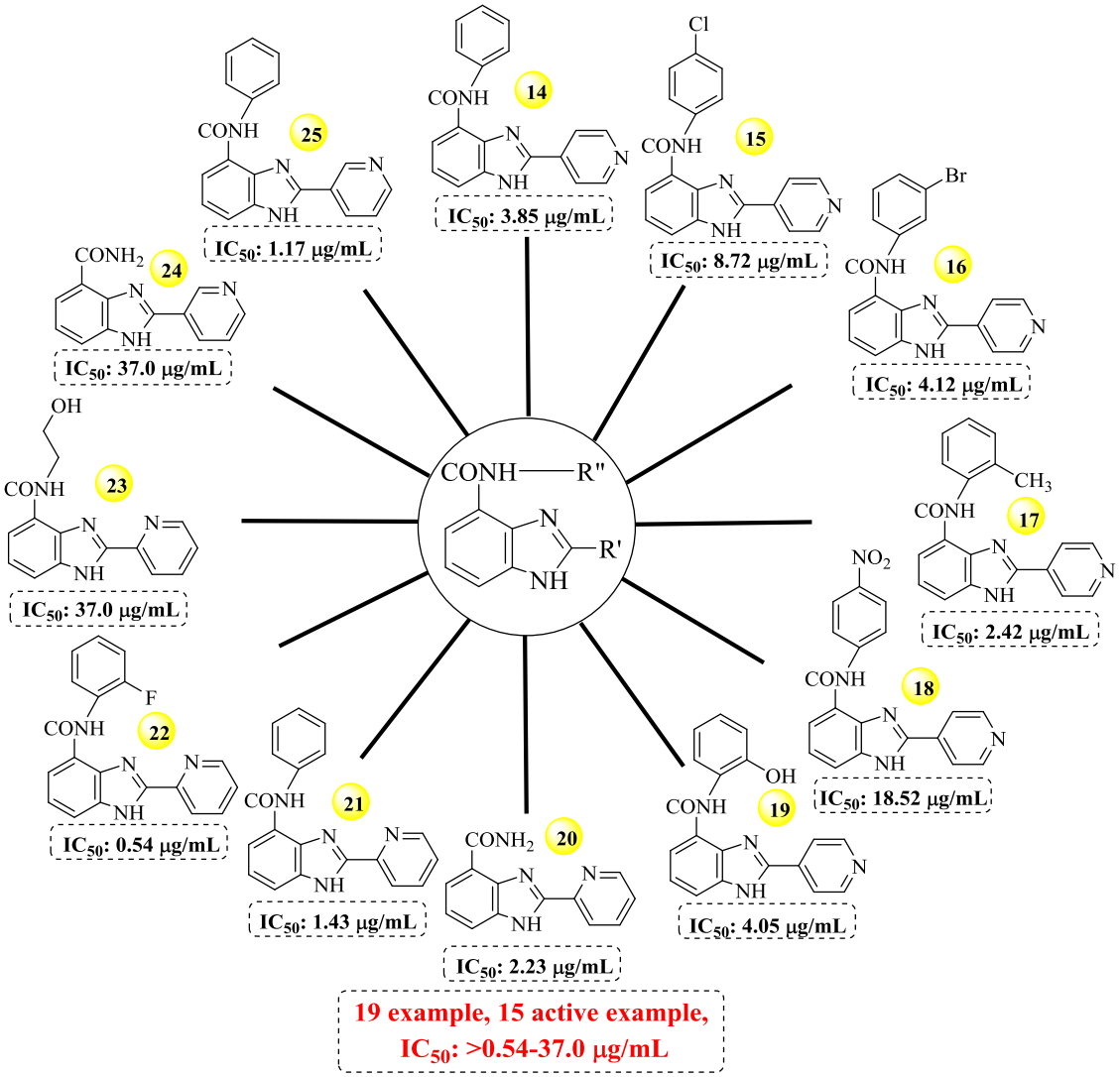

Figure 3. Some benzimidazole derivatives with activity against CVB3 (Coxsackievirus B3).

In 2007, Starcevic et al. were also proposed the synthesis of some substituted benzimidazoles derivatives and further submitted for the valuation of antiviral and antitumor activities, for the evaluation of *in vitro* antiviral inhibitory activity HeLa (human cervical carcinoma) and GMK cell lines were used [32]. Total four Virus strains were used, adenovirus 5 (ATCC VR-5) and herpesvirus 1 (ATCC VR-1545) were grown on HeLa cells on the other hand coxsackie B5 (ATCC VR-185) and echovirus 7 (ATCC VR-1047) were grown on GMK cells. Among the series of substituted benzimidazoles, **29, 32, 33,** and **34** compounds exhibited good activity against all the virus strains without cytotoxicity (Fig. 4). In the same year, Li et al. (2007) were also proposed a series of newly synthesized benzimidazoles derivatives and evaluated their HBV (hepatitis B virus) inhibition potential. Their results are displayed that **38** and **44** compounds exhibited excellent anti-HBV effectiveness with the IC_{50} values 0.70 and 0.70 µg/mL and all the findings were also compared with standard drug Lamivudine and Adefovir [33] (Fig. 5).

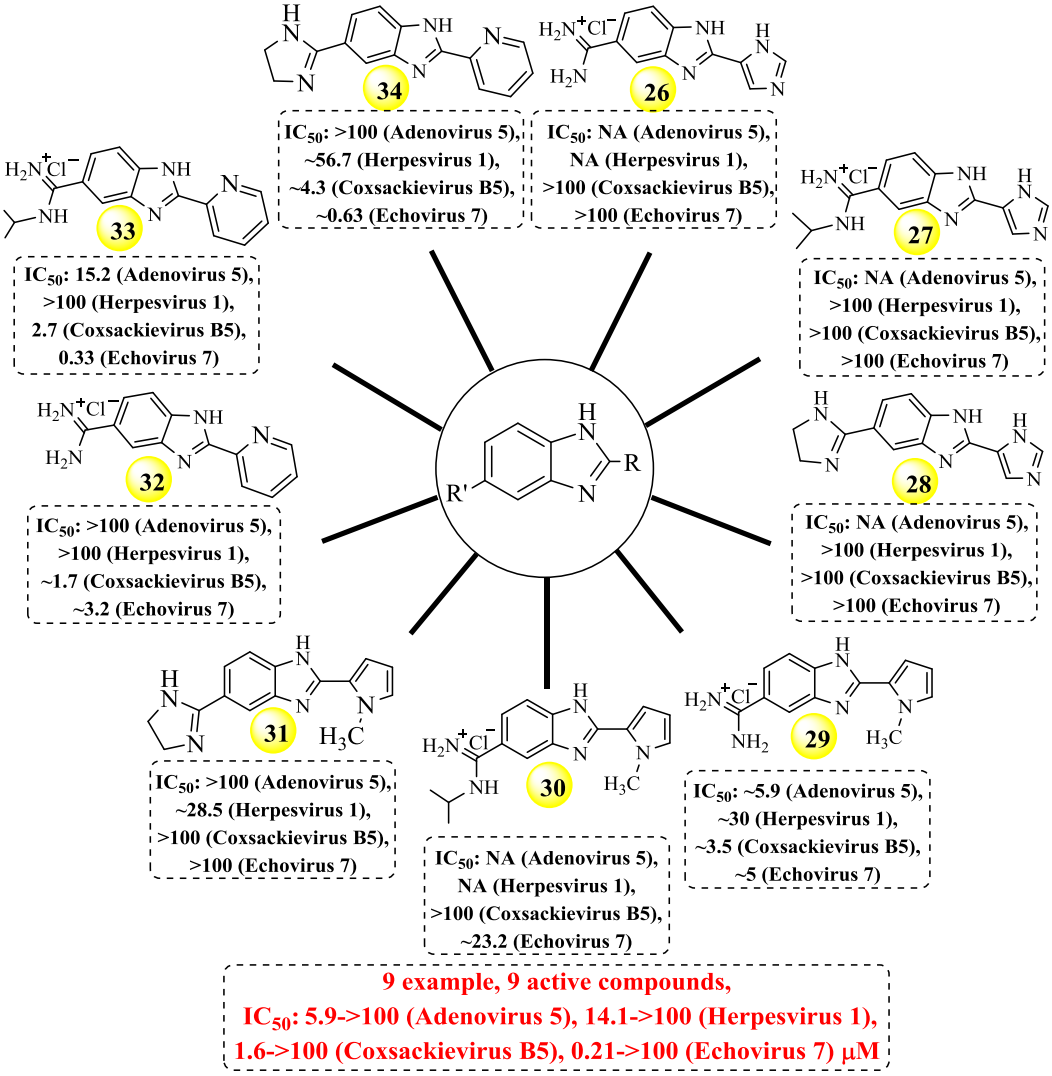

Figure 4. Some benzimidazole derivatives with activity against four virus strains (adenovirus 5 (ATCC VR-5) and herpesvirus 1 (ATCC VR-1545) were grown on HeLa cells and coxsackie B5 (ATCC VR-185) and echovirus 7 (ATCC VR-1047) were grown on GMK cells).

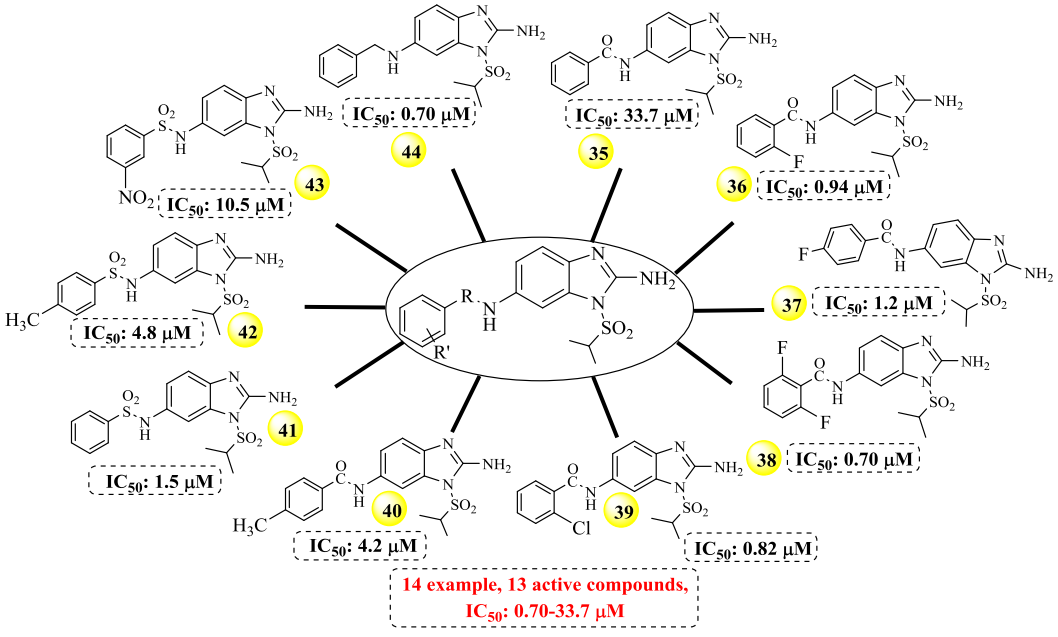

Figure 5. Some benzimidazole derivatives with activity against HBV (hepatitis B virus).

Hwu et al. were also synthesized numerous novel benzimidazole derivatives in 2008 associated with the coumarin ring scaffolds. Synthesized compounds were subjected to the assessed their antiviral activity *versus* the HCV (hepatitis C virus). Including a series of compounds, **52, 54,** and **56** derivatives were observed to be the highest active and revealed EC_{50} values 3.4, 2.3, and 3.1 μM [34] (Figs. 6a and 6b).

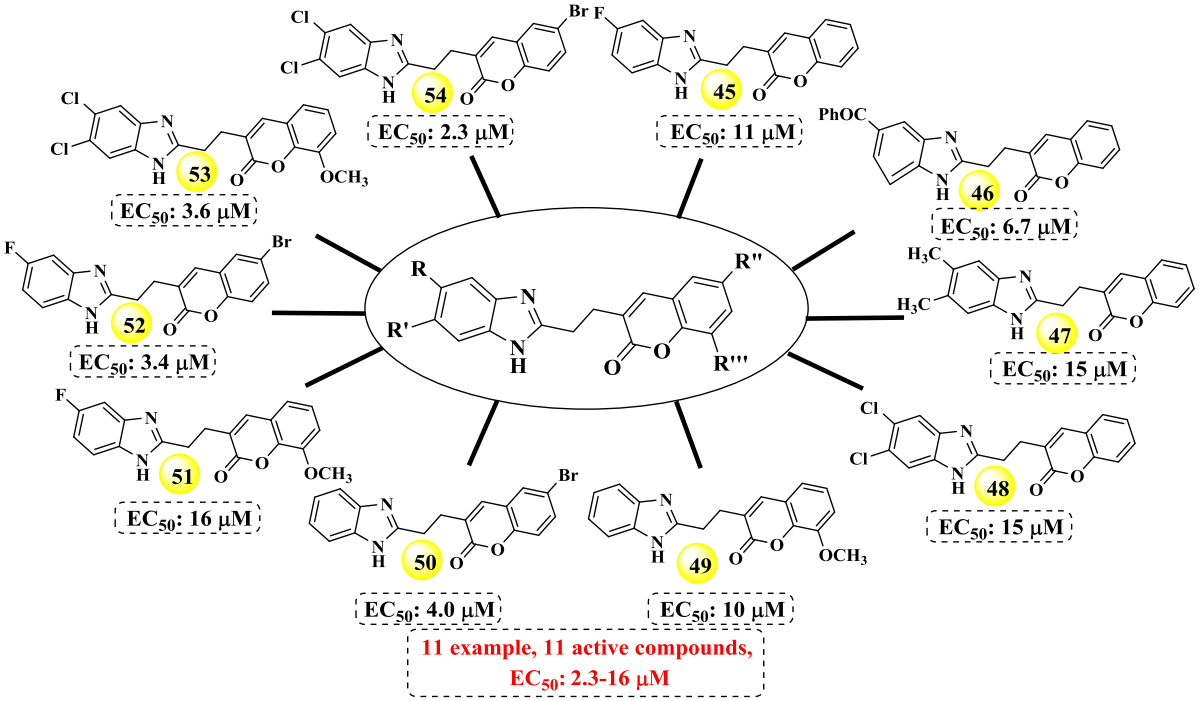

Figure 6a. Some benzimidazole derivatives with activity versus HCV (hepatitis C virus).

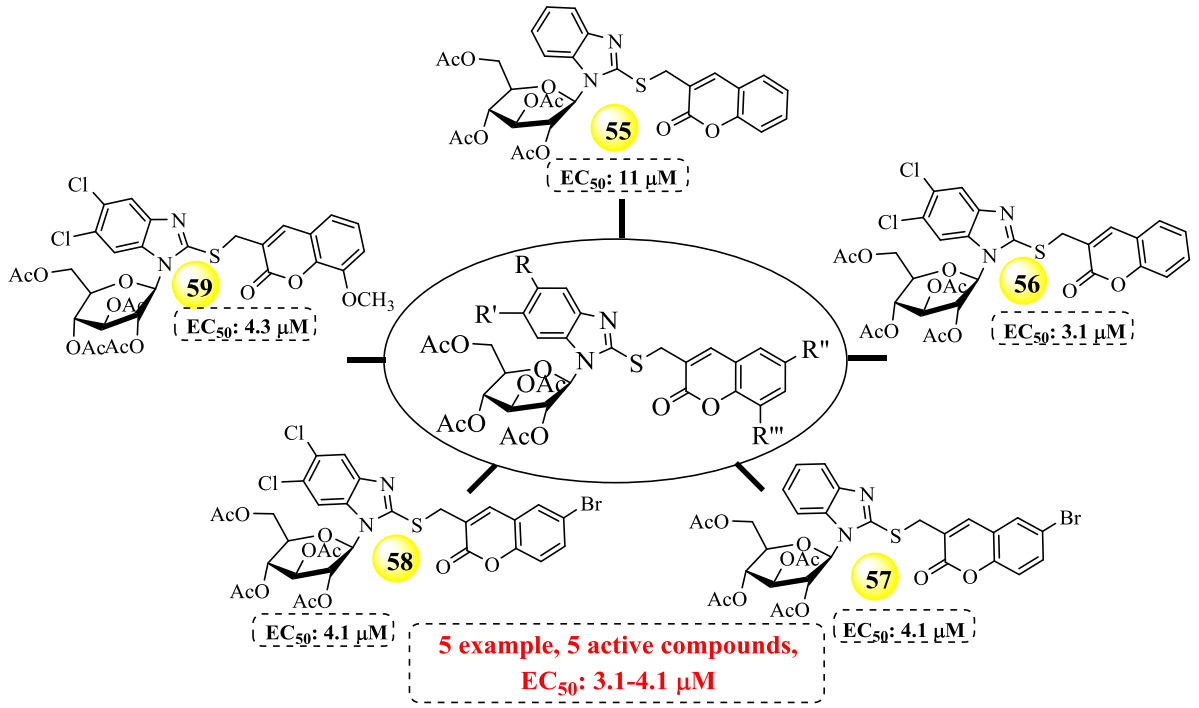

Figure 6b. Some benzimidazole derivatives with activity versus HCV (hepatitis C virus).

In 2009, Zhang et al. [35] were also proposed the synthesis of novel benzimidazole derivatives and further submitted to screen their antiviral activity against CVB3. Among the all synthesized compounds **60** and **62** presented good inhibitory potential with IC_{50} values

1.06 and 5.30 µg/mL as associated to standard drug RBV (IC_{50} value 353.33 µg/mL) [35] (Fig. 7).

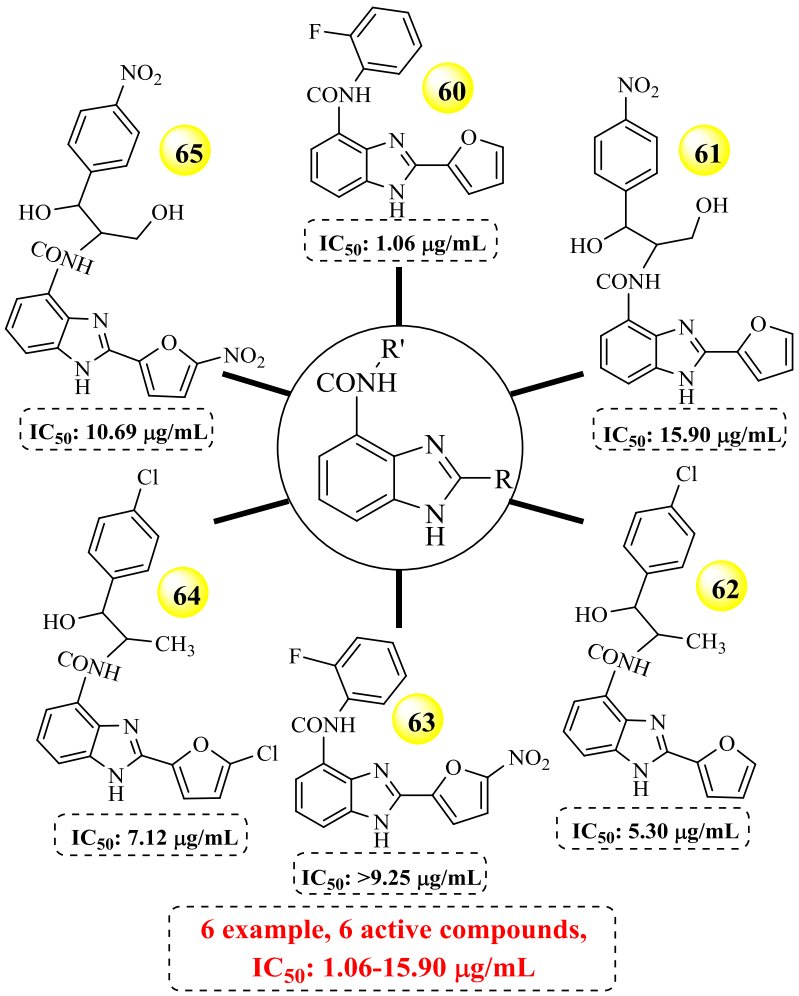

Figure 7. Some benzimidazole derivatives with activity against CVB3.

Miller et al. were proposed a synthesis of numerous N-substituted benzimidazoles in 2010 and screed as a CXCR4 receptor inhibitor. Among them, **66** compound displayed promising antiviral activity with IC_{50} value ~6.0 nM dual protein alters and 1000-fold cytotoxicity. Geometrical optimization as well as the alteration in the side chain have an advantage to considerable improvement in the effectiveness and protein shift to afford molecule with minimum nanomolar anti-HIV potential [36] (Fig. 8). Luo et al. were also reported a new synthesis of benzimidazole compounds in 2010 and synthesized compounds were subjected to screen their HBV as well as cytotoxicity in HepG 2.2.15 cells. Among the series of compounds, **72** compound shows the highest antiviral potential with IC_{50} value < 0.41 µM and results compared with Lamivudine as a reference [37] (Fig. 9).

In 2014, Monforte et al. were described a synthesis of new benzimidazoles and estimated their HIV-1 (human immunodeficiency virus type-1) inhibitor potential. Among all the compounds **78, 80,** and **82** derivatives were observed to be the highest active without toxicity with IC_{50} values 0.18, 0.55, and 0.12 µM. Obtained results are compared with the standard drug Nevirapine and Efavirenz [38] (Fig. 10). Recently, Francesconi et al. (2020) described the synthesis of various new (thio)semicarbazone-based benzimidazoles derivatives as potential antiviral agents *versus* the human respiratory viruses such as RSA, Influenza A/H1N1, Influenza A/H3N2, and Coronavirus 229E. Among the series of compounds, 86, 87 and 92 benzimidazole derivatives display potential antiviral properties [39] (Fig. 11).

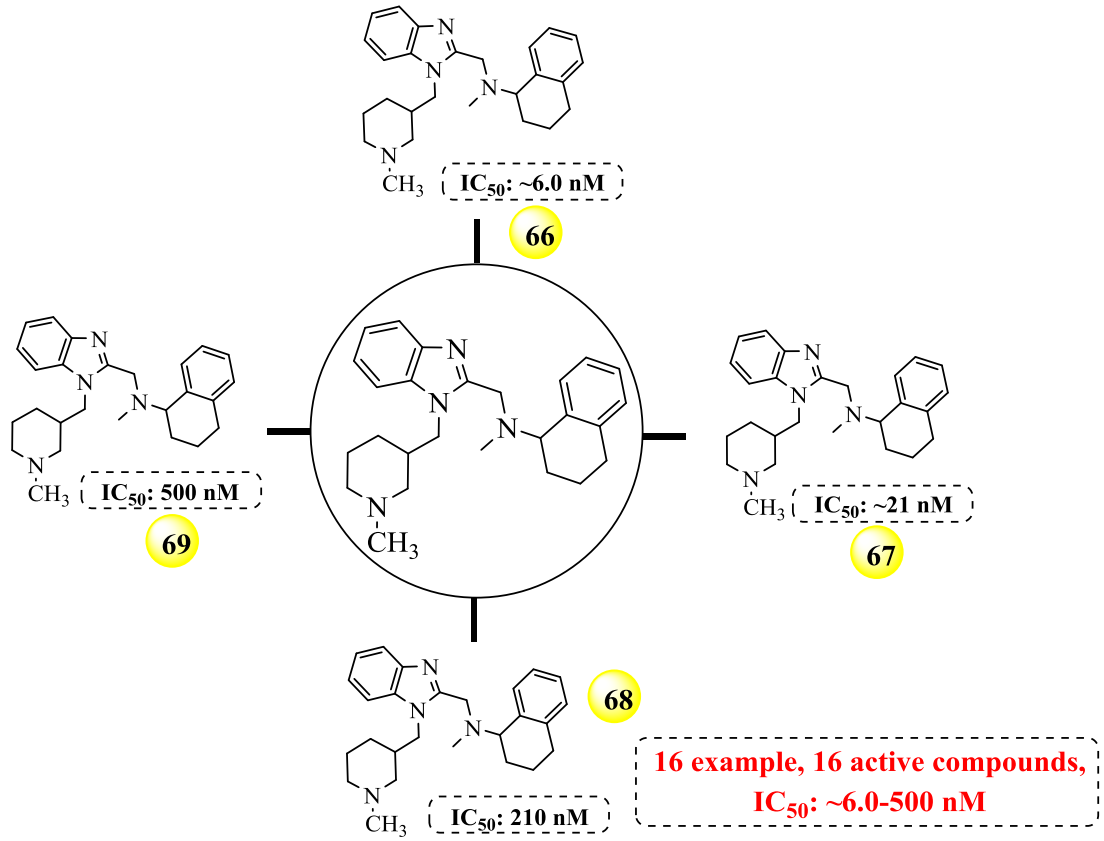

Figure 8. Some benzimidazole derivatives with activity against CXCR4 receptor inhibitor.

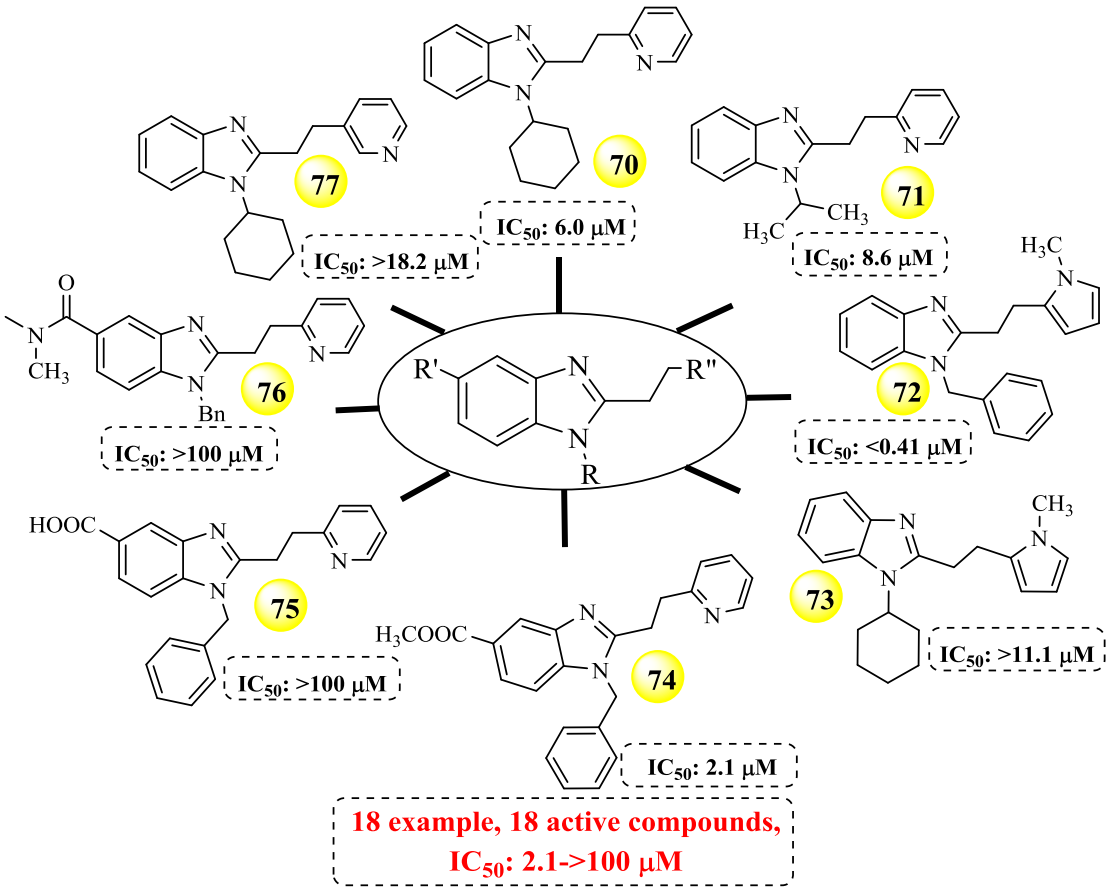

Figure 9. Some benzimidazole derivatives with activity against HepG 2.2.15 cells.

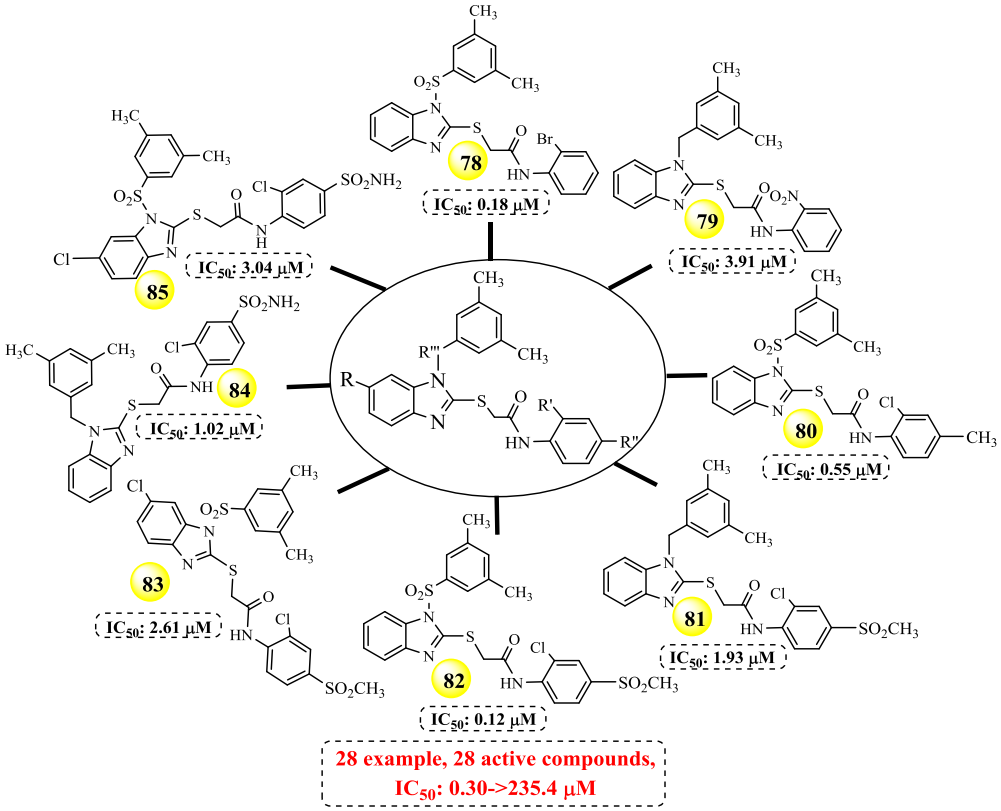

Figure 10. Some benzimidazole derivatives with activity against HIV-1 (human immunodeficiency virus type-1).

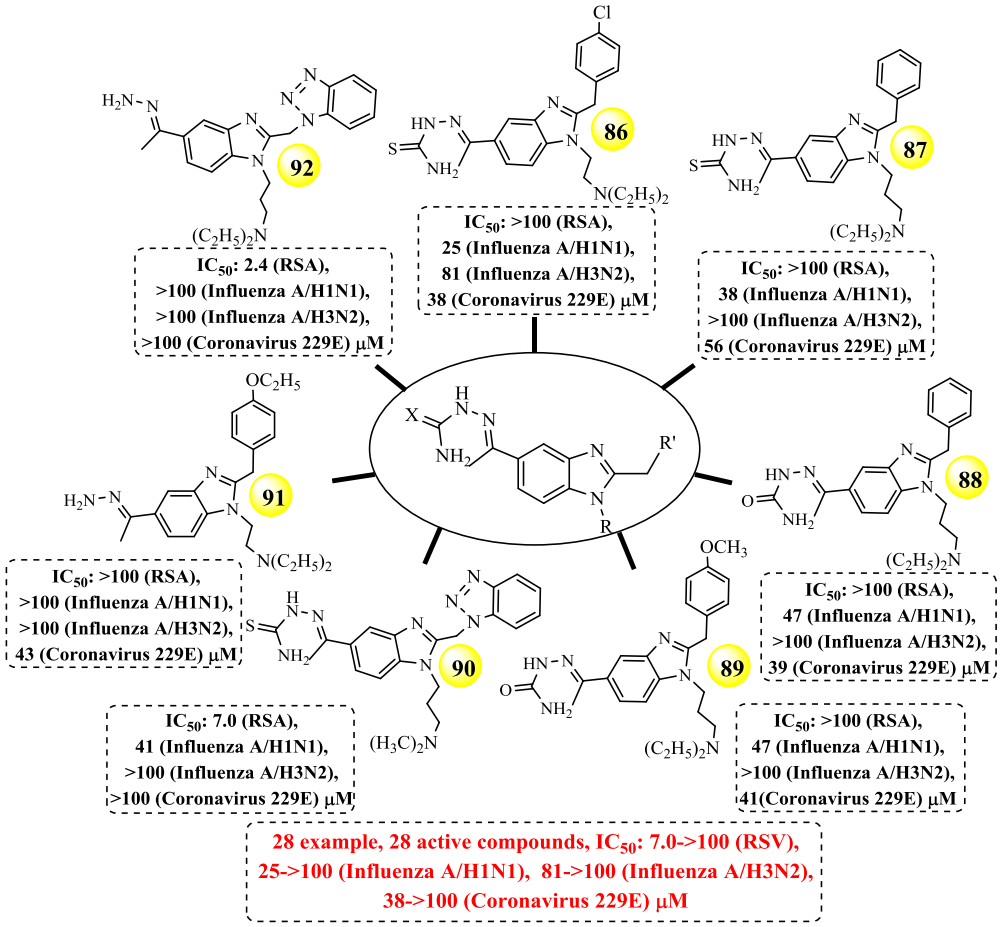

Figure 11. Some benzimidazole derivatives with activity against RSA, Influenza A/H1N1, Influenza A/H3N2, and Coronavirus 229E.

4. FUTURE ASPECTS

Benzimidazole shows, its structural comparison with some natural nucleotides. Hence, it is a widely distributed class of naturally active heterocycles that display an extensive range of biological potentials such as anticancer activity, antifungal activity, antitumor activity antihistamine activity, and antiviral activity [40]. The current review is described as the antiviral potential of well-known substituted benzimidazole derivatives and found that many of them show effective antiviral potential. Thus, the benzimidazole scaffold attracts the attention of researchers for drug design and discovery of the novel antiviral drug.

5. CONCLUSION

Benzimidazole scaffold is the main skeleton for numerous heterocycles that is significantly contributes in the naturally active of important compounds and are remarkably useful with their limited substitutions and promising outcomes. This review described substituted benzimidazole derivatives which exhibited considerable antiviral potentials. We expect this article may be valuable in the finding and synthesis of novel benzimidazole derivatives as a promising antiviral agent in the future.

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