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Mini-review

Imidazole and its derivatives as potential candidates for drug development

Imidazole and its derivatives as potential candidates for drug development

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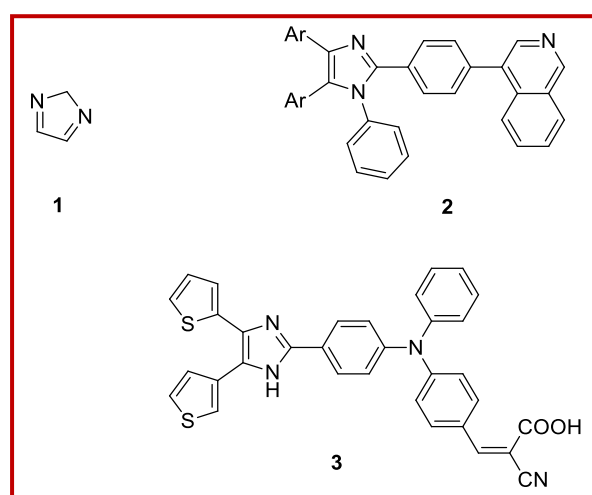
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Abstract

Imidazole and its derivatives are the pharmacological significant scaffolds with the broad spectrum of activities can be synthesized in the laboratory in the single step by the action of the catalyst. The current review summarizes the role of the imidazole and its derivatives during the last decade (2005-2014) for the treatment of many diseases. Review highlights their significant contribution towards the drug development for the treatment of some fatal diseases like HIV, cancer, tuberculosis and hepatitis C. As imidazole and its derivatives continue to play an important role for the treatment of many diseases so there is a need to trigger research in this field.

Introduction

Synthetic organic chemistry is playing a significant role in the development of new drugs. In this regard, nitrogenous heterocycles have a long history in the biomedical research and always remained on the front line (Anderson and Long, 2010). Imidazole a five-member nitrogenous heterocycle constitutes the part of many essential amino acids histidine, bovine and vitamin B12 (Bellina et al., 2007; Anderson and Long, 2010; Uçucu et al., 2001). Imidazoles (1) and their derivatives (2-3) have attracted the attention of scientists due to their significant importance for designing the targeted molecules of medicinal importance (Nagarajan et al., 2014b; Chen et al., 2014; Nagarajan et al., 2014a) which relates to the presence of polar imidazole ring, with two nitrogen atoms separated with a methylene, hydrogen bonds in which one amino hydrogen behaves as the donor while the other amino nitrogen as the acceptor (Anderson and Long, 2010). Due to the unusual ring structure many pharmaceutical



activities are associated with imidazole and its derivatives, antifungal, antibacterial (Nagarajan et al., 2013), antitumor (Chen et al., 2013b), antiviral (Sharma et al.,



2009), anti-oxidant (Sorrenti et al., 2006) and anti-depressant (Dostert et al., 1990) are the known examples.

Synthesis of imidazole ring and its derivatives is carried out by using one-step condensation of diketone with aldehyde, ammonium acetate and primary aromatic amine in the presence of nanocrystalline magnesium aluminate (Safari et al., 2013), supported ionic liquid-like phase (Saffari Jourshari et al., 2013), SiO₂-Pr-SO₃H (Ziarani et al., 2013), clay supported titanium catalyst (Kannan and Sreekumar, 2013), brønsted acidic ionic liquid, (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogen sulfate (Banothu et al., 2013), nano-TiCl₄.SiO₂ (Mirjalili et al., 2012) I₂/Cs₂CO₃ (Xue et al., 2014) and sulfonic acid functionalized SBA-15 nanoporous material (SBA-Pr-SO₃H) catalyst (Ziarani et al., 2013).

As imidazole and its derivatives are associated with a number of biological significances so the current review will emphasized on the role of imidazole and its derivative as potential candidate for the development of drugs to treat some fatal diseases including HIV-AIDS (de Walque, 2014), cancer (Fraser et al., 2014), hepatitis-C (Linan et al., 2014) and tuberculosis (Zoraghi and Reiner, 2013), etc.

Pharmacological Significances

From the literature, it is found that imidazole and their derivatives they possess potent activities against fetal diseases and playing a significant role in a fight against them.

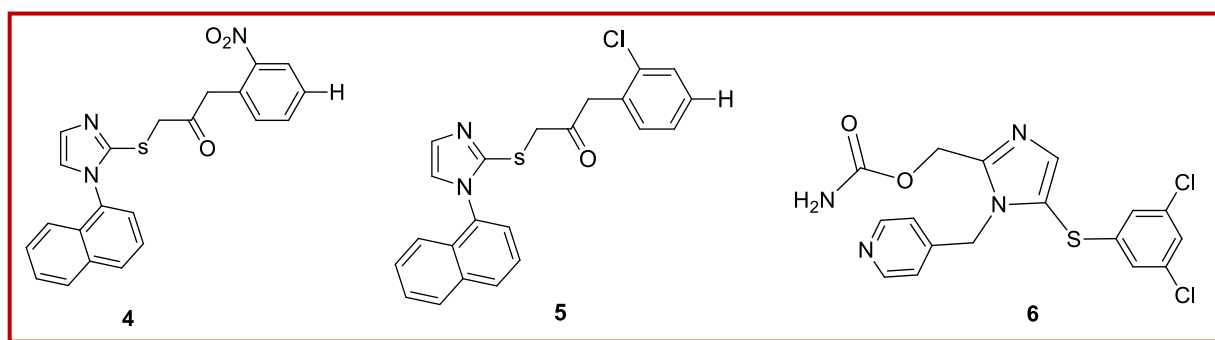
Anti-HIV activity

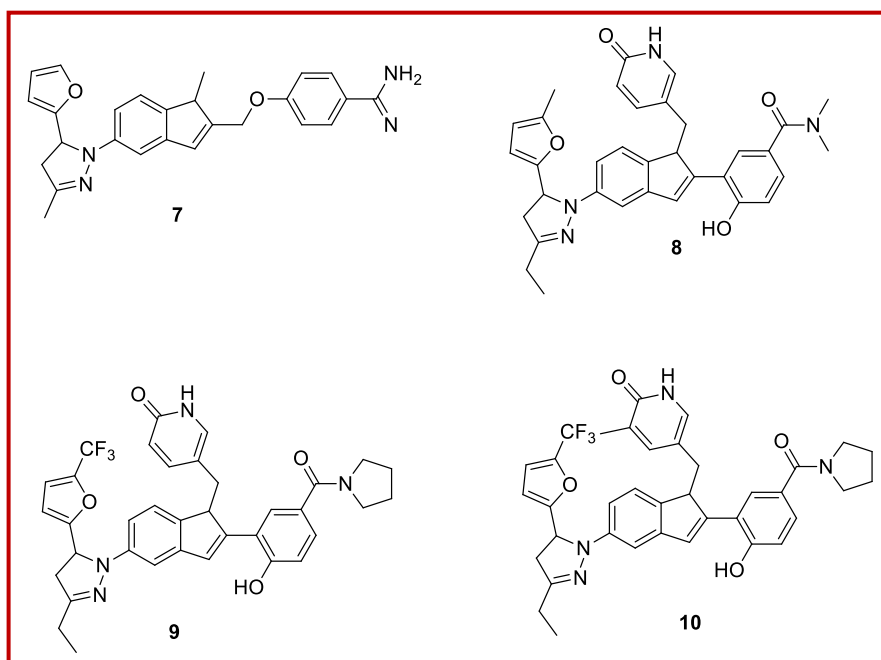
Acquired immunodeficiency syndrome (AIDS) is a viral disease caused due to the special virus Human Immunodeficiency Virus type 1 (HIV-1) (Basu et al., 2009). The HIV-1 type virus destroys the lymphocytes the 'helper cell' which fight against the infections (Roy and Leonard, 2005). According to World Health Organization report, three million people were suffering from AIDS and more than five million people acquire the AIDS in the single year (AIDS, 2003). As the HIV-AIDS is increasing globally and there is a need to introduce some new drugs to help in a fight against this

fatal disease. In this regard imidazole and their derivatives are playing a significant role in the treatment of disease. During the course of drugs for the treatment of HIV-AIDS, the activity is mainly focused on the interaction of the compound with the active site of the viral enzyme to inhibit its growth (Serrao et al., 2013). Derivatives of 2-(1-aryl-1H-imidazol-2-ylthio)acetamide [imidazole thioacetanilide (ITA)] was evaluated against Human Immunodeficiency Virus type-1 (HIV-1). The most significant activity was observed by compound **4** (EC₅₀ = 0.18 LM) with electron withdrawing nitro group, and compound **5** (EC₅₀ = 0.20 LM) with electron donating group at meta positions of the compounds. These two compounds were found more active as compared to the reference drugs nevirapine and delavirdine (Zhan et al., 2009).

Some 5-carbonyl-1H-imidazole-4-carboxamides were developed which were the potent inhibitor for HIV-1 integrase-LEDGF/p75 (Serrao et al., 2013) because of the presence of the imidazole moiety. Some butterfly-like inhibitors of N-benzyl-imidazole derivatives were synthesized and subjected to HIV-1 inhibition activities and were found potent inhibitor due to the specific shape (Ziółkowska et al., 2010). Another target for the development of the anti HIV-1 drug is the attack of the drug on the capsid protein of the HIV virus which plays an important role in the early and later stage of the HIV -I virus life cycle. With the advancement of the organic synthesis modification on the C2, C16 and N1 of the benzimidazole group more efficient compounds with potent anti-HIV activities were formed. In this regard, series of 5-(5-furan-2-ylpyrazol-1-yl)-1H-benzimidazole (**7**) were synthesized and showed excellent inhibition against the assembly of HIV capsid. Modifications of the compounds at C2, C16, and N1 position enhanced the antiviral activities and compounds (**8-10**) after modification showed maximum inhibition at EC₅₀ values (Tremblay et al., 2012).

Caparavarin (**6**) is a non-nucleoside drug having imidazole moiety and is under the process of drug development for the treatment of AIDS but its use is being restricted due to some side effect like inflammation etc. Loksha et al synthesized the analogs of caparavarin and tested them against different wild types of HIV viruses. It was found that the compounds





similar to the caparavarine structure showed maximum activity against the virus (Loksha et al., 2005). Computational studies also confirm the imidazole moiety as a potential candidate for the treatment of HIV-AIDS. In this regard, a study was done using Levenberg-Marquardt Algorithm trained Neural Network (ANN) for the QSAR of 5-phenyl-1-phenyl-amino-1H-imidazole compounds. Imidazole is the potential candidate for the treatment of AIDs (Chamjangali et al., 2007). As imidazole and its derivatives show significant activity, so there is a need to explore more in this field to introduce a drug for the treatment of HIV-AIDS.

Anti-cancer

Cancer is a disease which accompanied by the mortality causes due to the malfunctioning of the cells. The need of time is to develop some new drugs which can bind to the proteins of the infected cells and help to destroy their regeneration. Synthetic chemists are trying to produce some new drugs to treat the cancer patients. Nitrogenous compounds are found to be very good anti-cancerous agents. In this regard a natural product with the imidazole moiety(-)-dibromophakellstatin (**11**) isolated from the marine sponges, was tested against 36 different cancerous cell line. The more resistance was observed for the ovarian OVXF 899L (Zöllinger et al., 2007).

Some derivatives of the acetylhydrazole containing 2-(phenylthiomethyl)-1H-benzo-[d]-imidazole were synthesized and tested against five cancerous cell lines including PC-9, A549, A375, HCT116, and HepG2. Activity was determined by using MTT analysis. It was found that among them the two compounds N-(5-bromo-2-hydroxybenzylidene)-2-(2-(phenylthiomethyl)

-1H-benzo[d]-imidazol-1-yl)acetohydrazide (**12**) and N-(2,4-dihydroxybenzylidene)-2-(2-(phenylthiomethyl)-1H-benzo[d]-imidazol-1-yl)acetohydrazide (**13**) showed excellent activities against all the five cancer cell lines (Liu et al., 2012). Özkay et al., synthesized some derivatives of imidazole i.e imidazole-(benz)azole and imidazole piperazine and tested them against the breast (MCF-7) carcinoma and colon (HT-29) cancerous cell line. Compounds with the triazole moiety showed maximum cytotoxic activity against the colon cancer cell lines (Özkay et al., 2010). Tert-butyl-2(4,5-dihydrogen-4,4,5,5-tetramethyl-3-O-1H-imidazole-3-cationic-1-oxyl-2)-pyrrolidine-1-carboxylic ester (L-NNP) (**14**) is a stable nitroxyl nitroxide radical possess a activity against the human breast cancer MCF-7 and MDA-MB-231 cell lines. When this compound was tested against the isogenic human hepatoma HepG2 cell lines it showed activity and found as a potent inhibitor for the lung cancer cell line (Guo et al., 2012).

Sulfa drugs are famous for the broad spectrum of activities. Amidosulfonamidomethane linked bis-imidazoles (**15**) were synthesized and found potent against the colon, prostate and lungs cancer cell lines (Premakumari et al., 2014). Anthra[1,2-d]imidazole-6,11-dione derivatives were synthesized and tested for their cytotoxic activities. Maximum derivatives were found active against different cancerous cell lines (Chen et al., 2013a). Some derivatives of 2-[(4,5-dimethyl-1-(aryl-amino)-1H-imidazol-2-yl)thio]-1-(aryl)ethanone were synthesized and evaluated them for anti-cancerous activities by brine shrimp lethality assay and found active (Yurttas et al., 2013). Copper complex of imidazole with taurine Schiff base was synthesized and tested for its cytotoxic analysis. Due to specific S shape molecule, it was found that the copper complex of

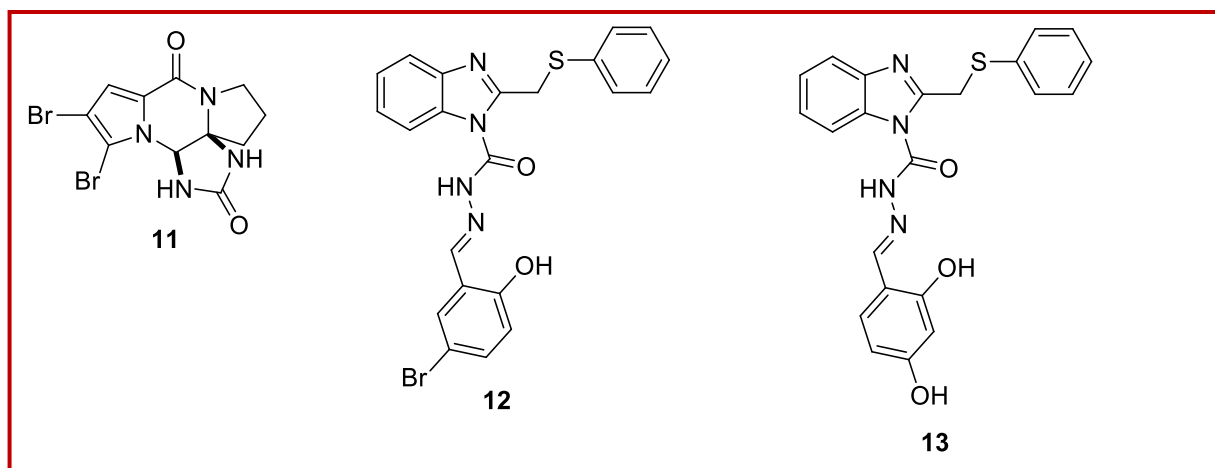
imidazole showed maximum inhibition against the human tumor cell lines *in vitro* (Li et al., 2014). The hybrid between imidazole and 2-phenylbenzofuran (**16**) was synthesized and evaluated against the cancerous cell lines. It was proposed that the molecules in which imidazolyl-3-position is substituted with a naphthylacyl or bromophenacyl group show maximum inhibition against the liver carcinoma (SMMC-7721) cell-lines (Yang et al., 2012). A series of 4-aryl-5-(3,4,5-trimethoxy-phenyl)-2-alkylthio-1H-imidazoles were synthesized and *in vitro* tested against the four cancerous cell lines including HT-29, MCF-7, NIH-3T3, AGS. It was found that the compound with the 3,4,5-trimethoxy substitution is more active against the all four cell lines (Assadieskandar et al., 2013). Derivatives of 2-(phenyl)-3H-benzo[d]imidazole-5-carboxylic acids were synthesized and *in vitro* studied against the three breast cancer cell lines MDA-MB231, MDA-MB468, and MCF7. Compound with the 5-fluoro-2-hydroxyphenyl (**17**) substituent was found to be the most active derivative of the series with GI50 values of 6.2, 4.1 and 0.2 LM against MDAMB468, MDA-MB231, and MCF7 breast cancer cell lines, respectively (Karthikeyan et al. 2013). Some amino substituted xantheno[1,2-d]imidazole derivatives were synthesized and tested against the breast cancer cell lines (Kostakis et al., 2008). The compound with substituted at the 2 and 5 position of the imidazole showed maximum inhibition and it was found that with the increase of the N-alkyl basity increase in activity was observed metal complex of chlorido-[1,3-dimethyl-4,5-diarylimidazol-2-ylidene] were synthesized and tested for their cytotoxic activity against four human cancer cell lines and found active candidate for the treatment of cancer (Kaps et al., 2012). A series of N-heterocycle carbene silver complexes with 4,5-di(p-isopropylphenyl)-1H-imidazole and 4,5-di(p-chlorophenyl)-1H-imidazole show activity against the human breast cancer cell lines (Streciwilk et al., 2014). Imidazole polyamide conjugates linked with pyrrolo [2,1][1,4] benzodiazepine (PBD) dimers were synthesized by the Lown group possess the potent anti-cancer

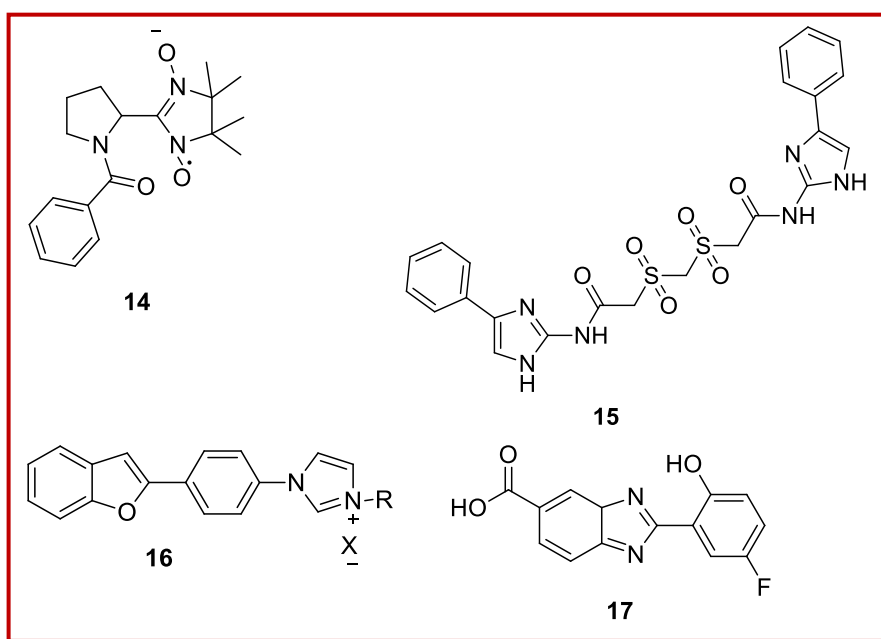
activities against many cancer cell lines (Kumar and Lown, 2005). From the literature, it is found that in near future imidazole substituted group can be used for the introduction of new drugs for the treatment of cancer especially for the treatment of breast cancer.

Antitubercular

Xiaoyun Lu et al. tested the 4-(2,6-dichlorobenzoyloxy) phenylimidazoles and their derivatives against the *Mycobacterium tuberculosis* H37Rv using the microplate alamar blue assay (MABA) for anti tuberculosis activities compounds were found to possess good activities (Lu et al., 2012). Moura et al (2012) synthesized the naphthoimidazoles (**18-21**) starting from the beta-lapachone. These compounds were tested for TB analysis against the *M. tuberculosis* H37Rv (pansusceptible), rifampicin-resistant (RIFr, ATCC 35338) and isoniazid-resistant (INHr, ATCC 35822) strains of bacteria among them the compounds with imidazole units showed good to moderate activity against these strains (Moura et al., 2012).

A series of N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)amide (**22**) and N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl) sulfonamide (**23**) derivatives showed potent antitubercular activities activity against *M. tuberculosis* H37Rv, *M. smegmatis*, *M. fortuitum* and MDR-TB strains (Ranjith et al., 2014). Jadhav et al (2009) has synthesized a series of 2-[4-(1H-[1,2,4]-triazol-1-yl)phenyl]-1-substituted-4,6-difluoro-1H-benzo[d]imidazole derivatives by the alkylation of 2-[4-(1H-[1,2,4]-triazol-1-yl)phenyl]-4,6-difluoro-1H-benzo[d]imidazole with substituted alkyl and aryl halides. They preliminary tested their compounds against different strains of bacteria including *Escherichia coli*, *Salmonella typhosaand*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and after then screened compounds were tested for their antitubercular activity against *M. tuberculosis* H37Rv strain by broth microdilution assay method. After the antibacterial evaluation, it was found that the compounds having electronegative substituents possess promising antimicrobials. It was also observed





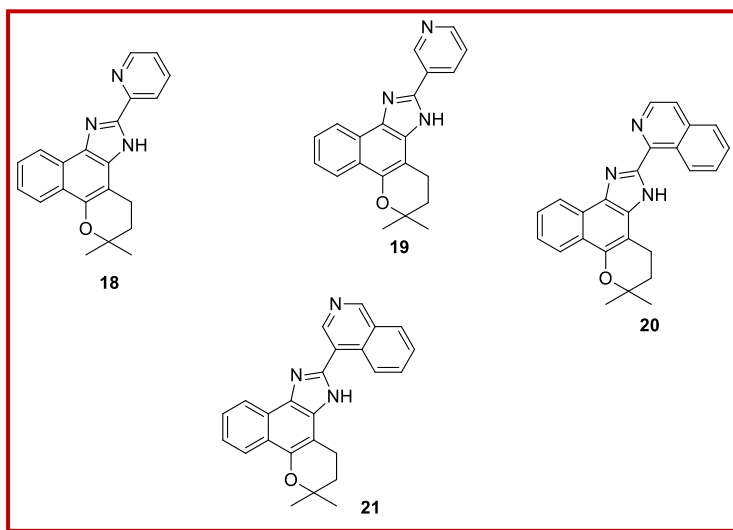
that the compounds with good antimicrobials activities can possess better antimycobacterials activity as well (Jadhav et al., 2009). Marrapu et al. synthesized some chalcone substituted imidazole and found active against the virulent *M. tuberculosis* (Marrapu et al., 2011). Some tetrazolo[1,5-a]quinoline based tetra-substituted imidazole derivatives were synthesized and tested for their anti-TB analysis approximately all the compounds were active against the bacteria (Mungra et al., 2012).

Some pyridine substituted imidazoles were synthesized but unfortunately, these compounds could not show good activity against the different strain of bacteria (Sirisha et al., 2011). A series of 51 benzimidazoles starting from the 4-floro-3-nitrobenzoic acid (**24**) were synthesized (Yoon et al., 2015). Among these 51 imidazoles, the ethyl 2-(4-(trifluoromethyl)phenyl)-1-(2-morpholinoethyl)-1H-benzo[d]imidazole-5-carboxylate found most active on IC₅₀ member against the *M. tuberculosis* H37Rv strain of bacteria. From the observation, it was found the lead compound could be used for the future analysis to introduce a new TB drug in the market (Yoon et al., 2015). Thiadiazole and imidazoles show a broad spectrum of bioactivities (Bhongade et al. 2013). Imidazo(2,1-b)-1,3,4-thiadiazole were synthesized and tested against *in vitro* anti-tubercular activity against *M. tuberculosis* H37Rv strain of bacteria (Patel et al., 2013). Among them the compound 2-(1-methyl-1H-imidazol-2-yl)-6-(4-nitro-phenyl)imidazo[2,1-b][1,3,4]thiadiazole showed maximum inhibition. Filament temperature sensitive protein Z (FtsZ) are very famous protein and used as a target for the treatment of TB. A series of 2,5,6-trisubstituted imidazoles (**25**) were synthesized and tested against the Fts Z protein and most of the derivatives show MIC values of 0.63–12.5 Lg/mL range (Park et al., 2014). N'-

substituted-2-(5-nitrofuran or 5-nitrothiophen-2-yl)-3H-benzo[d]imida-zole-5-carbohydrazide derivatives shows maximum inhibition activity against the mycobacterial cell (Camacho et al., 2011). As bacteria are becoming resistant to the available drugs and there is a need to introduce more drugs so literature shows that imidazole scaffold can help to lessen this problem.

Anti-hepatitis C

An important trauma of the world is facing today is to establish drugs against hepatitis C virus (HCV). More than 170 million people across the world are affected by this fatal disease. The standard treatment of this disease is a combination of ribavirin with pegylated interferon-alpha. Unfortunately, these medicines show activity only against type 2 and 3 and found to be inactive against 1 and 4 genotypes of HCV virus. Due to this lack of activity, some severe side effects are also being spread. In order to cope and stop this adverse effect, there is a need for the development of new drugs (Gamble et al., 2009). The computational study showed that imidazole compounds have a tendency to play a significant role in the introduction of new drugs for the treatment of antiviral drugs especially for hepatitis C (Srivastava and Shukla, 2013). Imidazole derivatives of L-ascorbic acid and imino-ascorbic acid possess strong activity against the hepatitis C virus (HCV) replication (Wittine et al., 2012). Ujjinamatad et al. synthesized the imidazole derivative (**26**) and *in vitro* evaluated against four different viruses from Flaviviridae family, hepatitis C virus (HCV), West Nile virus (WNV), dengue virus (DENV), and the Japanese encephalitis virus (JEV), employing both an RNA and a DNA substrate. The compound showed maximum activity against WNV and HCV with an IC₅₀ of 23 and 37IM, in the presence of DNA substrate (Ujjinamatada et al., 2007).



In addition to promising antibacterial activities, sulfa drugs are also playing their significant role in the development of new drugs to cure hepatitis C. N-Phenylbenzene sulfonamides are considered as hepatitis C polymerase inhibitors (May et al., 2012). Hepatitis B is the world's 9th infection which is the cause of death. Sulfa drug with imidazole moiety 1-isopropylsulfonyl-2-amine benzimidazole derivatives shows potent inhibitory activity against hepatitis B (Li et al., 2007). Benzimidazole substituted with coumarin a natural product derivatives 1-[(2,3,4,6-tetra-O-acetyl)glucopyranosyl-1-yl]-2-[(6-bromocoumarin-3-yl)methylenethio]benzimidazole (27) and 2-[(6-bromocoumarin-3-yl)methylenethio]-5-fluorobenzimidazole show potent activity against the HCV (Hwu et al., 2008). 2-Iminobenzimidazole (IBI) is a well-known hepatitis C enzyme inhibitor. Some analogs of IBI with characteristic imidazole group were synthesized by Windisch et al. when tested against the hepatitis virus they showed maximum inhibition (Windisch et al., 2014). With the advancement in imidazole chemistry, there is a need to introduce new imidazole substituted compounds and tested them for the treatment of hepatitis C.

Conclusion

Imidazole and their derivatives are important scaffolds used in the treatment of many diseases like HIV-AIDS, cancer, tuberculosis and hepatitis C. Many derivatives possess the strong activities and some other are with moderate activity. They have a potential to be used as potential drugs in future.

Conflict of Interest

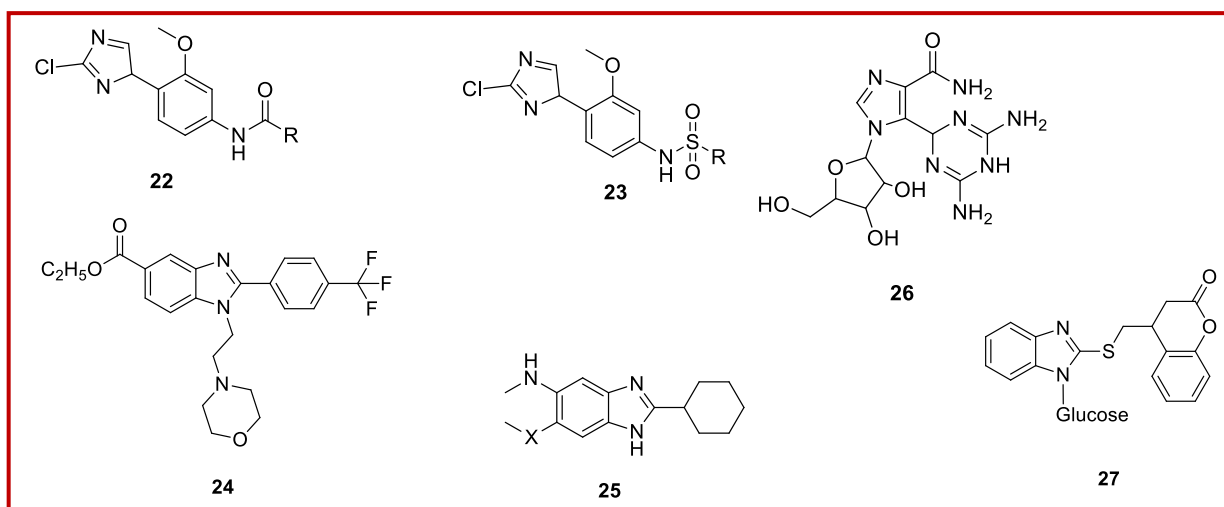
Authors declare no conflict of interest

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