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A Review On: Imidazole Derivatives As A Multifunctional Moiety

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Abstract
Imidazole nucleus has been potential studied member from heterocyclic compound family. Imidazole and its derivatives showing good pharmacological activities against various diseases. Imidazole is the heterocyclic molecule which having the interesting physical and chemical properties, in the present article focus lies on analysis of these properties which in turn may be exploited for different pharmacological activities, like compounds having a 3,4,5-trimethoxyphenyl ring linked to either N-1 or C-4 position of the imidazole entity gave an interesting profile of cytotoxicity with specific activity against leukemia cell lines, combination of indole-imidazole compounds formed demonstrated substantial in vitro anti proliferative activities against cancer cell lines, effective substitutions are also made in the entity which resembles structures of various natural compounds whose anti cancerous activity has already been examined. The present review study highlighting pharmacological potential of the imidazole. In present study we have discussed compounds synthesized with imidazole moieties as their structural framework. Thus can say imidazole is a moiety which had been exploited in the past years for synthesizing various compounds having versatile pharmacological activities, and still it can be further utilized for future prospective against various pathological conditions and other uses.

Keywords

Anticancer Activity, Heterocyclic compounds, Imidazole, Pharmacological activities.

Introduction

Many more heterocyclic compounds have been synthesized now a day due to having various biological activities. The heterocycles which contains nitrogen and oxygen such as oxazole, pyrazole and its derivatives possess many types of pharmacological activities. [1-4] Chemically imidazole is a planer, five membered heterocyclic molecule containing 3 carbon and 2 nitrogen atoms. The nitrogen atoms are present on 1st and 3rd position. Imidazole is 1, 3-diaza-2, 4-cyclopentadiene. [5, 6]

Imidazole ring is a main constituent of various types of natural products such as purine, histamine, histidine and nucleic acid etc. Due to polar and ionisable aromatic compound, imidazole having improved pharmacokinetics parameters as compare to the others. [7, 8]

Chemical Structure of Imidazole :

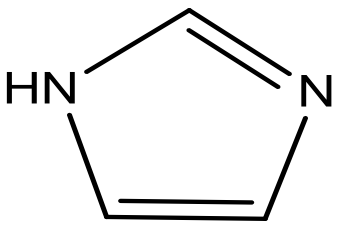

Figure 1: Structure of Imidazole [09]

Imidazole Characteristics [10, 11]

Table 1: Characteristics of Imidazole nucleus

Molecular Formula	$C_3H_4N_2$
Molecular Weight	68.077 g/mol
Color	Colorless solid
Melting Point	89-91 ^{0}C
Boiling Point	256 ^{0}C
Density	1.23 g/cm^3, solid
Solubility in water	633 g/L

Because of the special structural features and electron rich environment of the imidazole moiety having the ability to bind with the different therapeutic targets, and therefore the imidazole is having broad spectrum of bioactivities.[12,13]

Imidazole having huge variety of biological activities like anti- cancer, anti-microbial, anti-inflammatory, including their potential mechanisms such as topoisomerase II R catalytic inhibition, focal adhesion kinase (FAK) inhibition, G-quadruplex DNA stabilization etc. As per the above mentioned activities imidazole shows anti- microbial properties by breaking the DNA double strand helix and inhibiting protein kinase. And anti-inflammatory mechanisms involve COX-2 inhibition and generation of reactive oxygen species.[14,15] Other than this activities the imidazole and its derivative i.e. benzimidazole also act as a antileukemic activity, anti-malarial , anti-oxidant and antileishmanial activity, Analgesic, Anxiolytic, and Anti –diabetic activities also.[16,17]

BIOLOGICAL ACTIVITIES AND IMPORTANCE OF IMIDAZOLE NUCLEUS:

Cancer is a malignant type of disease which is characterized by the uncontrolled growth and proliferation of the cells. Depending on the type of cancer the growth may be rapid or slow. [18] Nearly, 13 members are identified as a cyclin – dependent kinase (CDKs) which is generally divided into the 2 groups depending on their role in the cell-cycle progression and transcription regulation. De-regulation of the different components which plays important role in cell-cycle controls in tumor pathogenesis. [19, 20] The signs and symptoms of cancer are new lumps formation, abnormal bleeding, prolonged cough, weight loss and alteration of bowel movement. Now days, various types of anti-cancer drugs are available in the market, though there are many issues related to the toxicity, low efficacy and solubility changes the overall therapeutic success [21-24]. So the selective drug's anticancer activity is depending in the substitution present on the imidazole nucleus. [25]

CHEMICAL SYNTHESIS AND PHARMACOLOGICAL ACTIVITIES OF IMIDAZOLE:

Imidazole and its derivatives showed the greater importance as an anti-cancer agent:

The recent study reveals that several methods are adopted for the synthesis of imidazole and its derivatives:

1. ANTI-CANCER ACTIVITY:

Jeany M. Rademaker-Lakhai, Desiree van den Bongard, *et al.*, (2004) pre-clinical studies, The novel ruthenium-containing compound , Imidazolium-trans- DMSO – imidazole- tetrachlororuthenate (NAMI-A) has demonstrated for antimetastatic activity. [26] The Phase I study was designed for the determination of maximum- tolerated dose(MTD) , adverse effect study and dose- limiting toxicity of NAMI-A in the patients having solid tumors. The NAMI-A can be administered through *i.v.* route as 3-h at a dose 300 mg/m^2 for 5 days and for every 3 weeks stated as a conclusion as a study. [27]

Ken-Ichi Shinoharaa, Toshikazu Bandoa and Hiroshi Sugiyama, *et al.,* (2010) were synthesized N-methyl imidazole polyamides are the small newly introduced compounds which bind to the minor groove of the DNA duplex within in sequence-specific fashion. [28] These agents are recruiting alkylating agents for their target sequence. In this research article a series of sequence-specific alkylating py-Im polyamide conjugates were synthesized for the alkylating predetermined DNA sequences. This type of alkylating agents alkylate tamplet strand coding region due to having gene-silencing activity. These agents are also having potency against human cancer cell lines and also xenografts having human cancer cells. [29]

Kallol Purkait, Subhendu Karmakar, Sudipta Bhattacharyya *et al.*,(2015) Π bonded arene bound Ru (II) complex having greater activity against different types of cancer. [30, 31] Imidazole-based Ru (II) arene complex i.e. [(L)Ru-II(η^6-p-cym)(CI)](PF_6) is a slow hydrolyzing substance having better stability in the extracellular chloride concentration . Under hypoxic condition it shows better activity under hypoxia and strong resistance to glutathione (GSH) *in vitro.* It showed its pharmacological action by arresting the cell in sub G1 and G2/M phases which results in apoptosis. [32]

Michael I. Webb, and Charles J. Walsbya *et al.,* (2015) developed NAMI-A i.e. imidazolium [trans-$RuCl_4$(1H-imidazole)(DMSO-S)] with other Ru(III) chemotherapeutic agents interact with the human serum albumin (HSA) .[33,34] In this article showed us idea about the characterization of coordination to HAS , using NAMI-A and its analogue labeled with deuterium , the electron paramagnetic resonance (EPR) and electron nuclear double resonance (ENDOR) spectroscopic analysis is carried out. The sample was prepared by using phosphate buffered saline solution in the presence of HAS, with the individual amino acids such as histidine, cysteine and alanine. The coordination of ligand was confirmed by the ^{14}N ENDOR signals. The ENDOR data said that, via histidine imidazoles , both complexes bind to HSA. [35]

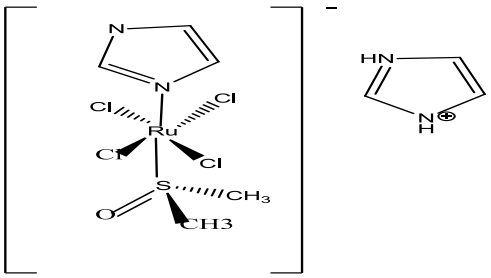

Figure 2 : NAMI-A

Arvind Negi a , Jimi Marin Alex a , Suyog M. Amrutkar *et al.*,(2015) synthesized 1-(2-Chlorobenzyl)-5-((3,5-dichloro-2-hydroxybenzylidene) amino)1H-imidazole-4-carbonitrile , 5-(((1H-Indol-2-yl)methylene)amino)-1-(2- chlorobenzyl)-1H-imidazole-4-carbonitrile and (N-(1-(2-Chlorobenzyl)-4-cyano-1H-imidazol-5-yl)- acetamide) in the synthesized series having promising antiproliferative activity *in vitro*, with a low micromolar IC_{50} values against different cancer cell lines such as, A-459(lungs) , Hep-G2(liver)etc. These compounds show their activity by increasing the ROS levels along with depolarization of mitochondrial membrane which results in the apoptosis. For the 1st time the anticancer activity of novel imine/amide-imidazole conjugates synthesized from the 5-amino-4-cyano-N1-substituted benzyl imidazole using microwave. [36-37]

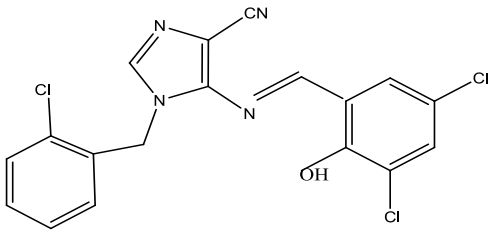

Figure 3: 1-(2-Chlorobenzyl)-5-((3, 5-dichloro-2-hydroxybenzylidene) amino)1H-imidazole-4-carbonitrile

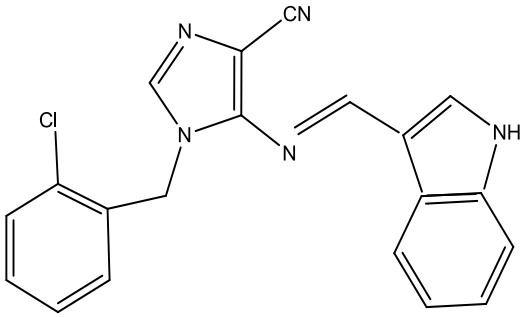

Figure 4 : 5-(((1H-Indol-2-yl) methylene)amino)-1-(2- chlorobenzyl)-1H-imidazole-4-carbonitrile

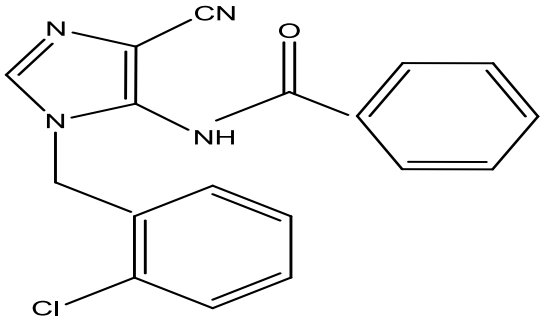

Figure 5: (N-(1-(2-Chlorobenzyl)-4-cyano-1H-imidazol-5-yl)-acetamide)

Fang Wang, Xue Wang, Min-Xia Zhang, *et al..*,(2015) introduced the series of novel compounds like 2-(benzo[*d*][1,3]dioxol-5-yl)-1-(2,6-dinitro-4-(trifluoromethyl)phenyl)-1*H*-benzo[*d*]imidazole, 2-(benzo[*d*][1,3]dioxol-5-yl)-1-(2,6-dinitro-4-(trifluoromethyl)phenyl)-5-methyl-1*H*-benzo[*d*]imidazole, and many more were designed and prepared . Between these synthesized compounds 1-(3-chloro-2,6-dinitro-4-(trifluoromethyl)phenyl)-2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1*H*-benzo[*d*]imidazole. Anti-tubulin polymerizing agents have ability to strongly inhibit the tubulin polymerization by binding to the colchicine binding site resulting in strong cytotoxicity against multiple human tumor.[38] Based on the 1H-benzo[d]imidazole. Having most potent in vitro growth inhibitory activity against cancer cell lines such as A549, MCF-7 , K562 with IC_{50} values 0.12μM,0.15 μM,0.21 μM respectively. The above mentioned compound also having tubulin polymerization inhibition activity and the 3D-QSAR modeling provide information about the determination of the probable binding model and having potent inhibitory activity in growth of tumor as an anticancer agent.[39]

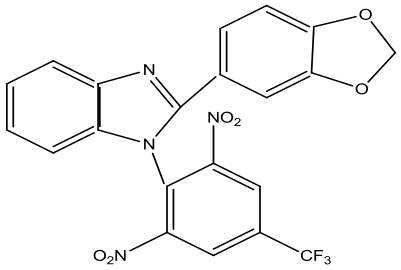

Figure 6 : 2-(benzo[*d*][1,3]dioxol-5-yl)-1-(2,6-dinitro-4-(trifluoromethyl)phenyl)-1*H* benzo[*d*]imidazole

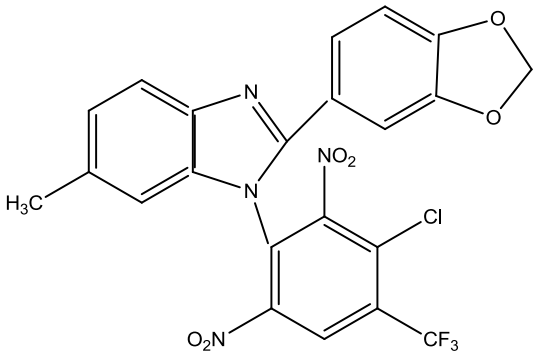

Figure 7 : 2-(benzo[*d*][1,3]dioxol-5-yl)-1-(2,6-dinitro-4-(trifluoromethyl)phenyl)-5-methyl-1*H*-benzo[*d*]imidazole

Romeo Romagnoli , PierGiovanni Baraldi , Filippo Prencipe , *et al.,* (2016) Depending on the 1-(3',4',5'-Trimethoxyphenyl)-2-Aryl-1H-imidazole moiety a novel series of polymerization inhibitors were designed as a cis-restricted combretastatin A-4 analogues.[40] This is used by the for the evaluation of the effect of different types of substitution on phenyl at position 2 of the imidazole ring. The chloro and ethoxy group at meta and para position gives the series containing more active compound i.e. 2-(3′-Chloro-4′-ethoxyphenyl)-1-(3′,4′,5′-trimethoxyphenyl)-1H-imidazole showed its IC_{50}value= 0.4-3.8 nM. This compound is effective against seven cancer cell lines. The mouse syngenic model used for the experiments demonstrated high antitumor activity of the *2*-(3′-Chloro-4′-ethoxyphenyl)-1-(3′, 4′,5′-trimethoxyphenyl)-1H-imidazole which significantly decreased tumor mass .[41]

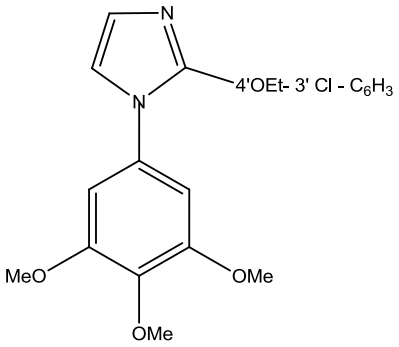

Figure 08 : 2-(3′-Chloro-4′-ethoxyphenyl)-1-(3′,4′,5′-trimethoxyphenyl)-1H-imidazole

Sobhi Mohamed Gomha, ,a Hassan Mohamed Abdel-aziz,b and Khaled Dessouky Khalila, *et al.,* (2016) Synthesized 1,3,4-thiadiazole nuclei and annulated 1,3,4-thiadiazoles possess antimicrobial, anti-inflammatory, anticancer, anticonvulsant, antidepressant, antioxidant, radio protective, and anti-leishmanial activities and many more. [42,43] By using most versatile and unreported 2-(5-oxo-4,4-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-*N*-phenylhydrazinecarbothioamide along with appropriate hydrazonoyl halides , a new series of 2-(2-(3-aryl-5-substituted-1,3,4-thiadiazol-2(3*H*)-ylidene)- hydrazinyl)-4,4-diphenyl-1*H*-imidazol-5(4*H*)-one derivatives were synthesized . The synthesized products were evaluated against HEPG2-1 i.e. liver carcinoma cell line against anticancer activity with their SAR also. From the evaluation study it was conclude that the thiazole-imidazole derivatives possess better anticancer activity. [44]

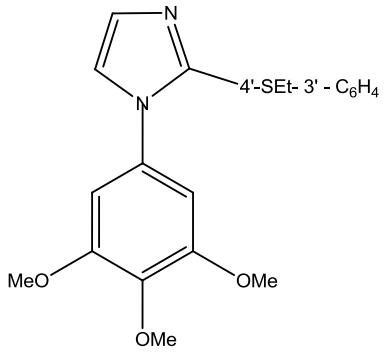

Figure 9 : 2-(3′-Chloro-4′-ethoxyphenyl)-1-(3′,4′,5′-trimethoxyphenyl)-1H-imidazole

Elvan Üstün, Aykut Özgür, Kübra A. Coşkun , *et al.,* (2016) The breaking down of heme in mammals gives CO, ferrous ion and biliverdin. [45, 46] The reaction is catalyzed by the heme oxygenase1 (HO-1). The increases the activity of HO-1 and inhibits the cell proliferation. The HO-1 plays important role against oxidative stress and it inhibits apoptosis, metastases, angiogenesis and proliferation of cells also. So the molecules which release CO have effective anticancer activity. For this purpose synthesized [Mn(CO)3(bpy)L]X manganese containing CORMs [bpy = 2,2'-bipyridine, X = hexafluorophosphate (PF6), trifluoromethanesulfonate (OTf), L = imidazole, methylimidazole, benzimidazole, N-benzylbenzimidazole, N-(4-chlorobenzyl)benzimidazole] for analyzing its activity on invasive ductal breast(MCF-7) cell lines. The in vitro study reveals that these compounds are possessing good anticancer activity against breast cell wall. As an alkylating cytotoxic agent, oxaliplatin forms adducts between two adjacent guanines or guanine plus adenine preventing DNA replication [47].

Sara Hadian Rasanani, Mahboube Eslami Moghadam, *et al.,* (2017) Oxaliplatin, (1R, 2R)- cyclohexanediamine-platinum(II) is known as third-generation of platinum cancer drug, and is widely used in cancer treatment. [48] Synthesized of two novel water-soluble fluorescent palladium and platinum complexes. These two having molecular formula i.e. [Pt(DACH)(FIP)](NO3)2 and [Pd(DACH)(FIP)](NO3)2,respectively. In that FIP means 2-(furan-2-yl)-1H-imidazo [4,4-f][1,10]phenanthroline and DACH means 1R,2R-diaminocyclohexane. From the flurescence spectroscopy , circular dichronism (CD), ionic strength , kinetic study , thermal denaturation measurement it was conclude that , groove binding of Pt comple on DNA and beacause of the binding of Pd complex, B form of DNA is converted into Z. The Pd and DNA complex, DNA form is converted which gives more enough space for the Pd complex for the insertion between base stacking of DNA. The cancer activities of the synthesized drugs are checked by MTT assay method on human colon cancer cell line for platinum complex along with molecular docking also. Docking showed higher negative energy and high tendancy for DNA binding to show anti-cancer effect. [49]

Mahboube Eslami Moghadam, Adeleh Divsalar, Marziye Shahraki Zare, *et al.,* (2017) Pt or Pd complexes of phen or modified phen ligand with large square surface in their structure bind to DNA by intercalation [50,51] .

The novel nickel (II) and copper (II) complexes containing (FIP) i.e. 2-(furan-2-yl)1H -imidazo[4,4-f][1,10]phenanthroline and 2-(thiphen-2-yl)-1H- imidazo[4'5-f][1,10] phenanthroline , 2-(thiophen-2-yl)-1Himidazo[4,5-f][1,10]phenanthroline (TIP) and imidazophen derivatives were prepared.The pharmacological activity of Ni and Cu complex as an anticancer agents were tested at micromolar concentration for chronic myelogenous leukemia cell line K562. Cc_{50} values for Cu and Ni (ii) were found to be 21 and 160 µM respectively. The activity of Cu (ii) and Ni (ii) against particular type of microorganism showed by Cu(ii) comple having antifungal and Ni (ii) complex have antibacterial activity. [52]

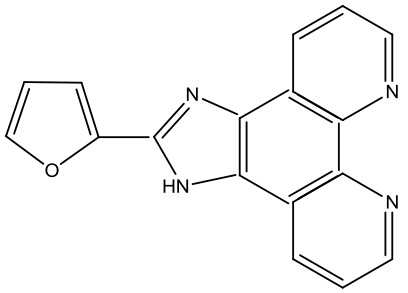

Figure 10 : 2-(furan-2-yl)1H -imidazo[4,4-f][1,10]phenanthroline and 2-(thiphen-2-yl)-1H- imidazo[4'5-f][1,10] phenanthroline (FIP)

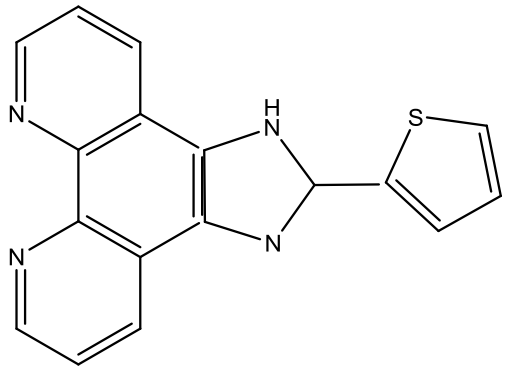

Figure 11: 2-(thiophen-2-yl)-1 Himidazo[4,5-f][1,10]phenanthroline (TIP)

Guanghua Yang, Nouredine Sadeg and Hafid Belhadj-Tahar, *et al.,* (2017) Hepatocellular carcinoma is the very common primary type of liver tumor.[53] Treatment for HCC is e transcatheter hepatic arterial infusion chemotherapy (TACE trans arterial chemoembolization) and radiofrequency ablation.[54-56] . Now a days direct intratumoral injection of non removable radioactive material has been invented for treatment of hepatic tumors like sulfide [188Re] rhenium colloidal or dendrimers loaded [188Re]rhenium complexes [57] . Therefore [^{188}Re] rhenium –imdendrim is an potential anticancer agent synthesized from [^{188}Re]rhenium-nitro-imidazole-methyl- 1,2,3-trazole-methyl-di-(2-pycolyl)amine , a radioactive ligand including 5th generation poly-L-lysine denrimer. The injected $5X10^6$ cells to the mice by sc route . After the tumor generation 4 mice treated with single dose of [^{188}Re] rhenium-imdendrim i.e. 37, 74, 92.5 and 111 mBq. The results showed that [^{188}Re] rhenium –imdendrim have greater anticancer activity at low dose i.e. 37 mBq [58]

Wen Gu , Ting-Ting Miao, Da-Wei Hua, *et al.,* (2017) Dehydroabietic and its derivatives possess a broad spectrum of biological activities such as antibacterial, antifungal, antiulcer, anti-aging, antifeedant and BK-channel opening activities with antitumor property by DNA binding, apoptosis or oncosis inducing mechanisms [59-62] synthesized the novel series of 1H-benzo[d]imidazole as a potent antitumor agents. Most

derivatives of dehydroabietic acid showed cytotoxic effect against two hepatocarcnoma cancer cell lines. Also showed activity against SMMC-7721 cells with IC_{50} =m0.36±0.13μM. This derivatives showed their anticancer activity by cycle arrest of SMMC-7721 cells at G2/M phase.[63]

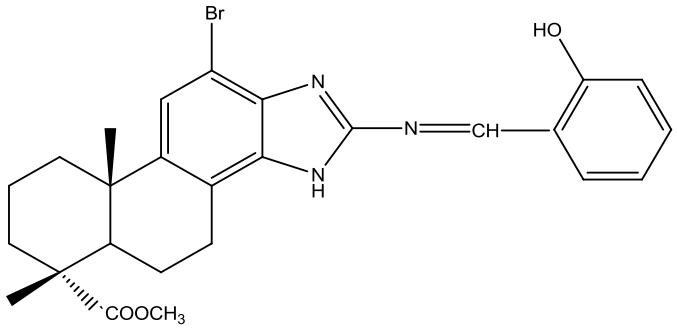

Figure 12 : Dehydroabietic acid derivative 01

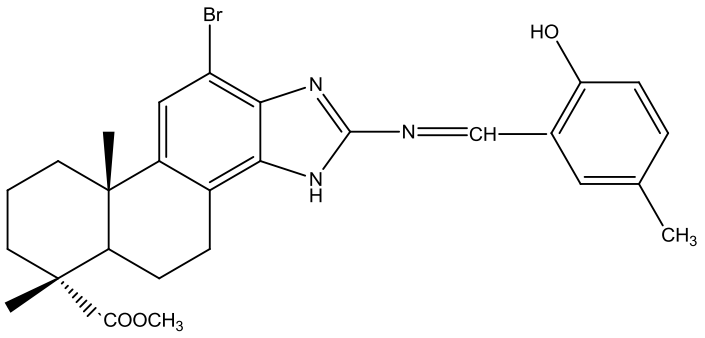

Figure 13 : Dehydroabietic acid derivative 02

Maura Pellei , Valentina Gandin, Cristina Marzano , *et al.,* (2017) NHC complexes of coinage metals is having different applications and diverse structural properties such as anti-cancer agents. The water solubility is achieved by the introduction of a hydrophilic moiety on the scaffold, such as P(O)(ONa)2, OH, NMe3 + and PMe3 + or sulfonate and carboxylate side chains.[64-66] Since by using sulphonated N-heterocyclic carbine precursors the novel 1st water soluble bis(NHCSO3)CuCl complexes (NHCSO3 = $NaIm^{Bn,PrSO3}$, $Na2(4-Me)Im^{PrSO3}$ and $Na2BzIm^{PrSO3}$) were synthesized. The compounds like Him $Bn,^{PrSO3}$ (3- (1- benzyl- 1H- imidazol- 3- ium- 3- yl)propane- 1- sulfonate), $Na(4- Me)HIm^{PrSO3}$ (sodium 3,3′- (4- methyl- 1H- imidazole- 3- ium- 1,3- diyl)dipropane- 1- sulfonate) and $NaHBzIm^{PrSO3}$ (sodium 3,3′- (1H- benzoimidazole- 3- ium- 1,3- diyl)dipropane- 1- sulfonate) were synthesized. The anti-tumor effects of the bis(NHC^{so3})cucl complexes determined by in vitro studies. This agent is also effective against different human tumour cell lines like lungs, colon, ovarian etc. NHC-copper complexes possessing induced cell killing effect against tumour cells along with greater IC_{50} . [67]

Reda Ahmed Haggam , Mohamed Gomma Assy , Mohamed Hassan Sherif , *et al.,* (2018) Azoles and azines of having good antitumor activity. The addition of nsemicarbazole or phenylhydrazine hydrochloride into thienoylisothiocyanate gives the derivatives of thiosemicarbazide , triazole , thiphene-2-carboxamide etc.

Various compounds were synthesized by using different methodology like synthesis of thiadiazine derivative is done by reaction of maleic anhydride in triethyl amine. The yield of the synthesized compounds was found to be to 61-91%. [68-70]

Zhanxiong Liua , Zhenfeng Zhangb , Wanbin Zhangab , *et al..*,(in 2018) introduced 2-Substituted-1-(2-morpholinoethyl)-1*H*-naphtho[2,3-*d*] imidazole-4,9-diones containing a N-(2-morpholinoethyl group and 2-substitited imidazole segment were synthesized and screened for the 3 types of human cancer cell lines- HeLa, A549,and normal cell line also. From all of the synthesized compounds 2-(3-chloro-4-methoxyphenyl)-1-(2-morpholinoethyl)-1*H*-naphtho[2,3-*d*]imidazole-4 9-dione possess better antiprolifertaive activity against MCF-7, HeLa with IC_{50}= 10.6,8.3,4.3 μM respectively. 2-morpholino ethylamino-substituted naphthoquinones were designed rationally as inhibitors for the dual specificity protein hosphatase CDC25, which is considered to be a potential target for anticancer agents. [71-73]

Sung Hun Bae, Ju Ho Park, Hyeon Gyeom Choi, *et al..*, (2018) showed that , The imidazole moiety containing drugs like clotrimazole and ketoconazole were evaluated again human breast adrenocarcinoma cells i.e.MCF-7 and MDA-MB-231 . This agents showed their effect by acting on cell proliferation, apoptosis, cell cycle etc. They also inhibit the motility of MDA-MB-231 cellsand G_1 phase arrest induced in MCF-7. These agents also suppressed invasiveness through matrix metalloproteinase 9 inhibition in above mentioned cell line. [74, 75]

Hangxia Zhao , Li Tao , Fengmin Zhang , *et al..*,(2019) stated that polyoxometalas having oxygen rich surfaces and possess very different physical & chemical properties like polarity, redox potential and also having sversatile bioactivity. Therefore H2[(CH3)4N]4-{[Na(H2O)4][Na0.7Ni5.3(imi)2(Himi)(H2O)2(SbW9O33)2]}_10H2O(i) and H3[(CH3)4N]4[Na0.7Co5.3(imi)2(Himi)(H2O)2(SbW9O33)2]_12H2O(ii) and many other derivatives of imidazole were prepared using tragonal cluster precursor i.e. [Na2Sb8W36O132(H2O)4]22_ {Sb8W36} . From the above 2 derivatives the compound (i) is found to be highly cytotoxic against gastric cancer cells. It shows action by targeting the cell cycle in S-phase and inducing apoptosis [76-78].

Sangeetha Meenakshisundaram , Manoj Manickam , Thanigaimalai Pillaiyar , *et al..*,(2019) introduced the new series of bis-imidazoles and bis-imidazo[1,2-α]pyridines such as 1,4- Bis(1- phenyl- 1H- imidazol- 5-yl)benzene and (E)- N- (3- (1- Phenyl- 1H- imidazol- 5- yl)benzylidene)aniline (18) were prepared using Schiff base dimers. This all derivatives checked for the various cancer cell lines such as, cervical(HeLa0, breast (MDS-MB-231) , renal(ACCN) cancer cell line. 1, 3- Bis(3- benzylimidazo[1,2- a]pyridin- 2- yl)benzene is having very good activity against breast cancer cell line.

The cellular process like cell proliferation and differentiation the protein or receptor dimerization have lot of importance. Due to this , this dimerization is important in the cancer treatment. [79-80]

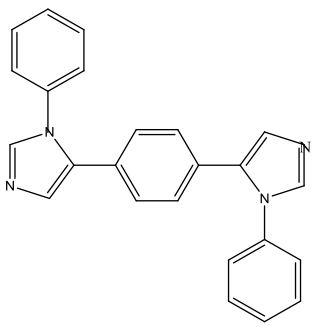

Figure 14 : 1, 4- Bis(1- phenyl- 1H- imidazol- 5- yl)benzene

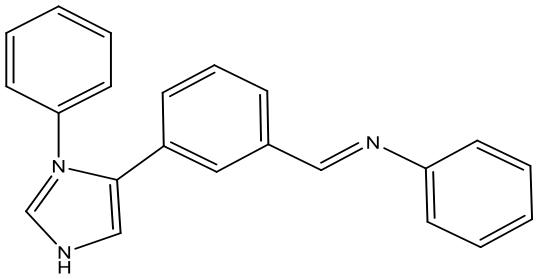

Figure 15 : (E)- N- (3- (1- Phenyl- 1H- imidazol- 5- yl)benzylidene)aniline

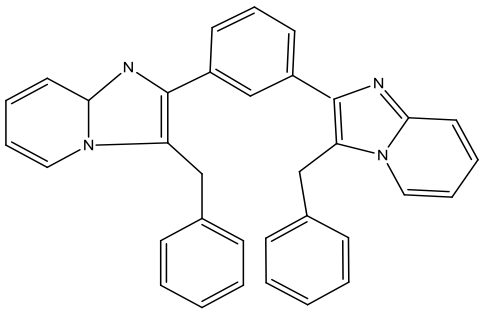

Figure 16: 1,3- Bis(3- benzylimidazo[1,2- a]pyridin- 2- yl)benzene

Ming Zhang, Yong Ding, Hong-Xia Qin, *et al.,* (2019) synthesized Pyrrole –imidazole using a post-ugi cascade reaction. The compound N‑ benz y l ‑ 2 ‑ (4 ‑ c h l o ropheny l)‑ 3 ‑ oxo ‑ 2 , 3 ‑ dihydro‑ 1H‑ pyrrolo[1,2‑ c]imidazole‑ 1‑ carboxamide showed anticancer active against human pancreatic cancer cell lines i.e. PANC and ASPC-I.

Ugi four-component reaction is a versatile and highly efficient synthetic route for heterocyclic compounds. [81-83]

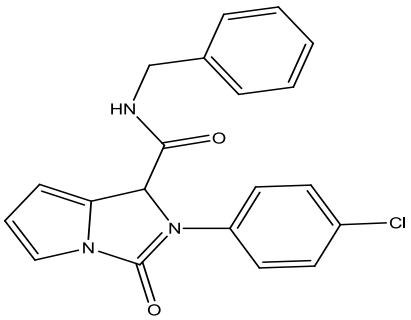

Figure 17:
N‑ benzyl‑ 2‑ (4‑ chlorophenyl)‑ 3‑ oxo‑ 2‑ dihydro‑ 1H‑ pyrrolo[1,2‑ c]imidazole‑ 1‑ carboxamide

Yibo Zhaoa,b Liqian Zhanga, Xu Lia , *et al.,* (2019) Ruthenium complexes is one of type of anticancer agents having greater activity for certain types of tumors and also work as a antimetastatic agent in cancer .[84,85] This article showed Synthesis of six rectangular metallacycles through the [2+2] coordination –driven self-assembly of 1,4-bis(imidazole-1-yl)benzene and 1,3-bis(imidazol-1-yl)benzene, along with dinuclear half-sandwich p-cymene ruthenium (II) acceptors [Ru2(μ-η4 oxalato)(η6-p-cymene)2](SO3CF3)2, [Ru2(μ- η4-2,5-dioxido-1,4-benzoquinonato)(η6-p-cymene)2](SO3CF3)2 and [Ru2(μ-η4-5,8-dioxido-1,4-naphtoquinonato)(η6-p-cymene)2](SO3CF3)2, respectively. The self-assembled macrocycles and cage which contain 5,8-dioxido-1,4-naphtoquinonato (donq) spacer having good anticancer activity against different cell lines such as HCT-116, MDA-MB-231,MCF-7 HeLa etc. with lower cytotoxicities in HBE and THLE-2 normal cells. [86]

Sourav Kalra,a Gaurav Joshi,b Manvendra Kumar, *et al..*,(2020) were synthesized various types of derivatives by using ethyl N-((Z)-2- amino-1,2-dicyanovinyl)formimidate. All the compounds were checked for activity against five cancer cell lines such as MDA- MA lines. 2-(3,4-Dimethoxyphenyl)-9-(4-fluorophenyl)-3,9-dihydro- 2H-purine-6-carboxamide and 9-(4-Fluorophenyl)-2-(4-isopropylphenyl)-9H-purine-6-carboxamide . This 2 molecules having good anticancer activity with does not having any toxic effect on normal cells and also showed inhibitory action on EGFR in vitro with IC_{50} 617.33 ± 0.04 nM for 1st molecule 710 ± 0.05 nM for second molecule as mentioned above. In this article the anticancer activity of imidazole and fused imidazole derivative was checked for their inhibitory action on epidermal growth factor receptor (EGFR) . EGFR plays important role in cell proliferation, migration and tumorigenesis. [87-90]

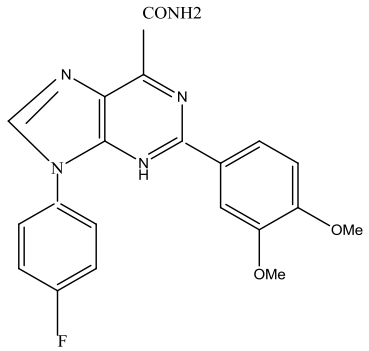

Figure 18: 2-(3,4-Dimethoxyphenyl)-9-(4-fluorophenyl)-3,9-dihydro- 2H-purine-6-carboxamide

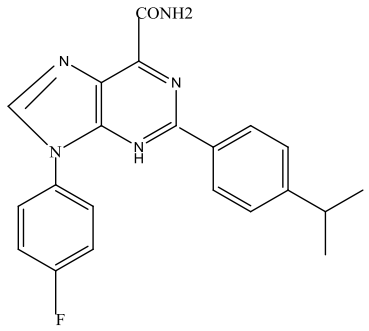

Figure 19 : 9-(4-Fluorophenyl)-2-(4-isopropylphenyl)-9H-purine-6- carboxamide

Behbood Taheri1, Mehdi Taghavi, Mansoreh Zarei , *et al..*,(in 2020) revels that imidazole derivatives showed cytotoxic activity against three human cancer cell lines such as MCF57(breast cancer) , HT29 (human colon cancer)and HeLa (Human cervical cancer) . As per the docking study DNA is set as a proposed target to check their binding interactions and binding energies and all the derivatives showed strong affinity to binds with DNA.

Carbacol is the major content in many natural alkaloids and synthetic derivatives and having anticancer (anti-microtubule agents) , anti-inflammatory[91-94]

Cigdem Karaaslan a , Fatima Doganc a , Mehmet Alp *et al..*,(in 2020) were performed by various types of compounds containing imidazole heterocycles e.g. Imidazopyridines , Imidazopyrimidines may exist more tautomeric form as compare to the benzimidazoles.[95] By using N-alkylations with 4- fluorobenzyl bromide under basic conditions i.e. K_2CO_3 their regioselectivities. As per this regioisomers were formed in the form of mixture and N-benzylation occurs on six membered heterocycles with greater ratio. The synthesized compounds also shows activity aginst human colon cancer and leukemia cell lines, as per the vitro study. 6-Bromo-2-[4-(4-methylpiperazin-1-yl)phenyl]-3H-imidazo [4,5-b]pyridine having bromine atom on 6^{th} position in the pyridine moiety having lowest IC_{50} value 6 to 7 µg/ ml against three types of cancer cell. [96]

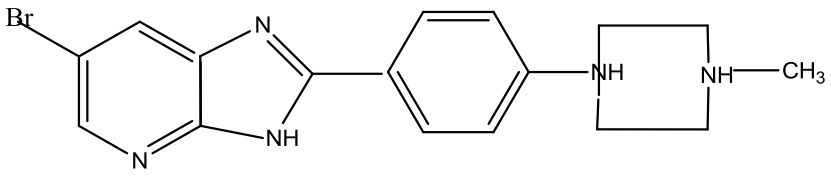

Figure 20 : 6-Bromo-2-[4-(4-methylpiperazin-1-yl)phenyl]-3H-imidazo [4,5-b]pyridine

Ya-Qun Yang, Hao Chen, Qing-Song Liu, Yue Sun, Wen Gu *et al..*,(in 2020) synthesized the 2-arylthio- and 2 arylamino -1H-Benzo [d] imidazole derivatives of dehydroabietic acid and characterized by using ^{1}H – NMR , IR , ^{13}C-NMR and MS analytical techniques. Some derivatives exhibit inhibitory activities against four types of cancer cell lines. They are HCT-116, MCF-7, HeLa and HepG2. From the all derivatives, Methyl (6R,9aS)-11-bromo-2-((4-cyanophenyl)amino)-6,9a-dimethyl-4,5,5a,6,7,8,9,9aoctahydro- 3H-phenanthro[1,2-d]imidazole-6-carboxylate shows very good activity with good IC_{50} values for 4 types of cancer cell lines. Along with this it increases intracellular reactive oxygen process, decrease the mitochondrial membrane potential etc. Phosphatidylinositol 3-kinase i.e (PI3K) is one of the most attractive therapeutic targets for cancer treatment by inhibiting cell growth, survival, proliferation, differentiation and invasion. [97-100]

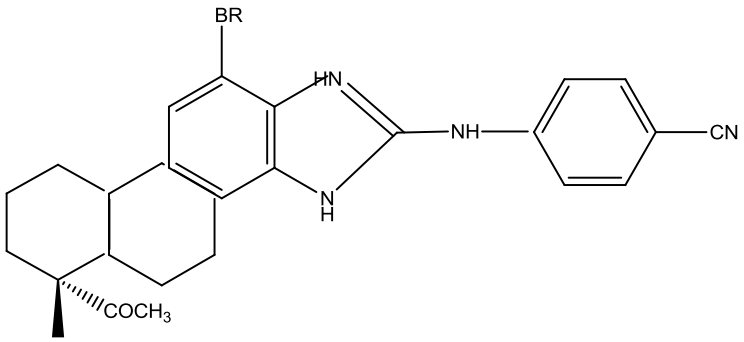

Figure 21 : Methyl (6R,9aS)-11-bromo-2-((4-cyanophenyl)amino)-6,9a-dimethyl-4,5,5a,6,7,8,9,9aoctahydro-3H-phenanthro[1,2-d]imidazole-6-carboxylate

Ali M. S. Hebishy, Mohamed Saleh Abdelfattah, Abdullah Elmorsy *et al..*,(in 2020) performed one-pot the synthesis of bis- and poly(imidazoles) was performes with three component reaction of 1,2-diketones with aldehydes and ammonium acetate using Zno as a catalyst was performed. The reaction is carried out by using

both conventional and microwave heating also [101,102] . The synthesized compounds were evaluated for human breast adenocarcinoma cell line, liver cell lines . Among from the synthesized compounds , the compound with bis(imidazole) i.e. bis(2-(4,5-di(furan-2-yl)-1H-imidazol-2-yl)phenoxy)alkanes analog containing 4,5-difuran rings shows potency against HepG-2 cancer cells with greater IC_{50} =8.14μM and high selectivity index SI= 27.47. The compound which contained six imidazole units means 2,2',2",2"',2""-((((6-((4-(4,5-diphenyl-1H-imidazol-2-yl)benzyl)oxy)benzene-1,2,3,4,5-pentayl)hexakis(methylene))hexakis (oxy))hexakis-(benzene-4,1-diyl))hexakis(4,5-diphenyl-1H-imidazole) shows greater activity against CaCo-2 cell line. [103]

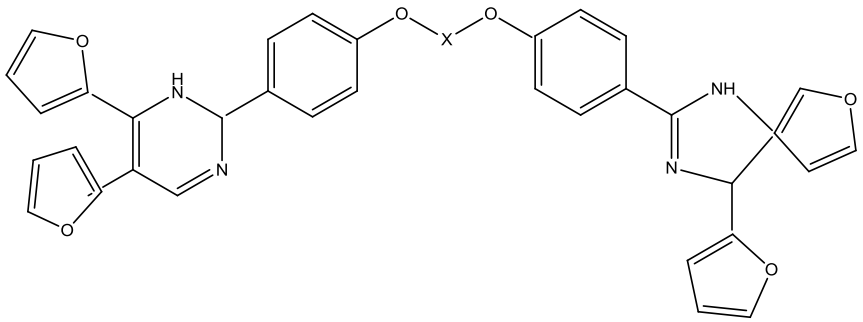

Figure 22 : bis(2-(4,5-di(furan-2-yl)-1H-imidazol-2-yl)phenoxy)alkanes

Fawzia Al-blewi , Salma Akram Shaikh , Arshi Naqvi *et al..*,(in 2021) reported the reaction of thiopropargylated – imidazole with organoazides in the presence of catalyst copper(I) . the reaction gave imidazole -1,2,3-triazole hybride containing various un or functionalized alkyl or aryl groups as a side chains, such as 4-(((1,4,5-Triphenyl-1H-imidazol-2-yl)thio)methyl)-1-undecyl-1H-1,2,3-triazole , 4-(((1,4,5-Triphenyl-1H-imidazol-2-yl)thio)methyl)-1-hexadecyl-1H-1,2,3-triazole, and 1-(4-Nitrophenyl)-4-(((1,4,5-triphenyl-1H-imidazol-2-yl)thio)methyl)-1H-1,2,3-triazole By using spectral techniques such as IR, NMR and elemental analysis all the derivatives were screened for their anticancer activity for four cancer cell lines by MTT assay method including $Caco_2$, HCT-116 , HeLa , MCF-7 etc. showed good activity. In the In- silico molecular modeling the prominent cancer target receptor i.e. glycogen synthase kinase-3β good binding ability with the potent compound i.e. 4-(2-(4-(((1,4,5-Triphenyl-1H-imidazol-2-yl)thio)methyl)-1H-1,2,3-triazol-1-yl)acetamido)benzoic acid. Depending upon the hybrid phamacophore approach , the library of novel imidazole -1,2,3 – triazole hybrids were designed and synthesized.[104-106]

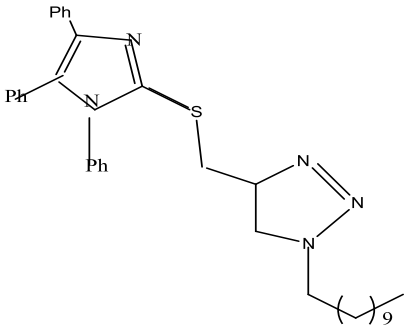

Figure 23 : 4-(((1,4,5-Triphenyl-1H-imidazol-2-yl)thio)methyl)-1-undecyl-1H-1,2,3-triazole

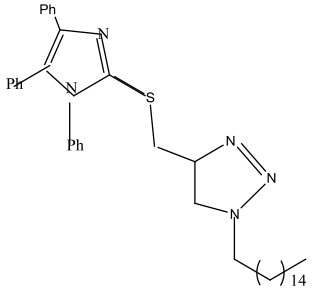

Figure 24: 4-(((1,4,5-Triphenyl-1H-imidazol-2-yl)thio)methyl)-1-hexadecyl-1H-1,2,3-triazole

Ameen Ali Abu-Hashem , Sami A. Al-Hussain and Magdi E. A. Zaki (in 2021) synthesiszed of new polycyclic aromatic compounds like, N-(thienotriazolopyrimidine) acetamide, 2-mercapto-thienotriazolopyrimidinones,2-(((thieno-triazolopyrimidine) methyl) thio) thieno-triazolopyrimidines and imidazopyrrolotriazolothienopyrimidines from the 2,3-diamino-6-benzoyl-5-methylthieno[2,3-d]pyrimidin-4(3H)-one as a starting material. These all compounds were screened for the various spectroscopic methods and elemental analysis. The series of Imidazole,Thiazine,Oxathii derivatives showed greater antiproliferative activity against, 4 types of human cancer cell lines – CNE2 (nasopharyngeal), KB(oral), MCF-7 (breast) and MGC-803 (gastric) carcinoma cells. 10-Benzoyl-9-Methyl-3-Phenyl-1H-[1,2,4]Triazolo[4’’’,3’’:1”,2”]Imidazo[4”,5”:30,40]Pyrrolo[1’,2’:2,3][1,2,4]Triazolo[1,5-a]Thieno[2,3-d]Pyrimidine-5,8-Dione and 7-Benzoyl-2-Mercapto-8-Methyl-1HImidaz [4”,5”:3’,4’]Pyrrolo[1’,2’:2,3][1,2,4]Triazolo[1,5-a]Thieno[2,3-d]Pyrimidine-9,12-Dione having good cytotoxicity for various types of human cancer cell lines. [107,108]

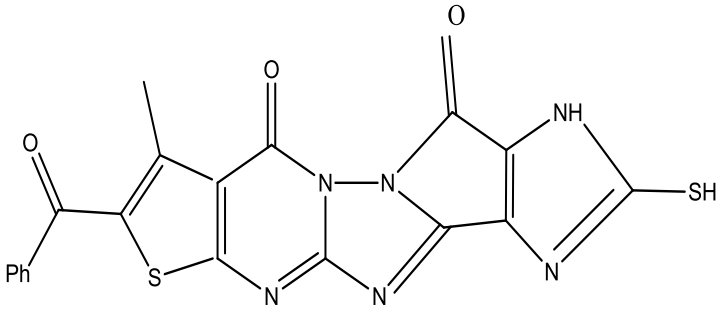

Figure 25 : 7-Benzoyl-2-Mercapto-8-Methyl-1HImidaz[4”,5”:3’,4’]Pyrrolo[1’,2’:2,3][1,2,4]Triazolo[1,5-a]Thieno[2,3-d]Pyrimidine-9,12-Dione

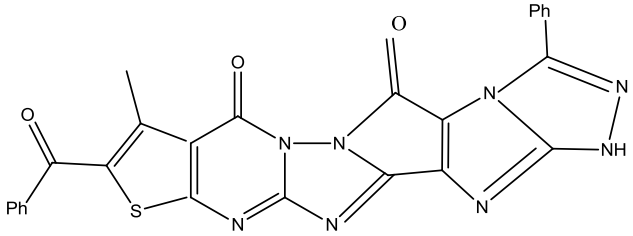

Figure 26 : 10-Benzoyl-9-Methyl-3-Phenyl-1H[1,2,4]Triazolo[4’’’,3’’:1”,2”]Imidazo[4”,5”:30,40]Pyrrolo[1’,2’:2,3][1,2,4]Triazolo[1,5-a]Thieno[2,3-d]Pyrimidine-5,8-Dione

Sara Rahimzadeh Oskuei a,b,1 , Salimeh Mirzaei c,1 , Mohammad Reza Jafari-Nik , *et al..*,(in 2021) showed that Normally, the imidazole-chalcone derivatives having more cytotoxic effect against A549 cancel cells as compare to the other 3 types. (E)-3-(1-benzyl-2-(methylthio)-1H-imidazol-4-yl)-1-(naphthalen- 2-yl)prop-2-en-1-one and (E)-3-(1-benzyl-2-(ethylthio)-1H-imidazol-4-yl)-1-(naphthalen-2- yl)prop-2-en-1-one having better cytotoxicity along with IC $_{50}$ = 7.05-63.43 μM on the 4 types of human cancer cell lines.These compounds also possess inhibitory action on tubulin polymerization. The antiproliferative activity of imidazole-chalcone was checked on different types of human cancer cell lines such as, A549 (adenocarcinoma human alveolar basal epithelial cells, HEPG2 (Human hepatocellular carcinoma cells) [109-110]

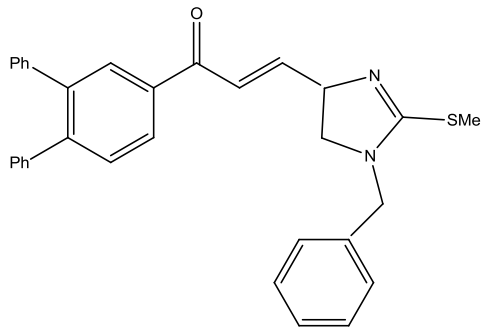

Figure 27: (E)-3-(1-benzyl-2-(methylthio)-1H-imidazol-4-yl)-1-(naphthalen- 2-yl)prop-2-en-1-one

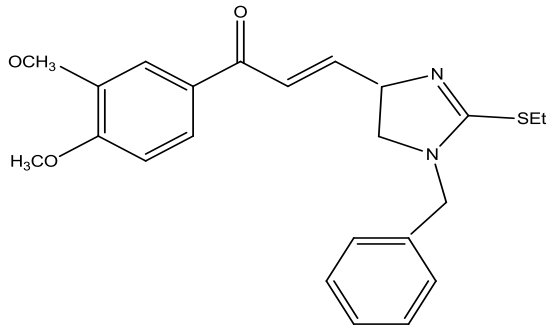

Figure 28 : (E)-3-(1-benzyl-2-(ethylthio)-1H-imidazol-4-yl)-1-(3,4,5- trimethoxyphenyl)prop-2-en-1-one

Eslam M.H. Ali , Mohammed S. Abdel-Maksoud *et al..*,(in 2021) developed potent BRAF ^{V600E} inhibitors. By using Dabrafenib , the series of of 38 4-(1-H- imidazole -5-yl)pyridine 2-amine derivatives were synthesized for the evaluation as an anticancer agents against human cancer cell line, NCI 60 . two compounds N-(3-((4-(4-(3-methoxyphenyl)-2-phenyl-1H-imidazol-5-yl)pyridin-2-yl)amino)propyl)-4-(trifluoromethyl)benzenesulfonamide (14h) and 3-chloro-N-(3-((4-(4-(3-hydroxyphenyl)-2-phenyl-1H-imidazol-5-yl)pyridin-2-yl)amino)propyl)benzenesulfonamide showed good anticancer activity with IC_{50} = 2.4μ M. and 3.6μM respectively. The compounds also having good activity against melanoma cell line. The compounds N-(2-((4-(4-(3-hydroxyphenyl)-2-phenyl-1H-imidazol-5-yl)pyridin-2-yl)amino)ethyl)-4-methoxybenzenesulfonamide showed AF^{V600E} kinase inhibitory action with IC_{50} values 76 nM. In RAF kinase the pathological mutation generally occurs to BRAF. [111] In various malignant tumours BRAF ^{V600E} mutation is detected. [112-114]

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ANTI ANGIOGENESIS ACTIVITY

Gopinath Gudipudi , Sagurthi Someswar. R , Shyam Perugu , *et al..*,(in 2014) synthesized 2-(substituted 2Hchromen-3-yl)-5-aryl-1H-imidazoles, a novel compound and its derivatives. Reaction of the chromene-3-carboxylic acids along with substituted acyl bromides in the presence of TEA. After that with NH4OAc in toluene. The compounds like (2H-chromen-3-yl)-5-phenyl-1H-imidazole and 5-(4-Chlorophenyl)-2-(2H-chromen-3-yl)-1H-imidazole were screened by in vitro for inhibition of KRAS/ Wnt and their anti-angiogenesis property. The compounds like 5-((Benzyloxy) phenyl)-2-(5-methoxy-2H-chromen-3-yl)-1H-imidazole having anti-angiogenesis when screened for the inhibition of KRAS/Wnt . Synthetic heterocyclic compounds containing N and O_2 are commonly used as anticancer agents with anti-angiogenesis as the mode of action. Tumor angiogenesis is a complex dynamic process required for the growth of all tumors. The imidazole moiety is present in a wide range of naturally occurring compounds such as isoflavones which are considered as a potential anti-angiogenic agent. 2-(substituted 2H-chromen-3-yl)-5-aryl1H-imidazoles are structurally similar to the isoflavones. [115-116]

Hakan Unkar, Gokhan Dikmen and Hulya Tuba Kiyan *et al..*,(in 2021) synthesized The 1-(4-(trifluoromethyl)benzyl)-1H-imidazole, ($ImCF_3$) and 2,2′-bipyridyl, (bipy) ligands coordinating copper(II) complex and characterized by using x-ray diffraction , FT-IR and UV-vis and elemental analysis techniques. The electrophilic and nucleophilic nature of Copper (II) complex were therotically determined along with its local and global chemical activity. From the anti-angiogenic activity results it was conclude that,Copper have very good anti-angiogenic activity as compared to that of activity of thalidomide (Average score for copper (II) is 1.06 ± 0.01.It also have no irritation potential and embryo toxicity .[117]

ANTI- OXIDANT ACTIVITY

Ramin Ghorbani-Vaghei, Jafar Mahmood *et al.*, (2018) Synthesized Tri- and tetra-substituted imidazole compounds by in situ oxidation–condensation in the presence of catalytic amount of $H_2PW_{12}O_{40}^-$ loaded on the ionic liquid-functionalized magnetic nanoparticles. Then the antioxidant and antifungal activities of the new imidazoles compounds were evaluated. The effectiveness of the samples as DPPH radical scavengers was confirmed by the measured IC_{50} values and thiophenyl-containing product 4,5-Diphenyl-2-(thiophen-2-yl)-1-(p-tolyl)-1H-imidazole showed the best IC_{50} of 0.12 when compared to the standard ascorbic acid.[118]

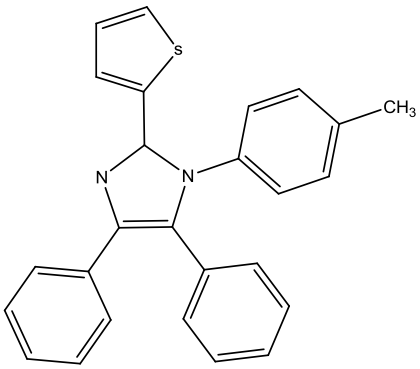

Figure 29 : 4,5-Diphenyl-2-(thiophen-2-yl)-1-(p-tolyl)-1H-imidazole

Harshad Brahmbhatt, Maja Molnar *et al.*,(2018) synthesized a reaction of benzil, ammonium acetate and different derivatives of 1*H*-pyrazole-4-carbaldehyde. Structures of the synthesized entities were confirmed with the support of modern techniques like elemental analysis (CHN) and spectral analysis (FTIR, ^1H and ^{13}C NMR and LC–MS). All compounds were screened for their biological potency: antibacterial activity using a serial

broth dilution method and antioxidant activity using the DPPH method. From all the synthesized compounds 4-(4,5-Diphenyl-1H-imidazol-2-yl)-1,3-di-p-tolyl-1Hpyrazole showed good antioxidant activity. [119]

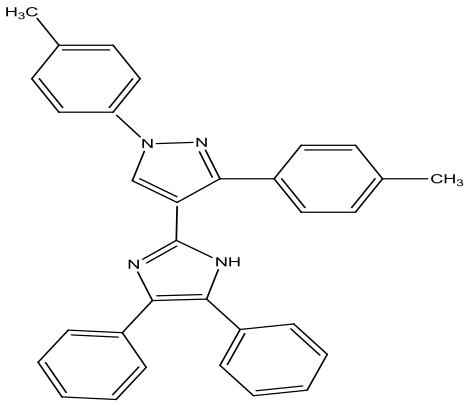

Figure 30 : 4-(4,5-Diphenyl-1H-imidazol-2-yl)-1,3-di-p-tolyl-1Hpyrazole

Samra Farooq , Ihsan-Ul Haq , Naseem Ullah *et al..*,(2021) synthesized a new series of mannich base derivatives of 2-phenyl-2-imidazoline. The synthesized compounds were characterized by using spectroanalytical techniques. These derivatives were evaluated for their anti-oxidant activity a-amylase enzyme inhibition, antimicrobial activity. 4-Methoxy-N-((2-phenyl-4, 5-dihydro-1H-imidazol-1- yl) methyl) aniline showed good activity in % FRSA against DPPH free radical at IC50 of 148.16 ± 2.81 mg/mL. N-(4-hydroxyphenyl)-N-((2-phenyl-4, 5-dihydro-1Himidazol-1-yl) methyl) acetamide showed good antioxidant activity in TRP assays. 4-((2-Phenyl-4, 5-dihydro-1H-imidazol-1-yl) methyl) morpholine and . 4-Bromo-N-((2-phenyl-4, 5-dihydro-1H-imidazol-1-yl) methyl) aniline exhibited potent effect against a-amylase enzyme at IC50 value of 9.20 ± 0.48 and 10.25 ± 0.43 mg/mL respectively. [120]

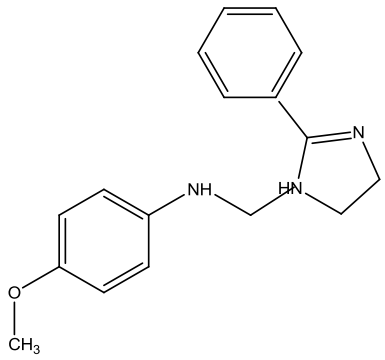

Figure 31: 4-Methoxy-N-((2-phenyl-4, 5-dihydro-1H-imidazol-1-yl) methyl) aniline

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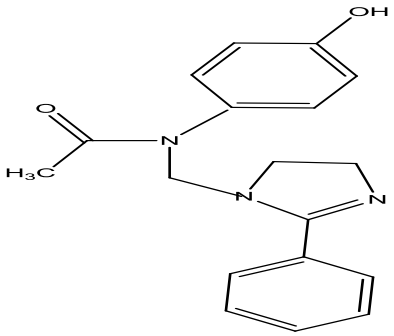

Figure 43: N-(4-hydroxyphenyl)-N-((2-phenyl-4, 5-dihydro-1Himidazol-1-yl) methyl) acetamide

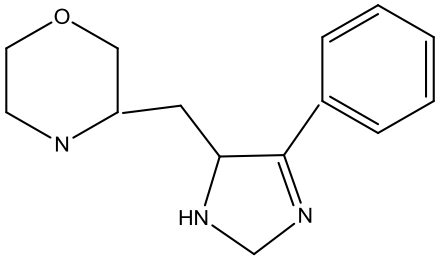

Figure 44: 4-((2-Phenyl-4, 5-dihydro-1H-imidazol-1-yl) methyl) morpholine

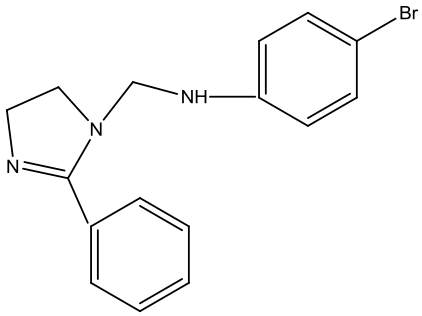

Figure 45: 4-Bromo-N-((2-phenyl-4, 5-dihydro-1H-imidazol-1-yl) methyl) aniline

Conclusion

The conclusion of this review article is to review and highlight the pharmacological activities of Imidazole heterocyclic nucleus as a multifunctional moiety. This article revels the study of Imidazole having as an anti-cancer , as an anti- oxidant and as an Anti-angiogenesis properties. This review also covers the synthesis methods for imidazole and its derivatives which are reported in recent years . This review article will be helpful to overlook the synthetical and pharmacological activity of imidazole and its various derivatives.

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The list of references should only include works that are cited in the text and that have been published or accepted for publication. Examples of the ***Journal of Medicinal and Chemical Science***s reference style are shown below (**Font:** Time New Roman 9).

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