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AN ACUMEN INTO ANTICANCER EFFICACY OF IMIDAZOLE DERIVATIVES: A REVIEW

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ABSTRACT

Imidazole, a 1,3-dinitrogen containing five membered heterocyclic ring, is constantly attracting scientists towards its various medicinal properties. Imidazole elicits various pharmacological properties such as antibacterial, analgesics, anti-HIV and anti-cancer *etc*. It is a part of many marketed formulations where it is used as an antifungal drug (e.g., Clotrimazole, Bifonazole *etc*.). Much lately a lot of work has been done in the towards determining the anticancer propensity of the imidazole ring. The present review covers the work done in the recent years by various researchers towards its anti-cancer acumen.

KEYWORDS: Heterocyclic; Imidazole; Pharmacological Activity; Anticancer, 1,3-dinitrogen, Antifungal.

1. INTRODUCTION

Cancer is one of the deadliest diseases, accounted as second most leading cause of deaths globally with 8.8 million deaths in 2015.[1] and

can lead to 13 million deaths by 2030.[2,3] as predicted by World Health Organization (WHO). Reports confirm that one in every five individuals suffers from cancer during their lifetime.[4] It is caused due to uncontrolled growth of the cells as there are abnormalities in essential enzymes and other proteins which control cell division and their proliferation.[5,6] Many efforts are being done in the direction of cancer treatment but not all patients respond positively towards the treatment therapy. Despite this, chemotherapy the adopted approach of choice in the direction of cancer treatment.[7] The major hurdle in the effectiveness of chemotherapy is the resistance towards anticancer agents and the drug toxicities associated with the use of high dose chemotherapeutic agents.[8,9] Accordingly, the discovery of new anticancer agents with promising activity and high therapeutic and safety index at war footing is a necessity for combating this malice.[10]

Imidazole is a five membered aromatic heterocyclic compound having 6π electrons and nitrogen atom on 1st and 3rd position of the ring (**Figure 1**). These two nitrogen atoms help imidazole to serve as an integral part of effective drugs used in treatment of various disease conditions. This is known to elicit a spectrum of pharmacological activities such as antifungal,[11] antiprotozoal,[12] antitrypanosomal,[13] anti-inflammatory,[14] antihypertensive,[15] antihistaminic,[16] antiepileptic.[17] and anticancer.[18]

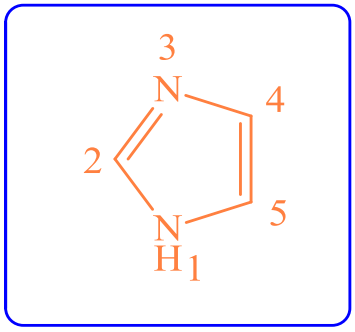
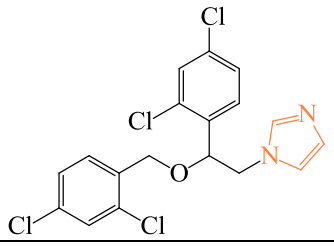
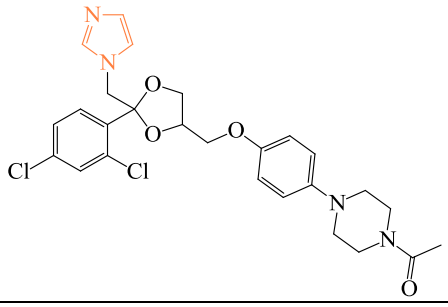
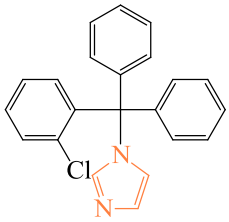
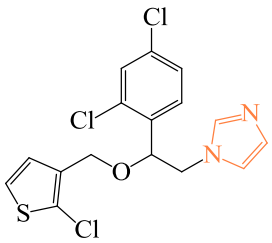
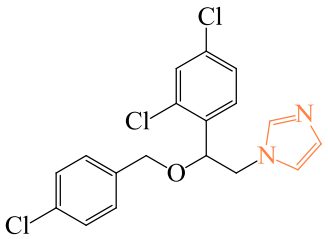
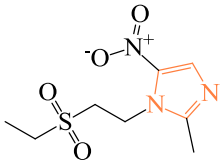
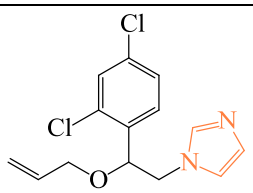
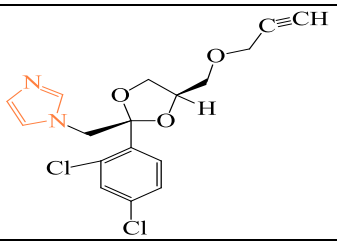
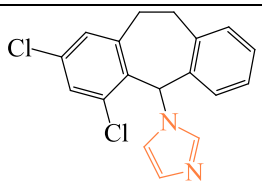
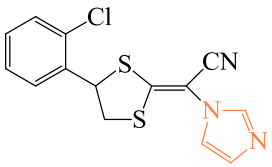
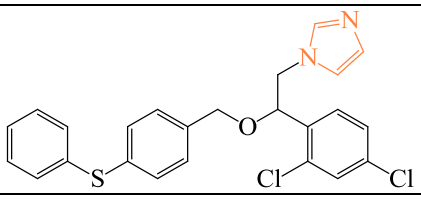
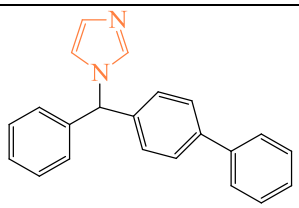
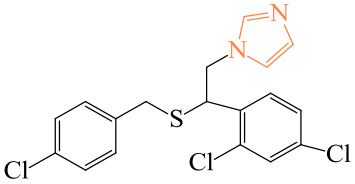
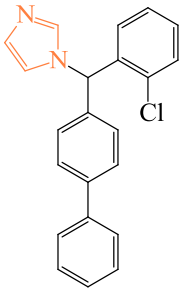
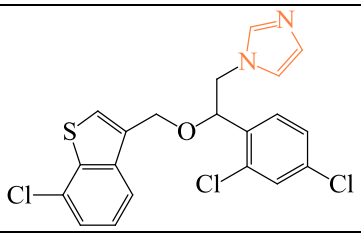
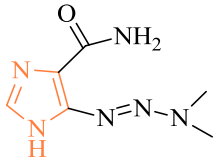


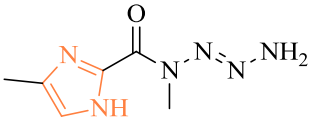
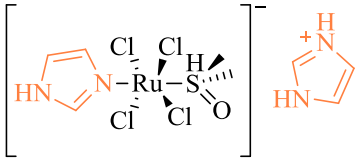
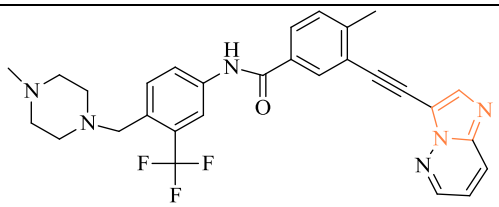
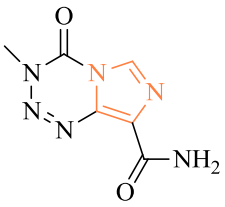
Figure 1: Imidazole ring.

Various imidazole-based compounds with anticancer potential, recently developed by the researchers have been discussed in the subsequent section. This moiety is also present in a number of marketed formulations mentioned in **Table 1**.

Table 1: Commercially available Imidazole containing drugs.

S. No.	Name of the Drug	Structure	Pharmacological Action
1.	Miconazole		Antifungal.[19]
2.	Ketoconazole		Antifungal.[20]
3.	Clotrimazole		Antifungal, Antimalarial.[21]
4.	Ticonazole		Antifungal.[22]
5.	Econazole		Antifungal.[23]
6.	Tinidazole		Antiprotozoal, Antibacterial.[24]
7.	Enilconazole/ Imazalil		Antifungal.[25]

8.	Parconazole		Antimycotic.[26]
9.	Eberconazole		Antifungal.[27]
10.	Lanoconazole		Antifungal.[28]
11.	Fenticonazole		Antifungal.[29]
12.	Bifonazole		Antifungal.[30]
13.	Sulconazole		Antifungal.[31]
14.	Lombazole		Antifungal.[32]
15.	Setraconazole		Antifungal.[33]
16.	Dacarbazine		Anticancer.[34]

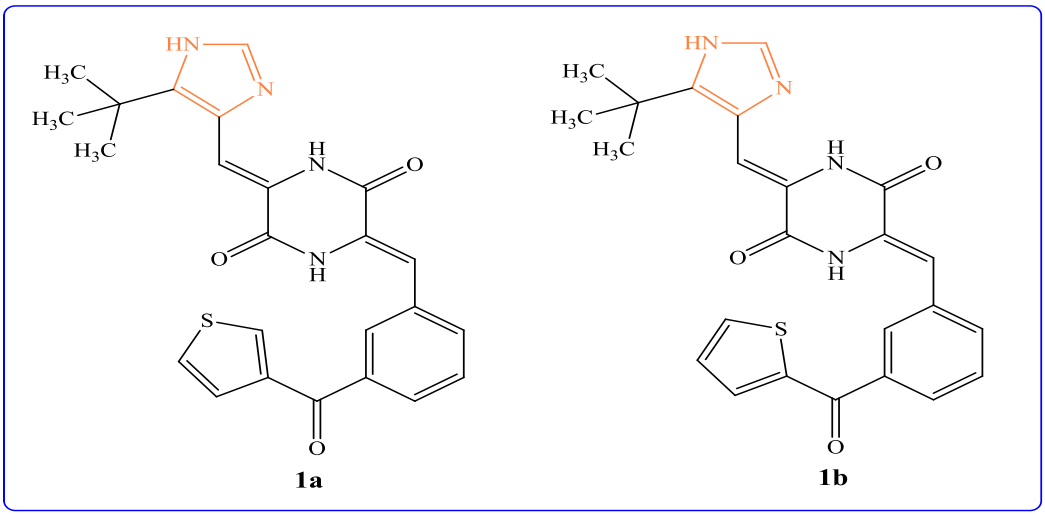
17.	Dimethyl Triazeno Imidazole Carboxamide		Anticancer (Phase 1 & Phase 2).[35]
18.	Imidazolium-*trans*-DMSO-imidazole-tetrachlororuthenate		Anticancer (Phase 1).[36]
19.	Iclusig (Ponatinib)		Thyroid Cancer[37]
20.	Temozolomide		Glioma (Brain Tumor)[38]

Few patents were also filed in the past highlighting various therapeutic and industrial uses of this moiety.[39-44]

2. Recent Advancements

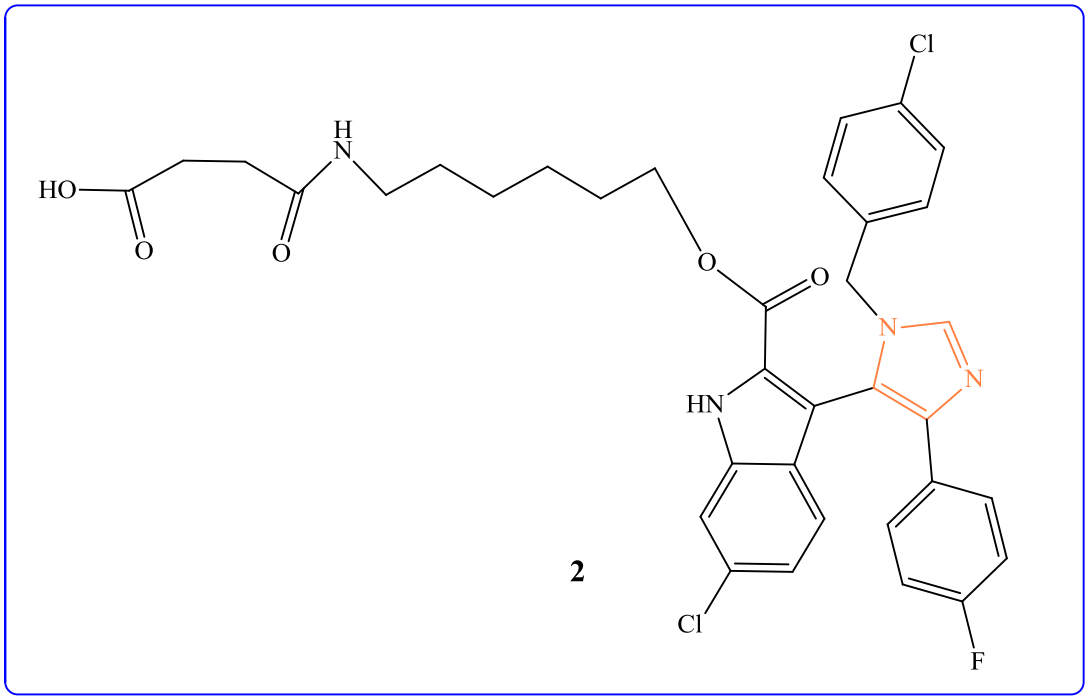
Various anticancer agents based on imidazole moiety reported in the recent past have been summarized here under.

Fu *et al.*[45] synthesized eighteen new plinabulin derivatives and tested their activity against BxPC-3 (Human Pancreatic Cancer) cell lines. Compounds **1a** and **1b** were the most potent agents with IC_{50} of 1.56nM and 1.72nM respectively.



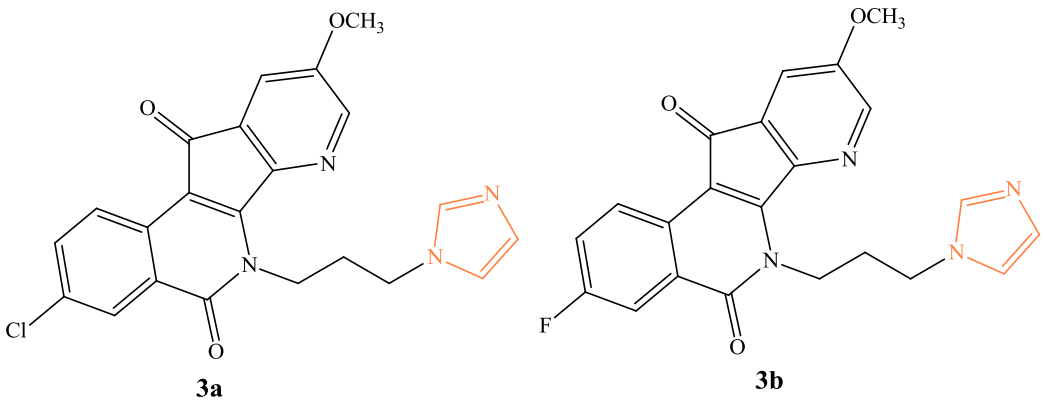
1a **1b**

Clapa *et al.*[46] synthesized various p53-MDM2/MDMX inhibitors which had 1,4,5-trisubstituted imidazole moiety as their basic structure and compound **2** was found to be the most potent. It was reported to act by tightly binding to MDM2 and thus activating p53 that leads to cell cycle arrest. This ultimately inhibited the growth of the cancer cells. IC_{50} of the compound was found to be 11.08µM.

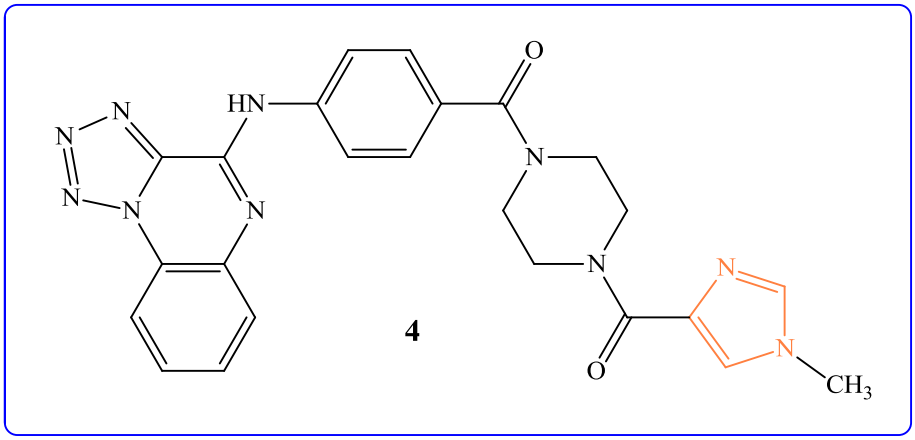


2

Elsayed *et al.*[47] studied and found that 3-nitro group containing 7-azaindenoisoquinoline Top1 inhibitors were highly toxic for the animal use though they have higher anticancer activity as well. To overcome this drawback chlorinated and fluorinated compounds were developed which reduced toxicity keeping the potency up to a similar extent as monitored by lethality in a zebrafish animal model. Out of the various developed compounds, **3a** and **3b** were most potent with GI_{50} values of 0.02 and <0.01 μM against lung cancer (HOP-62), 0.043 and <0.01 μM for prostate cancer (DU-145) respectively. IC_{50} was found to be <0.01 μM for in case of breast cancer cell lines (MCF-7).

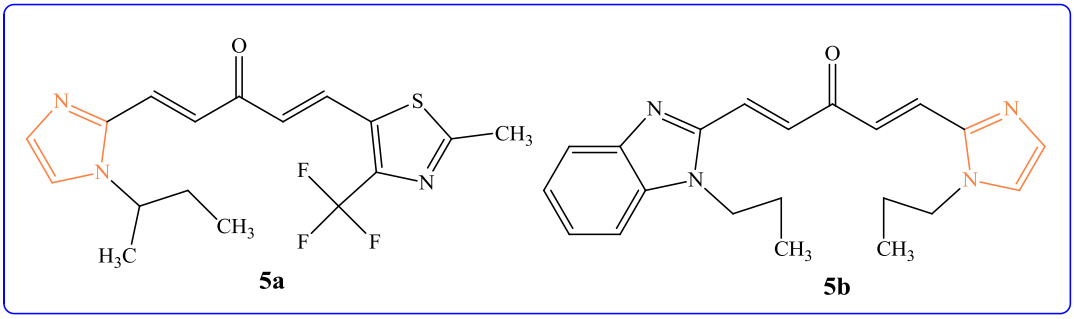


Thomson *et al.*[48] synthesized various selective tankyrase (TNKS) inhibitors as these compounds decrease the growth of various tumor cells. Compound **4** was the most potent agent due to its high selectivity towards tankyrase inhibition. Initially, it was concluded that any substitution in phenyl ring leads to a decrease in potency, while substitution of the piperazine moiety with an aliphatic straight chain or cyclic amide increases the potency when compared to that of unsubstituted piperazine. If the substitution is with a heteroaromatic amide, then it leads to special increase in the potency of compound. This substitution increases the potency as well as the binding affinity for tankyrase 1 (TNKS1). Compound **4** had pIC_{50} of 8.6 and 7.5 with TNKS-array-assay and Wnt-Reporter respectively.

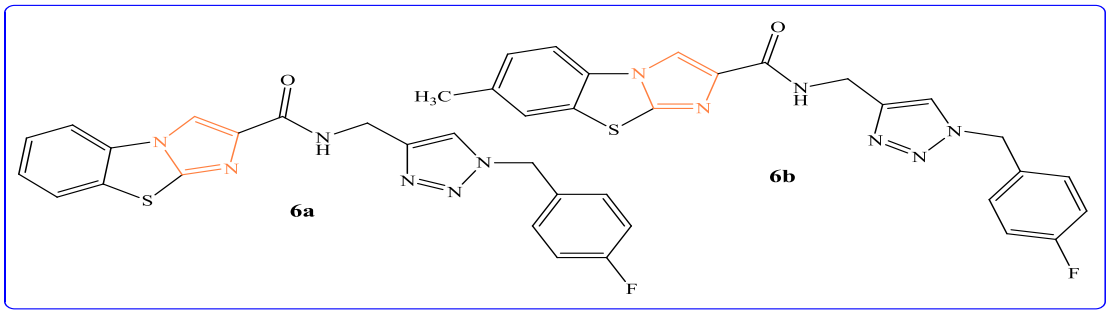


Zhang *et al.*[49] synthesized thirty-four curcumin mimics that are asymmetric 1,5-diheteroarylpenta-1,4-dien-3-ones and evaluated for their *in vitro* antiproliferative activity in one human non-neoplastic prostate cancer cell line and three human prostate cancer cell lines. These asymmetric dienones were found to be more potent when compared to curcumin but the compounds **5a** and **5b** were among the most potent. These compounds acted by inducing cell death in cancer cells by inducing PC-3 cell cycle regulation at the G_0/G_1 phase.

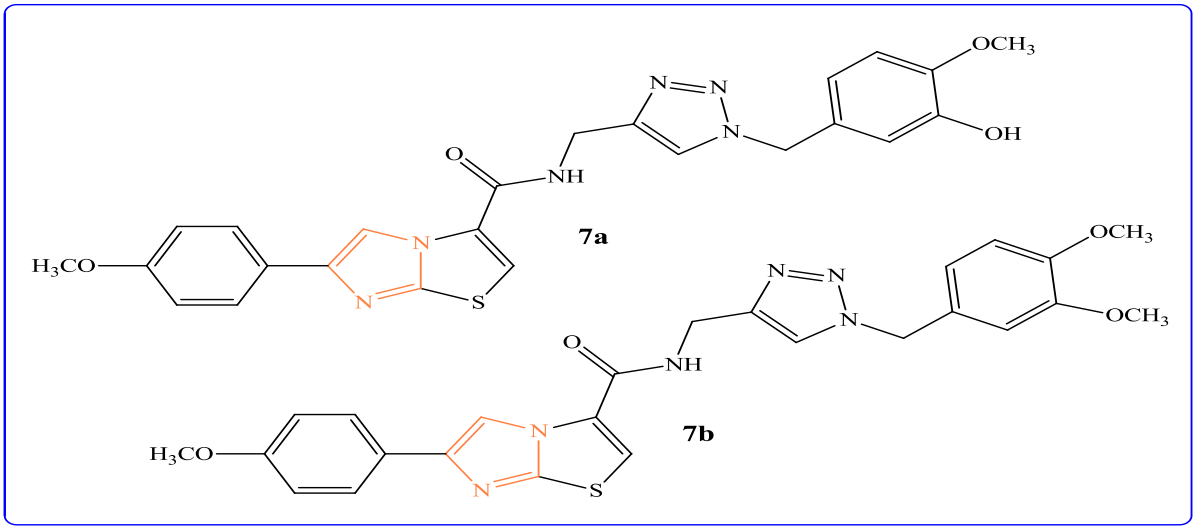
IC_{50} (µM) of compounds **5a** and **5b** against different Prostate Cancer cell lines was found to be 0.23 and 0.10 against PC-3 and 0.35 and 0.22 against DU145.



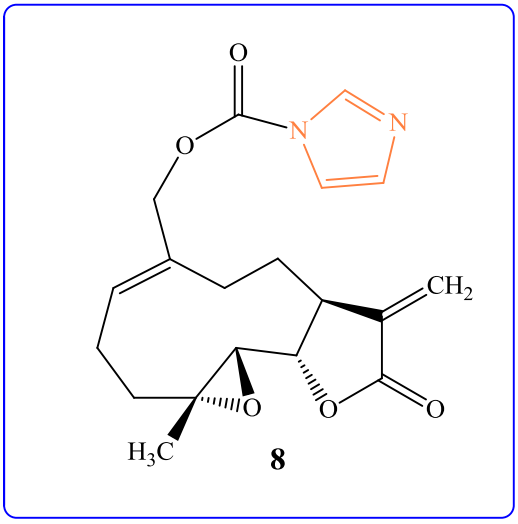
Shaik *et al.*[50] synthesized various 1,2,3-triazolo linked benzo[*d*]imidazo[2,1-*b*]thiazole conjugates and tested their cytotoxic profile against different human cancer cell lines *viz.* prostate (DU-145), cervical (HeLa), breast (MCF-7), liver (HepG2) and lungs (A549). Mechanism of action of these conjugates showed cell cycle arrest at G_2/M phase. IC_{50} of the most potent compounds **6a** and **6b** was found to be 1.23µM and 1.65µM respectively.



Shaik *et al.*[51] synthesized and evaluated the antiproliferative activity of novel imidazo[2,1-*b*]thiazole linked triazole conjugates and found that these compounds exhibited potent cytotoxicity against human lung cancer cell line (A549). These compounds acted by arresting cell cycle at G_2/M phase. Microtubule organization is also disrupted by these compounds in lung cancer cells. IC_{50} of compounds **7a** and **7b** was found to be 0.924µM and 0.788µM respectively against A549 cell line of human lung cancer.

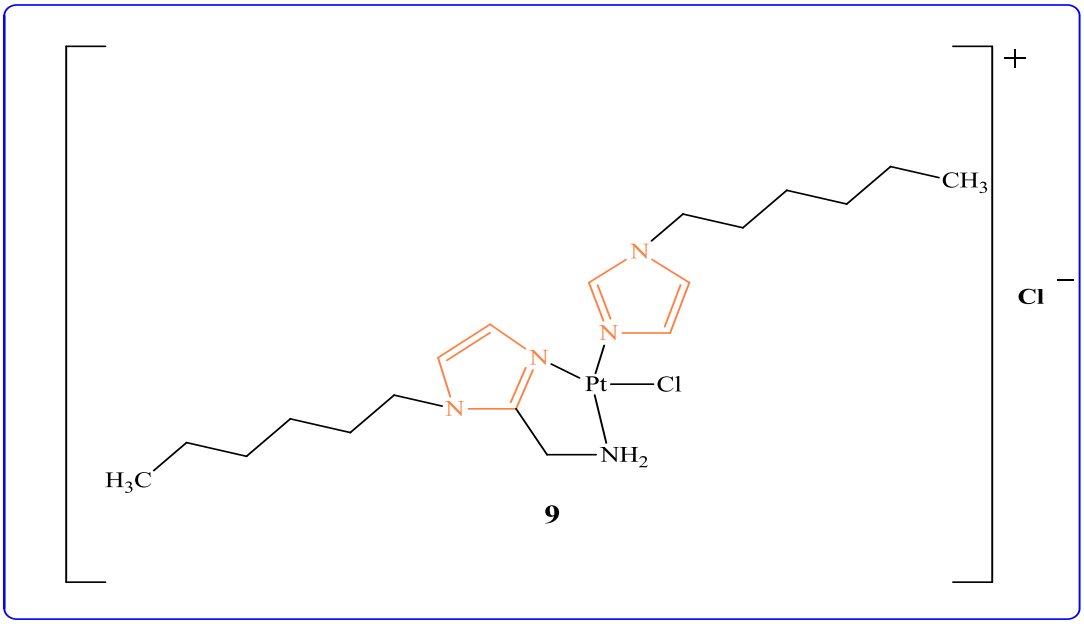


Albayati *et al.*[52] synthesized imidazole- and benzimidazole-carbamate analogs as potent MMB analogues. Compound **8** was the most potent agent with an EC_{50} of 0.9µM with respect to the parent MMB (EC_{50} = 7.0µM). When compared on the basis of the bioavailability of both compounds, compound **8** was found to have plasma bioavailability of 45.5% while for MMB, it was 6.7%. These results prove that compound **8** is a potential candidate against acute myelogenous leukemia.



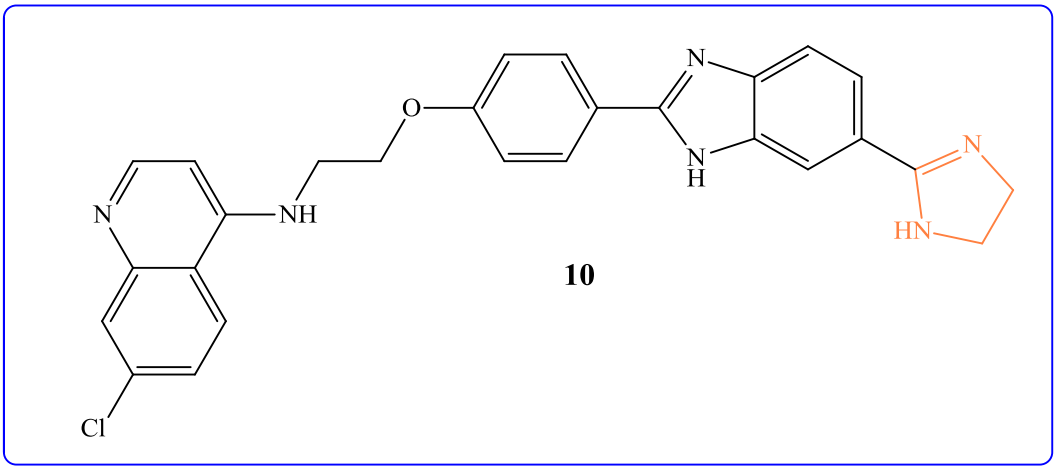
Rimoldi *et* al.[53] developed cationic platinum(II) complexes and their cytotoxic property was evaluated against triple negative breast cancer cell line (MDA-MB-231) and two other cell lines which were less responsive to cisplatin (DLD-1 and MCF-7). Out of the developed agents, compound **9** emerged as the potent agent interfering with the M phase of the cell cycle. IC_{50} of the compound was found to be 61.9µM for MDA-MB-231 cell line and

57.4µM and 79.9µM for DLD-1 and MCF-7 cell lines respectively. The results prove the effectiveness of these agents compared to cisplatin.



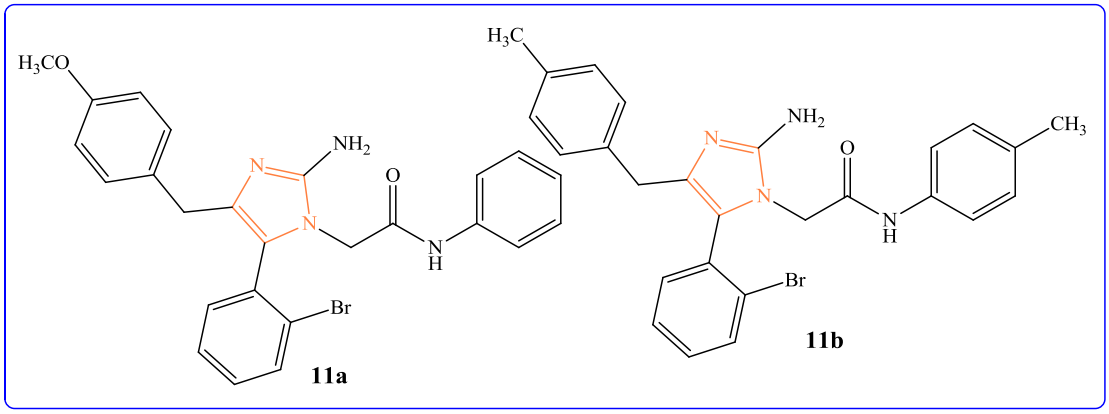
9

Krstulovic *et al.*[54] synthesized novel series of hybrids containing 7-chloroquinoline and arylamidine moieties. These compounds were tested for their binding properties towards DNA/RNA as well as cytotoxic profile against various human cancer cell lines. MTT assay was used to evaluate antiproliferative profile of the compounds against normal (MDCK1) as well as carcinoma (HeLa and CaCo2) and leukemia cell lines (Raji and K462). GI_{50} of most potent compound **10** was found to be 8.6µmol/dm against K562 and 27.5µmol/dm against Raji cell lines.

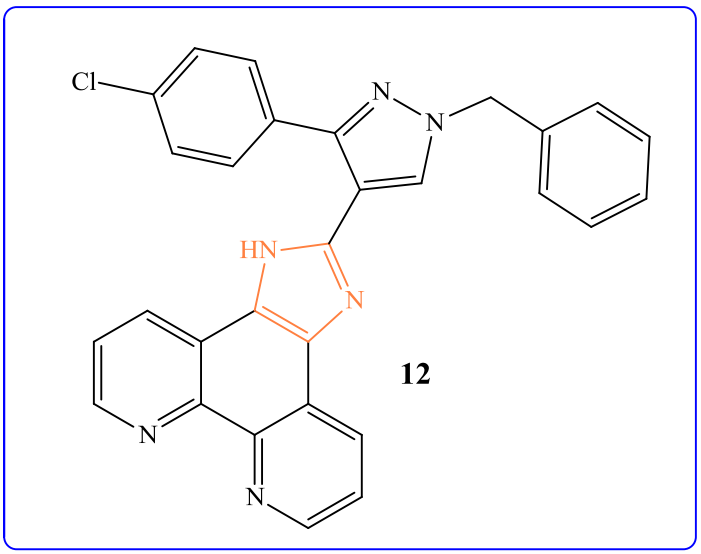


10

Gill *et al.*[55] synthesized a series of novel polysubstituted 2-aminoimidazoles which possess significant antiproliferative activity. Out of the synthesized compounds, **11a** and **11b** were the potent moieties which could induce G_2/M phase arrest in the cell cycle. IC_{50} of these compounds was found to be 1.4µM and 1.3µM respectively.

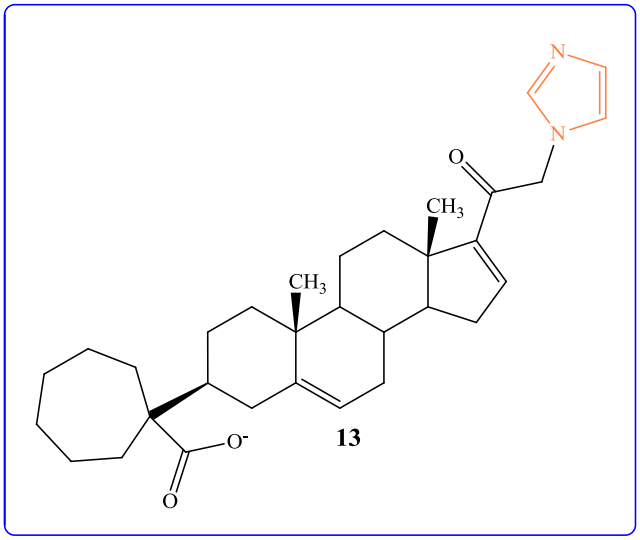


Liu *et al.*[56] developed a series of novel 2-(1*H*-pyrazol-4-yl)-1*H*-imidazo[4,5-*f*][1,10]-phenanthrolines and evaluated their antitumor activity against lung cancer cell lines (A549 & MRC-5). Various assays *viz.* CCK-8 assay and electrophoretic mobility shift assay (EMSA) along with UV-melting study and docking study were used to evaluate their anticancer property. Compound **12** was the potent with IC_{50} value of 1.48µM against A549 cell line and 3.83µM against MRC-5 cell line. However, cisplatin elicited IC_{50} values of 12.08µM and 21.55µM against the same cell lines.



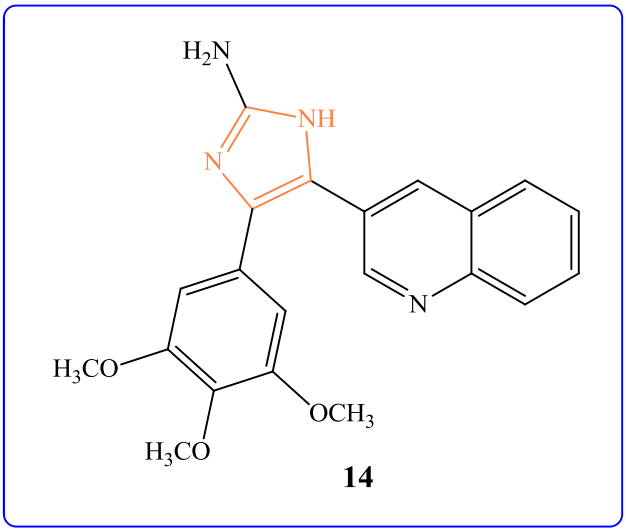
Silva-Ortiz *et al.*[57] synthesized 16-dehydroprepnenolone derivatives having an imidazole ring at C-21 and a different ester moiety at C-3 and studied their binding capacity to the

androgen receptor (AR). These agents acted as inhibitors of 5α-reductase 1 and 2. The most potent derivative compound **13** exhibited an IC_{50} of 29nM, inhibiting 5α-R2 successfully.



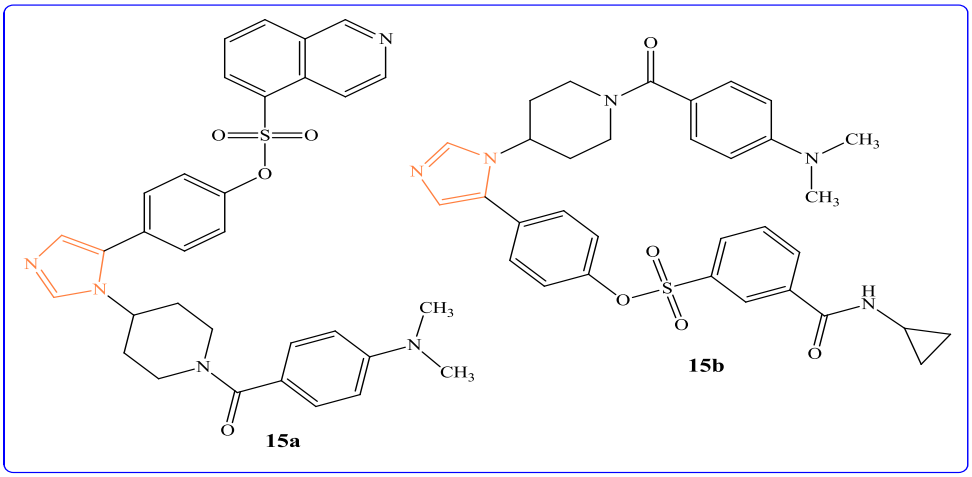
13

Chaudhary *et al.*[58] synthesized a series of new drugs that were analogs of combretastatin A-4 (CA-4) and comprised of 2-Aminoimidazole as replacement of a double bond in CA-4, 3,4,5-trimethoxyphenyl in ring A and various relevant arenes in ring B. Out of 15 compounds synthesized, four showed anti proliferative activity in nanomolar concentrations and compound **14** had the maximum potency against the five different cancer cell lines along with a drug resistant cell line. The IC_{50} of compound **14** was found to be 96nM against MDA-MB-231 cell line, 350nM against EMT6/AR1 cell line and 335nM against HuH-7 cell line whereas CA-4 demonstrated IC_{50} value of 331nM, 495nM and 430nM for CA-4 respectively against these cell lines.

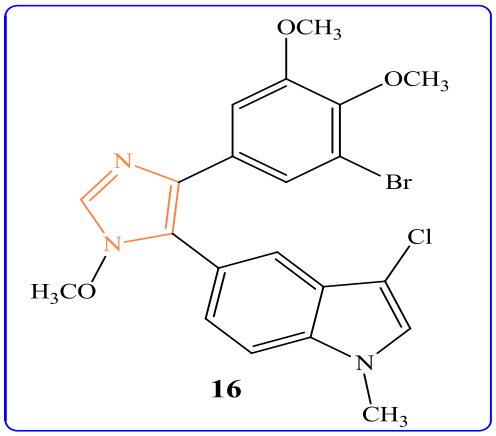


14

Park *et al.*[59] studied and developed various anticancer metastatic agents targeting P2X7 receptor by optimizing the core skeletons and side chains as the designing concept of conformationally constrained KN62 analogs which resulted in the development of potent P2X7 receptor antagonists of imidazole core with IC_{50} in subnanomolar range. Compounds **15a** and **15b** were the most potent when compared for the invasive capability for the metastatic breast cancer cell line (MDA-MB-231) with their IC_{50} at 2.679µM and 3.632µM respectively.

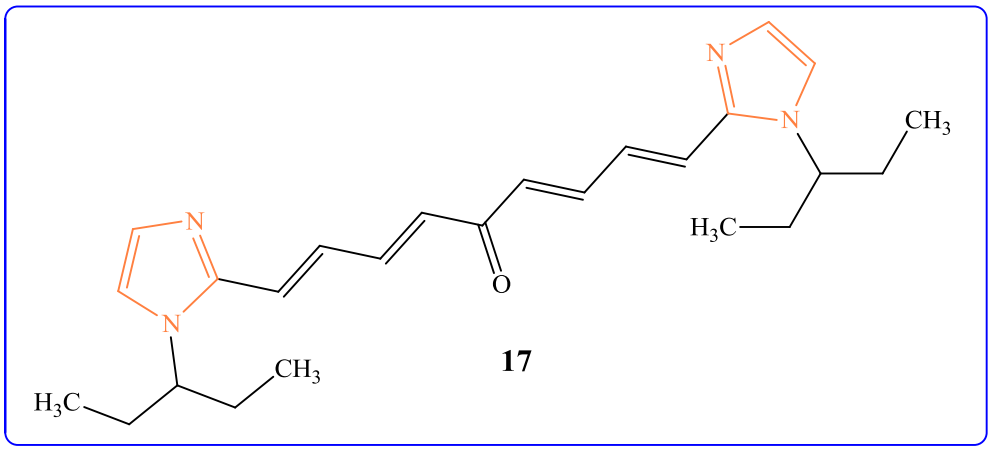


Mahal *et al.*[60] developed analogs of natural vascular-disrupting agent CA-4 and tested them. These, 5-(1-methyl-4-phenyl-imidazol-5yl) indole derivatives were more potent than CA-4 with low IC_{50} concentration. 3-Bromo-4,5-dimethoxyphenyl derivative was the most active compound among all compounds against multidrug-resistant KB-V1/Vbl cervix and MCF-7/Topo mamma carcinoma cells, and also against CA-4 resistant HT-29 colon carcinoma cells. Compound **16** also destroyed real blood vessels of choliroallantoic membrane (CAM) of fertilized chicken eggs and within tumor xenografts in mice leaving behind the embryo and mouse unharmed. IC_{50} of compound **16** was found to be 31.3nM and 25.4nM for HT-29 and KB-V1/Vbl cancer cell lines respectively, and 18.8nM for MCF-7/topo breast carcinoma.



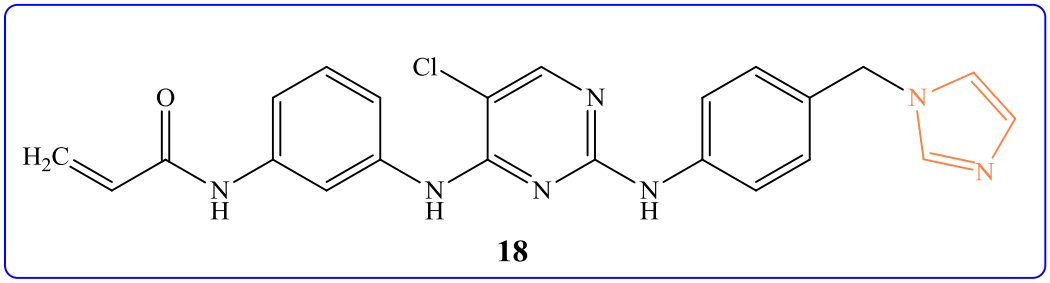
16

For the effective chemotherapeutics treatment of castration-resistant prostate cancer, Zhang *et al.*[61] synthesized twenty-five different curcumin analogues (1*E*,3*E*,6*E*,8*E*)-1,9-Diarylnona-1,3,6,8-tetraen-5-ones having two identical terminal heteroaromatic rings. The WST-1 cell proliferation assay was used to assess the anti-proliferative effects of the compounds towards both androgen-insensitive and androgen-sensitive human prostate cancer cell lines. Twenty-three of these twenty-five compounds were new and eighteen of them possessed improved potency when compared against curcumin. Compound **17** suppressed PC-3 cell proliferation by activating cell apoptosis and by arresting cell cycle in the G_0/G_1 phase. IC_{50} of compound **17** was found to be 1.21µM and 2.43µM against human androgen-insensitive prostate cancer cell lines and human androgen-sensitive prostate cancer cell lines respectively.



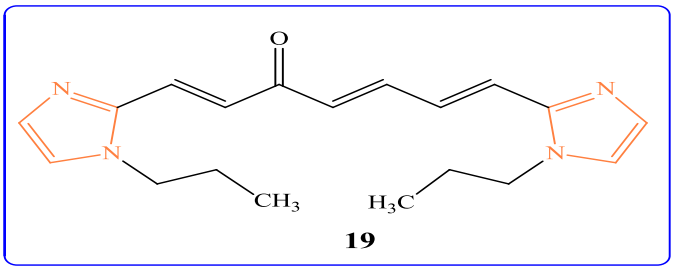
17

Song *et al.*[62] developed azole-diphenylpyrimidine derivatives (AzDPPYs) which were evaluated against $EGFR^{T790M/L858R}$ kinase. IC_{50} of compound **18** was found to be 3.3nM and thus termed as the most potent inhibitor of $EGFRT^{790M/L858R}$. Compound **18** also showed higher selectivity and thus proved to be least toxic and produced lesser side effects which is further confirmed by its selectivity index (SI) value of 299.



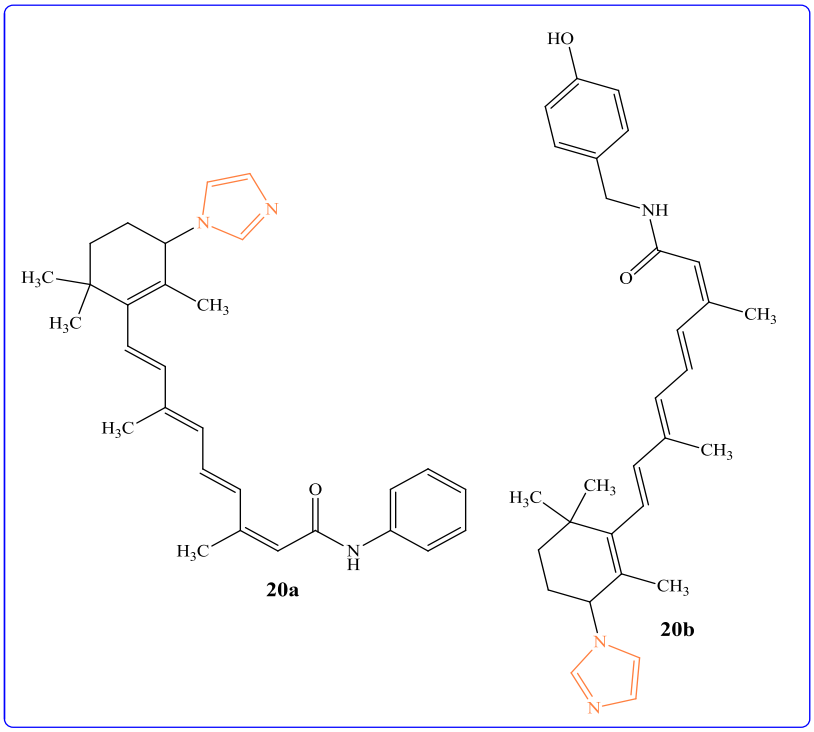
18

Wang *et al.*[63] synthesized (1*E*,4*E*,6*E*)-1,7-diaryl-1,4,6-heptatrien-3-ones as curcumin based anticancer agents on the basis that they have similarity in their structures to the enol-tautomer of curcumin. These compounds were developed using Aldol condensation and Horner-Wadsworth-Emmons reaction. Ten compounds were found to be significantly more cytotoxic when evaluated against the androgen-dependent and androgen-independent prostate cancer cell lines along with HeLa human cervical cancer cells. These compounds were found to be 5- to 36-times more potent than curcumin. Compound **19** exhibited inhibitory rate of 91, 84, 95, 98 against human androgen-insensitive prostate cancer cell lines (PC-3 & DU145), human androgen-sensitive prostate cancer cell lines, human aggressive cervical cancer cell lines respectively.

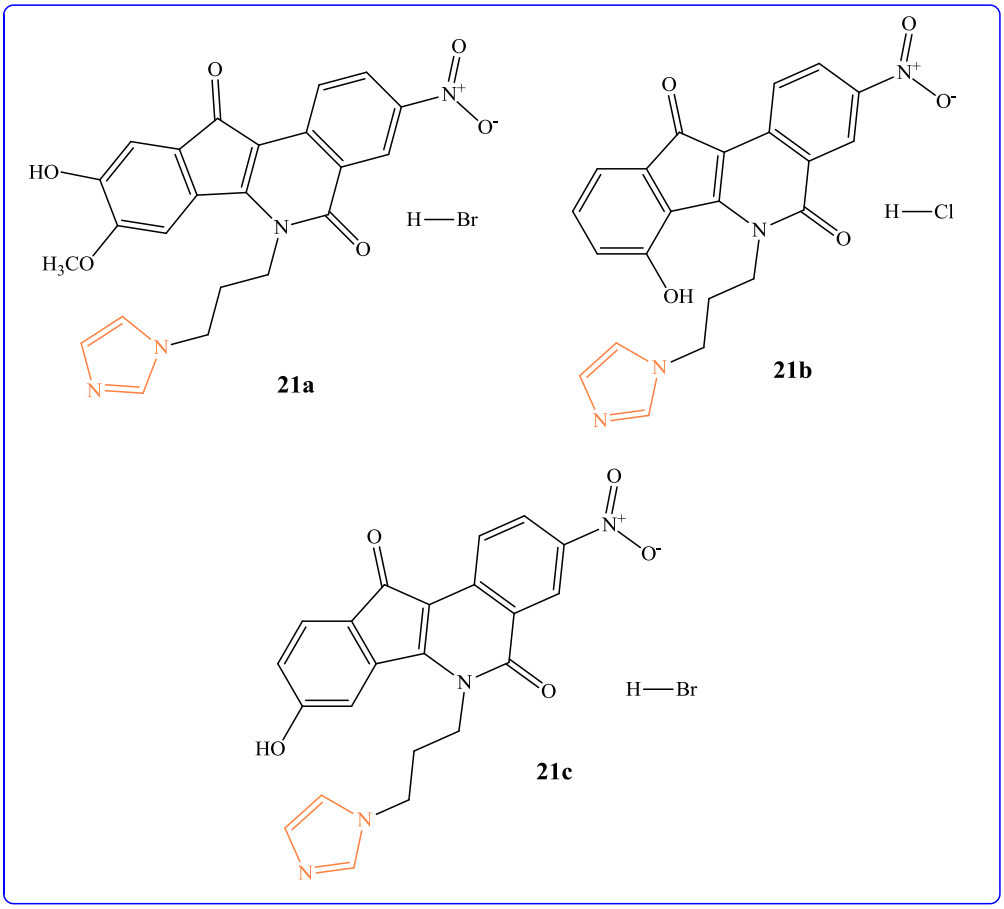


19

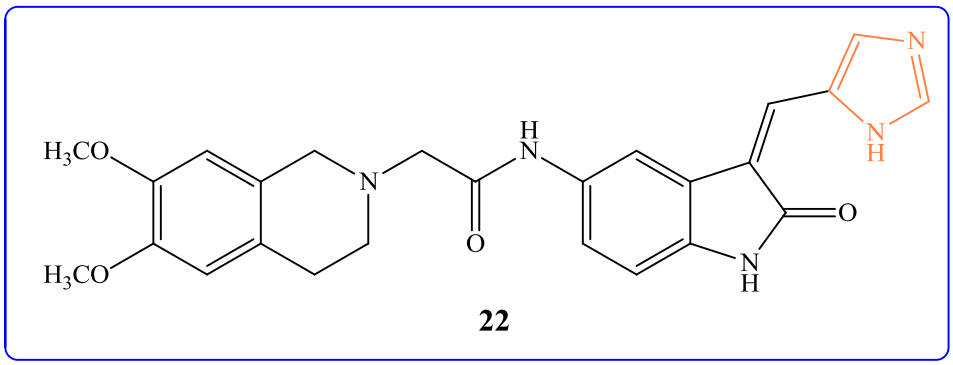
Mbatia *et al.*[64] synthesized a series of compounds for their anti-prostrate and anti-breast cancer activity. Compounds **20a** and **20b** were the most potent with their activity being attributed to the presence of 1*H*-imidazole. They exhibited GI_{50} values of 1.90µM and 0.16µM against MCF-7, 1.74µM and 2.23µM against MDA-MB-231, 2.54µM and 2.70µM against MDA-MB-468 and 1.73µM and 2.45µM against SKBR-3 cell lines respectively.



Nguyen *et al*.[65] synthesized a series of nitrated 7-, 8-, 9-, and 10-hydroxyindeno isouinolines and evaluated them for their dual inhibition of top1 and TDP. Out of these synthesized compounds, **21a** and **21b** were found to have GI_{50} value < 0.01µM against HOP-62 (lung cancer), HCT-116 (colon cancer), SF-539 (CNS cancer), UACC-62 (melanoma cancer) whereas compound **21c** exhibited GI_{50} value <0.01µM for SN12C (renal cancer), DU-145 (prostrate cancer), MCF-7 (breast cancer).

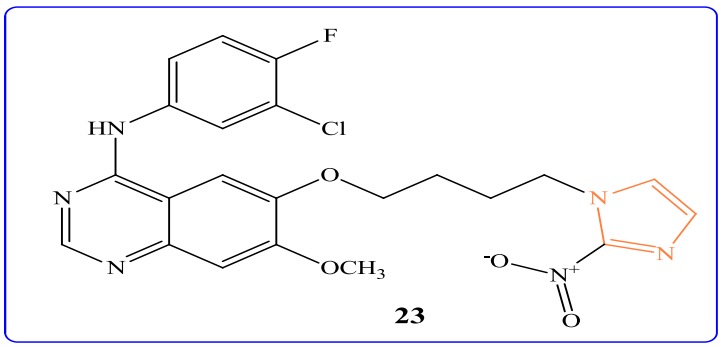


Sestito *et al.*[66] designed and developed a series of 2-oxindole derivatives which inhibited PDK1/Akt and thus was helpful in the treatment of Glioblastoma multiforme (GBM). Among these compounds, **22** was found to have potent activity against two different human glioblastoma cell lines *viz*. ANGMS-CSS (GI_{50} 7.73µM) and U118MG (GI_{50} 14.6µM).



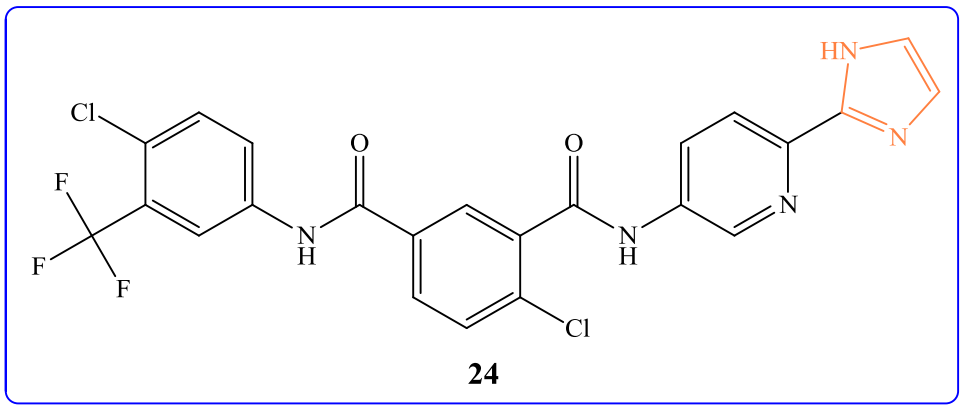
A new family of 6-(nitroimidazole-1*H*-alkyloxyl)-4-anilinoquinazoline derivatives was developed by Cheng *et al.*[67] and evaluated for their EGFR inhibitory and anti-proliferative activities. Out of these compounds, **23** was the most potent with IC_{50} of 0.47nM against

EGFR kinase and 2.21µM and 1.62µM against HT-29 cell line under the normal oxygen state and deficient oxygen states respectively.



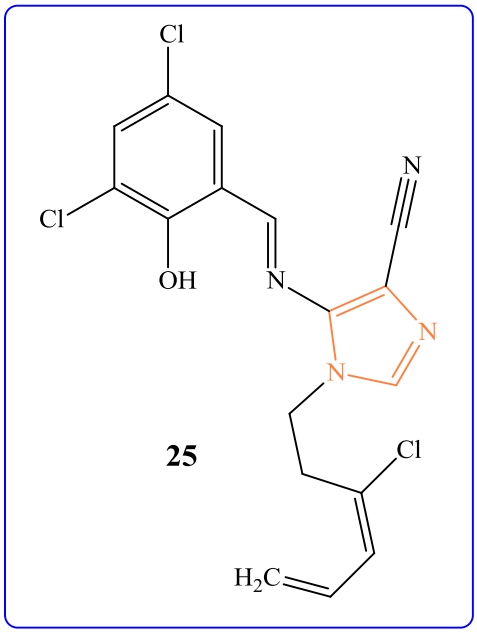
23

Jiao *et al.*[68] synthesized certain 2-(1*H*-imidazol-2-yl) pyridine derivatives and evaluated them for inhibition of BRAF kinase and found out that the compound **24** was the most potent among the designed derivatives. The IC_{50} value of for this compound was found to be 2.93µM against A375 cell line.



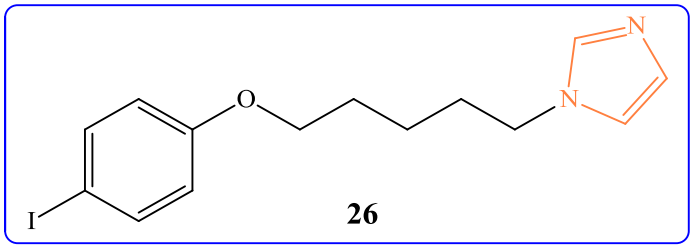
24

Negi *et al.*[69] developed new imine/amide-imidazole derivatives and evaluated their anticancer property against different cancer cell lines. Compound **25** was found to be most potent with its IC_{50} 7.5µM against A-549 (lung cancer), 12µM and 11.2µM against two liver cancer cell lines - Hep-G2 and H-460 respectively.



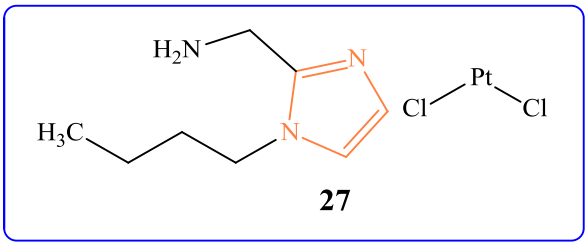
25

Salerno *et al.*,[70] developed various novel imidazole derivatives which inhibit heme oxygenase-1 (HO-1) and heme oxygenase-2 (HO-2) enzymes and thus were found to be potent cytotoxic agents. Compound **26** was the most potent with IC_{50} of 44µM for HO-1 and 0.9µM for HO-2.



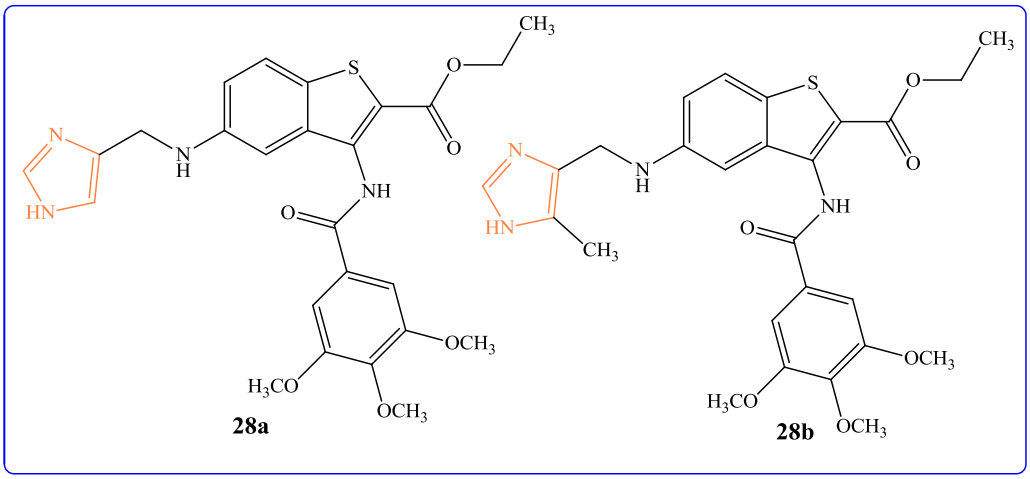
26

Ferri *et al.*[71] developed various imidazole-based complexes and determined their anticancer activity against HCT-116 cell line. The IC_{50} of the most potent complex, **27** was found to be 38µM.

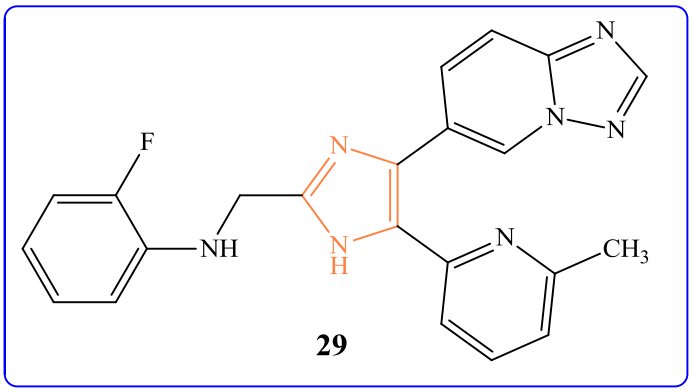


27

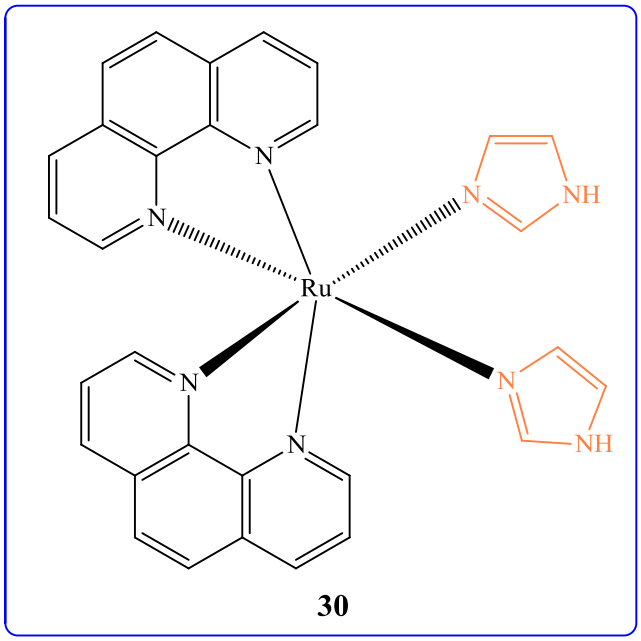
Martorana *et al.*[72] synthesized a new series of 3-benzoylamino-5-imidazol-5-yl-benzo[*b*]thiophenes and evaluated their topoisomerase Ⅱ inhibitory activity and found that the compounds **28a** and **28b** exhibited best activity with percentage affinities of 62.67 % and 61.32 % respectively.



Jin *et al.*[73] synthesized various 2-substituted-4-([1,2,4] triazolo[1,5-*a*]-pyridin-6-yl)-5-(6-methylpyridin-2-yl) imidazoles and evaluated their TGF-β type I receptor kinase (ALK5) inhibition. Among all compounds, **29** was found to have maximum inhibitory IC_{50} value of 13nM against ALK5, 12.1nM against 4T1 stable cells and 16.5nM against HaCaT stable cells.

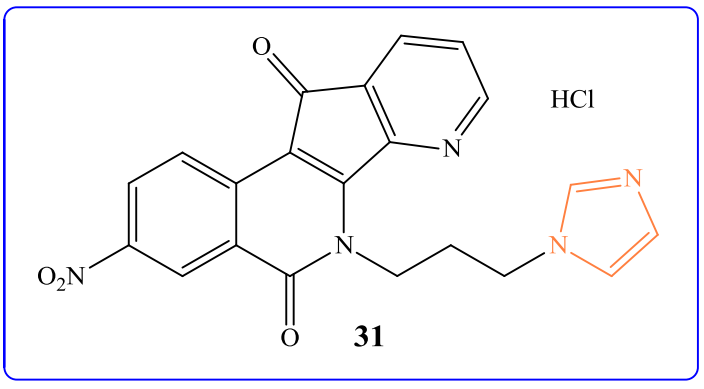


Various water-soluble ruthenium complexes were synthesized by Cardoso *et al.*[74] and their characterization was done by different spectroscopic techniques (e.g., NMR). Among the derivatives, compound **30** was found to have best cytotoxicity against proliferation of $HCT116p53^{+/+}$ and $HCTp53^{-/-}$ with IC_{50} 0.1µmol/L and 0.7µmol/L respectively.



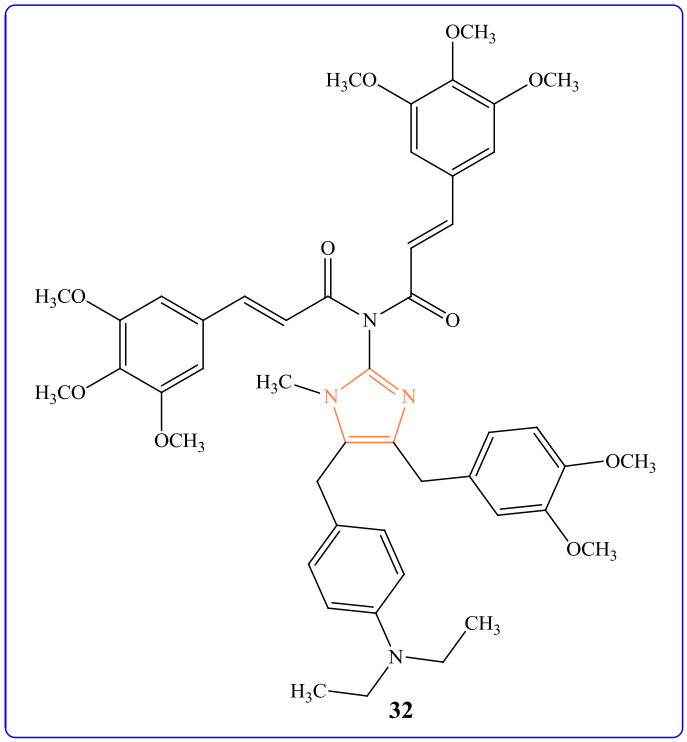
30

Kiseley *et al.*[75] optimized lactam ω-aminoalkyl substituents in a series of 7-azaindenoisoquinolines which resulted in the production of better anti-cancer agents with enhanced Top1 inhibitory activity. Among the derivatives, compound **31** was found to have mean GI_{50} values of 21-71nM in the NCI panel which has 60 human cancer cell cultures. GI_{50} (μM) values for different cancer cell lines for compound **31** was <0.01 against HOP-62 (lung cancer), HCT-116 (colon cancer), SF-539 (CNS cancer), MCF-7 (breast cancer), SN12C (renal cancer), DU-145 (prostate cancer), UACC-62 (melanoma cancer) and 0.025µM against OVCAR-3 (ovarian cancer).



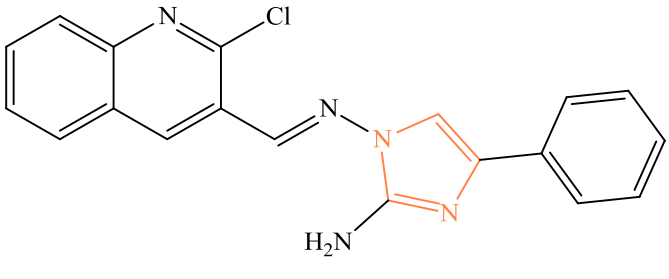
31

A series of novel 4,5-di-substituted benzyl-1-methyl-1*H*-imidazol-2-substituted amines was designed by Zhang *et al.*[76] and evaluated for their P-gp-mediated MDR reversal activity. Compound **32** showed best P-gp modulating activity when compared at 1µM concentration. IC_{50} **32** was found to be 9.1µM for LCC6MDR (breast cancer).



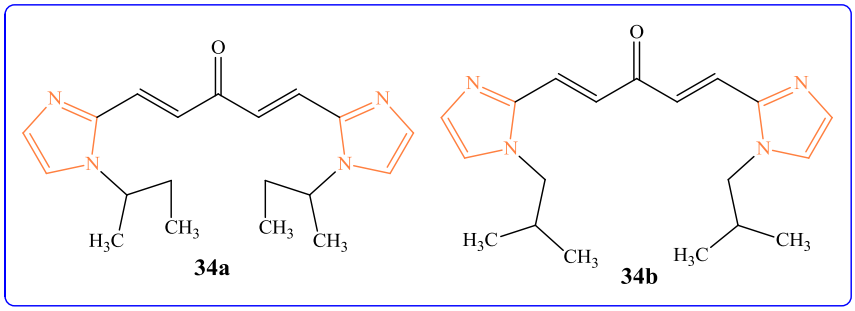
32

Singh *et al.*[77] synthesized sixteen new compounds by combining two different heterocyclic moieties - 2-aminoimidazole and quinoline. Compound **33** was selective against human colon cancer cell line (HCT-116, DLD-1) over breast cancer cell line (MDA-MB-231) and emerged as the most potent scaffold amongst the sixteen derivatives with IC_{50} of 6.92µM, 16.37µM and 49.04µM against HCT-116 and DLD-1 and MDA-MB-231 cell lines respectively.

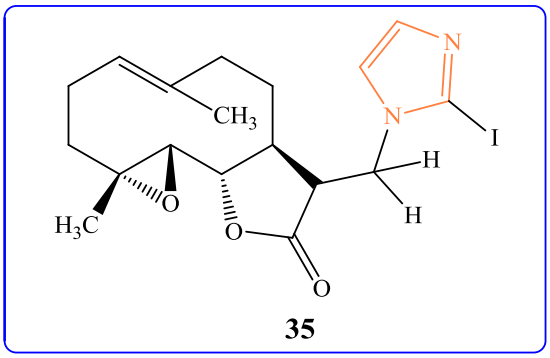


33

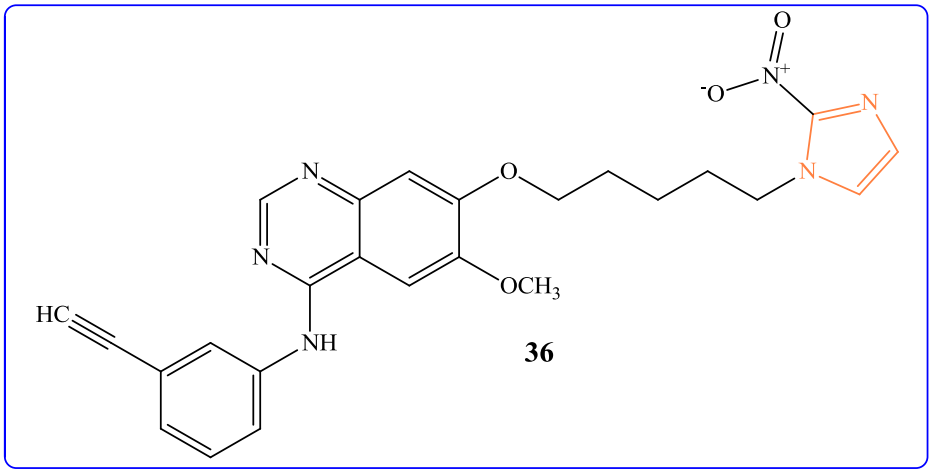
Samaan *et al.*[78] synthesized a novel derivative with different monoketone linkers and evaluated their cytotoxic profile against PC-3 and DU-145 (prostate cancer cell lines). Compounds **34a** and **34b** were found to be the most potent with IC_{50} values of 0.035µM and 0.057µM against DU-145 and 0.063µM and 0.046µM against PC-3 cell lines respectively.



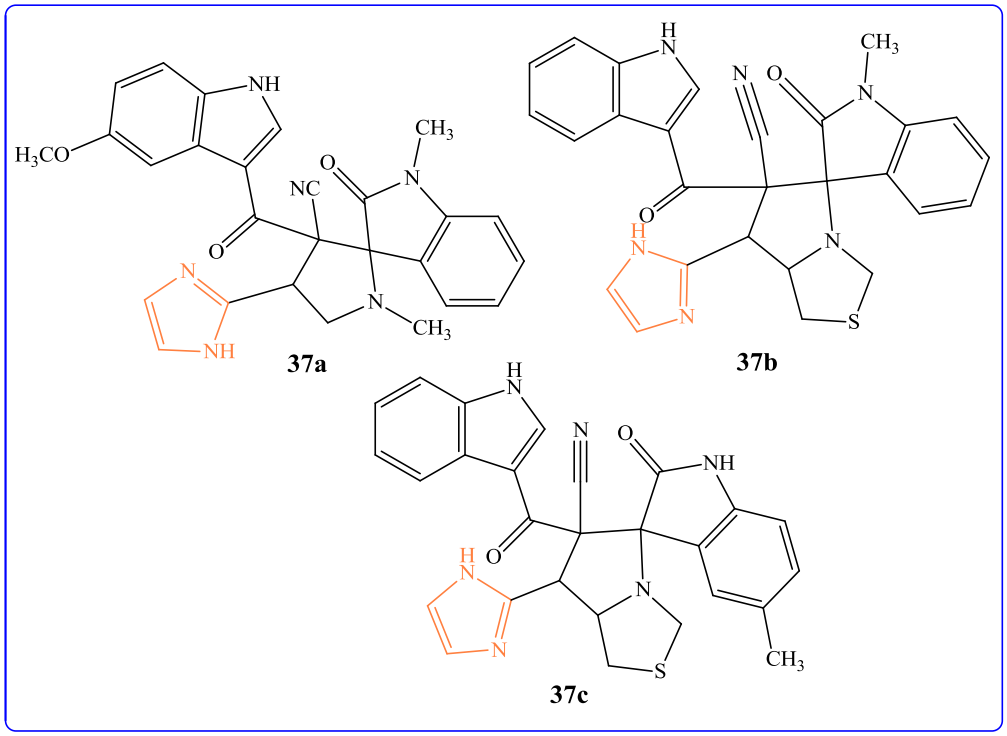
Penthala *et al.*[79] designed various (*E*)-13-(aryl/heteroaryl)parthenolides and found that compound **35** exhibited significant inhibition of growth against various selective cancer cell lines among the panel of 60 cancer cell lines. GI_{50} value for compound **35** was found to be 6.13µM and 6.90µM for CCRF-CEM & HL-60(TB) (leukemia cancer cell lines), 6.85µM against OVCAR-3 (ovarian cancer cell line), 6.61µM against CAKI-1 (renal cancer cell line), 9.79µM against MCF-7 (breast cancer cell line).



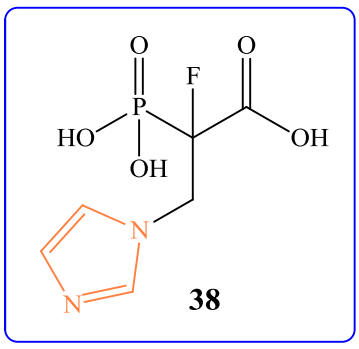
Cheng *et al.*[80] synthesized a new series of 4-anilinoquinazoline derivatives and the most potent compound **36** showed considerable EGFR inhibition. IC_{50} of this compound was found to be 0.47nM.



Arun *et al.*[81] designed and developed compounds and evaluated them for their percentage inhibition of A539 human lung adenocarcinoma cancer cell lines. Among these compounds, **37a**, **37b** and **37c** were found to have very high inhibition even at low concentrations (25µg/mL) 66.3%, 64.8% and 66.3% respectively.

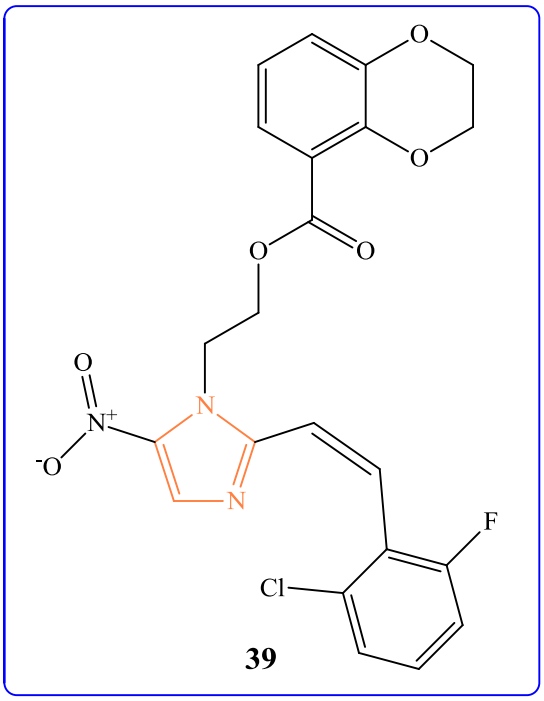


Coxon *et al.*[82] synthesized new phosphonocarboxylate (PC) analogs which selectively inhibited Rab geranylgeranyl transferase (RabGGTase, RGGT), an enzyme which is responsible for various cancers, like ovarian, breast and skin. Compound **38** was the most potent with an IC_{50} for Rab5a and Rab21 to be 40µM and 72µM respectively.



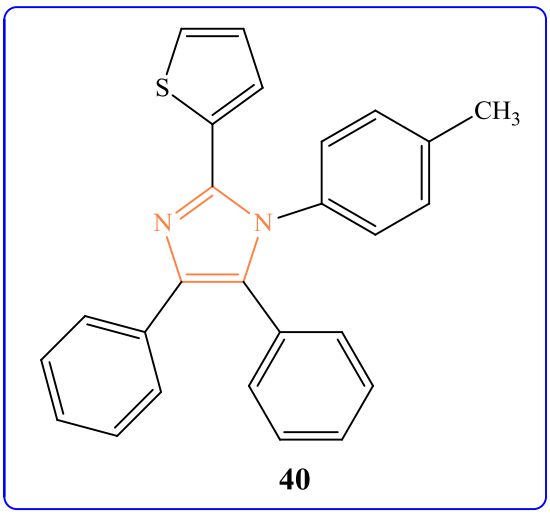
Duan *et al.*[83] designed and developed a series of 2-styryl-5-nitroimidazole derivatives having 1,4-benzodioxan moiety and their anti-proliferatory activity was evaluated. Compound **39** was found to exhibit good FAK (Focal Adhesion Kinase) inhibitory activity

with IC_{50} 0.45µM. Compound **39** exhibited best IC_{50} of 3.11µM and 2.54µM against A549 and Hela cancer cell lines respectively.



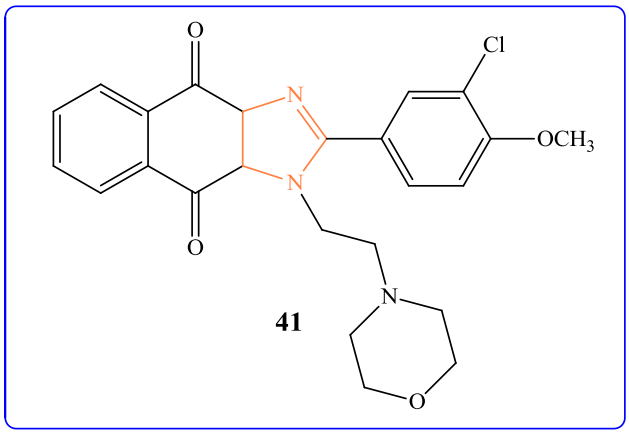
39

Vaghei *et al.*[84] synthesized and demonstrated the antioxidant activity of certain novel 4,5-diphenyl imidazole derivatives by DPPH free radical scavenging assay. The free radical scavenging was studied against the standard ascorbic acid. The results indicated 4-5-diphenyl imidazole flanked by thiophene at C-2 gave better inhibitors compared with other aryl derivatives. The best compound **40** exhibited an IC_{50} of 0.12.



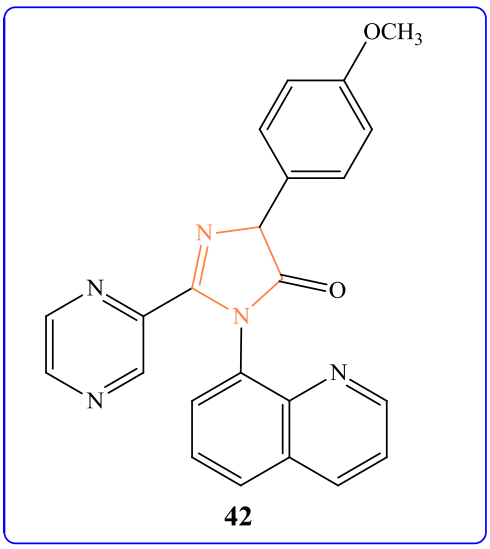
40

Liu *et al.*[85] demonstrated the antiproliferative propensity of series of novel 2-substituted imidazole derivatives fused with napthoquinone moiety on one side and flanked by morpholine on other side. The C-2 position of imidazole was substituted with different substituents which included alkyl, alkenyl and aryl groups, with aryl substituents showing better inhibitory profiles when tested against MCF-7, HeLa, A549 and L929 human cancer cell lines with minimum cytotoxicity towards normal cells. The best active compound **41** bore a perfect balance between cytotoxicity and inhibitory activity with an IC50 of 4.3µM against A549.



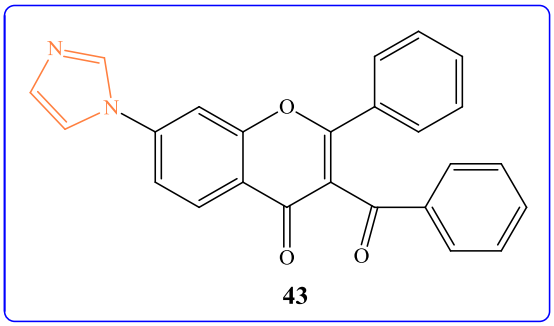
41

Rajurkar *et al.*[86] synthesized novel series of substituted imidazoles following the principles of Green Chemistry and tested these derivatives against different human cancer lines. They postulated that these compounds could act as template for the development of newer imidazole anticancer agents. Compound **42** exhibited growth % in the range of -38.07 to 80.33.



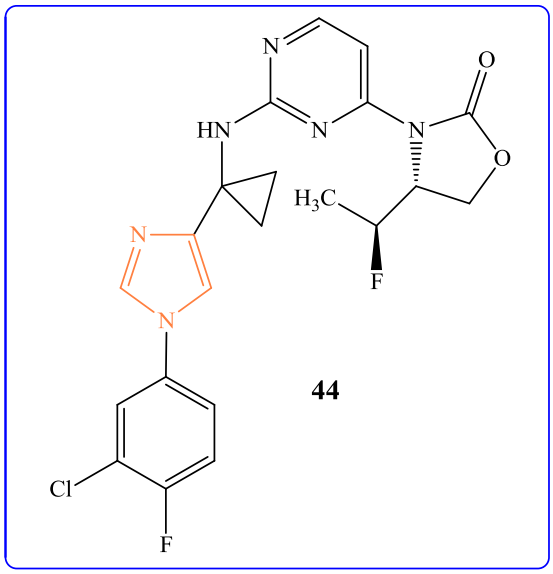
42

Sable *et al*.[87] developed flavone derivatives of imidazole and demonstrated their aromatase inhibitory action and anti-breast cancer activity against MCF-7 cancer cell line. The compounds were postulated to have three pharmacophore features *viz*. heme coordination moiety (imidazole ring), hydrophobic spacer (flavone ring) and hydrogen bond acceptor (aromatic rings). The aromatic ring flanked on flavone skeleton was substituted with different moieties among which the unsubstituted derivative compound **43** exhibited the best IC_{50} of 15.88µM.



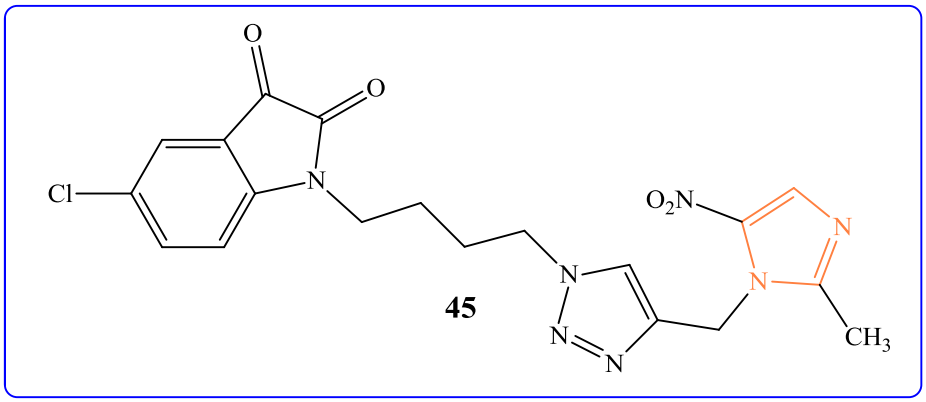
43

Zheng *et al*.[88] developed a novel series of imidazole cyclo-propyl amine analogues which could act as inhibitors of different isoforms of isocitric dehydrogenase. The derivative was prepared by considering experimental drug IDH305 as the template. The addition of cyclopropyl at benzyl position of IDH305 reduces the oxidative metabolism and epimerization of the drug. The derivatives showed promising inhibitory action with compound **44** exhibited an *in vitro* IC_{50} of 25nM. The compounds were also found to inhibit 2-hydroxyglutarate production, which further potentiated their inhibitory action.



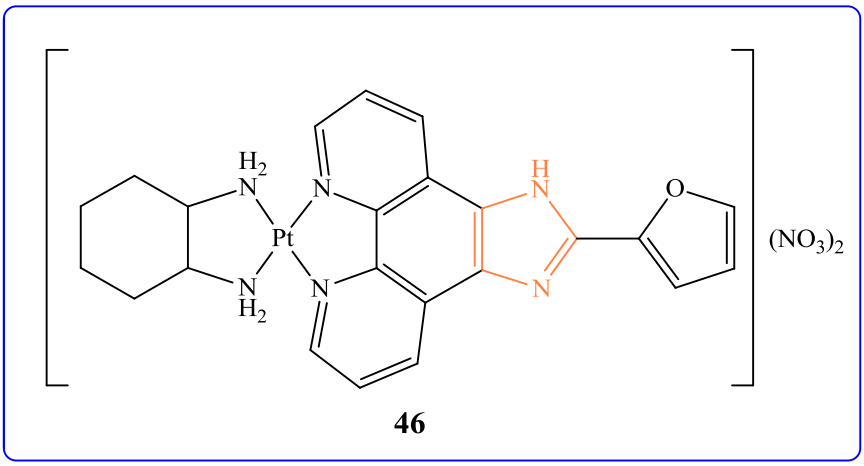
44

Kumar *et al.*[89] synthesized and demonstrated the anti-breast cancer proclivity of a novel series of complex nitroimidazole conjugates flanked by triazole and isatin and thiosemicarbazone against MCF-7 and MDA-MB-231cell lines. The docking studies were also performed to determine the binding sites of insulin growth factor-1. The chain length between isatin and imidazole played a crucial role for exhibiting the inhibitory activity, with compound **45** having butyl chain showing an IC_{50} of 54.25µM and 26.12µM against the two above mentioned cell lines respectively.



45

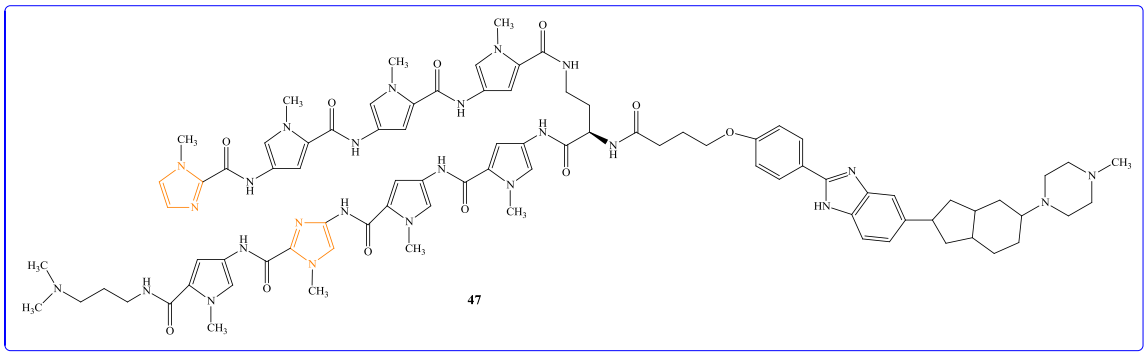
Rasanani *et al.*[90] synthesized palladium and platinum complexes of diaminocyclohexane bearing imidazole. The studies revealed that these agents under appropriate conditions denature DNA thus causing cell death. The anticancer activity was studied against HCT116 cell line. The results indicated that Platinum complex exhibited a stronger growth suppression compared to Palladium complex. Compound **46** exhibited a CC_{50} of 80µM.



46

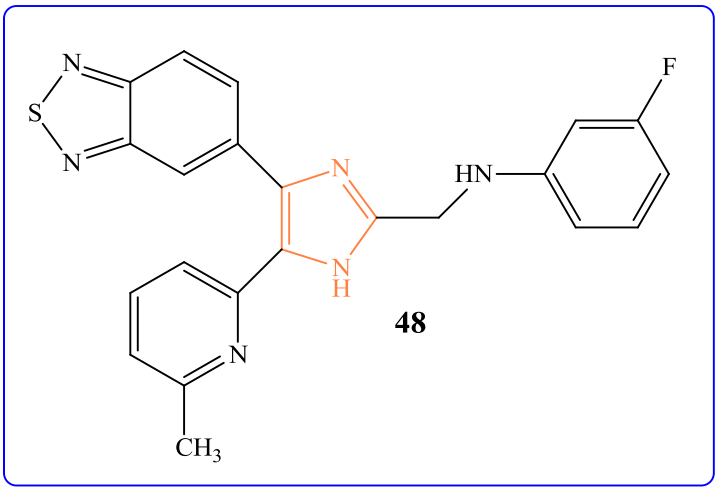
Cheng *et al.*[91] synthesized pyrrole-imidazole polyamide which could interfere with the binding of EBV nuclear antigen 1, expressed in Epstein-Bar virus tumor cells, to virus

plasmid replication. The compound **47** was tested for the inhibitory potential in *in vitro* as well as in *in vivo* mice model and was found to suppress EBV replication and virus dependent cell proliferation.



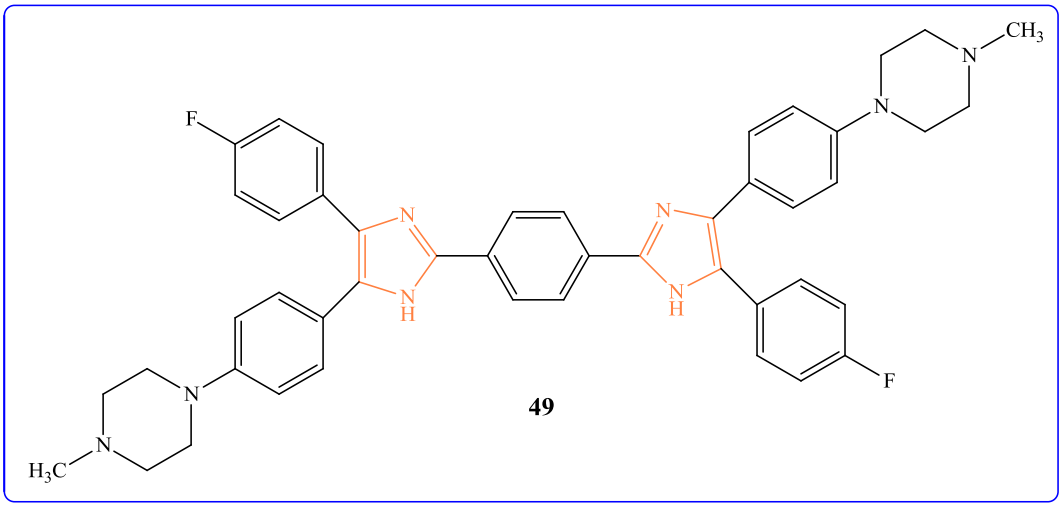
47

Guo *et al.*[92] synthesized and demonstrated the anti-cancer activity of a novel series of imidazole derivatives which acted by inhibiting ALK5 kinase. The compounds in addition to showing exhibiting the anti-cancer potential were also found to be highly selective against the tumor cells. Compound **48** was found to be highly potent with an IC_{50} of 0.008µM against ALK5 kinase. *In silico* evaluation also established that these derivatives exhibited good pharmacokinetics properties.



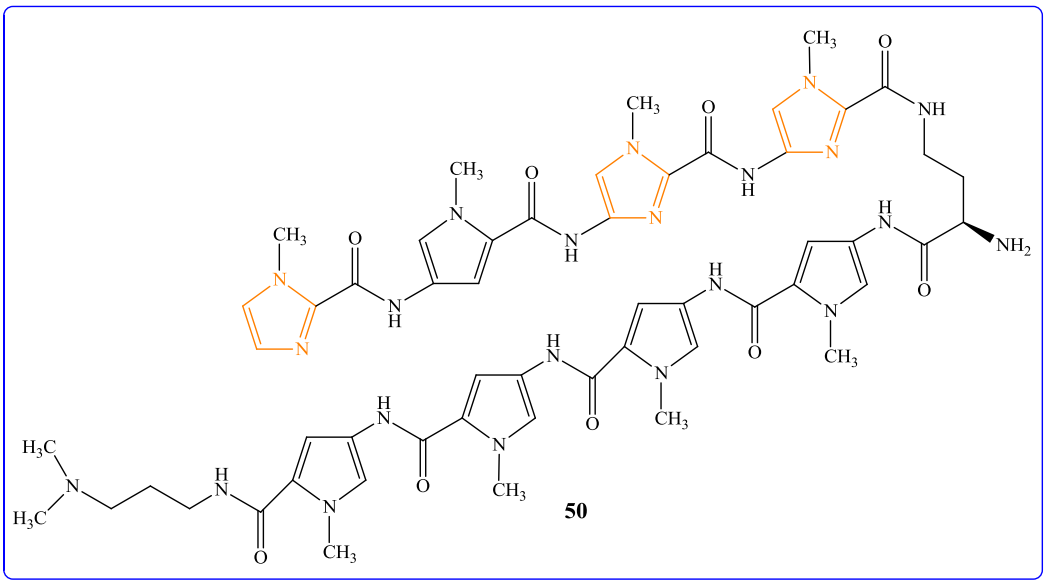
48

Hu *et al.*[93] developed aryl substituted imidazole as selective telomeric multimeric G4 ligand. The novel derivative suppressed cell proliferation by inducing cell cycle arrest and apoptosis when tested against ALT cancer cell line with minimum cytotoxicity to the normal cells. The inhibitory action was induced by accumulation of cells in S phase. Among the four derivatives synthesized, compound **49** showed the most potent inhibitory effect.



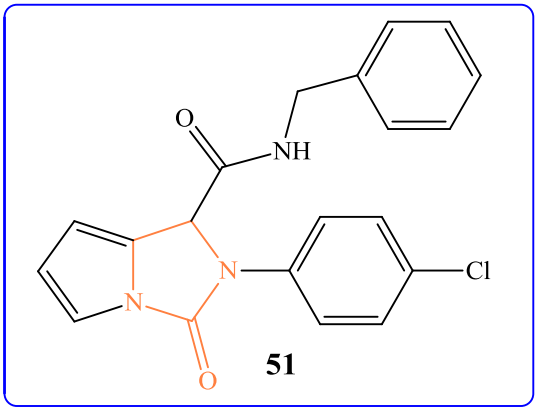
49

Hayatigolkhatmi *et al.*[94] developed novel imidazole-based polyamides which regulates the expression of E2F1-controlled genes which causes restriction of KCL22 BC-CML cells and postulated that these agents could act as adjuvant therapy for CP-CML (chronic phase chronic myeloid leukemia) and BC-CML (blast crisis-chronic myeloid leukemia). Compound **50** down-regulates the expression of E2F1-controlled genes.



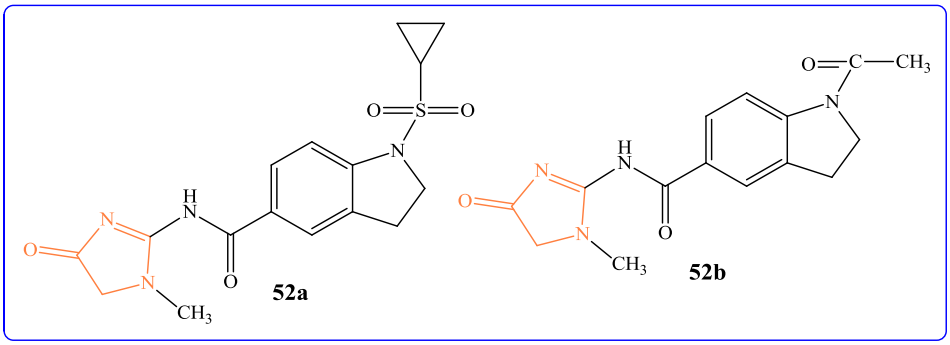
50

Zhang *et al.*[95] synthesized fused pyrrole-imidazole derivatives through one pot synthesis. The compounds were tested for their anticancer propensity against pancreatic cell lines PANC and ASPC-1. Compound **51** exhibited the most potent activity against PANC and ASPC-1 cell lines with IC_{50} of 63nM and 62nM respectively.



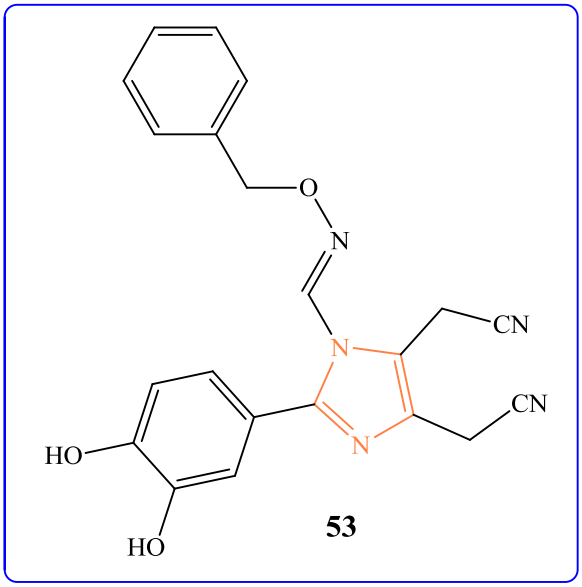
51

Ashok *et al.*[96] synthesized imidazole-4-ones and demonstrated their anti-breast cancer propensity against MCF-7 cancer cell lines. The activity was attributed to inhibition of PAR1 and PI3Kinase facilitated *via* G-Protein coupled receptor. Docking studies were also performed and binding affinity in the range of 0.25µM to 1.75µM for PAR1 were obtained. Compounds **52a** and **52b** gave promising results and also showed minimum toxic effects against normal cells.



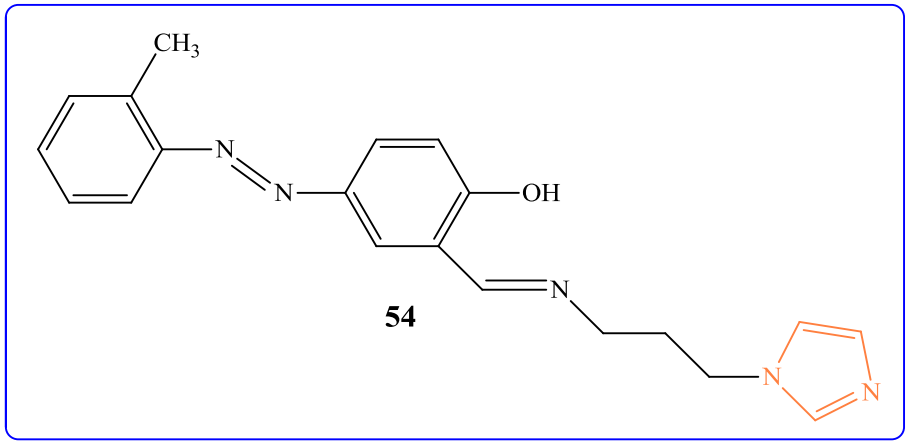
52a **52b**

Bettencourt *et al.*[97] developed a novel series of phenolic imidazoles and tested their antioxidant penchant by cyclic voltammetry, DPHH radical assay and deoxyribose degradation assay and got promising results with activity higher than the reference Trolox. IC_{50} of compound **53** was 7.3µM in DPHH assay.



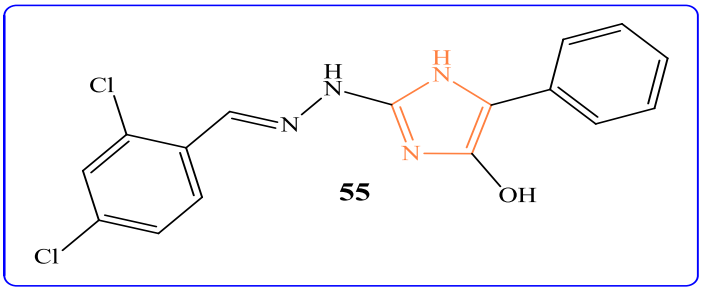
53

Slassi *et al.*[98] synthesized imidazole derivatives bearing an azo moiety and Schiff bases and determined their DPPH radical scavenging propensity. The activity was attributed to the hydroxyl group present in these derivatives which is an active group for DPHH scavenging. Promising results were obtained though activity was lower than the standard ascorbic acid. The ligands differed in the presence of methyl group with compound **54** exhibiting an IC_{50} of 94.48µgmL^{-1}.



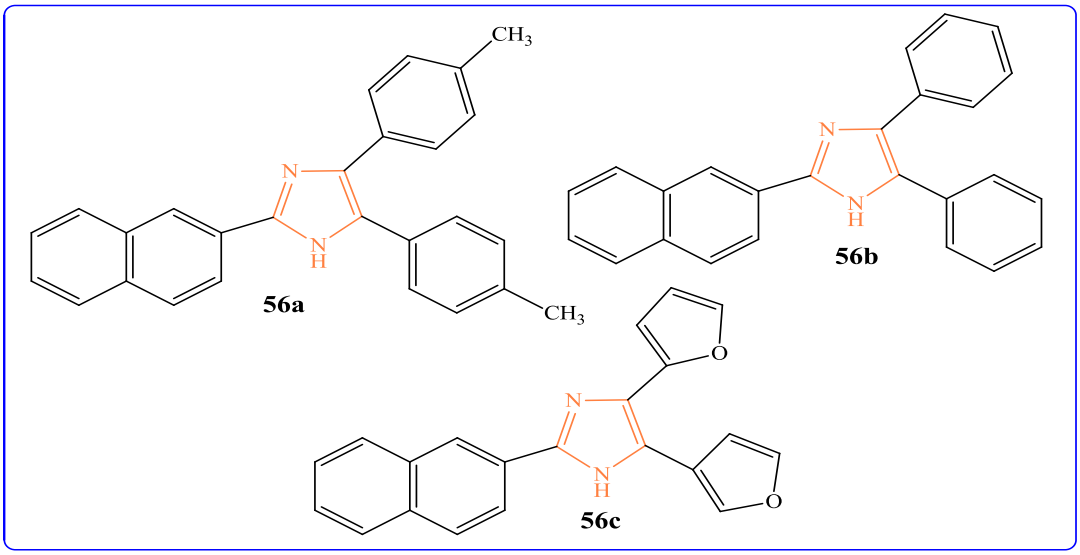
54

Yavuz *et al.*[99] synthesized certain novel imidazole derivatives and studied there *in vitro* anticancer potential against MCF-7 and HepG2 cell lines *via* MTT assay. The derivatives were found to exhibit profound cytotoxicity with inhibitory potentials better than the standard. Compound **55** displayed an IC_{50} of 14.80µM and 40.34µM against MCF-7 and HepG2.



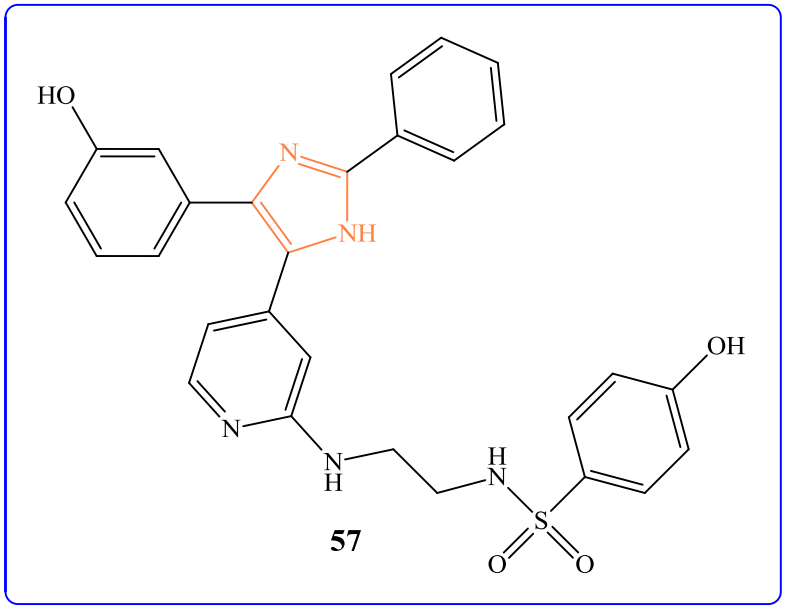
55

Somashekara *et al.*[100] synthesized novel naphthalene containing trisubstituted imidazole derivatives and determined their *in vitro* antioxidant propensity by DPPH assay. The compounds **56a**, **56b** and **56c** exhibited good antioxidant activity at concentration of 100µg/mL.



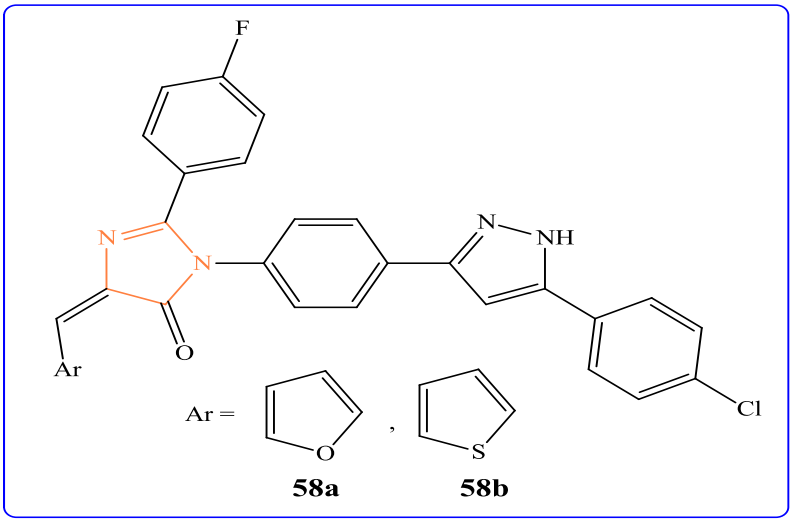
56a **56b** **56c**

Ali *et al.*[101] taking Dabrafenib as the template, developed a series of imidazole derivatives as BRAF inhibitors which are indicated in treating various types of cancers. The present series were tested against NCI 60 human cancer cell lines which encompassed different cell lines *viz.* leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer, most of these cell lines showed high sensitivity towards these derivatives. Compound **57** exhibited an IC_{50} of 32nM against BRAF.



57

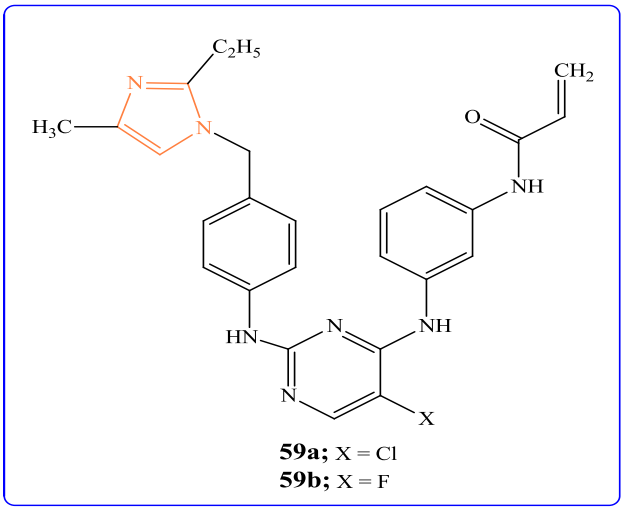
Lawal *et al.*[102] described the anti-breast cancer activity against MCF-7 human cancer cell lines for a novel series of imidazolones via *in silico* studies. Docking studies revealed that compounds agents acted *via* binding at Polo-like kinases receptors (Plk1), proven as a target for breast cancer treatment. The binding affinities of these compounds were higher than the standard Doxarubicin, with compounds **58a** and **58b** exhibiting a docking score of -8.8kcal/mol and 9.1kcal/mol respectively. The peer group postulated that these agents could act as a template for the development of newer molecules, active against estrogen positive breast cancer.



58a **58b**

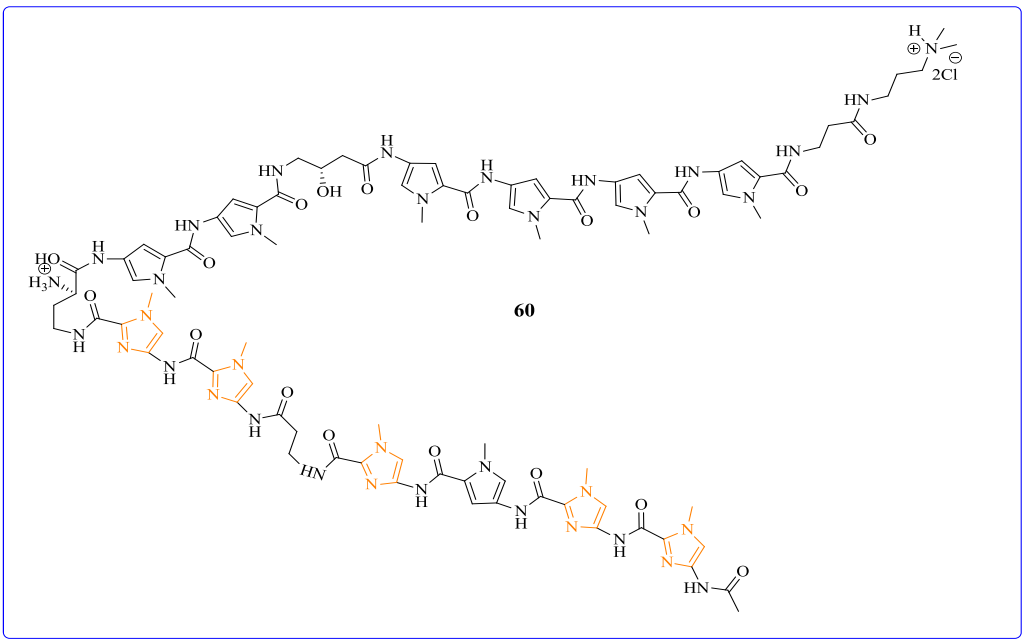
Li *et al.*[103] synthesized and demonstrated the inhibitory potential of certain complex imidazole substituted derivatives against B-cell lymphoma and acute myeloid leukemia by

acting as BTK (Bruton's tyrosine kinase) inhibitors. The activity was attributed to cell cycle arrest caused at G1/G0 or G2/M phase by these agents. Compounds **59a** and **59b** exhibited an activity which was better compared to the standard ibrutinib and were also less cytotoxic to the normal cells.



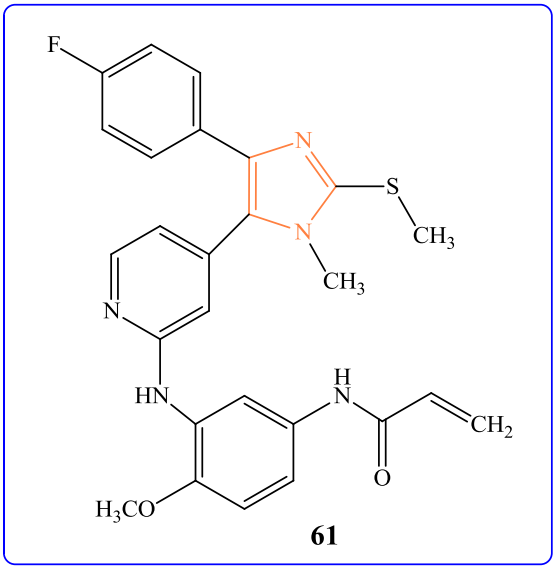
59a; X = Cl
59b; X = F

Zhang *et al.*[104] designed and synthesized pyrrole-imidazole polyamides which could act by inhibiting the c-kit kinase expression. These agents bind to the DNA sequence in the oncogenic c-kit promoter region, thus inhibiting transcription and translation resulting in cessation of cell proliferation and causing cell apoptosis. These agents were studied against A549 and SGC-7901 cells. Compound **60** could greatly reduce proliferation thus eliciting a decent response on the target.



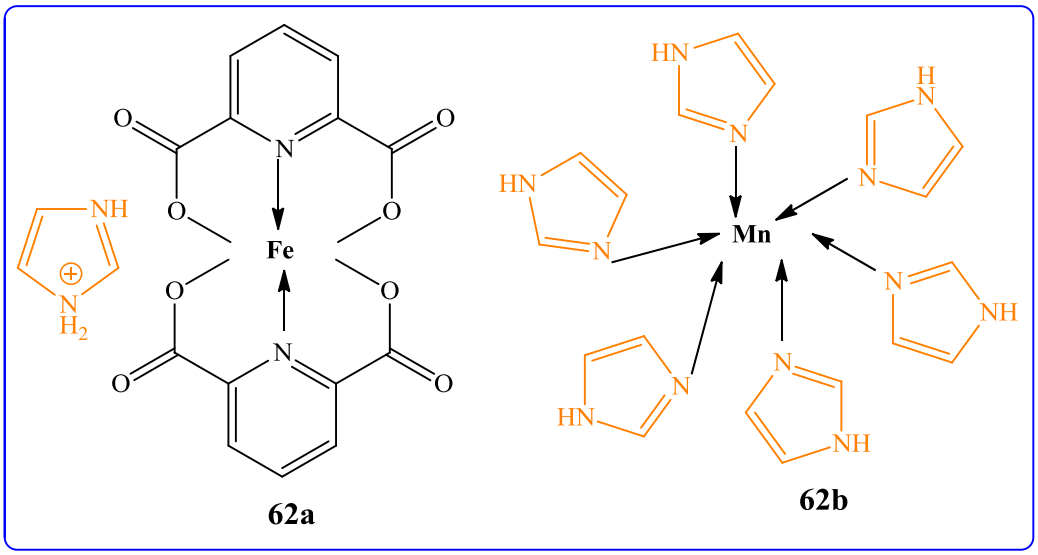
60

Heppner *et al.*[105] demonstrated the reversible non-covalent inhibitory action of trisubstituted imidazoles against epidermal growth factor receptor (EGFR), which was better than Osimertinib, a third generation EGFR tyrosine kinase inhibitor. Compound **61** was hypothesized to aid the development of newer entities which could help in the treatment of EGFR mutant non-small cell lung cancer.



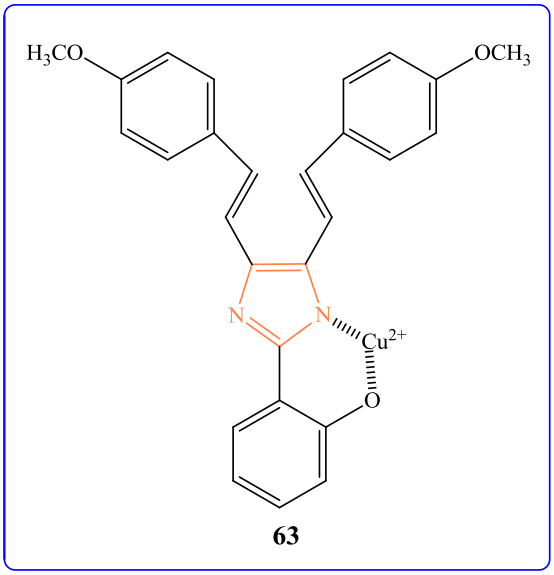
61

Khan *et al.*[106] describe the anticancer potential of imidazole-based Iron and manganese coordination complexes against RAW 264.7 cell lines. The anticancer activity was determined through MTT assay. IC_{50} of compounds **62a** and **62b** was found to be 7.89µM and 15.98µM. Docking studies revealed binding energy for iron complexes was more than the manganese counterpart when docked in the minor region of B-DNA.



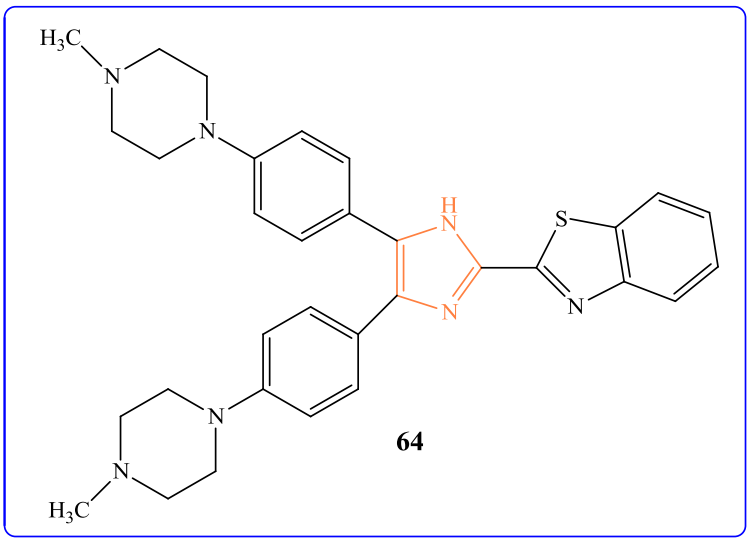
62a **62b**

Savithri *et al.*[107] developed a selective imidazole based fluorescent probe and demonstrated the *in vitro* anti-cancer activity of this molecule against human liver (HepG2) and lung (A549) cancer cell lines *via* MTT assay. It was found to elicit the inhibitory response in a dose dependent manner. Compound **63**, referred to as BMIP displayed an IC_{50} of 11µM and 12µM against liver and lung cells respectively, which was equivalent to cisplatin. Furthermore, BMIP did not show any toxicity against the normal human embryonic kidney cells.



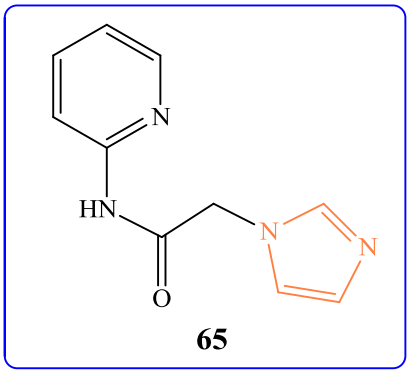
63

Wu *et al.*[108] demonstrated the *c*-MYC oncogene suppression of novel imidazole-based compound. The derivative acted by downregulating the *c*-MYC transcription thus causing cell cycle arrest and apoptosis. Compound **64**, was found to inhibit the tumour growth in B16 tumour-bearing mouse model.



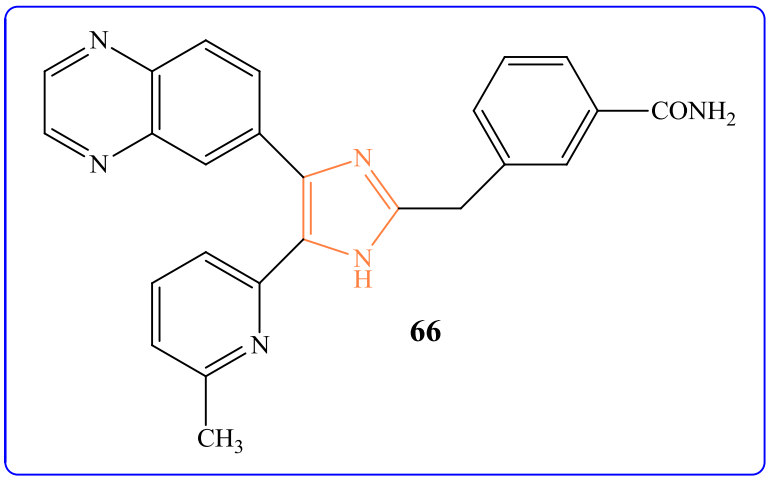
64

Lungu *et al.*[109] synthesized hybrid imidazole-pyridine derivatives which could act as DNA intercalators. The compounds were tested for their activity against NCI60 cell screen line. Compound **65**, was found to be active on different tumour cell lines and QSAR model agreed with the experimental results. Computational studies further revealed excellent pharmacokinetics properties of these newer derivatives.



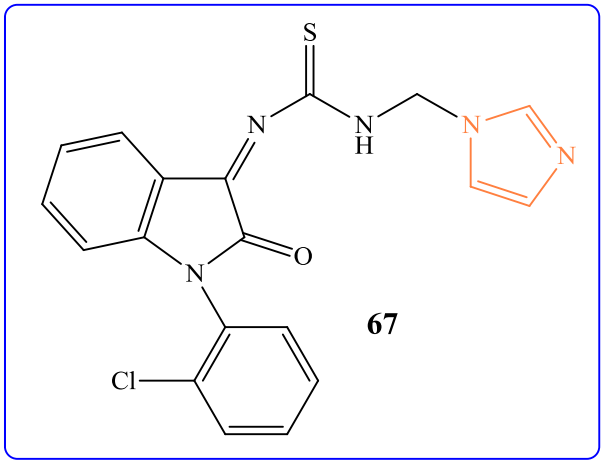
65

Park *et al.*[110] synthesized substituted imidazoles as ALK5 inhibitors. The derivatives were synthesized *via* structural modification of Vactosertib, an active ALK5 inhibitor under Phase 1b/2a clinical trials. The inhibitory potential of the derivatives was determined by enzyme assay and cell-based luciferase reporter assay. The IC_{50} of compound **66**, was found to be 0.036µM.



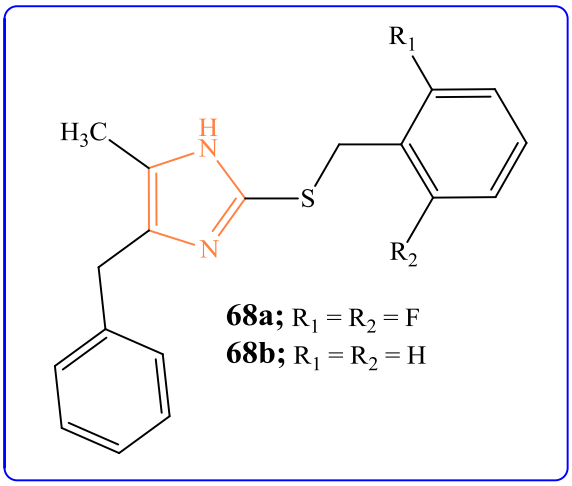
66

Kumar *et al.*[111] synthesized imidazole-isatin hybrids and demonstrated their anti-cancer activity against MCF-7. Best active compound **67**, with an IC_{50} of 0.75µM showed an activity better than the standard wortmannin.



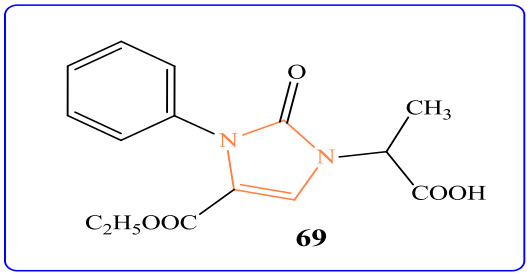
67

Beshay *et al.*[112] designed and synthesized substituted imidazoles and determined their anti-breast cancer propensity which acted by inhibiting STAT3 signalling which is associated with tumorigenesis. Appreciable activity was observed with compound **68a** exhibiting an IC_{50} of 6.66µM against 4 T1-Luc2 and compound **68b** showed an IC_{50} of 8.26µM against MDA-MB-231 cell line. Furthermore, docking studies were also performed with the compounds showing good binding affinities in the active site of STAT3-SH2.



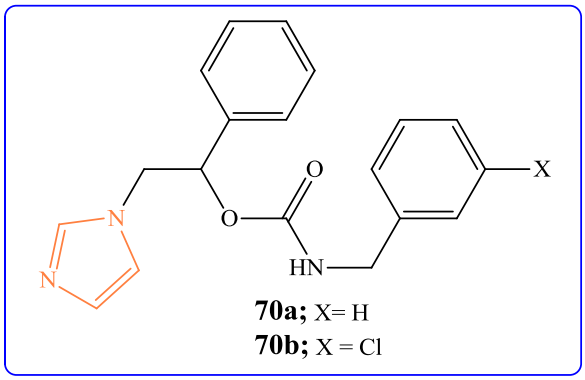
68a; $R_1 = R_2 = F$
68b; $R_1 = R_2 = H$

Ghazvini *et al.*[113] envisaged the synthesis of certain imidazole derivatives catalysed by zinc oxide nanoparticles and reported their antioxidant propensity. The antioxidant activity was determined *via* DPHH assay with compound **69** exhibiting good radical trapping relative to the standards butylated hydroxytoluene (BHT) and 2-tert-butylhydroquinone.



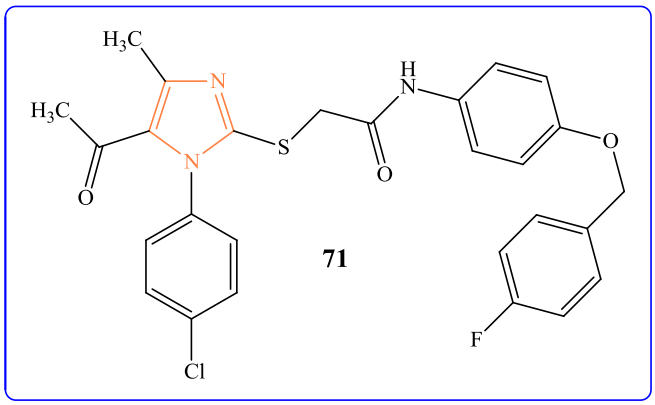
69

Ammazzalorso *et al.*[114] synthesized and described the aromatase inhibitory proclivity of imidazole tethered carbamate derivatives. The compounds were tested for their anti-breast cancer activity against MCF7 cell lines. Compounds **70a** and **70b** when tested for their aromatase inhibitory action, showed an inhibition of 81% and 72% compared to letrozole and IC_{50} values for these compounds was found to be 0.82µM and 0.86µM.



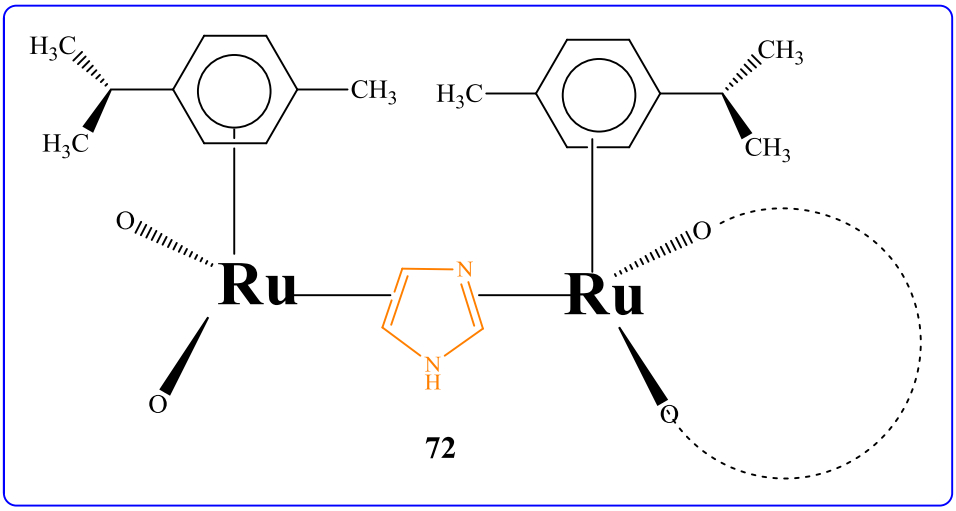
70a; X= H
70b; X = Cl

Daraji *et al.*[115] synthesized and tested the antioxidant activity of a novel series of imidazole derivatives by DPPH, nitric oxide and hydrogen peroxide radical scavenging assay. Although the derivatives exhibited a lower antioxidant potential then the standard ascorbic acid but the results were appreciable with compound **71** being the most active scavenger of the free radicals at 100 dilution value by all the three methods.



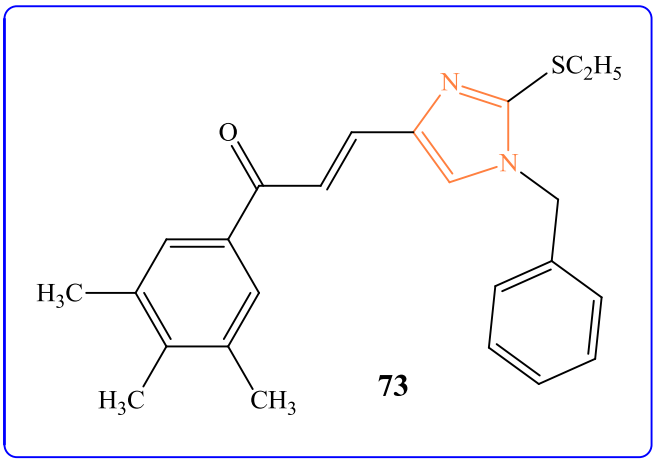
71

Khanvilkar *et al.*[116] developed binuclear ruthenium (II) complexes of *p*-cymene, lemofloxacin, levofloxacin, ciprofloxacin and moxifloxacin with imidazole acting as a bridge between the two nuclei. The *in vitro* cytotoxicity of these agents was determined by MTT colorimetric assay against HeLa cell lines. These agents were found to be DNA intercalators with compound **72** having the strongest binding constant of the order 2.5 x 105/M.



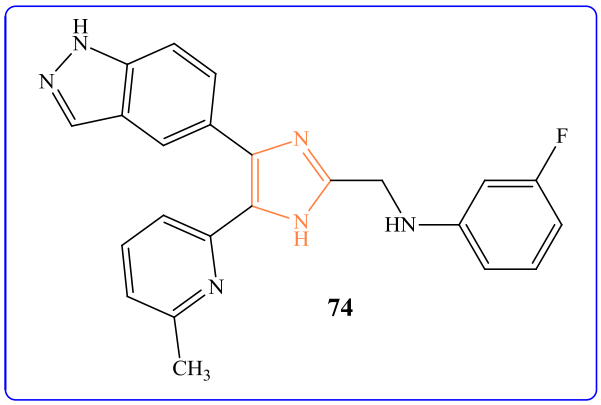
72

Oskuei *et al.*[117] designed and synthesized imidazole-chalcone derivatives and tested them against different human cancer cell lines *viz.* A549, MCF-7, MCF-7/MX and HEPG2. The *in vitro* studies demonstrated that these novel chalcones were more active against A549 cell lines as compared to other cell lines, with compound **73** showing an IC_{50} of 7.05µM. Studies also revealed that they acted by causing cell cycle arrest at the G2/M phase. Docking studies indicated that these derivatives bind to the colchicine-binding site of tubulin.

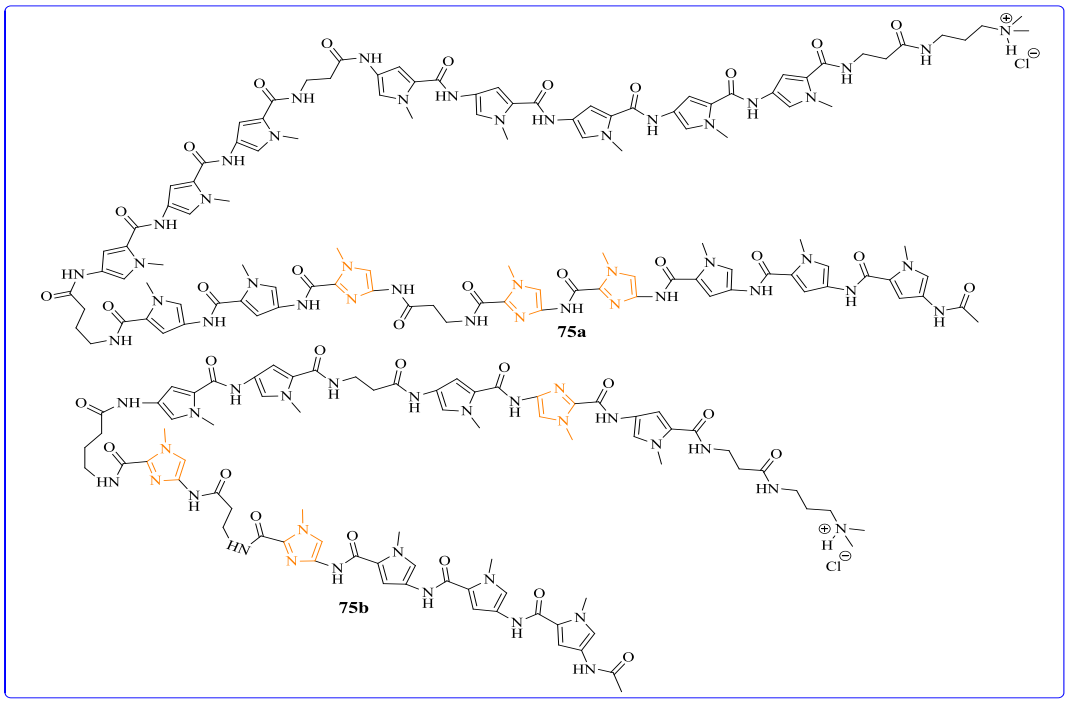


73

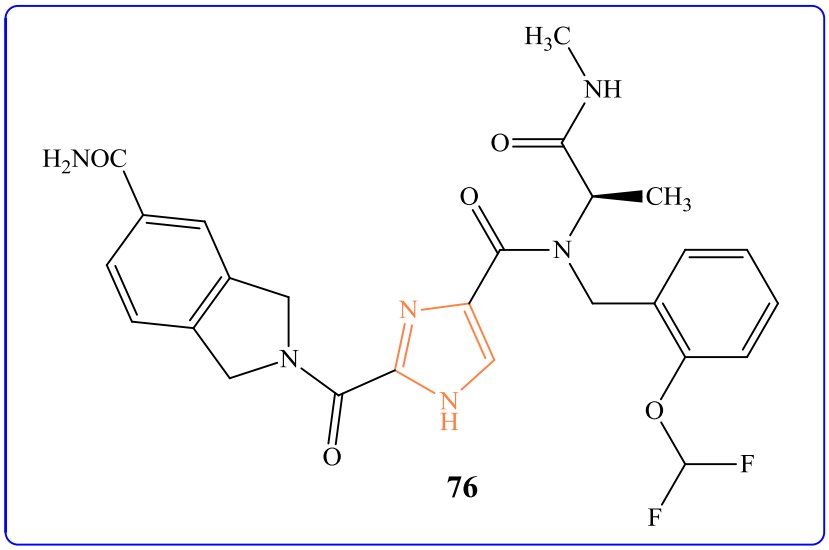
Liu *et al.*[118] synthesized and evaluated the ALK5 and p38α protein kinase inhibitory action of a new series of indazole derived imidazoles. Compound **74** exhibited the most potent derivative with an IC_{50} of 0.004μM in both ALK5 kinase inhibition and p38α kinase inhibition activities in enzyme assay. It was also shown that the compounds could inhibit EMT and invasiveness in glioma cells *in vitro*.



Wang *et al.*[119] established pyrrole-imidazole polyamides which could act as STAT3 signalling inhibitor by binding at the double stranded DNA resulting in inhibition of angiogenesis thus, causing apoptosis and cell death. The agents could downregulate PD-L1 expression at both transcriptional and translational levels; these are transmembrane proteins which modulate T cell function resulting in cytotoxicity. Polyamides **75a** and **75b** could also inhibit the expression of Akt/Caspase-3.

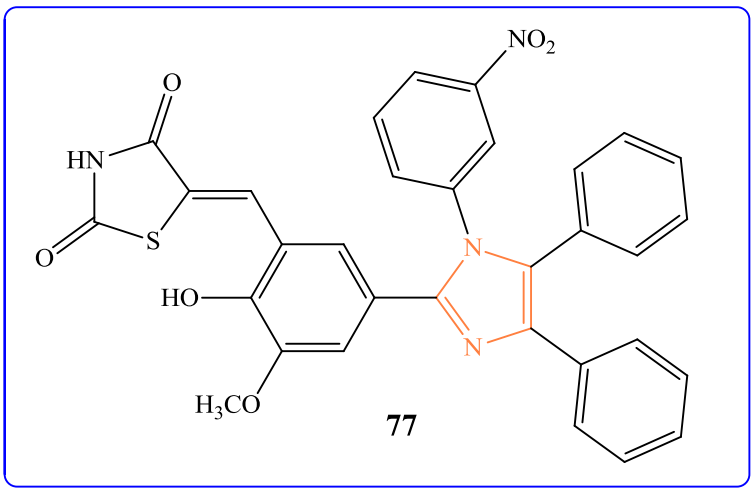


Veerman *et al.*[120] demonstrated the TAK1 inhibition of novel imidazole carboxamides with compound **76** showing an IC_{50} of 0.002µM.



76

Nyaki and Mahmoodi.[121] determined the antioxidant and cytotoxic propensity of new imidazole derivatives. The radical scavenging potential was determined *via* DPPH assay. The IC_{50} of compound **77** was found to be 1768µM which was much higher than the standard ascorbic acid. Additionally, the cytotoxic activity was also determined for these series against MCF-7 cell line and appreciable activity was obtained, with compound 47 exhibiting an IC50 of 85.6µ/mL.



77

3. CONCLUSION

Imidazole, a 1,3-dinitrogen containing five membered heterocyclic moiety finds its worth in treatment of various cancers. The demand of imidazole-based moiety is constantly increasing

due to its activity against various cancer cells *via* different mechanisms of action. This review highlights the current status and ongoing development in the direction of developing various imidazole based anticancer compounds that can be used in the near future to combat this disease.

4. CONFLICT OF INTEREST

The Authors have declared no conflict of interest.

5. ACKNOWLEDGEMENTS

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Abbreviations

AR	Androgen receptor
AzDPPYs	Azole-diphenylpyrimidine derivatives
BC-CML	Blast crisis-chronic myeloid leukemia
BTK	Bruton's tyrosine kinase
BxPC-3	Human Pancreatic Cancer cell lines
CA-4	Combretastatin A-4
CAM	Choliroallantoic membrane
CP-CML	Chronic phase chronic myeloid leukemia
DU-145	Prostate cancer cell lines
EGFR	Epidermal growth factor receptor
EMSA	Electrophoretic mobility shift assay
FAK	Focal Adhesion Kinase
GBM	Glioblastoma multiforme
HeLa	Cervical cancer cell lines
HepG2	Liver cancer cell lines
HO-1	Heme oxygenase-1
HO-2	Heme oxygenase-2
HOP-62	Lung cancer cell lines
MCF-7	Breast cancer cell lines
PC	Phosphonocarboxylate

PC-3	Prostate Cancer cell lines
Plk1	Polo-like kinases receptors
RabGGTase	Rab geranylgeranyl transferase
SI	Selectivity index
TNKS	Tankyrase inhibitors
TNKS1	Tankyrase 1 inhibitors
WHO	World Health Organization

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