



## Imidazoles as potential anticancer agents†

Cite this: *Med. Chem. Commun.*, 2017, 8, 1742

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Cancer is a black spot on the face of humanity in this era of science and technology. Presently, several classes of anticancer drugs are available in the market, but issues such as toxicity, low efficacy and solubility have decreased the overall therapeutic indices. Thus, the search for new promising anticancer agents continues, and the battle against cancer is far from over. Imidazole is an aromatic diazole and alkaloid with anticancer properties. There is considerable interest among scientists in developing imidazoles as safe alternatives to anticancer chemotherapy. The present article describes the structural, chemical, and biological features of imidazoles. Several classes of imidazoles as anticancer agents based on their mode of action have been critically discussed. A careful observation has been made into pharmacologically active imidazoles with better or equal therapeutic effects compared to well-known imidazole-based anticancer drugs, which are available on the market. A brief discussion of the toxicities of imidazoles has been made. Finally, the current challenges and future perspectives of imidazole based anticancer drug development are conferred.

Received 7th February 2017,  
Accepted 21st March 2017

DOI: 10.1039/c7md00067g

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### Introduction

In the 21st century, cancer is still a problem. It is a genetic disease that progresses *via* development of multistep carcinogenesis with the participation of various physiological systems in the human body, such as cell signaling and apoptosis, and as a result, cancer is extremely complicated to combat.<sup>1</sup> Generally, cancer begins as a local disease, but it metastasizes over time, making it difficult to cure. It is the leading cause of death in developed countries. The possible signs and symptoms of cancer are new lumps, abnormal bleeding, prolonged cough, unexplained weight loss, and change in bowel movements, among others.<sup>2</sup> However, it is not presently clear how nutritional imbalance affect one's cancer risk.<sup>3</sup> Globally, cancer is the second leading cause of death, and it is the number one cause in the US.<sup>4–6</sup> From all over the world, cancer has drawn unusual attention, and extensive research (radiation and chemotherapy) has been devoted towards the development of effective anticancer modalities.<sup>7</sup> As per the prediction of the World Health Organization in 2012, the number of annual cancer cases will rise from 14 million to 22 million within the next 2 decades.<sup>8</sup> According to a 2014 UN DESA report, the world population of 7.3 billion is expected to reach 8.5 billion by 2030, 9.7 billion in 2050 and 11.2 billion in 2100. Out of these, about 1.5 billion cancer cases are expected

with about 1.2 billion deaths.<sup>9</sup> Moreover, total deaths are expected to reach 2.14 billion in the year 2030 with an expected 8.5 billion population.<sup>10,11</sup> Breast and lung cancers are the common causes of deaths (a total of 522 000 deaths in 2012) in women and men, respectively. These two types of cancers are most frequently diagnosed in about 140 countries.<sup>12</sup>

Despite the accessibility of several anticancer drugs, common problems like multi-drug resistance, less therapeutic efficacy, solubility, adverse side effects, and/or poor bio-availability issues necessitate the development of new anticancer agents.<sup>13,14</sup> For more than a century, heterocyclic compounds (particularly bearing nitrogen atoms) have been the major molecules in organic chemistry because of their remarkable pharmaceutical activities, especially their anticancer properties.<sup>15–17</sup> Since the discovery of imidazole in the 1840s, the research and development of imidazole based compounds have been interesting and active fields of research.<sup>18–22</sup> Imidazole (five membered aromatic ring) is an organic alkaloid that acts as an important pharmacophore in drug discovery. The imidazole ring is present in various natural<sup>23–25</sup> and synthetic<sup>26–29</sup> bioactive compounds. Natural compounds include biotin, essential amino acids, histidine, histamine, and pilocarpine alkaloids, and the synthetic compounds include cimetidine, losartan<sup>26</sup> fungicides, herbicides,<sup>27</sup> plant growth regulators<sup>28</sup> and therapeutic agents.<sup>29</sup> Imidazoles have a wide range of biological activities, such as anticancer,<sup>30</sup> antifungal,<sup>31</sup> antiviral,<sup>32</sup> antibacterial,<sup>33</sup> antitubercular,<sup>34</sup> antiparasitic,<sup>35</sup> antihistaminic,<sup>36</sup> anti-inflammatory,<sup>37</sup> antineuropathic,<sup>38</sup> anti-obesity,<sup>39</sup> and antihypertensive,<sup>40</sup> and other medicinal

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† The authors declare no competing interests.

properties.<sup>41–47</sup> Among various pharmaceutical activities, imidazoles have been used as effective anticancer agents. Presently, several imidazoles, dacarbazine, temzolomide, zoledronic acid, mercaptopurine, nilotinib, tipifarnib *etc.*, are being used in clinics to cure various cancers (Fig. 1). Briefly, these molecules have remarkable pharmaceutical potencies to control cancer. The interesting anticancer properties of imidazoles inspired the prevalent development of their derivatives with the hope of increasing the efficiency and lowering the side effects. The experimental evidence indicated that the different types of cancers originate because of a change in the structure and function of DNA (deoxyribonucleic acid), VEGF (vascular endothelial growth factor), topoisomerase I & II, mitotic spindle microtubules, histone deacetylases, receptor tyrosine kinases, topoisomerases, CYP26A1 enzyme, *etc.* Among the various targets, DNA is one of the leading targets for anticancer molecules. Thus, it has become the epicenter of attraction for the scientific community to identify and characterize the interactions of small molecules with DNA to help design new and efficient therapeutic agents for controlling gene expression.<sup>48–50</sup> Remarkably, imidazoles interact with DNA *via* covalent or non-covalent interactions (electrostatic, intercalation and groove binding) and halt cell division.<sup>51</sup> In comparison to other heterocyclic molecules, imidazoles easily binds to protein molecules,<sup>52</sup> and some imidazole drugs at high concentrations directly inhibit the synthesis of essential cell membrane components without interference from sterols and sterol esters.<sup>53</sup>

The literature survey revealed around 1180 research papers on imidazoles with interesting anticancer results. An analysis of the number of publications on “imidazoles as

anticancer agents” from 2002 to 2016 indicated steadily growing interest in research on this topic. The period from 2002 to 2016 was divided into three intervals, *viz.* 2002–06, 2007–11 and 2012–16, (Fig. 2). It is clear from Fig. 2 that there were 261 publications during 2002–2006, 420 during 2007–2011 and 500 from 2012–2016. Further, the literature indicated that some review papers on related topics have appeared on imidazoles.<sup>54–57</sup> However, none of the articles discussed the classes of imidazoles as anticancer agents based on the mode of action, and a review has not appeared since 2010. Therefore, an updated review of the recent advances in this field is missing. Thus, it was thought worthwhile to address the recent advances in the development of imidazoles as anticancer agents of clinical interest. In this review, the recent advances with a special emphasis on the structural, chemical, and biological features of imidazoles are addressed. Attempts have been made to outline the mechanism of action of imidazoles, and careful observations of pharmacologically active imidazoles with better or equal therapeutic effects to that of the standard drugs have been presented. In addition, the issues of the toxicity of imidazoles have been highlighted. Finally, market status, current challenges and future perspectives have been addressed. We hope that this paper will open new opportunities for researchers to design future generation novel and potent imidazole containing anticancer drugs.

## Imidazole: an exciting heterocyclic moiety

Imidazole is an important chemical ring that is present in many existing drugs.<sup>58</sup> This ring exists in two equivalent tautomeric forms as the hydrogen atom is located on either of the two nitrogen atoms. In 1858, imidazole was first synthesized by Heinrich Debus<sup>59</sup> from glyoxal and formaldehyde (Scheme 1a). The % yield in this protocol was quite low, but the protocol is still being used to create C-substituted imidazoles. Later, in 1977, Van Leusen synthesized imidazole using a three component reaction



Fig. 1 Market faces and chemical structures of some imidazole-based anticancer drugs.

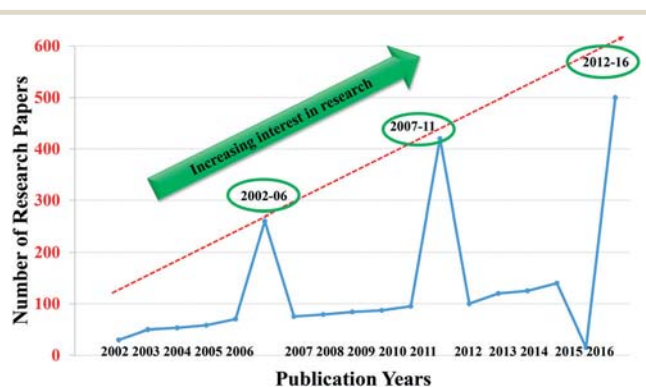
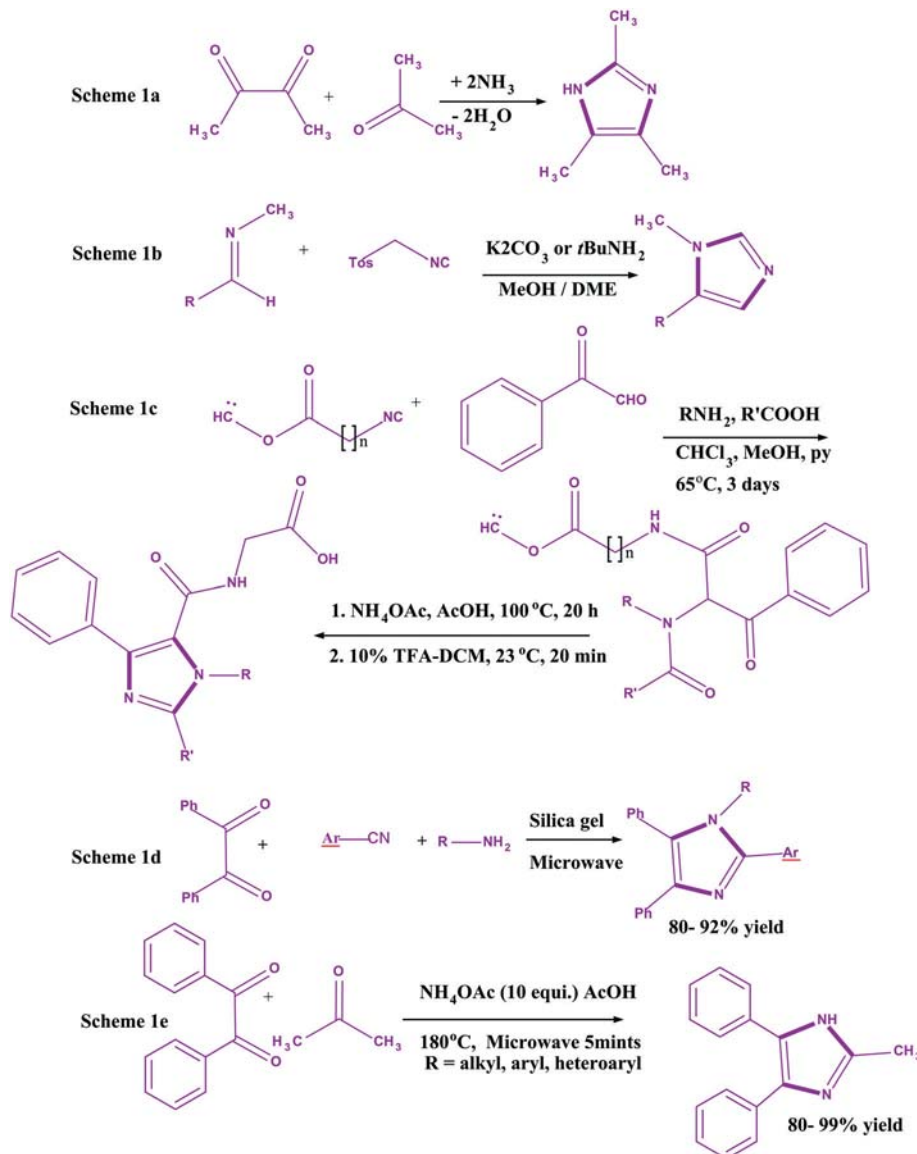


Fig. 2 A graphic representation of the increasing interest in research on imidazoles as anticancer agents from 2002–06 through 2007–11 to 2012–16.



**Scheme 1** Heinrich debus synthesis **1a**, Van Leusen three-component reaction (vl-3CR) **1b**, synthesis of imidazoles via Ugi reaction on Wang resin **1c**, one pot synthesis **1d** and short synthesis **1e**.

with aldimines and tosylmethyl isocyanide (Scheme 1b).<sup>60</sup> However, the yield was low. Therefore, the thrust of its synthesis continues. Consequently, in 1996, Zhang *et al.*<sup>61</sup> reported a constructive approach for imidazoles syntheses (16–56% overall yields) *via* a Ugi four component reaction of arylglyoxals, primary amines, carboxylic acids, and isocyanide on a Wang resin (Scheme 1c). Initially, keto-amides were formed, which were treated with 60 equivalent of  $\text{NH}_4\text{OAc}$  in  $\text{AcOH}$  at  $100^\circ\text{C}$  for 20 h, followed by reaction with 10% TFA-DCM at  $23^\circ\text{C}$  for 20 min for cyclization of the corresponding imidazoles. The Ugi reaction was carried out in a mixture of  $\text{CHCl}_3$ – $\text{MeOH}$ –pyridine (1:1:1) at  $65^\circ\text{C}$  for 3 days. With the passage of time, high yielding productive approaches were given in the mid-2000's. In the year 2003, a novel one pot synthesis of tetra substituted imidazoles under solvent-free conditions

and microwave irradiation was reported by Balalaie *et al.*, (Scheme 1d) and the yield of imidazoles was quite high (80–92%).<sup>62</sup> Another efficient, simple, and high yielding constructive approach for synthesis of imidazoles from 1,2-diketones and aldehydes in the presence of  $\text{NH}_4\text{OAc}$  was reported by Wolkenberg *et al.* (Scheme 1e). Under microwave irradiation, alkyl, aryl, and heteroaryl substituted imidazoles were formed in yields ranging from 80 to 99%.<sup>63</sup> Besides, there are many other methods available for the synthesis of imidazoles with good yields.<sup>64–70</sup>

At the molecular level, medicinal chemistry is concerned with the discovery, development, interpretation, and identification of the mechanism of action of biologically active compounds.<sup>71</sup> As already noted above, this exciting heterocyclic moiety constructs several compounds that possess an extensive spectrum of pharmacological activities. This paper aims

to review the anticancer activities of imidazoles during the past years.

## Imidazoles as anticancer agents

Many research papers have revealed that imidazoles possess anticancer drug potentials. The success of imidazoles as anticancer agents started with dacarbazine, which triggered interest in the development of imidazole agents. Several classes of various structured heterocyclic molecules, which include imidazoles, for different types of cancer treatment have been designed and developed to cure cancer *via* various targets.<sup>12</sup> Imidazoles have the potential to overcome the various drawbacks of currently available clinical drugs and to develop anticancer agents. Therefore, attempts have been made to highlight some important classes of imidazoles based on mechanisms of action *via* various targets like DNA, VEGF, mitotic spindle microtubules, histone deacetylases, receptor tyrosine kinases, topoisomerases, CYP26A1 enzyme, rapid accelerated fibrosarcoma (RAF) kinases, *etc.*

## Imidazoles as antiangiogenic agents

Angiogenesis is essential to the growth of cells and tissues.<sup>72-75</sup> Tumors cannot grow through a defined volume if they are not vascularized. The vascular endothelial growth factor (VEGF) is an important angiogenic factors secreted by tumor cells. Most human cancer cells express elevated levels of VEGF and VEGF receptors on their surface. An antiangiogenic drug (*e.g.*, bevacizumab) impairs the VEGF pathway and tumor vasculature by targeting VEGF<sup>76</sup> or their receptors. In the last two decades, several small molecules have been evaluated as antiangiogenic agents, but only a few molecules have worked.<sup>77</sup> For example vincristine, taxol and etoposide are currently being used for the treatment of acute lymphocytic leukemia, ovarian, and lung cancers, respectively.<sup>78-80</sup> Several imidazoles have been explored as anticancer agents with antiangiogenesis as the mode of action. Hansen *et al.* reported a series of levamisole derivatives 1-4i (Fig. 3) for the *in vitro* inhibition of angiogenesis.<sup>81</sup> The authors summarized the morphological effect of the three groups of

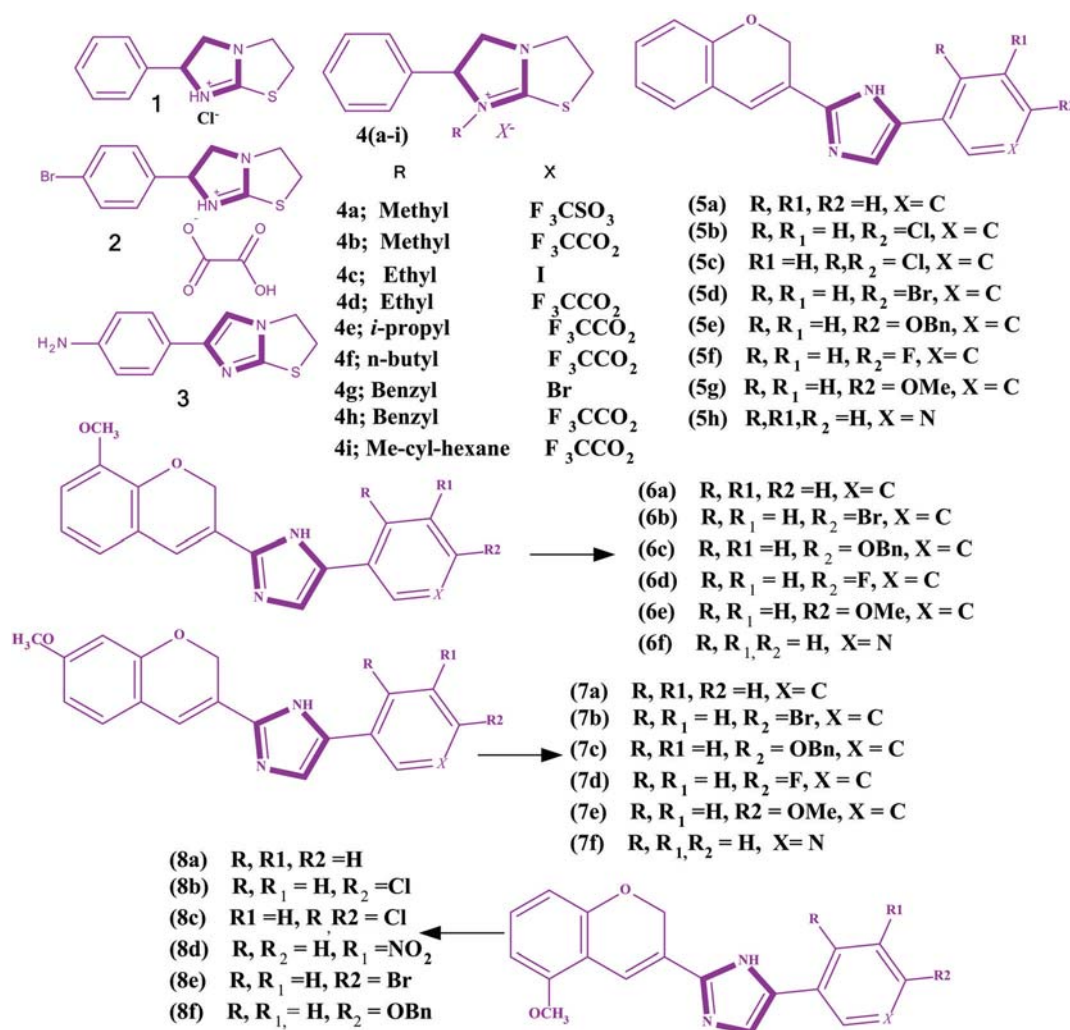


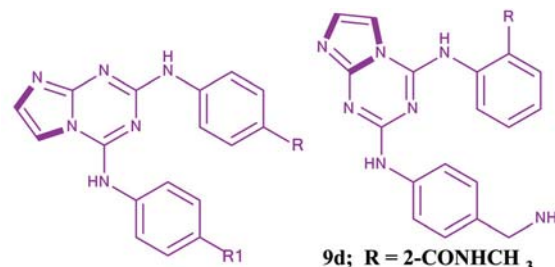
Fig. 3 Imidazoles reported as antiangiogenic agents.

levamisole. In the first group, the authors found *p*-bromolevamisole **2** was an equivalent angiogenic agent to levamisole, and *N*-methyllevamisoles **4a** and **4b** were more potent than the parent inhibitor, levamisole. In the second one, bromolevamisole was highlighted as having a higher antiangiogenic agent than levamisole. Finally, the third group comprised *N*-alkylated analogues, and they were considered good inhibitors of angiogenesis. Gopinath *et al.*<sup>77</sup> constructed another series of imidazoles **5a–8f** (Fig. 3) by the reaction of chrome-3-carboxylic acids with substituted acyl bromides in the presence of TEA followed by reflux with NH<sub>4</sub>OAc in toluene. The reported imidazoles were screened *in vitro* for the inhibition of KRAS/Wnt and their anti-angiogenesis properties. In addition, they carried out a molecular docking analysis and found the higher binding affinity of **8f** with KRAS/Wnt and VEGF. Finally, based on the angiogenesis inhibition mechanism, it was concluded that imidazole **8f** is a potent anticancer agent.

The focal adhesion kinase (FAK) enzyme is a key pathogenic mediator of various diseases, including cancer. It stimulates the tumor progression and metastasis *via* regulation of the cell migration, invasion, extracellular matrix, and angiogenesis. Therefore, this enzyme is a promising therapeutic target, as it is highly expressed at both the transcriptional and translational levels in various cancers.<sup>82–84</sup> In this countenance, Dao *et al.* highlighted the anticancer efficiencies of imidazoles (triazines incorporated with imidazole rings) and explored their anti-angiogenic activities against human umbilical vein endothelial cells and anticancer efficacy against several cancer cell lines with the aid of focal adhesion kinase (FAK) inhibition.<sup>85</sup> Besides, the authors checked the *in vitro* enzymatic activities of the developed imidazole based heterocyclic compounds with reference to the standard inhibitor TAE-226. It is an ATP competitive FAK inhibitor that has shown potent anti-proliferative and antitumor effects *in vitro* and *in vivo* in several malignancies, including brain tumors, esophageal cancer, breast cancer, ovarian cancer, and gastrointestinal stroma tumor. The IC<sub>50</sub> value of the standard TAE-226 is 0.007 ± 0.002 μM. The series of compounds displayed IC<sub>50</sub> values in the range of 10<sup>-7</sup>–10<sup>-8</sup> M. Among the series, several inhibitors, **9a–9d** (Fig. 4), showed high anticancer activities against four cancer cell lines (U87-MG, HCT-116, MDA-MB-231, and PC-3).

## Imidazoles as antiproliferative agents

Among various cancer cures, the antiproliferative approach is one of the significant ways to control this deadly disease. The various heterocyclic molecules, particularly imidazoles, have great antiproliferative potential. Chen *et al.*<sup>86</sup> reported seventeen molecules of imidazole and imidazoline analogues as antiproliferative agents for melanoma. In this work, the authors investigated the antiproliferative activi-



**9a;** R = 2-CONHCH<sub>3</sub> and R<sub>1</sub> = 3,4,5-trimethoxy  
**9b;** R = 2-CONHCH<sub>3</sub> and R<sub>1</sub> = 2-OCH<sub>3</sub>-4-morpholino  
**9c;** R = 2-CONHCH<sub>3</sub> and R<sub>1</sub> = 4-CH<sub>2</sub>NHAlloc  
**9d;** R = 2-CONHCH<sub>3</sub>

S.No	IC <sub>50</sub> (μM)			
	U-87MG	HCT-116	MDA-MB-231	PC-3
<b>9a;</b>	4.2+/- 0.3	0.95+/- 0.2	>10	0.35+/- 0.19
<b>9b;</b>	2.31+/- 0.2	0.34+/-0.08	>10	0.27+/- 0.08
<b>9c;</b>	2.89+/-0.3	0.52+/- 0.21	0.80+/- 0.27	0.29+/-0.17
<b>9d;</b>	0.37+/- 0.04	0.31+/-0.18	1.08+/- 0.45	1.27+/-0.28
<b>TAE-226</b>	1.2+/- 0.3	0.4+/- 0.08	2.8+/- 0.2	1.6+/- 0.2

Fig. 4 Potent antiangiogenic imidazoles.

ties of these imidazole and imidazoline analogs in two melanoma cell lines (human A375 cells and mouse B16 cells) using a fibroblast cell line as a control unit. The authors studied the anticancer activities of **10a–10g** imidazoles (Fig. 5) using the standard sulforhodamine B (SRB) assay and sorafenib (Bay43-9006) as a reference standard drug. As per the authors, 10 μM concentrations of some imidazoles showed good activity. Moreover, a few analogues had similar activities to the sorafenib standard drug. The IC<sub>50</sub> values of the reported compounds are given in Fig. 5. It is clear from this figure that these values ranged from 16.1 to >100 μM.

Jamalian and his colleagues<sup>87</sup> demonstrated in their review that the potential of 1,8-acridinones as anti-proliferative agents could be enhanced by incorporating imidazole moieties bearing electron withdrawing groups. In this regard, Sarkarzadeh *et al.*<sup>88</sup> investigated a series of heterocyclic molecules containing imidazole moieties for their antiproliferative effects on cervical (HeLa), colon (LS180), breast (MCF-7) and Jurkat human cancer cell lines by MTT assay. Interestingly, the authors found that the compounds **11a–11c**, bearing the imidazole-2-yl moiety on the C11-position of the dihydropyridine ring, exhibited superior antiproliferative activities compared to cis-platin, especially in the Jurkat cell line. The chemical structures of the potent imidazoles along with the IC<sub>16</sub> and IC<sub>50</sub> values are given in Fig. 5. Benzimidazoles are complex compounds with a broad range of pharmacological properties, like antitumor.<sup>89</sup> These compounds have been studied extensively and are reported to be very potent cytotoxic agents against various cancer cell lines.<sup>90</sup> Roopashree *et al.* investigated the antiproliferative effect of newly synthesized benzimidazole derivatives **12a–12d** (Fig. 6) on Hela cells.<sup>91</sup> Although the reported compounds were found to be less effective with reference to IC<sub>50</sub> > 50, the

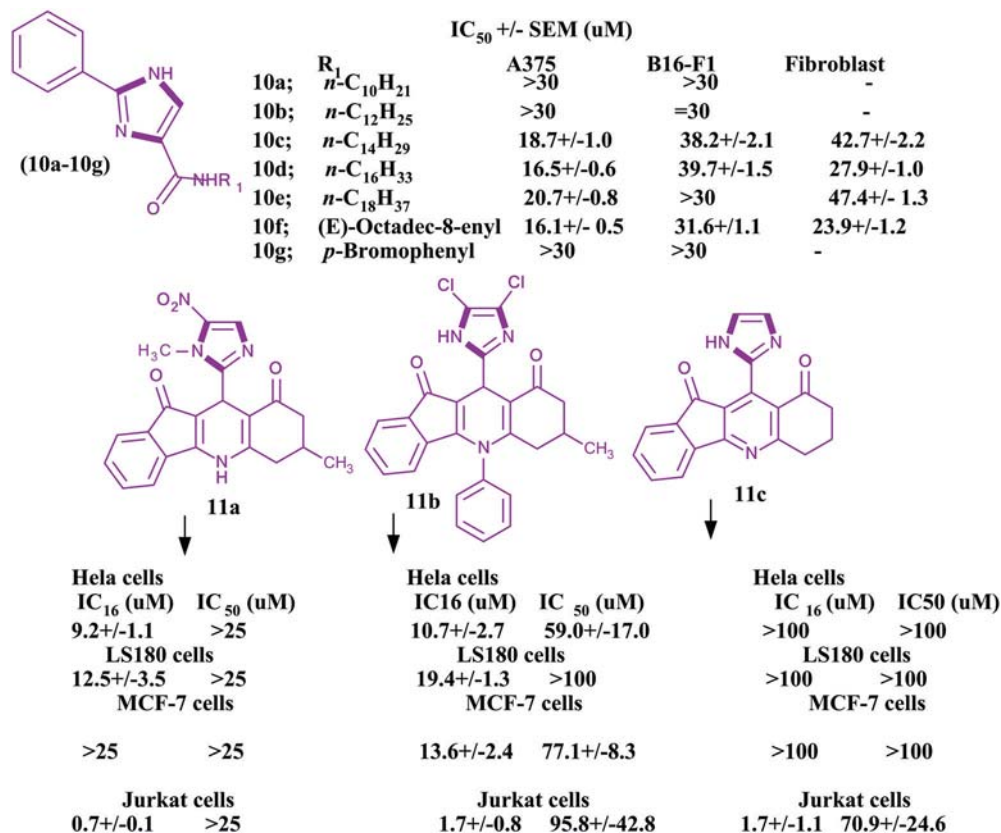


Fig. 5 Potent antiproliferative imidazoles.

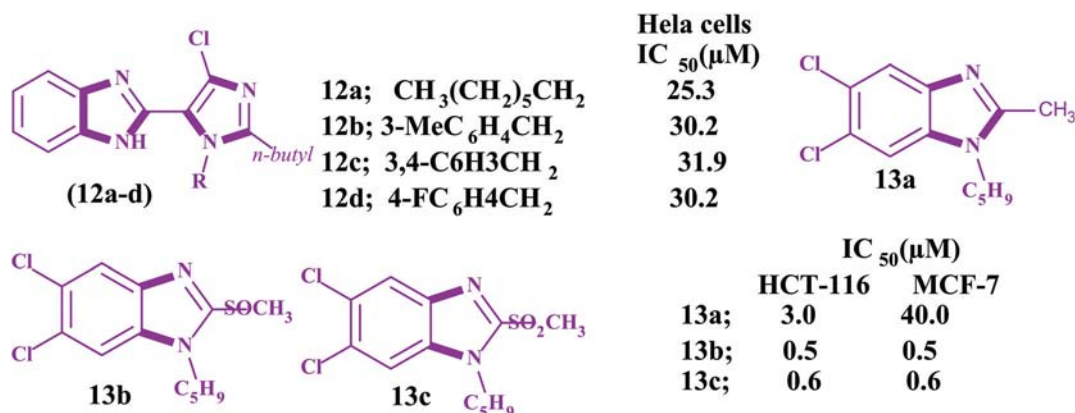


Fig. 6 Antiproliferative benzimidazoles.

compound 12a, with a high alkyl group, was considered more potent than the standard drug with an IC<sub>50</sub> = 25.3 μM. In addition, the compounds 12b–12d were found to be good cytotoxic agents with IC<sub>50</sub> = 30.2 μM, 31.9 μM, and 30 μM, respectively. Due to the close structural similarities of benzimidazoles with the purine nucleotide, these moieties are applied for multiple targeting, especially in antitumor activity, which make these heterocycles good pharmacophores. Alkahtani *et al.* synthesized another series of benzo[*d*]imidazoles and evaluated their anticancer

activities.<sup>92</sup> In this work, the authors found some imidazoles 13a–13c (Fig. 6) carrying chloro, cyclopentyl, –CH<sub>3</sub>, –SOCH<sub>3</sub> and –SO<sub>2</sub>CH<sub>3</sub> substituents as potent antiproliferative agents in cancer cell lines.

## Imidazoles as CYP26A1 enzyme inhibitors

All trans retinoic acids (ATRA), physiological metabolites of vitamin A, are useful in the treatment of cancer,<sup>93–95</sup> skin

related diseases, and neurodegenerative and autoimmune diseases, particularly in oncology against acute promyelocytic leukemia (APL). ATRAs can change the prognosis of APL from fatal to highly curable.<sup>96–99</sup> However, the emergence of resistance has severely hampered clinical applications along with the easily metabolism of ATRAs into 4-hydroxyl-RA by the CYP26A1 enzyme. Therefore, inhibition of the CYP26A1 metabolic enzyme denotes a promising strategy for the discovery of new specific anticancer agents. Few research papers have been published wherein imidazoles have been reported as inhibitors of the CYP26A1 enzyme. Several families of retinoic acid metabolism blocking agents (RAMBAs) targeting the CYP26A1 enzyme with imidazoles have been exploited from generation to generation. The first generation imidazoles as RAMBAs were ketoconazole, miconazole and liarozole<sup>100,101</sup> (Fig. 7), which were evaluated as potent blocking agents to inhibit CYP26A1 activities. However, the lack of CYP26 isoform specificity and the extensive structure activity relationship (SAR) studies on imidazoles led to the discovery of the second generation CYP26A1 inhibitors [OSI Pharma, naphthyl compound (Fig. 7)] and other azoles.<sup>102–105</sup> It was found that these second generation RAMBAs exhibited higher potency and better specificity against the CYP26A1 enzyme than the first generation compounds, and some proceeded to clinical studies where they showed encouraging preclinical and clinical results with improved specific activities.<sup>106,107</sup> Recently, Sun *et al.* described the synthesis and biological evaluation of fifteen imidazoles 14a–14o (Fig. 8) as retinoic acid metabolism blocking agents (RAMBAs) towards the CYP26A1 enzyme.<sup>108</sup> It was found that all the compounds exhibited applicable activities towards the CYP26A1 enzyme with  $IC_{50}$  values ranging from 0.22–1.11  $\mu\text{M}$ . Additionally, the authors observed that 14f and 14i were promising inhibitors with  $IC_{50}$  values of 0.22 and 0.46  $\mu\text{M}$  towards the CYP26A1 enzyme, re-

spectively. Furthermore, these two compounds were evaluated for CYP selectivity and the metabolic profile of ATRA and found to show higher selectivities for CYP26A1 in comparison to CYP2D6, CYP3A4. Gomaa *et al.* synthesized another series of imidazoles<sup>109</sup> (Fig. 9). The imidazoles were evaluated for their ability to inhibit CYP26-mediated retinoic acid metabolism (CYP26) inhibitory activity using a cell-free microsomal assay with the standards liarozole ( $IC_{50} = 540$  nM) and R116010 ( $IC_{50} = 10$  nM). All the imidazoles showed poor response, but two imidazoles, namely 3-[4-(6-bromopyridin-3-ylamino)-phenyl]-3-imidazol-1-yl-2,2-dimethyl-propionic acid methyl ester 15a and 3-[4-(benzo[1,3]dioxol-5-ylamino)-phenyl]-3-imidazol-1-yl-2,2-dimethyl-propionic acid methyl ester 15b, exhibited potent activities against the CYP26 enzyme. The chemical structures of the potent imidazoles are shown in Fig. 9.

Gomaa *et al.* synthesized 3-(1*H*-imidazol)-2,2-dimethyl-3-(4-(naphthalen-2-ylamino)phenyl)propyl derivatives 16a–16k (Fig. 9) and carried out a MCF-7 CYP26A1 microsomal assay for the assessment of anticancer activities.<sup>110</sup> Almost all the compounds have shown good CYP26A1 inhibitory activities compared to the standard drugs (liarozole and R116010). Amongst all the compounds, 2-[3-imidazol-1-yl-5-(naphthalen-2-ylamino)-phenyl]-2-methyl-propionic acid methyl ester 16a had the most promising  $IC_{50}$  value, which was less than the standard drug.

## Imidazoles as topoisomerase inhibitors

DNA topoisomerases are the enzymes that regulate DNA strand supercoiling by catalyzing winding and unwinding. These have been accepted as an important target in anticancer drug discovery.<sup>111–115</sup> There are several clinically

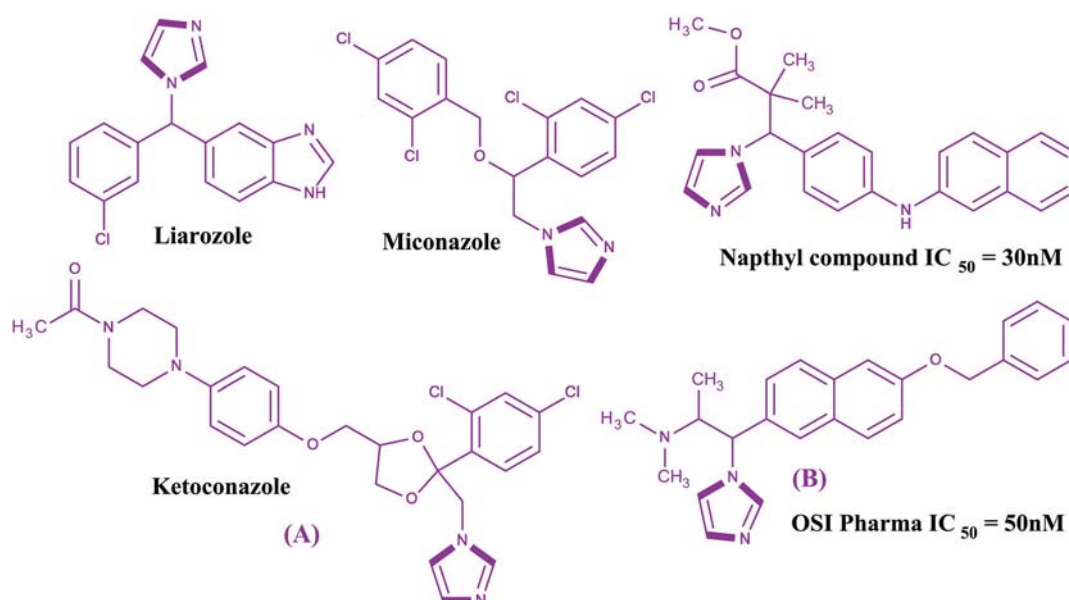


Fig. 7 Chemical structures of the first generation (A) and second generation (B) imidazoles as CYP26A1 inhibitors.

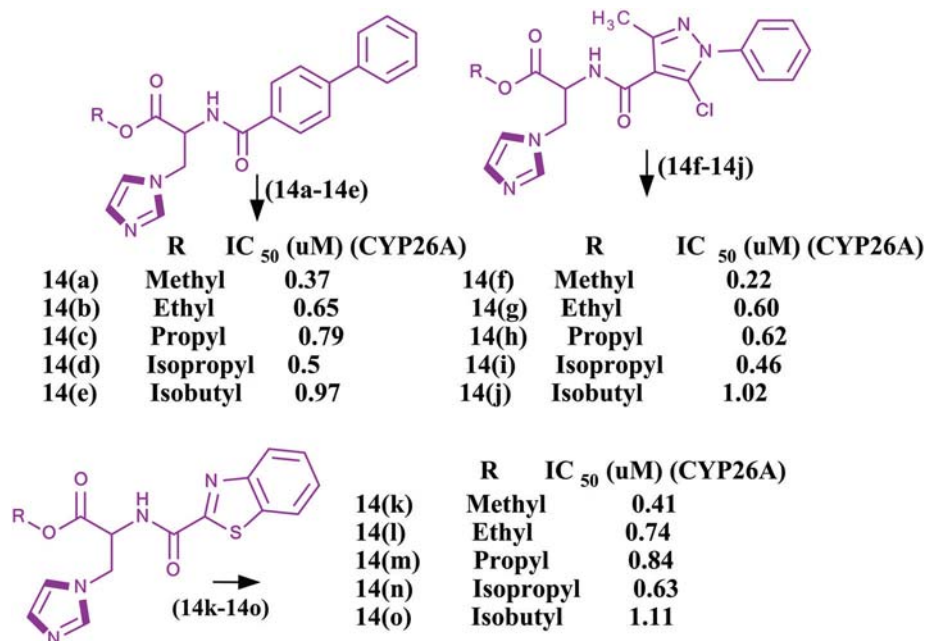


Fig. 8 Imidazoles as CYP26A1 inhibitors.

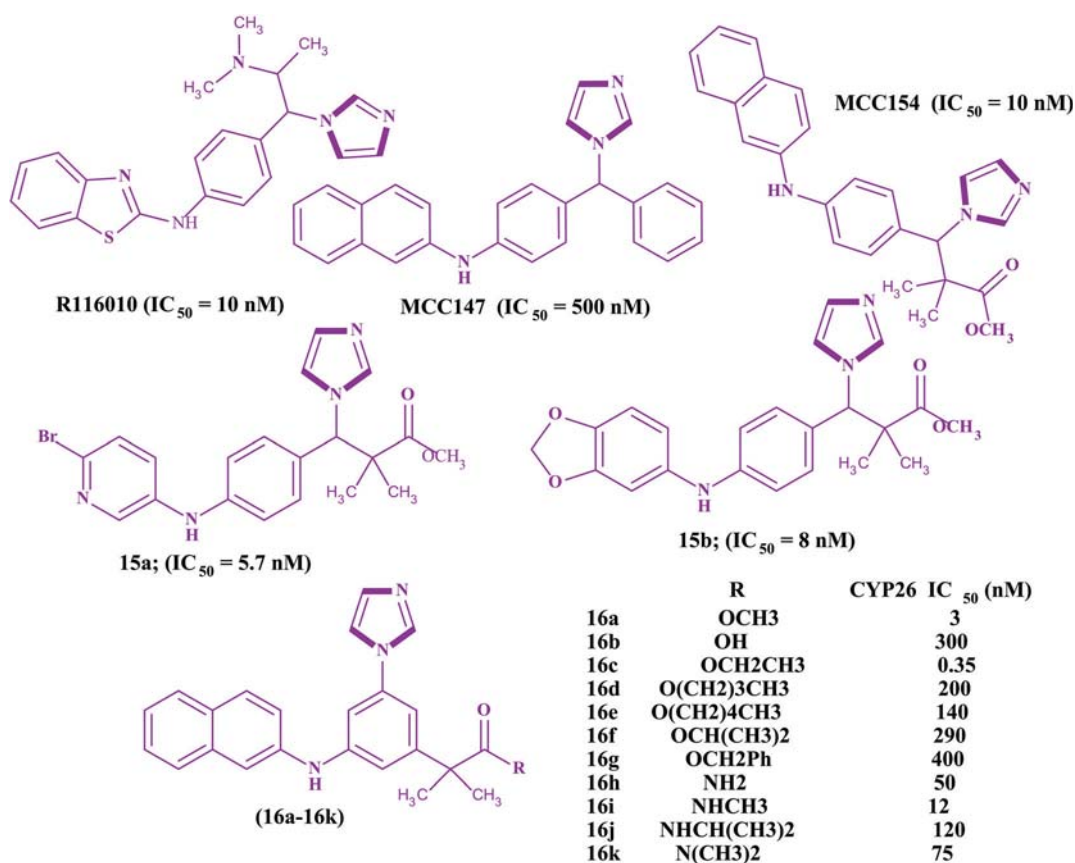


Fig. 9 Imidazoles as CYP26A1 inhibitors.

important classes of antitumorals drugs like anthracycline (doxorubicin and daunorubicin), epipodophyllotoxin (etoposide and teniposide), mitoxantrone, amonafide,

topotecan, irinotecan, camptothecin and amsacrine classes that are considered topoisomerase (TOP) inhibitors.<sup>116-119</sup> About 50% of anticancer agents available target cancer *via*



inhibition of the topoisomerase mechanism.<sup>120,121</sup> However, high toxicity, the poor solubility and short action duration hinders their continuous use. Many efforts have been devoted to searching for safer and more effective TOP inhibitors. Due to two typical nitrogen atoms, imidazoles can form hydrogen bonds, which are favorable for the water solubility of the target compounds. For this reason, imidazole has been considered as a structural fragment and is frequently introduced into other bioactive skeletons. By multiple component reactions, Baviskar *et al.* constructed a series of *N*-fused imidazoles and evaluated them against human topoisomerase II $\alpha$  (hTopoII $\alpha$ ) in decatenation, relaxation, cleavage complex, and DNA intercalation *in vitro* assays.<sup>122</sup> The results of the study revealed that five imidazoles 17a–17e (Fig. 10) acted as potent DNA non-intercalating topoisomerase II $\alpha$  catalytic inhibitors. In addition, the authors observed higher anticancer activities compared to etoposide and 5-fluorouracil in kidney and breast cancer cell lines with an apoptotic effect in the G1/S phase. Besides, these imidazoles showed low toxicity to normal cells. Recently, Negi *et al.* reported the microwave synthesis of ten imidazoles conjugated with imine/amides and screened them for anticancer activities with seven cancer cell lines (A-459, Hep-G2, H-460, HeLa, MCF7, PC3 and IGROV-1).<sup>123</sup> Only three imidazoles 18a–18c (Fig. 10) showed promising *in vitro* anticancer activities with low micromolar IC<sub>50</sub> values against A-459, Hep-G2 and H-460 cancer cell lines.

Indimitecan 19a is a clinical anticancer candidate with good solubility to treat refractory solid tumors. It has improved stability without the lactone moiety in comparison to the conventional Top-I inhibitors. Moreover, it can induce

long lasting DNA breaks and Top-I cleavage strands at unique genomic positions. Besides, it can bind with various targeting sites and cause cell cycle arrest in both the S and G(2)-M phases,<sup>124</sup> which reveals its robust potency to overcome drug resistance.

Camptothecin (CPT) was the first effective TOP-I inhibitor derived from the plant alkaloid *Camptotheca acuminata*, but its lower water solubility largely limits drug administration.<sup>125</sup> Introduction of ethyl and imidazolyl groups into camptothecin at the 7- and 10-positions yielded compound 19b. Due to these groups, it was observed that both the water solubility and TOP I inhibitory ability of CPT were improved. The IC<sub>50</sub> values (0.16 and 0.06  $\mu$ M) of 19b were low against breast (MCF-7) and colon cancer cell lines (HCT-8), and they were comparable to topotecan (0.15 and 0.07  $\mu$ M) but inferior to camptothecin (0.02 and <0.01  $\mu$ M), respectively.<sup>125</sup> In addition, the research revealed that the *E*-lactone ring in camptothecin is unstable and produced toxic carboxylates in the human body. However, 19c and 19d with the imidazolyl at the 20-position were found to increase the stabilities of the lactone rings and decrease the toxicity. Besides, both exhibited stronger anticancer potencies than camptothecin towards the PC-3, MCF-7 and HCT-8 cancer cell lines.<sup>126</sup> Cinelli *et al.* reported imidazole based aromathecine 19e, which had a better target TOP I inhibitory activity than aromathecine (non-CPT TOP I inhibitor).<sup>127</sup> Indenoisoquinolines without the unstable hydroxyl lactone are also an important non-CPT TOP I inhibitors. However, the imidazole analog 19f displayed better water solubility and affinity towards DNA than the indenone analog (19g), due to the interaction of the incorporated NH moiety with the phosphates of the DNA backbone.

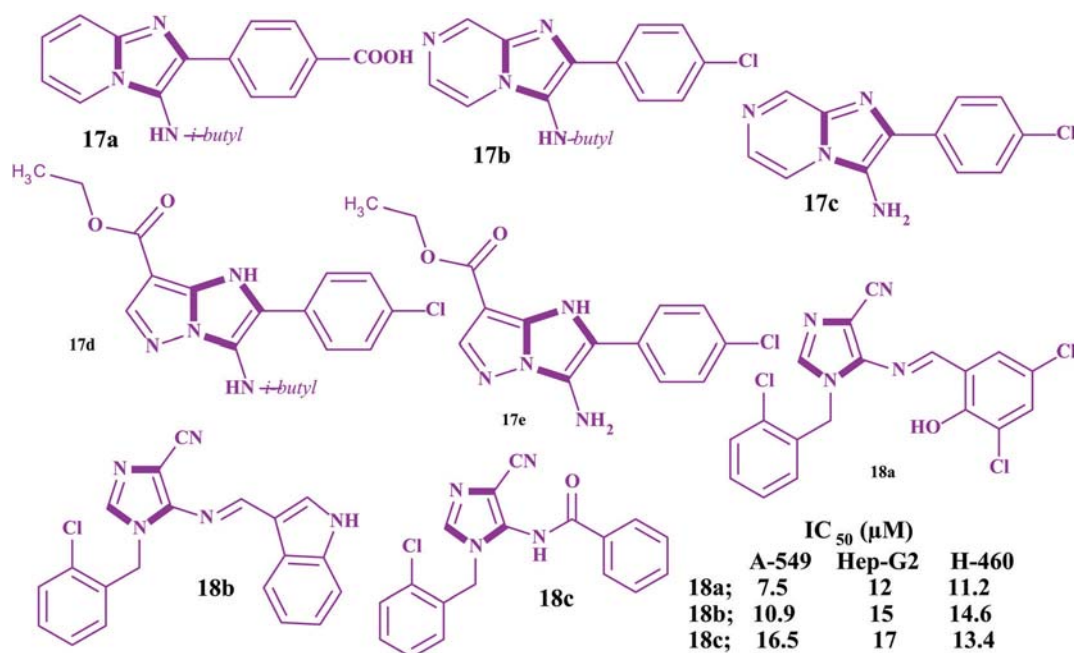


Fig. 10 Topoisomerase-II- $\alpha$  inhibitors.

Podophyllotoxin derivatives have showed encouraging clinical efficacy toward several types of neoplasms by inhibiting DNA-TOP II. However, their imidazole derivative displayed more potent anticancer activities towards human cell lines, *i.e.*, HeLa, K562, and K562/ADM, than etoposide.<sup>128</sup> It is well established that acridine derivatives like amsacrine are a class of DNA-TOP II inhibitors as they can intercalate into the DNA base pair, leading to cell cycle arrest and apoptosis. The acridine-based imidazole **19h** can satisfy the stereochemical and electronic requirements of the target receptor in a suitable way and displayed better anticancer activity towards MCF-7, HEP-2,

COLO-205, HCT-15, A-549, and IMR-32 human cancer cell lines at a concentration of 10  $\mu$ M in comparison to adriamycin.<sup>129</sup> This result suggested that the introduction of an imidazole ring into the 9-amino acridine is an effective approach to exploit new anticancer drugs. Norindenoisoquinolines were also found to be a novel class of TOP I inhibitors with poor solubility. The imidazole derivative (**19i**) showed good water solubilities and improved anticancer efficacies towards MCF-7, IGROVI, HCT-116, and SN12C.<sup>130</sup> The chemical structures of the podophyllotoxin derivatives (**19j–19n**) and imidazoles as topoisomerase inhibitors are shown in Fig. 11.

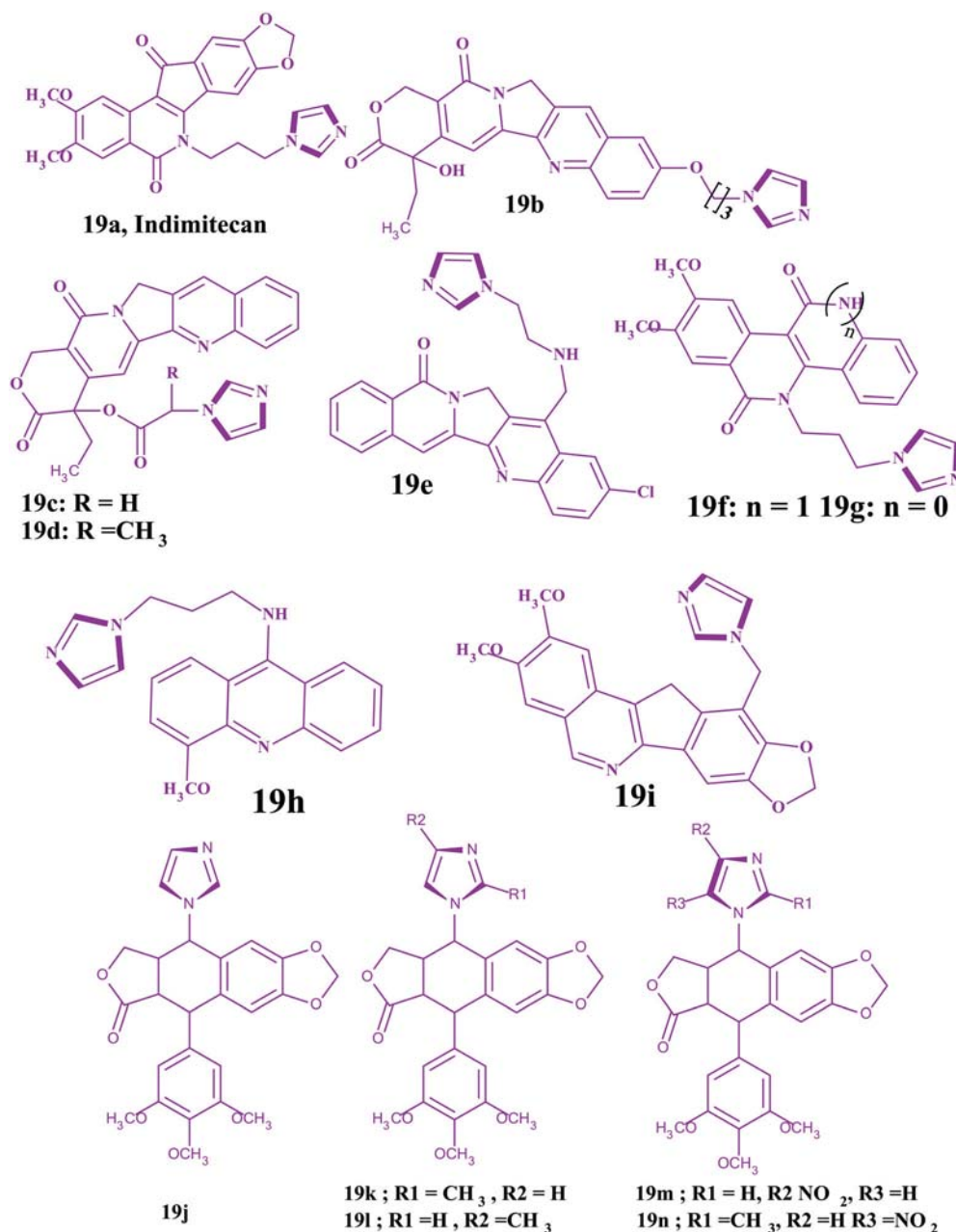


Fig. 11 Imidazoles as topoisomerase inhibitors.

## Imidazoles as rapid accelerated fibrosarcoma (RAF) kinase inhibitors

Among important biological targets in the discovery of anti-cancer drugs, RAF kinases (A, B and C) are regarded as attractive targets because of their relationship with cell growth, differentiation and proliferation. Currently, sorafenib is clinically available for the treatment of renal cancer as an RAF inhibitor.<sup>131</sup> However, its imidazole analogs **20a** and **20b**, possessing an amide linker and urea bridge, respectively, were found to possess remarkable CRAF inhibitory efficiency and more anticancer activities with  $GI_{50}$  values of 0.62 and 0.65  $\mu\text{M}$ , respectively, compared to sorafenib ( $GI_{50} = 0.78 \mu\text{M}$ ) towards the melanoma cancer cell line WM3629. Particularly, compound **20a** showed a 99% inhibitory efficacy towards CRAF at a concentration of 10  $\mu\text{M}$  with high selectivity. Astonishingly, for **20b**, the substitution of the chlorine atom of the benzene ring decreased the bioactivities.<sup>132</sup> All these findings revealed that imidazole analogs have great potential to act as RAF inhibitors for the treatment of melanoma. In another work reported by Rajitha *et al.*, imidazole **20c** was identified to be an excellent RAF inhibitor and exhibited superior anticancer activities towards the A549 and DLD-1 cell lines compared to sorafenib.<sup>133</sup> Furthermore, notable anti-proliferative activity was obtained when it was tested against acute myeloid leukemia (MV4-11) and compared to sorafenib. Moreover, modeling studies of **20c** were carried out, and they showed the compound occupying the ribose position of the ATP binding pocket, which is necessary for anticancer activity. Yu *et al.* reported some imidazoles incorporated pyrazole moieties.<sup>134</sup> This work revealed that the compound **20d** exhibited 96% inhibitory activity towards CRAF at a concentration of 10  $\mu\text{M}$  and good antiproliferative activities with  $GI_{50}$  values of 2.24 and 0.86  $\mu\text{M}$ , respectively, in contrast to sorafenib ( $GI_{50} = 5.58$  and 0.65  $\mu\text{M}$ ) against the human melanoma cell lines A375P and WM3629. Niculescu-Duvaz *et al.*

reported the imidazole containing pyrazole tricyclic derivative **20e** to be an active BRAF inhibitor for melanoma with good cellular activity ( $IC_{50} = 0.24 \mu\text{M}$ ) and a pharmacokinetic profile.<sup>135</sup> Furthermore, the study indicated that both the pyrazole tricyclic moiety and imidazole ring played crucial roles in exerting bioactivity. The replacement of the tricyclic pyrazole by a tricyclic triazole or six membered ring decreased the inhibitory potency. This might be attributed to the steric clash or unfavorable electrostatic interaction with the BRAF binding pocket. The structures for imidazoles as RAF inhibitors are shown in Fig. 12.

## Imidazoles as microtubule destabilizing anticancer agents

Microtubules, the important cytoskeletal filaments in cells, are assembled by polymerized tubulins. These filaments are proven molecular targets for anticancer drugs.<sup>136–140</sup> The tubulin binding agents interact with the tubulins on the binding sites and cause aberrations in the tubulin assembly kinetics and, thus, alter the stabilities of the microtubule structure. The inhibition of tubulin polymerization or interfering with microtubule disassembly disturbs some cellular functions, like cell motility and mitosis. There are a number of microtubule targeted tubulin binding agents that are clinically effective drugs in cancer treatments, like vincristine, vinblastine, a third-generation vinca alkaloid (vinorelbine), combretastatin A-4 phosphate (under clinical trial), paclitaxel, docetaxel, epothilones, *etc.*<sup>131–136</sup> Paclitaxel has a specific binding site on the microtubule polymer that makes it unique among chemotherapeutic agents, and the ability of paclitaxel to polymerize tubulin in the absence of cofactors like guanosine triphosphate and microtubule-associated proteins is unusual. It blocks cells in the G2/M phase of the cell cycle, and such cells are unable to form a normal mitotic apparatus. Vincristine also works *via* a microtubule

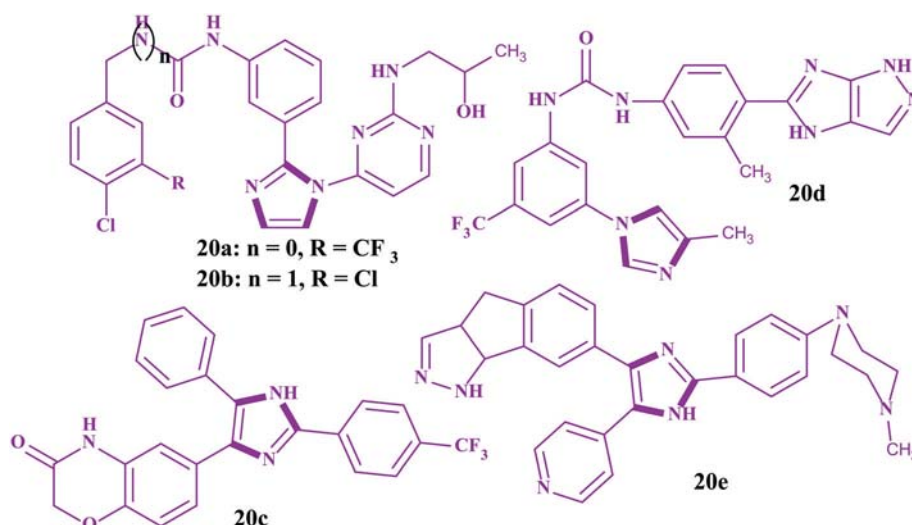


Fig. 12 Imidazoles as rapid accelerated fibrosarcoma kinase inhibitors.

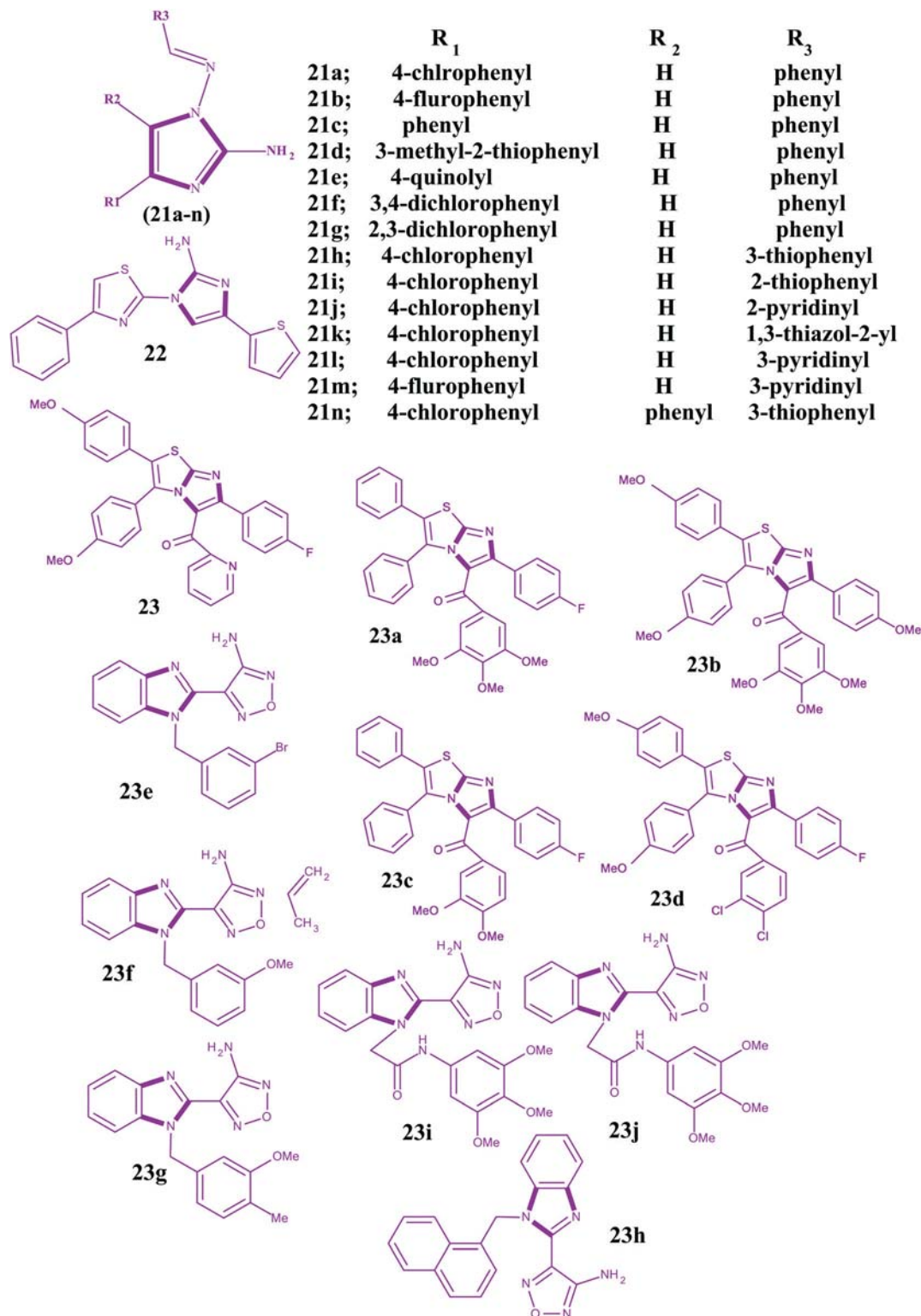


Fig. 13 Imidazoles as microtubule-destabilizing agents.

destabilizing mechanism, *via* binding to the tubulin protein, and stopping the cell from separating its chromosomes during the metaphase; the cell then undergoes apoptosis.

Some papers<sup>141–146</sup> have been published under the context of microtubule destabilizing agents in which the anticancer

potencies of imidazoles are well addressed. The structures for imidazoles as microtubule destabilizing agents are shown in Fig. 13. In 2010, Li *et al.* reported 2-amino-1-arylidenaminoimidazoles as orally active anticancer agents *via* a microtubule target mechanism.<sup>147</sup> In this work, the

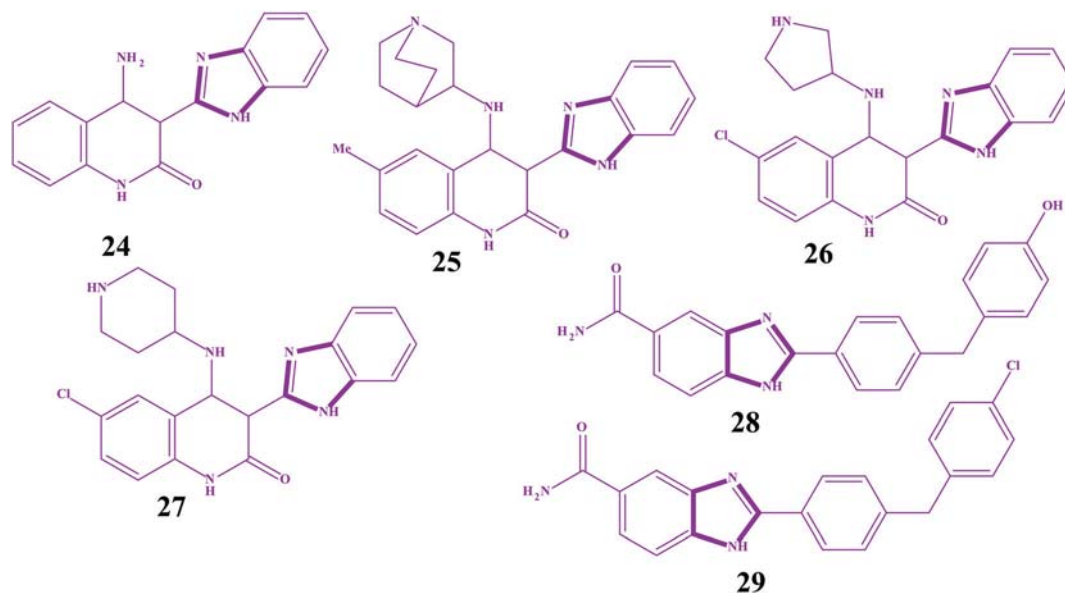


Fig. 14 Imidazoles as CHK-1 and CHK-2 inhibitors.

authors used a high throughput screening platform for the discovery of these imidazoles. The reported imidazoles were initially evaluated for cytotoxicity in the human gastric cancer NUGC-3 cells. The NUGC-3 cells were immunostained for microtubules by fluorescein isothiocyanate (FITC) and treated with one of the imidazoles at 1.0  $\mu\text{M}$  for 16 h, and a DMSO vehicle control was included. Compared to the well-arranged microtubule structures in the untreated cancer cells, the disarranged microtubule structures were observed as diffused green fluorescent tubulinimmunoreactive activities. Therefore, the molecular interaction effects of 2-amino-1-arylideneaminoimidazoles on targeted microtubules were visualized by fluorescence imaging. It has been found that the substituents on the phenyl ring of arylidene **21a** and **21b** indicated comparable activities with  $\text{IC}_{50}$  values of 0.06 and 0.05  $\mu\text{M}$ , respectively. However, imidazoles **21c**, **21d** and **21e**, containing arylidene substituents of phenyl, 3-methyl-2-thiophenyl, and 4-quinolyl, respectively, exhibited cytotoxic  $\text{IC}_{50}$  values of 0.84, 0.91, and  $>10$   $\mu\text{M}$  against NUGC-3 cancer cells. Among these, the phenyl substitution was superior to the others. So, substitution at the 4-position of the phenyl ring played a critical role in the cytotoxicity. The authors also observed a similar phenomenon with substituents of 3,4-dichlorophenyl **21f** and 2,3-dichlorophenyl **21g** on arylidene and showed  $\text{IC}_{50}$  values of 0.74 and 5.12  $\mu\text{M}$ , respectively. Furthermore, it has been observed that imidazoles **21h** and **21i** containing 3-thiophenyl and 2-thiophenyl at the 4-position of the imidazole ring exhibited the most potent cytotoxic activities against the NUGC-3 cancer cells, more than **21j** and **21k** containing 2-pyridinyl and 1,3-thiazol-2-yl, respectively. Compound **21l**, with a 3-pyridyl group at the 4-position of the imidazole, revealed a similar activity to **21j**, containing a 2-pyridyl group. In addition,

**21m**, with a substitution of the 4-fluorophenyl of arylidene and 3-pyridyl group at the 4-position of imidazole, exhibited a potent cytotoxic  $\text{IC}_{50}$  of 0.06  $\mu\text{M}$ . Substitution on the 5th position of the imidazole caused a loss of activity, like that shown by compound **21n**. In this work, the authors also carried out tubulin polymerization assays to access the anticancer activities of 2-amino-1-arylideneaminoimidazoles regarding colchicine and found imidazoles **21a** and **21l** were potent microtubule assembly inhibitors. In addition, in this study, an *ex vivo* antitumor activity assessment was performed against histocultured human gastric (MKN-45) and colorectal (SW-480) tumors with some imidazoles for 96 h and a reduction in the number of MKN-45 and SW-480 tumor cells was observed. The inhibition on the tubulin polymerization and colchicine binding kinetics provided evidence at the molecular level for interference in the microtubule assembly, which is one of the proven molecular mechanisms of anticancer action for the compounds presented in the study.

In another work, a group of imidazoles linked with a thiazole moiety were promoted as orally active microtubule destabilizing anticancer agents.<sup>148</sup> The reported imidazoles were evaluated for cytotoxic activity against the human gastric cancer NUGC-3 cells. Among the group, compound **22** (1-(4-phenylthiazol-2-yl)-4-(thiophen-2-yl)-1*H*-imidazol-2-amine) with an  $\text{IC}_{50}$  value of 0.05  $\mu\text{M}$  was found to be potent against human cancer cells. Its anticancer action was explained based on interferences in the colchicine binding sites of tubulins and the kinetics of microtubule assembly, which cause cell cycle arrest at the G2/M phase, inhibition of tumor cell proliferation, and induction of tumor cell apoptosis. Besides, **22** showed oral activity and significantly prolonged (75% longer compared to that of the vehicle control group vinblastine 83%) the lifespan of leukemia mice.

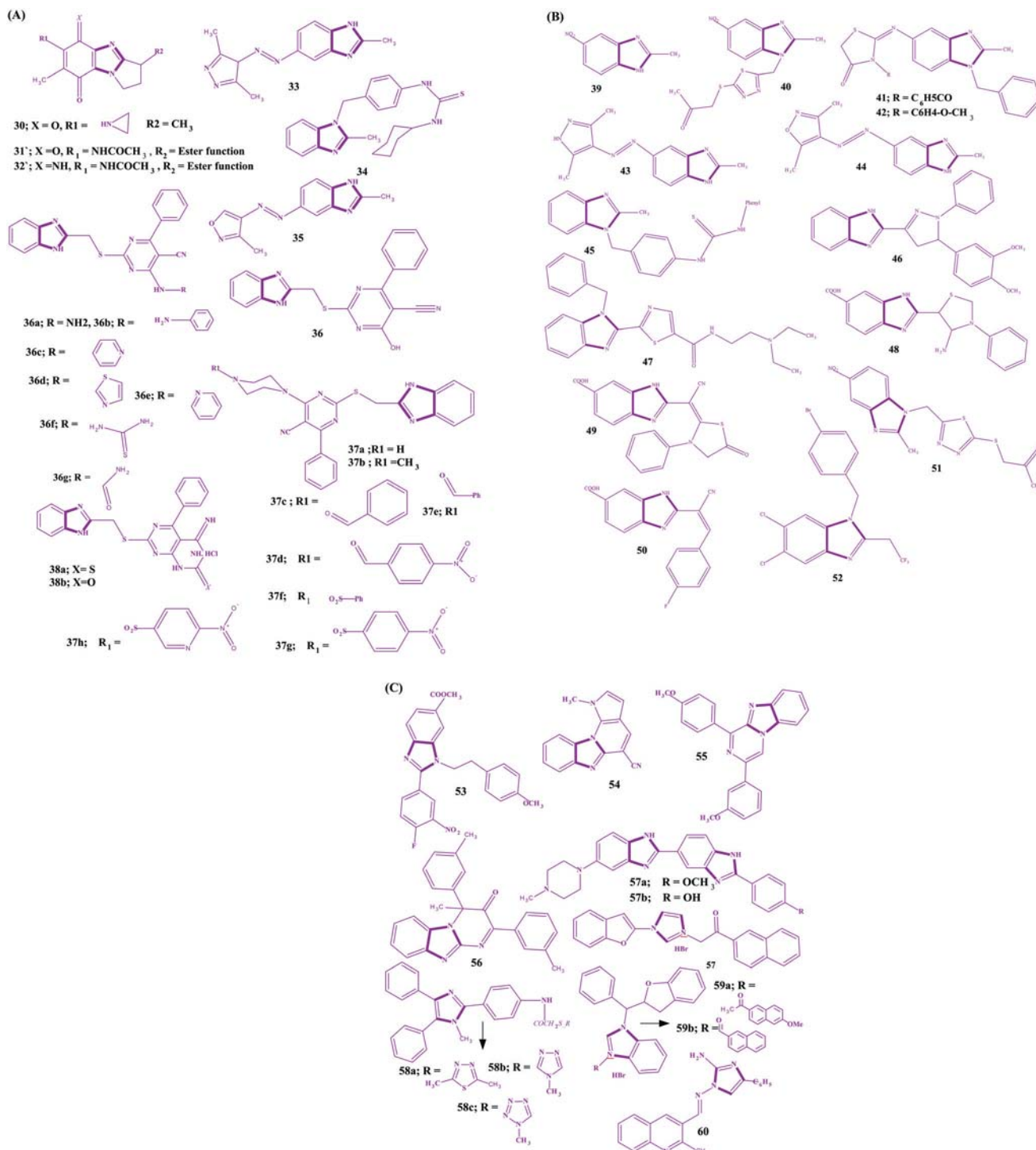


Fig. 15 (A): Benzimidazoles as potent anticancer agents. (B): Benzimidazoles as potent anticancer agents. (C): Benzimidazoles as potent anticancer agents.

In one more study, Kamal *et al.* constructed chalcone conjugates featuring the imidazo[2,1-*b*]thiazole scaffold and evaluated their cytotoxic activities against five human cancer cell lines (MCF-7, A549, HeLa, DU-145 and HT-29) as inhibitors of microtubules.<sup>149</sup> Promising cytotoxic activities with IC<sub>50</sub> values ranging from 0.64 to 30.9  $\mu\text{m}$  were ob-

served. The imidazole 23 showed significant activity against the five human cancer cell lines and among the tested cancer cell lines. A549 cells were the most sensitive to 23 (IC<sub>50</sub> = 0.64  $\mu\text{m}$ ). Furthermore, a flow cytometric analysis was also carried on 23, which resulted in cell cycle arrest in the G<sub>2</sub>/M phase, leading to apoptotic cell

death. Besides, Hoechst staining, activation of caspase-3, DNA fragmentation analysis, Annexin V-FITC assay and molecular docking studies were carried out to support the results. Finally, it was concluded that the combo of imidazole and chalcone is a potent tubulin polymerization inhibitor (23a–23d). Recently, Stepanov *et al.* reported a series of benzoimidazolyl furazanamines and evaluated their microtubule destabilizing properties in the sea urchin embryo model and in cultured human cancer cell lines.<sup>150</sup> Some imidazoles were studied *in vitro* using a tubulin polymerization assay and cell cycle distribution analysis. Further, these compounds were screened against a panel of human cancer cell lines to assess their cytotoxicities. The authors followed a simple protocol that includes a fertilized egg test for antimetabolic activity and the compounds displayed cleavage alteration/arrest and swimming pattern observation of blastulae treated by the compounds after hatching. The lack of forward movement, settling to the bottom of the culture vessel, and rapid spinning of the embryos around the animal vegetal axis suggested the microtubule destabilizing activity caused by the molecule (video illustrations are available at <http://www.chemblock.com>). The attainment of a specific tuberculate shape of the arrested eggs (typical for microtubule destabilizing agents) was considered indirect evidence of targeting microtubules.<sup>151,152</sup> In this work, the authors found some imidazoles 23e–23j very interesting and considered them as active microtubule destabilizing agents. In the experiment, it was found that the arrested sea urchin eggs acquired a tuberculate shape typical of microtubule destabilizers.<sup>151–153</sup>

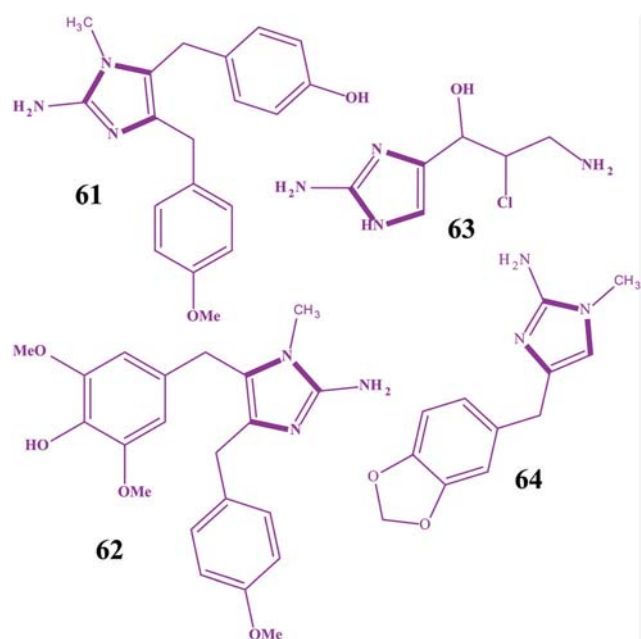


Fig. 16 Some naturally occurring 2-aminoimidazoles as anticancer agents.

## Imidazoles as CHK-1 and CHK-2 inhibitors

The checkpoint kinases (CHK-1 and CHK-2) are serine/threonine protein kinases, which function as key regulatory kinases in cellular DNA damage response pathways limiting cell-cycle progression in the presence of DNA damage. The development of checkpoint kinase inhibitors for the treatment of cancer has been a major objective in drug discovery over the past decade, as evidenced by three checkpoint kinase inhibitors entering clinic trials since late 2005.<sup>154–158</sup> Since cell cycle arrest is a mechanism by which tumor cells can overcome the damage induced by cytotoxic agents, abrogation of the G2/M checkpoint with novel small compounds may increase the sensitivity of p53-deficient tumors to chemotherapy. Importantly, in contrast to many current therapies for cancer, this mechanism potentially carries with it only a low risk of toxicity against nonmalignant cells, as CHK-1 inhibition is most effective in p53-defective cancer cells. The major advantage of CHK-1 inhibitors in the treatment of cancer is their selective activity in conjunction with cytotoxicity, such as DNA-damaging reagents. Until now, several CHK-1 inhibitors have been reported, but UCN-01 (7-hydroxystaurosporine) has been found to be a potent inhibitor ( $K_i = 5.6$  nM) that has modest selectivity among other kinases of CHK-1 and is currently under clinical trials.<sup>159–165</sup> However, the checkpoint kinase CHK-2 is activated by ATM (ataxia-telangiectasia mutated) in response to DNA damage and controls the downstream p53-dependent apoptosis machinery.<sup>166</sup> Deletion of CHK-2 in mice blocks apoptosis after lethal radiation in several cell types and increases cell survival.<sup>167,168</sup> Tumor tissue is, generally, more apoptosis resistant than normal cells. Generally, inhibition of CHK-2 would not protect these tissues and becomes an important target for anticancer drugs. However, imidazole analogues also showed potency as CHK inhibitors. Ni *et al.* constructed a series of benzimidazoles as serine/threonine checkpoint kinase (CHK-1) inhibitors with synergistic effects and DNA-damaging agents in tumor cells.<sup>169</sup> Among the series, the unsubstituted benzimidazole linked with quinolone 24 showed moderate activity ( $IC_{50} = 0.73$   $\mu$ M) against CHK-1. However, its substitution by various heterocyclic rings increased the activity potencies by more than 10 fold. Replacement of the amine hydrogen with the aza-bicyclo-octane ring 25 increased the potency ( $IC_{50} = 0.35$  nM). Moreover, the imidazoles containing methyl 26 and chloro 27 groups also showed high potential against CHK-1 with  $IC_{50} = 0.50$  nM and  $IC_{50} = 0.32$  nM, respectively. In another work, the imidazoles 28 ( $IC_{50} = 2$  nM) and 29 ( $IC_{50} = 15$  nM) were identified as potent inhibitors of CHK-2.<sup>170,171</sup> Based on molecular modeling, it was predicted that the high affinity of compound 28 was potentially due to a hydrogen bonding interaction between an active site residue (histamine 157) and the hydroxyl group of the terminal phenol. In view of the potencies of the 28 and 29 imidazoles, Neff *et al.* exploited a series of benzimidazoles as CHK-2 inhibitors.<sup>172</sup> All compounds showed

significantly less inhibitory activity than **28** and **29** but more overall solubility. The structures for imidazoles as CHK-1 and CHK-2 inhibitors are shown in Fig. 14.

## Miscellaneous biological targets of imidazoles

Benzimidazole is an important scaffold in various biological active molecules. It is an isostere of a purine based nucleic acid and is extensively explored for the development of anti-cancer agents. Earlier benzimidazoles **30–32** as anticancer agents act *via* a DNA alkylation mechanism through cleavages of the G and A bases.<sup>173–175</sup> Various benzimidazole substituted derivatives **33–35** are reported as cytotoxic against lung and breast cancers.<sup>176,177</sup> Abdel-Mohsen *et al.* developed benzimidazoles conjugated with pyrimidine and explored their anticancer activities for twelve carcinoma cell lines (KB, SK OV-3, SF-268, NCI H460, RKOP27 HL60 U937 K562 G361 SK-MEL-28 GOTO NB-1).<sup>178</sup> Compound **36** emerged as the most active against non-small lung cancer (NCI H460), ovarian carcinoma (SK OV-3) and leukemia (HL60) but was still less active than the standards. Compound **36a** was observed as the most active against cervical carcinoma (KB), and the phenylhydrazino compound **36b** was one of the most active compounds against melanoma (G 361) and neuroblastoma (NB-1). In addition, the 4-aminopyridino compound **36c** and the 2-aminothiazolo compound **36d** were found to be the most active compounds against CNS cancer (SF-268), while the 2-aminopyridino compound **36e** was the most active against leukaemia (U937) and neuroblastoma (GOTO). The thiosemicarbazido compound **36f** was one of the most active compounds against neuroblastoma (GOTO), while the uryl compound **36g** was one of the most active compounds against colon adenocarcinoma (RKOP27). Compound **37a** was the most active against melanoma (SK-MEL-28), and the *N*-methylpiperazino compound **37b** was the most active among the series against leukemia (K562) and neuroblastoma (NB-1). The *N*-benzoylpiperazine compound **37c** and the 4-nitrobenzoylpiperazino compound **37d** were found to be the most active compounds against melanoma (G 361), and the phenylacetylpiperazino compound **37e** was active against leukemia (U937). The benzenesulfonylpiperazino compound **37f** was among the most active compounds against cervical carcinoma (KB) and non-small lung cancer (NCI H460), and the tosyl piperazine compound **37g** was one of the most active compounds against colon adenocarcinoma RKOP27. The 2-nitrobenzenesulfonylpiperazino compound **37h** was among the most active compounds against neuroblastoma (NB-1). Compound **38a** was one of the most active compounds against colonadenocarcinoma (RKOP27), and **38b** was one of the most active compounds against cervical carcinoma (KB). In other work, benzimidazole derivatives were synthesized, and compounds **39** (IC<sub>50</sub> = 4.2 μM) and **40** (IC<sub>50</sub> = 8.29 μM) were found to have high cytotoxic activity against breast cancer (MCF7).<sup>179</sup> Compounds **41** and **42** possess significant inhibitory activity against Burkitt's lymphoma promotion,<sup>177</sup>

and **43**, **44** (log GI<sub>50</sub> = -5.61) and **45** have high cytotoxic activity against non-small lung cancer and breast cancer, **43** (log GI<sub>50</sub> = 5.77) and **44** (log GI<sub>50</sub> = 5.36).<sup>176,178</sup> Development of benzimidazoles is a continuous goal of researchers, and its pyrazoline **46** analogues<sup>180</sup> and thiazole **47** derivatives<sup>181</sup> have been developed as potent anticancer agents for various cancer cell lines. Furthermore, another series of benzimidazoles as anti-tumour agents have been reported by Refaat,<sup>182</sup> and some imidazoles, 4-amino-thioxothiazole **48**, 4-oxothiazolidine **49**, 4-fluorobenzylidene **50**, and cycloalkylidene were found to be potent anti-tumour agents. Ramla *et al.* evaluated the anti-tumor activity of benzimidazoles and revealed the imidazole **51** incurs the maximum antitumor activity.<sup>179</sup> Ng *et al.* explored some 2,5,6-trihalogenobenzimidazoles as androgen receptor antagonists for their use in prostate cancer and revealed that benzimidazole possessed the 1-(4-bromobenzyl) substituent (**52**) as the most potent androgen receptor antagonist.<sup>183</sup> Similarly, another series of benzimidazoles containing 5-carboxylic acid have been evaluated as anti-leukemic agents by Gowda *et al.*, and compound **53** was found to activate apoptosis.<sup>184</sup> Hranjec *et al.* reported a series of benzimidazoles covalently linked to a quinolone ring and found compound **54** (IC<sub>50</sub> of 0.8–30 μM) was the most potent on all cancer cell lines.<sup>185</sup> This potency was predicted *via* the potential to insert into the space between the base pairs of DNA, resulting in DNA cleavage. Recently, more fused planar benzimidazole derivatives have been reported to exhibit potent cytotoxicity. The exemplaries include **55** (pyrimido[1,2-*a*]benzimidazole-3(4*H*)-one)<sup>186</sup> and **56** (1,3-diarylpiazino[1,2-*a*]benzimidazole).<sup>187</sup> Bis-benzimidazoles are another class of compounds exploited for the discovery of anticancer agents. Hoechst-33342 **57a** and Hoechst-33258 **57b** are the first of this series exhibiting *in vitro* antitumor as well as DNA top I inhibitory activities.<sup>188–192</sup> Yang *et al.* synthesized novel hybrid compounds between imidazole and 2-phenylbenzofuran, and imidazole **57** with the 2-bromobenzyl group was the most active potent compound against four human tumor cell lines (SMMC-7721, SW480, MCF-7 and HL-60) and more active than cisplatin (DDP).<sup>41</sup> Ozkay *et al.* constructed a series of 2-substituted-*N*-[4-(1-methyl-4,5-diphenyl-1*H*-imidazole-2-yl)-phenyl] acetamide derivatives and revealed that three compounds **58a–58c** were the most active anticancer agents against HT-29 and MCF-7 carcinoma cell lines amongst the series.<sup>193</sup> Wang *et al.* reported another series of imidazoles covalently linked with 2-benzylbenzofurane and found two imidazoles, **59a** and **59b**, were the most potent against five human tumor cell lines (HL-60, A549, SW480, MCF-7 and SMMC-7721).<sup>194</sup> In addition, these two compounds were more active than cisplatin (DDP). In another research article reported by Singh *et al.*, novel imidazole conjugates were designed and synthesized regioselectively; wherein, compound **60** was found as the most potent cytotoxic scaffold against HCT-116, DLD-1 cell lines and relatively non-toxic to MDA-MB-231 and HUVEC cell lines.<sup>195</sup> The structures for benzimidazoles as potent anticancer agents are shown in Fig. 15(A–C). Copp *et al.* reported 2-aminoimidazole alkaloid



naamidine A 61, which was isolated from a Fijian *Leucetta* species sponge as an inhibitor of the epidermal growth factor (EGF) receptor.<sup>196</sup> In this part of the work, the authors claimed that the compound exhibited a potent ability to inhibit the EGF signaling pathway and was more specific for the EGF-mediated mitogenic response than for the insulin-mediated mitogenic response. Furthermore, 85% growth inhibition at the maximal tolerated dose of 25 mg kg<sup>-1</sup> was observed after the evaluation of an A431 xenograft tumor model in athymic mice. In another research article by Hassan *et al.*, extraction of Naamine G 62 from Indonesian Sponge *Leucetta chagosensis* has been reported, and it revealed a mild cytotoxicity against mouse lymphoma (L5178Y) and human cervix carcinoma (HeLa) cell lines.<sup>197</sup> Similarly, giroline 63 and preclathridine A 64, the other two important natural imidazoles as anticancer agents, have been reported.<sup>198–200</sup> The structures of some naturally occurring 2-aminoimidazoles as anticancer agents are shown in Fig. 16.

## Market status of Imidazole-based anticancer drugs

Imidazole-based anticancer drugs possess remarkable potential due to their ability to interfere first with DNA synthesis and then halt the cell growth and division. Until now, many imidazole-based anticancer drugs: azathioprine, misonidazole, pimonidazole, nilotinib, tipifarnib, fadrozole, indimitecan, acadesine, bleomycin, bombesin, dacarbazine, zoledronic acid, clotrimazole, mitozolomide, mercaptopurine, pilocarpine, radotinib, plinabulin, SB-431542, temozolomide, etanidazole and bendamustine, have been developed and play an important role in the clinic (Table 1). Dacarbazine is an alkylating agent that destroys cancer cells by adding an alkyl group to DNA. It has applications for metastatic malignant melanoma, hodgkin lymphoma, sarcoma and islet cell carcinoma of the pancreas.<sup>201</sup> Azathioprine is a prodrug of mercaptopurine that has applications for the treatment of childhood acute lymphoblastic leukemia.<sup>202</sup> Moreover, 2-nitroimidazoles (misonidazole, etanidazole and pimonidazole) act as radiosensitizers of hypoxic tumor cells.<sup>203</sup> Pimonidazole is reduced in hypoxic environments, as in tumor cells, and it can be used as a hypoxia marker.<sup>204</sup> Bendamustine is an alkylating agent synthesized in the 1960s by Ozegowski and Krebs in East Germany,<sup>205</sup> which is used in the treatment of chronic lymphocytic leukemia and lymphomas.<sup>206,207</sup> Etanidazole also possess potential applications in cancer chemotherapy by depleting the glutathione concentration, and it inhibits glutathione transferase. This enhances the cytotoxicity of ionizing radiation.<sup>208</sup> Zoledronic acid is an inhibitor of osteoclast mediated bone resorption and is used in the management of patients with cancer. It slows down bone resorption, allowing the bone forming cells time to rebuild normal bone and bone remodeling.<sup>209</sup> Nilotinib is a novel and selective small molecule Bcr-Abl; whereas, tipifarnib is a non-peptidomimetic quinolone analog of imidazole and a potent farnesyl transferase inhibitor

developed by Johnson & Johnson Pharmaceutical for the treatment of acute myeloid leukemia.<sup>210</sup> Fadrozole is of great interest to medicinal chemists as it has been recommended as a first-line drug in the therapy of breast cancer.<sup>211</sup> Furthermore, indimitecan has been demonstrated to inhibit topoisomerase-I enzyme by intercalating between the DNA base pairs and stabilizing a ternary complex. Also, it produces a unique pattern of DNA cleavage sites relative to camptothecins and may target genes differently, which could result in a spectrum of anticancer activities.<sup>212</sup> Attempts have been made to compile the imidazole drugs available in the market and clinical trials and are given in Table 1.

## Toxicity issues of imidazoles

While developing anticancer drugs, toxicity is one of the serious issues of importance. Drug toxicity is acceptable when the drugs are less harmful than the disease. The main toxicities associated with the use of imidazoles are nausea, vomiting, and hepatic dysfunction. Toxicity of imidazoles interfere with steroid biosynthesis that may result in impaired reproduction, alterations in (sexual) differentiation, growth, and development and the development of certain cancers. The toxicity of imidazole entities (1-alkyl-3-methylimidazolium) increases with the length of the side chain alkyl groups. Similar results were also found for the 1-vinylimidazole cation. At the same time, the toxicity of 1-alkyl-3-methylimidazolium and 1-vinylimidazole ionic liquids also depends on the associated anion species. The EC<sub>50</sub> values are largest for tetrafluoroborate, whereas bis(trifluoromethylsulfonyl) imide results in the lowest EC<sub>50</sub> value.<sup>213</sup> In 1969, Nishie *et al.* reported the convulsant and lethal effects of imidazoles in mice. The authors found methylimidazole as the most potent convulsant. Furthermore, it was observed that the imidazoles tested at high dosage levels produced varying degrees of tremor, restlessness, running, sialorrhea, opisthotonus, straub tail and tonic extensor seizure terminating in death, whereas at lower doses, a loss of balance was the common finding. Toxicity experiments were carried out in 3 species, rabbit, mouse, and chicken, and the toxic manifestations, like abrupt paralysis of respiration, cyanosis, and gradual cardiac arrest, were observed in rabbit and mice. In addition, in rabbits, the heart rate decreased on the order of 33% below the control, while the respiratory rate increased to three times the normal values.<sup>214</sup> Generally, the use of higher concentrations of any drug is always a problem. Norregaard *et al.* carried out an experiment in which the toxicity of temozolomide on U87MG glioblastoma cells was studied in order to confirm the activity of the drug, and the toxic effects of TMZ were observed at 50 and 500 μM concentrations.<sup>215</sup> Moreover, Sing *et al.* reported the regioselective synthesis of aminoimidazole quinoline hybrids and cytotoxic evaluation against two cancer cells and toxicity against normal endothelial cells (HUVEC) and found some imidazoles 65a–65f had a good cytotoxicity against the cancer cell line. However, unfortunately against the HUVEC cells, the IC<sub>50</sub>

**Table 1** The chemical structures and applications of imidazole drugs in cancer chemotherapy

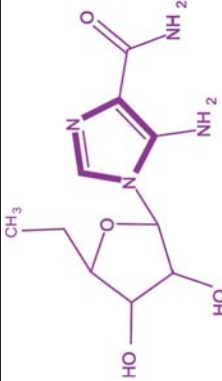
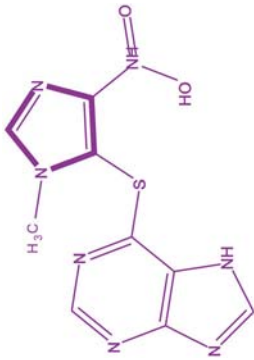
S. no	Drugs	Structures and chemical names	Brand names	Market status	Applications
1	Acadesine	 5-Amino-1-[(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i> )-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-1 <i>H</i> -imidazole-4-carboxamide	—	Phase III	Acute lymphoblastic leukemia
2	Azathioprine	 6-[[1-Methyl-4-nitro-1 <i>H</i> -imidazol-5-yl]sulfanyl]-7 <i>H</i> -purine	Imuran	Phase I	Childhood acute lymphoblastic leukemia

Table 1 (continued)

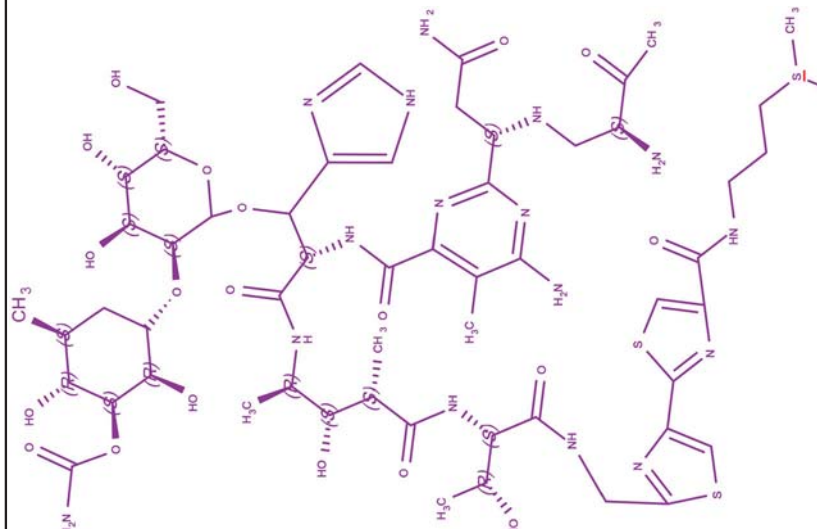
S. no	Drugs	Structures and chemical names	Brand names	Market status	Applications
3	Bleomycin	 <p>(3-[[[2'-{(5<i>S</i>,8<i>S</i>,9<i>S</i>,10<i>R</i>,13<i>S</i>)-15-{6-Amino-2-[(1<i>S</i>)-3-amino-1-[[[(2<i>S</i>)-2,3-diamino-3-oxopropyl]amino]-3-oxo propyl]-5-methylpyrimidin-4-yl]-13-[[[(2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>S</i>,6<i>S</i>)-3-[[[(2<i>R</i>,3<i>S</i>,4<i>S</i>, 5<i>R</i>,6<i>R</i>)-4-(carbamoyloxy)-3,5-dihydr oxy-6-(hydroxymethyl) tetrahydro-2<i>H</i>-pyran-2-yl]oxy]-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2<i>H</i>-pyran-2-yl]oxy} (1<i>H</i>-imidazol-5-yl)methyl]-9-hydroxy-5-[(1<i>R</i>)-1-hydr oxyethyl]-8,10-dimethyl-4,7,12,15-tetraoxo-3,6,11,14-tetraazapentadec-1-yl]-2,4'-bi-1,3-thiazol-4-yl]carbon yl]amino)propyl]dimethylsulfonium</p>	Blenoxane	US-FDA approval in 1973	Hodgkin's lymphoma, non-Hodgkin's lymphoma, testicular, ovarian and cervical cancer

Table 1 (continued)

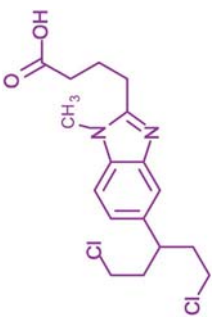
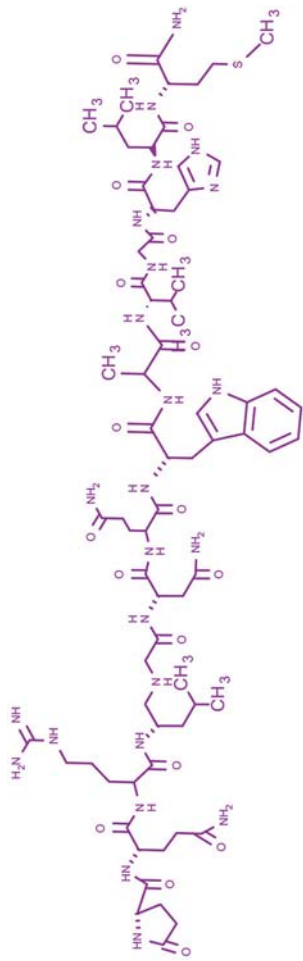

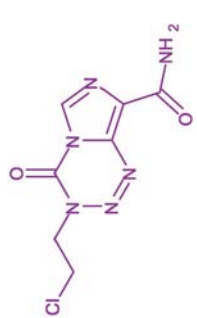
S. no	Drugs	Structures and chemical names	Brand names	Market status	Applications
4	Bendamustine	 4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid	Treanda	US-FDA approval in 2008	Chronic lymphocytic leukemia and lymphomas
5	Bombesin	 4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid	—	Phase-III	Small cell carcinoma of lung, gastric, pancreatic and neuroblastoma
6	Dacarbazine	 Pyr-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH <sub>2</sub> Fig. 1 5-(3,3-Dimethyl-1-triazenyl)imidazole-4-carboxamide	DTIC-Dome	US-FDA approval in 1975	Malignant melanoma, Hodgkin's lymphoma, sarcoma and islet cell carcinoma of the pancreas
7	Mitozolomide	 3-(2-Chloroethyl)-4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide Fig. 1 3,7-Dihydropurine-6-thione Fig. 1 4-Methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[(4-pyridin-3-yl)pyrimidin-2-yl]amino]benzamide	—	Discontinued during phase II	—
8	Mercaptopurine		Purinethol	Phase I	Acute lymphocytic leukemia
9	Nilotinib		Tasigna	US-FDA approval in 2009	Philadelphia chromosome(Ph <sup>+</sup> )-positive chronic myelogenous leukaemia

Table 1 (continued)


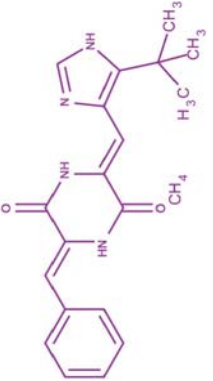
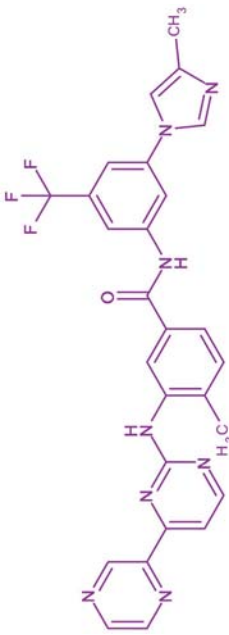
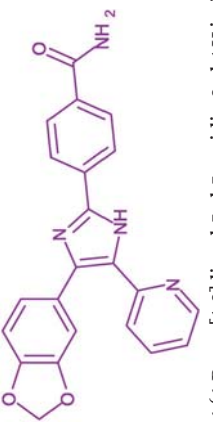
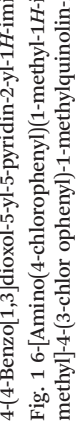

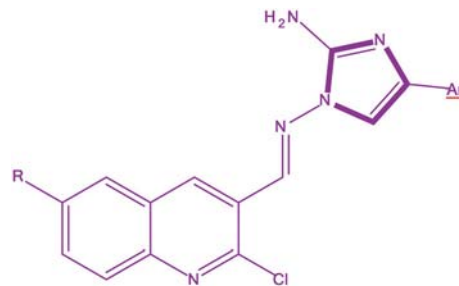
S. no	Drugs	Structures and chemical names	Brand names	Market status	Applications
10	Pilocarpine	 3-Ethyl-4-((1-methyl-1 <i>H</i> -imidazol-5-yl)methyl)dihydrofuran-2(3 <i>H</i> )-one	Salagen	Under clinic	As a side effect of radiation therapy for head and neck cancer
11	Plinabulin	 3-Benzylidene-6-((5-(2-methyl-2-propanyl)-1 <i>H</i> -imidazol-4-yl)methylene)-2,5-piperazinedione		Phase I and II	Non-small cell lung cancer
12	Radotinib	 4-Methyl- <i>N</i> -(3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-[[4-pyrazin-2-yl]pyrimidin-2-yl]amino]benzamide	Supect	Phase II	Chronic myeloid leukemia
13	SB-431542		—	No clinical trials	It suppress the TGF-beta-induced proliferation of osteosarcoma cells in humans
14	Tipifarnib	 4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1 <i>H</i> -imidazol-2-yl)-benzamide	Zarnestra	US-FDA disapproval in 2005	Acute myeloid leukemia
15	Temozolomide	 Fig. 1 4-Methyl-5-oxo-2,3,4,6,8-pentaza bicyclo[4.3.0]nona-2,7,9-triene-9-carboxamide	Temodar		Astrocytoma and glioblastoma multiforme

Table 1 (continued)

S. no	Drugs	Structures and chemical names	Brand names	Market status	Applications
16	Zoledronic acid	 Fig. 1 1-Hydroxy-2-(1H-imidazol-1-yl)ethane-1,1-diy]bis(phosphonic acid)	Zometa	Under clinic	In management of patients with multiple myeloma and prostate cancer
17	Indimitecan		—	Phase I	Topoisomerase-I inhibitor
18	Fadrozole	 4-(5,6,7,8-Tetrahydroimidazo[1,5-a]pyridin-5-yl)benzonitrile	Afema	Under clinic	Breast cancer



65a; R = Me, Ar = C<sub>6</sub>H<sub>4</sub>(Me)<sub>4</sub>  
 65b; R = Me, Ar = C<sub>6</sub>H<sub>4</sub>OMe  
 65c; R = Me, Ar = C<sub>6</sub>H<sub>4</sub>Cl  
 65d; R = Me, Ar = C<sub>6</sub>H<sub>4</sub>Br(4)  
 65e; R = Me, Ar = 1-naphthyl  
 65f; R = Me, Ar = 2-naphthyl

Fig. 17 The chemical structures of imidazoles that are less toxic to cancer cells and more toxic to normal cells.

values decreased and resulted in an increment in the toxicity, which is a matter of concern.<sup>216</sup> Furthermore, compound 60 showed selective toxicity against colon cancer cells and was relatively non-toxic to breast cancer cells. Moreover, the imidazole substituted with the theinyl moiety at position-4 reduces the anticancer activity of the imidazole derivative, and substitution of the imidazole derivative on the phenyl ring at position-4 leads to a decrease in the anticancer potential and, unfortunately, increases the toxicity to normal cells. The chemical structures of compounds 61–6f are shown in Fig. 17. Based on toxicological evaluation of imidazole and the latest update in 2006 ([www.bgchemie.de/toxicologicevaluations](http://www.bgchemie.de/toxicologicevaluations)), it has been found to be harmful *via* oral administration with signs of intoxication including salivation, ophisthotonus, decreased food consumption, increased blood pressure, disturbance of balance, vasodilatation, apathy, accelerated breathing, dyskinesia, lethargy, effects on liver enzyme, convulsion, tremors, *etc.* In addition, imidazole had an analgesic, anti-inflammatory, mild antipyretic, vasodilatory effect in animals and inhibition of platelet aggregation.

It is clear from the discussion that some imidazole derivatives exhibit toxic effects towards normal cells. Some of the derivatives are mildly toxic, while some exhibit pronounced toxicities. However, there are limited studies available on this subject, and more investigations are needed to further comment on this issue. Besides, there is a need to carry out toxicity studies of imidazole derivatives both *in vitro* and *in vivo* to visualize the potential of such compounds in anticancer chemotherapy.

## Molecular physicochemical properties and topological steric effect indexes

Molecular docking is a useful tool for selecting molecules with a certain structure. It is also necessary to consider other theoretical tools to estimate pharmacological activity.

With the use of online software's important pharmacological properties, including absorption, bioavailability, permeability, blood brain barrier penetration, metabolism, and excretion, to achieve greater affinity for the biological receptor, lower toxicity and better scores can be considered. Therefore, the physicochemical properties of some of the most potent imidazole based anticancer agents discussed in this article were theoretically studied. The different properties were the atom & bond count (A&BC), dreiding & MMFF94 energy, van der Waals volume (VWV), polar surface area (PSA), number of rotatable bonds (NB), the partition coefficient ( $\log P$ ), distribution coefficient ( $\log D$ ), donor & acceptor count (D&AC) and donor & acceptor sites (D&AS). These results demonstrated that the future of imidazoles is quite bright in the field of medicinal chemistry. In addition, a drug should obey Lipinski's rule (Rule of Five), which states that most molecules with good membrane permeability have  $\log P < 5$ , molecular weight  $< 400$ , number of hydrogen bond acceptors  $< 10$ , and number of hydrogen bond donors  $< 5$ . This rule is widely used as a filter for drug-like properties. An analysis of small drug-like molecules suggests a filter of  $\log D > 0$  and  $< 3$ , which enhances the probability of a compound to exhibit good intestinal permeability. A poor permeation or absorption is more likely when there are more than 5 H-bond donors and 10 H-bond acceptors. It is clear from Table 2 that imidazole based compounds have obeyed the 'Rule of Five' with  $\log P$  values  $< 5$  and HBAs  $\leq 10$ .

## Current challenges and future perspectives

In the last couple of decades, there have been mammoth advances in the era of science, but, despite that, the advance in the cure for cancer remains a major challenge.<sup>217</sup> Cancer is a leading threat to human beings and a serious challenge to scientists and society. The uses of the presently available anticancer drugs are limited due to their side effects, and other drug issues and higher numbers of deaths are reported compared to the cases of survival. Moreover, these drugs are too expensive and cannot be afforded by everyone. Until now, there have been significant advances in the understanding of the molecular etiology of cancer, but ultimate therapeutic strategies are still largely missing. Therefore, it is very crucial to develop new therapeutic agents against this vulnerable disease. Anticancer drugs with rapid action, selective nature, efficient bioavailability and reduced or no side effects (magic bullets) are the needs of the present day. So, it would be beneficial to explore imidazoles with various molecular features and topologies as anticancer drugs. Besides, targeting and activation strategies may be helpful in the development of future generations of anticancer drugs with ability to overcome the disadvantages of the already available conventional drugs. The novel imidazoles should be obtained with a broad spectrum of activity, no onset of drug resistance and fewer or no side effects. In the modern era of science, methods like density functional theory (DFT), molecular operating

**Table 2** Molecular physicochemical and topological properties of some selected potent imidazoles

	Mol. wt	ABC, rotatable bond count	PSA (2D)	$\log(P)$	$\log(D)$	No. of HBD's	No. of HBA's	Drieding & MMFF94 (kcal mol <sup>-1</sup> )	VWV
<b>8f</b>	410	53, 57, 6	56.37	4.93	4.92	1	4	95.88 & 106.53	366.45
<b>9d</b>	388	49, 52, 6	123.88	2.86	0.75	5	8	53.58 & -27.78	337.88
<b>11c</b>	390	47, 51, 2	107.13	1.45	1.45	1	9	91.94 & 66.28	324.89
<b>13b</b>	319	35, 36, 5	54.10	3.88	3.88	0	9	59.7 & 39.7	262.32
<b>14a</b>	349	45, 47, 7	73.22	2.44	2.37	1	5	95.33 & 63.58	317.03
<b>14f</b>	387	45, 47, 7	91.04	1.33	1.26	1	9	69.97 & 76.06	322.95
<b>16a</b>	385	56, 59, 6	46.92	4.38	4.30	1	4	142.58 & 85.21	371.68
<b>19a</b>	483	57, 62, 6	107.80	0.82	0.75	0	9	219.3 2 & 90.52	407.10
<b>19i</b>	427	53, 58, 4	82.45	1.80	1.74	1	9	197.15 & 85.83	366.33
<b>20c</b>	435	48, 52, 4	67.01	5.14	5.14	2	9	120.79 & 120.28	354.00
<b>20e</b>	475	65, 71, 4	73.64	3.67	3.11	2	6	123.79 & 111.28	388.00
<b>21a</b>	310	37, 39, 3	57.45	4.02	3.83	2	6	96.22 & 78.31	270.39
<b>21b</b>	294	37, 39, 3	57.45	3.56	3.37	2	6	96.22 & 78.31	270.39
<b>24</b>	278	35, 38, 1	85.42	1.68	0.75	4	4	60.31 & 54.62	240.48
<b>25</b>	401	57, 62, 3	77.63	3.00	1.57	3	5	147.01 & 100.72	370.63
<b>27</b>	395	50, 54, 3	86.42	2.18	-0.48	4	8	120.81 & 43.48	343.41
<b>36</b>	359	39, 42, 4	123.78	4.31	4.31	2	8	127.81 & 43.48	363.41
<b>36a</b>	373	42, 45, 5	141.60	4.00	4.00	4	8	75.82 & 41.19	312.83
<b>37a</b>	437	52, 66, 5	123.40	4.19	2.78	2	8	95.64 & 74.00	370.77
<b>37b</b>	441	55, 59, 5	110.03	4.57	4.40	1	8	101.48 & 76.03	388.03
<b>48</b>	340	40, 43, 3	124.99	2.78	0.50	4	9	86.78 & 30.73	285.90
<b>49</b>	376	39, 42, 3	138.21	3.56	3.25	2	9	94.11 & 76.56	301.71
<b>50</b>	307	33, 55, 3	92.60	3.49	2.97	2	9	71.79 & 46.86	251.19
<b>53</b>	449	53, 56, 8	96.49	5.45	5.45	0	9	114.11 & 76.56	341.71

ABC = atom & bond count, PSA = polar surface area,  $\log(P)$  = the partition coefficient,  $\log(D)$  = distribution coefficient, HBDs = number of hydrogen bond donor sites, HBAs = number of hydrogen bond acceptor sites, VWV = Van der Waals volume.

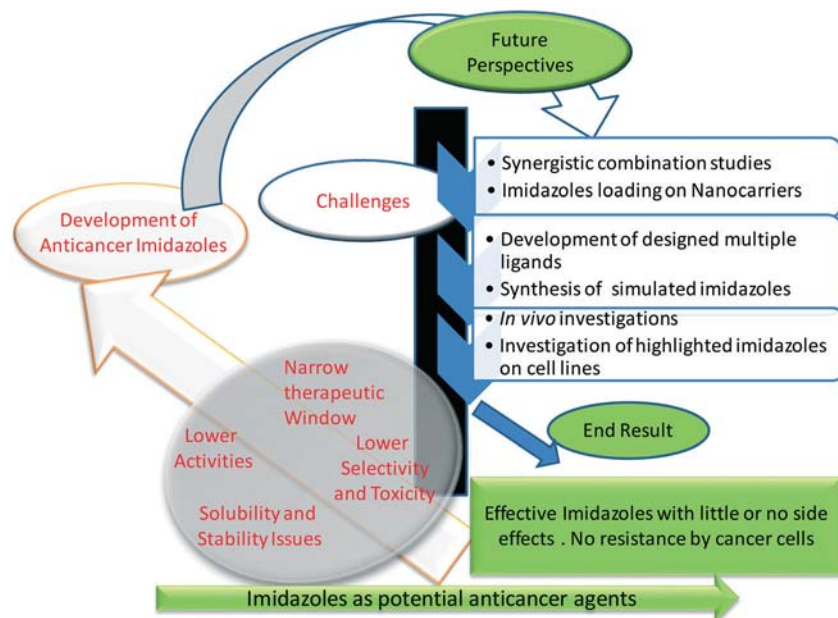


Fig. 18 A pictorial depiction of the current challenges and future perspectives of the development of imidazole based anticancer drugs.

environment (MOE) and techniques like high resolution electrospray mass spectrometry and multinuclear polarization transfer NMR (nuclear magnetic resonance) spectroscopy are significantly helpful and can surely improve our understanding of the chemical and biochemical reactivity of drugs, which might help in establishing some meaningful structure activity relationships. Thus, the chemical studies of anticancer agents under physiologically-relevant conditions (*e.g.*, biological screening conditions) become very important in drug development rationales. Nanotechnology has brought a grand revolution in the pharmaceutical field, especially in drug delivery, and resolves several issues of chemotherapeutic agents. The nanodrugs showed some advantages over conventional drugs, such as controlled drug release, enhanced permeability, and tumor specific targeting. Besides, nanodrugs exhibit few or no side effects to normal cells with the potential to cross the barriers of cancer cells easily.<sup>218</sup> Hence, it would be of great interest if anticancer agents are trapped in nanocages, which might avoid their poor bioavailability and ensure the selective, specific, and fast action of the trapped drugs. Nanocapsules of imidazoles may be expected to be effective replacements of their conventional counterparts. In the present, science, software, and simulation programmes can be used to estimate a drug therapeutic efficiency even before their actual syntheses. Hence, simulated drugs with good bioavailability, maximum solubility, remarkably fewer side effects, and higher efficiency need to be designed and developed. In view of the discussion in this section and the understanding of the molecular mechanism of action in cancer by imidazoles, we foresee the design and development of novel imidazoles along with the development of nanocounterpart imidazoles. Throughout the world, scientists and researchers are currently working on the development of safe and effective

anticancer agents (either in the nano regime or the normal size range), and it will be great to see how they work. Briefly, the future of imidazole-based drugs is quite bright for the treatment of cancer. A pictorial depiction of the current challenges and future perspectives of the development of imidazole-based anticancer drugs is shown in Fig. 18.

## Concluding remarks

The above critical assessment about various imidazoles is a significant class of heterocyclic compounds. It has been perceived so far that amendments on the imidazole core displayed promising anticancer activities, and it is interesting to observe that many imidazoles possess stimulating pharmacological profiles. Furthermore, it is still to be revealed the best mode of action of imidazoles, and it will be interesting to observe that in the future many new pharmacological profiles will be added as leads for future development of safer and more effective compounds. Therefore, we strongly suggest that imidazoles be used in pre-clinical and clinical studies at both the conventional and nano levels.

## Conflict of interest

Authors declare that there is no conflict of interest regarding the publication of this article.

## Acknowledgements

Mohammad Nadeem Lone acknowledges the UGC, New-Delhi for providing UGC-BSR Meritorious research fellowship.



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