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# A short overview of N-Heterocycle based FDA approved anti-cancer drugs

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**Abstract:** As per WHO report 202, cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths. Socancer remains one of the major public health burdensworldwide. It is characterized by the abnormal growth of cells that can affect any part of the body. Thereare drugs available in the market to treat the various types of cancer but none of drugscan be considered as fully effective and safe. So efforts are on to develop new molecules which can be safer and more effective. The present review article describes the status of FDA approved drugs and their synthetic methods.

## 1.1. Introduction

Cancer is a bunch of diseases resulting from the abnormal growth of the cells. Basically, the cells are the basic units of life and they grow and multiply according the need of the body in a regulated manner. Cancer starts when the cells grow uncontrollably and this uncontrolled growth leads to the formation of a mass termed as tumour.[1] Based on its potential to spread cancer is of two types-[2]

1. benign is a tumour that can grow but cannot spread to the other body parts and

2. malignant is a tumour that can grow as well as can spread to the other body parts and hence called cancerous tumour.

The spreading of tumour or cancerous cells to the other body parts through blood stream is known as metastasis. Medically, there are four types of cancers-[3]

1. Carcinomas includes prostate cancer, breast cancer, lung cancer, and colorectal cancer generally occurs in the skin of the internal organs and glands.

2. Sarcomas occurs in the connective tissues like fat, muscles, nerves, tendons, joints, blood vessels, lymph vessels, cartilage, or bone,

3. Leukaemia includes acute lymphocytic leukaemia, chronic lymphocytic leukaemia, acute myeloid leukaemia, and chronic myeloidleukaemia and is a cancer of the blood and

4. Lymphomas arises in the lymphatic system causing Hodgkin lymphoma and non-Hodgkin lymphoma. According to the recent report by World Health Organization, cancer is the second leading cause of death worldwide and in 2018, 9.6 million deaths were estimated. In India, 375,500 deaths of males and 326,300 deaths of females were reported by 2014 caused by this disease.[4]

In India, males are generally suffered by mouth, oropharynx, trachea, bronchus and lungs while females are suffered by cancer of breast and cervix uterine (http://www.who.int/cancer/country-profiles/en/). The factors causing cancer include chemicals also known as carcinogens (like tobacco causes 90% of lung cancer and 25-30 % deaths occur in tobacco consuming cases), obesity (30-35 % cancer deaths are related to physical activity), infection (18 % deaths), radiation (10 % deaths), heredity and hormones.[5]

## 1.2 Biology of cancer

There are six main hallmark features of cancer –

**1.** Immortality

The absence of ageing is biological immortality. In particular, it is the lack of a consistent rise in death rate as a function of chronological age. A cell or organism is biologically immortal if it either never ages or eventually stops ageing.[6]

**2.** Growth factors from oncogenes i.e., It Produces 'Go' signals.[7]

**3.** Anti-growth signals from tumour suppressor genes i.e., Dominate 'Stop' signals.[8]

**4.** Apoptosis i.e., Multicellular organisms experience a sort of planned cell death.[9]

**5. Angiogenesis**

The generation of new blood vessels is known as angiogenesis. Endothelial cells, which line the inside of blood arteries, move, proliferate, and differentiate throughout this process. Chemical cues in the body govern the angiogenesis process.[10]

**6. Metastasis**

In normal cells, the cell division is based on telomeres which are present in the form of hexanucleotide repeated sequence of DNA at the end of chromosomes. During cell division, some of the repeats are lost at the time of replication as DNA polymerase is not able to replicate DNA at the end and thus telomeres become sorter.[11] On the other hand, cancer cells activate telomerase, an enzyme that synthesise telomeres at the end and hence cancer cells are able to divide limitlessly. In general, the cells grow in the presence of growth factors using proper signalling with growth factor receptors and intracellular signalling molecules. However, cancer cells are able to produce mutant proteins called as oncogenic proteins which in normal case

are known as proto-oncogenic proteins. These oncogenic proteins are formed by mutations, chromosomal rearrangements, viral insertion, gene amplifications etc. and resemble growth signals. Therefore, cancer cells can grow indefinitely as not dependent on growth factors to divide.

These growth factors include the EGF, FGF, IGF, PDGF receptors (Epidermal Growth Factor, Fibroblast Growth Factor, Insulin Growth Factor, Platelet-Derived Growth Factor respectively). In some cases, overexpression of growth factor receptor leads to uncontrolled growth of cancer cells (like HER2/ neu receptor). C-crk (cell cycle related kinases) proteins function as to transfer substrate proteins to the tyrosine kinase receptors (TKR). The viral oncoprotein, Bcr-Abl, mimics substrate for c-crk, resulting in indefinite activation of the tyrosine kinase receptors leading to cell proliferation as in case ofchronic myelogenous leukaemia (CML).

Ras is another oncogenic protein that is generated through point mutation of normal Ras leading to constant activation of proliferation status.[12] Unlike to growth factors that signal cells to grow there are signals that tell cells to stop growing. These genes are known as Tumour suppressor genes that encode proteins involve in checking cell division in normal case. Conversely, in cancer cells mutation in these genes occurs which leads to loss of function in proteins encoded by these genes resulting in constant growth. Two examples of tumour suppressor protein are retinoblastoma (Rb) protein (paediatric tumours found in the retina of the eye) and p53 (its loss of function leads to tumour formation).[13] Programmed cell death or apoptosis is a suicidal process that occurs to maintain cellular homeostasis.

Cancer cells can avoid apoptosis to happen in several ways.

The four ways we discussed above are involved in the progression of cancer cells or we can say in tumour formation. Now the point is how tumours survive.

All the cells and tissues get their nutrients and oxygen to survive from nearby blood supply or capillaries the term known as angiogenesis.[14] Cancer cells activate signalling molecules involved in angiogenesis and hence turn on this process. It has been shown that without angiogenesis tumour cannot grow larger than the size of pea.[15] We discussed about how tumour is formed and grown now we talk about its spreading also known as metastasis.

The tumours originate at one place but spread to other body parts where these are termed as secondary tumours or metastases. These metastases are actually responsible for about 90 % of death due to cancer. Metastasis involves processes such as invasion to break membrane barrier, intravasation to get into circulatory system, transport, extravasation to enter new tissue environment, micrometastasis and colonization. Several molecules generally participate to accomplish these processes such as cell-cell adhesion molecules and integrins for invasion, and Matrix MetalloProteinases for colonization.[16]

Collectively, we can say that there are a number of signalling molecules as well pathways that are involved in tumour formation and its progression. Cancer is

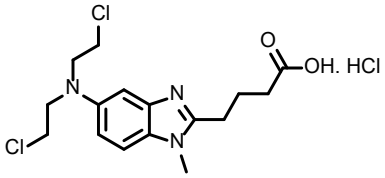
a complex disease and hence to treat it there are multiple ways to target. Several drugs have been approved by FDA (Food and Drug Administration) to treat cancer targeting any of hallmarks described above.

Clones with unfavourable compositions of genetic or epigenetic alterations (blue) will be eliminated after primary therapy. Resistant clones (pink) with survival advantages are indicated. Orange: normal cells; coloured-outline: pre-malignant lesion, blue, pink, green, dark brown: different malignant.[17]

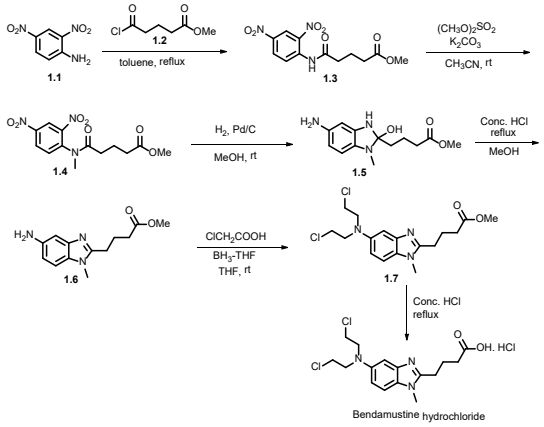
In view of our review literature, we will be discussing FDA approved drugs containing five membered heterocyclic rings. Additionally, we will be explaining their mode of action and pharmacological properties subsequently. The significant use of these drugs indicates how important is to study and synthesise molecules having five membered rings.

## 1. Bendamustine

Bendamustine (Treanda, Cephalon, U.S. Biopharmaceutical Company) was approved by FDA on March 2008 to cure chronic lymphocytic leukaemia (CLL) (FDA022249s014). Moreover, on October 2008 it got the approval for the treatment of indolent B-cell non-Hodgkin's lymphoma. In addition, it is also used in lung cancer and multiple myeloma in combination therapy. It was synthesized in 1963 by Ozegowski and Krebs in East Germany.[18] Since it belongs to a class of nitrogen mustard it causes some adverse effects like nausea, fatigue, vomiting, and loss of appetite, cough, fever and constipation.[19] Though its mode of action is not clear to date yet it causes DNA damage and inhibition in DNA repair in cancer cells.[20]



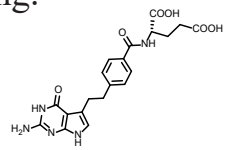

The synthesis of **bendamustine** involved six step processes. Firstly, the 2, 4-dinitroaniline is treated with methyl glutaryl chloride in toluene under reflux condition forming intermediate **1.3**. In the next step, the methylation of intermediate **1.3** with dimethyl sulphate occurs and a base potassium carbonate in acetonitrile for the formation of intermediate **1.4**. Then, the hydrogenation and cyclization were carried out with Pd/C in methanol at room temperature leading to the formation of intermediate **1.5**. Subsequently, dehydration process with conc. HCl of **1.5** takes place which leads to the formation of intermediate **1.6**. Thereafter, a mixture of **1.6**, chloroacetic acid and THF was stirred to dissolve solids and then Borane-THF was added for 1-3 h, at RT to afford compound **1.7**. **Bendamustine Hydrochloride** was prepared from **1.7** and conc HCl (3 L) and then it was heated to reflux for 4 h.[21]



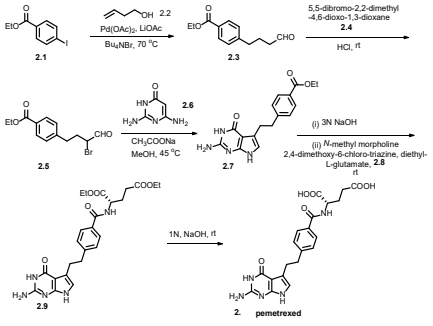

**Scheme 1: Synthesis of Bendamustine**

## 2. Pemetrexed

Pemetrexed (Alimta, Eli Lilly and Company) was approved previously to treat malignant pleural mesothelioma on February 2004 however in September 2008 it got approval for metastatic non-small cell lung cancer (NSCLC) generally in combination with Cisplatin.[22] Since it has chemical resemblance with folic acid it can inhibit thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase enzymes of nucleotide synthesis and hence inhibit DNA and RNA synthesis. Conversely, it shows few side effects such as loss of appetite, mental fatigue, low blood count nausea and vomiting.[23]



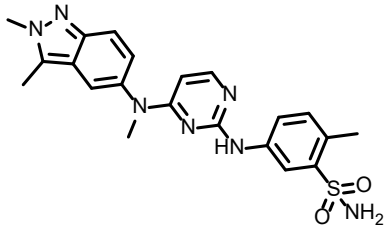
The synthesis of Pemetrexed is revealed in **scheme 2**. The first step of this reaction is Heck coupling reaction betweenethyl 4-iodobenzoate**2.1**and commercially available prop-2-en-1-ol**2.2** in the presence of palladium acetate, lithium acetate and tetra-butyl ammonium bromide at 70 °C affording the unsaturated, coupled alcohols that reorder to the vinyl alcohols and tautomerise to give aldehydes**2.3**. α-Bromonation of **2.3**with 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane to give **2.4**in hydrochloride at room temperature afforded α-bromo aldehydes **2.5**. Subsequently, compound **2.7**synthesize by condensation of **2.5** with 2,6-diamino-6,4-oxopyrimidine**2.6** at 45 ° C in the presence of sodium acetate.In the next step, hydrolysis with 3 N NaOH followed by coupling with diethyl L-glutamate using *N*-methylmorpholine and 2,4-dimethoxy-6-chlorotriazine **2.8**as theactivating agents corresponding**2.9**. Final saponification of the **2.9** with 1 N NaOH deliver target compound**2.**[24]



**Scheme 2: Synthesis of pemetrexed**

## 3. Pazopanib

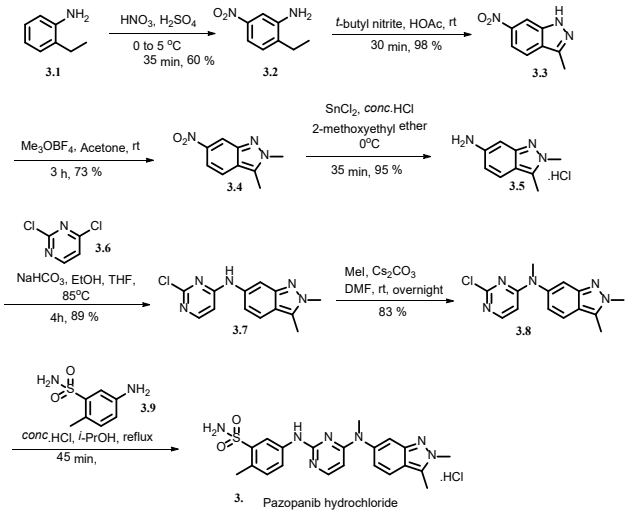
Pazopanib(Votrienttm,laxoSmithKline) was first approved by FDA on October 2009 for renal cell carcinoma and soft tissue sarcoma.



In strongly inhibits tyrosine kinase thereby inhibiting growth of tumour and it also impedes angiogenesis. Together with targeting tyrosine kinase it also inhibits other kinases like c-KIT, FGFR, PDGFR and VEGFR.[25] It has not shown activity against adipocytic STS or gastrointestinal stromal tumours (GIST). However, its overdose causes hypertension and fatigue.[26]

Pazopanib **3.10** is earlier synthesised by a route displayed in **Scheme 3**. In the first step the nitration of 2-ethyaniline takes place with the nitric acid and sulphuric acid at 0-5 °C to form compound **3.2**. Then the synthesis involves cyclization of 2- ethyl-5-nitroaniline **3.2** which is used

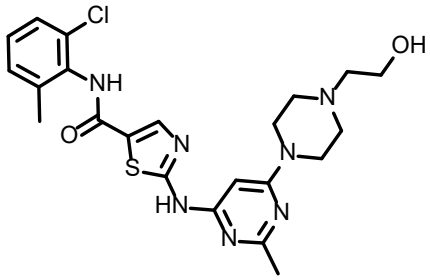
as a diazotizing reagent tert-butyl nitrite to afford 3-methyl-6-nitro-1Hindazole **3.3**. Regioselective methylation of **3.3** with trimethyl oxoniumtetraflouroborate provides intermediate **3.4**. The nitro functionality of **3.4** is reduced using tin (II) chloride to create 6-amino-2,3-dimethyl-2H-indazole hydrochloride **3.5** and subsequent addition of a 2,4-dichloropyrimidine **3.6** in the presence of sodium bicarbonate to the **3.5** afford **3.7**. Methylation of **3.7** with methyl iodide and cesium carbonate in DMF generate N-(2- chloropyrimidin-4-yl)-N,2,3-trimethyl-2H-indazol-6-amine **3.8**. Finally, condensation of N-(2-chloropyrimidin-4-yl)- N,2,3-trimethyl-2H-indazol-6-amine **3.8** and 5-amino-2-methylbenzenesulfonamide**3.9**in the presence of a catalytic amount of HCl is execute to afford pazopanib **3.** in six steps overall.[27,28]



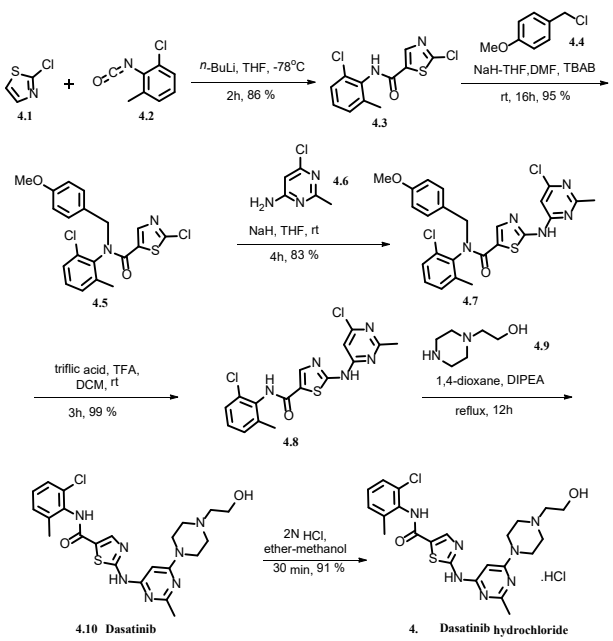

**Scheme 3: Synthesis of Pazopanib**

## 4.Dasatinib

**Dasatinib (**Sprycel by Bristol-Myers Squibb) was approved by FDA on October 2010 to cure blood cancer. It is an oral medication used to treat chronic myelogenous leukaemia (CML) and acute lymphoblastic leukaemia generally for those who are positive for Philadelphia chromosome.[29] Since it is a tyrosine kinase inhibitor it can block Bcr-Abl and the Src kinase family and hence hamper tumour growth.[30] Despite its common use it can lead to abnormally high blood pressure of lungs (pulmonary hypertension) as announced by FDA in 2011.



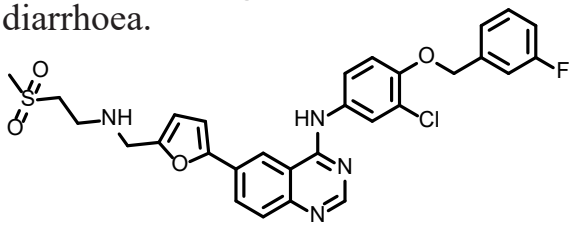
The process to make dasatinib monohydrate is shown in **Scheme 4**. The first step of synthesis in Scheme 4 is of 2-chlorothiazole **4.1** which underwent subsequent nucleophilic reaction with 1-chloro-2-isocyanato-3-methylbenzene **4.2** to afford the compound 2-chloro-N-(2-chloro-6-methylphenyl) thiazole-5-carboxamide **4.3**. Then protection of amide group in **4.3** with 4-methoxybenzylchloride **4.4** gives intermediate **4.5**. Compound 4.5 and 6-chloro-2-methylpyrimidin-4-amine **4.6** under basic medium give an intermediate compound **4.7**. Furthermore, deprotection of the para-methoxybenzyl group of **4.7** in the presence of triflic acid provide the last but one intermediate, **4.8**, which on coupling with 2-(piperazin-1- yl) ethan-1-ol (HEP) **4.9 in** dioxane, afford dasatinib-free base **4.10**. **4.10** in 2N HCl, ether/methanol medium transformed into hydrochloride salt **4.**[31,32]



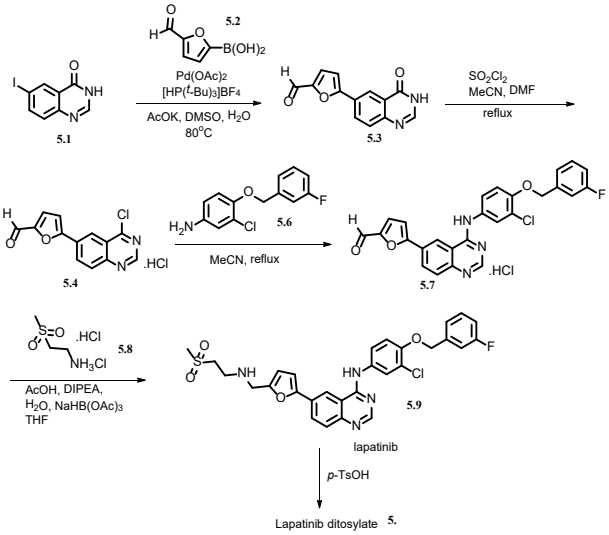

**Scheme 4: Synthesis of Dasatinib**

## 5. Lapatinib

Though Lapatinib (Tykerb by GlaxoSmithKline) was granted FDA approval on March 2007 for breast cancer but in 2010 it got accelerated approval to treat postmenopausal women with hormone receptor positive metastatic breast cancer withup regulated HER2 receptor in combination with letrozole [Femara, Novartis Pharmaceuticals Corp.].[33] It has been shown to inhibit tyrosine kinase inhibitor related to EGFR (epidermal growth factor receptor) and HER2/neu (human EGFR type 2).[34] In spite of its common use it has adverse effects like fatigue, nausea, rashes and diarrhoea.



The synthetic route of Lapatinib is described in **Scheme 5**. Initial step is coupling reaction between commercially available starting material 6-iodoquinozolinone **5.1** and 5-formyl-furon-2-ylnoronic acid **5.2** in the presence of palladium metal and phosphine ligand afforded intermediate **5.3.** Then, the chlorination of compound **5.3**with the sulfonyl chloride provides intermediate **5.4**. Subsequently, **5.4** treats with compound **5.6** in acetonitrile under the reflux condition to produce compound **5.7** thereafter 2-(methylsufonyl) ethanamine**5.8** reacts with compound **5.7** to provide lapatinib **5.9**. Final step of the formation of lapatinib ditosylate is the reaction of **5.10** with **5.9** along with TsOH.[35,36]

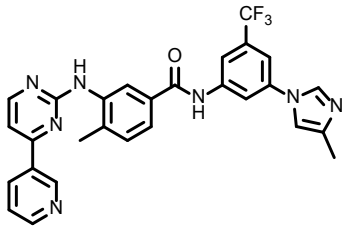



**Scheme 5: Synthesis of Lapatinib**

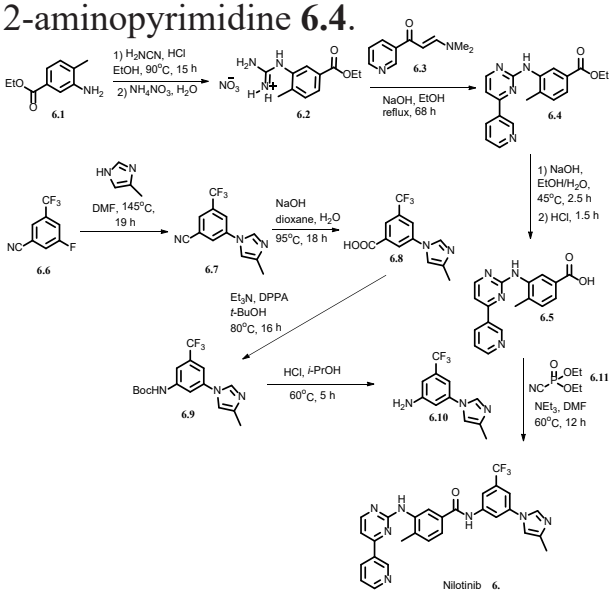
## 6. Nilotinib

**Nilotinib (**AMN107, trade name Tasigna by Novartis Pharmaceuticals Corporation**)** is an orally administered drug which was earlier approved by FDA in 2007 to treat chronic phase chronic myeloid leukaemia (CP-CML) but got accelerated approval in2010

forPhiladelphia chromosome positive CML.[37] It is a tyrosine kinase inhibitor but mainly inhibit Bcr-Abl kinase.[38] Though it shows fewer pulmonary related affects but shows diffuse alveolar haemorrhage of patients administered with nilotinib.



The synthesis of Nilotinib is explained in **Scheme 6**. Initial step is guanidine formation by ethyl-3-amino-4-methylbenzoate **6.1** and cyanamide provided the nitric acid salt of **6.2**which was easily isolated by filtration. In next step, a standard condensation reaction between enone**6.3** and the guanidine **6.2**, analogous generates the 2-aminopyrimidine **6.4**.

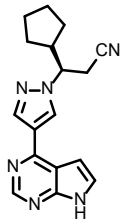



**Scheme 6: Synthesis of Nilotinib**

The ethyl ester group of compound**6.4** is then hydrolysed to the resultant carboxylic acid **6.5** and coupled with aniline fragment **6.10** using diethylphosphorocyanidate**6.11** as the agent to yield nilotinib **6.12**. A four-step procedure to produce the aniline fragment **6.10**starting from the commercially available 3-fluoro-5-trifluorobenzonitrile **6.6** is also designated. The first step includes nucleophilic aromatic substitution of 5-methylimidazole to give intermediate **6.7**. Then the hydrolysis of the nitrile takes place to produce compound **6.8**. 6.8 is further processed via Curtius rearrangement in the presence of triethylaminein *t*-BuOHresulting in the formation of the Boc protected aniline **6.9**. The desired compound **6.10** was acquired after simple acid catalysed deprotection with hydrochloride.[39,40]

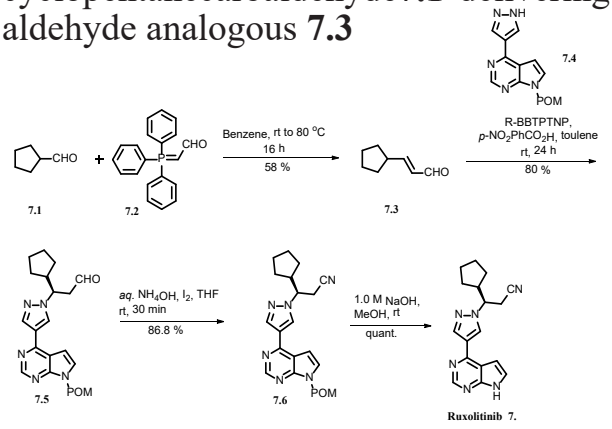
## 7. Ruxolitinib

Ruxolitinib (Jakafi oral tablets by Incyte Corporation) is an oral drug used to treat ntermediate and high-risk myelofibrosis, including primary myelofibrosis, post-polycythemiavera myelofibrosis and post-essential thrombocythemia myelofibrosis (bone marrow cancer) approved by FDA on November 2011. In addition, in 2014 it was approved for polycythemiavera (it is condition where bone marrow produces large number of RBCs). It targets janus kinase pathway leading to irregularities in JAK signalling associated with myelofibrosis.[41] Besides, it shows some side effects such as thrombocytopenia, pancytopenia, anaemia and neutropenia.



The process for synthesis of Ruxolitinib was defined in **scheme 7**.[42] The synthesis

is started with Wittig olefination of cyclopentanecarbaldehyde**7.1** delivering aldehyde analogous **7.3**

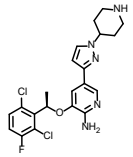



**Scheme 7: Synthesis of Ruxolitinib**

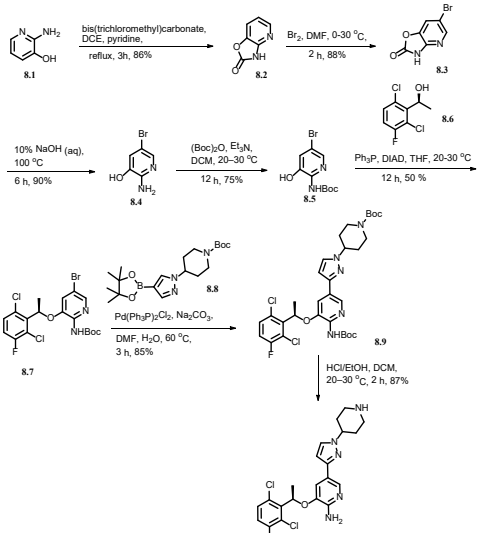
which was followed by aza-Micheal addition reaction with POM-protected **7.4** to produce intermediate **7.5.7.5** further reacts with ammonium hydroxide which converts aldehyde group to corresponding nitrile group. In the next step, the POM group is removed from compound **7.6** by sodium hydroxide leading to the formation of **Ruxolitinib**.

## 8.Crizotinib

Crizotinib ((XALKORI Capsules, Pfizer Inc.) got FDA approval for the treatment of non-small cell lung carcinoma (NSCLC) associated with mutation in anaplastic lymphoma kinase (ALK) gene on August 2011. It inhibits ALK to suppress tumour growth. Basically, its aminopyridine structure binds competitively within ATP-binding pocket of target kinase enzyme.[43] Moreover, in 2016 FDA announced its use for ROS1 (proto-oncogene tyrosine-protein kinase ROS)-positive non-small cell lung cancer.[44] The common side effects include vomiting, nausea and diarrhoea.



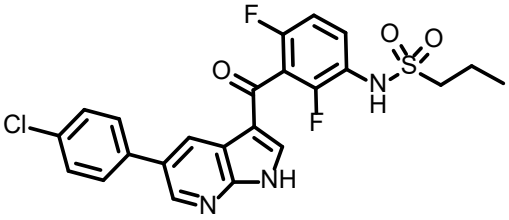
The routes of **Crizotinib**synthesis aredescribed in **scheme 8**.[45] The synthesis is initiated with 2-aminopyridin-3-ol **8.1**, (which is commercially available) react withbis(trichloromethyl)carbonate (BTC) to provide oxazole compound **8.2** in 86% yield. Bromination of **8.2** takes placeregioselectively by reacting with bromine at 0-30 °C to generate bromide **8.3** in 88% yields. Then the hydrolysis of **8.3**occursin the presence of 10%NaOH solution to afford**8.4** in 90% yield, which was followedby the protection of amino group in **8.4**by Boc group to give**8.5** in 75% yield. After that**8.5** and **8.6**are coupled*via*Mitsunobucondition to generate intermediate **8.7** in 50% yield. This reaction was followed suzuki coupling reaction of intermediate **8.7** with boronate analogous **8.8** by using $Pd(Ph_3P)_2Cl_2$ as catalyst in DMF, to produce Di-Boc protected compound **8.9** in 85% yield. Finally, removal of the Boc groups from **8.9** with HCl in ethanol occurs to create **Crizotinib8** in 87%.



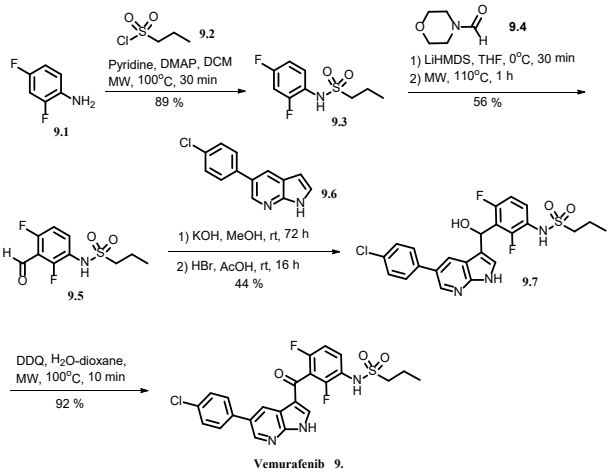

**Scheme 8: Synthesis of Crizotinib**

## 9. Vemurafenib

FDA approved Vemurafenib (Zelboraf, Hoffmann-La Roche Inc.)on August 2011 for the treatment melanoma of late-stage. It impedes the activity of a B-Raf enzyme encoded by BRAF gene which is essential for the growth of the cells.



Basically, if BRAF is mutated it causes cancer. This drug is applicable to melanoma caused by V600E BRAF mutation and in some cases V600K BRAF mutationhowever can trigger growth of tumor with other mutations. Moreover, in 2017 this drug got approval for histiocytic neoplasm.[46]

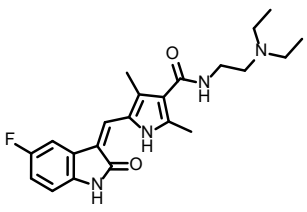



**Scheme 9: Synthesis of Vemurafenib**

The synthesis of Vemurafeenib is explained in **Scheme 9** which initiates with reaction of 2, 4-difluoroaniline **9.1** and propane-1-sulfonyl chloride **9.2** in the presence of anhydrous methylene chloride, dimethyaminopyridine (DMAP), and pyridine resulting in the formation of intermediate **9.3**.Next step is formylation of intermediate **9.3** with morpholine-4-carbaldehyde using LiHMDS in THF which subsequently is heated in MW at 100 °C to provide intermediate **9.5** which further react with **9.6** in the presence of potassium hydroxide and methanol, frequently yielding mixed by-products.Besides, deprotection of the methyl ether intermediate (structure not shown) with aqueous hydrogen bromide and acetic acid to the compound**9.7**. Compound **9.7**is oxidised to **Vemurafenib9.**[47]

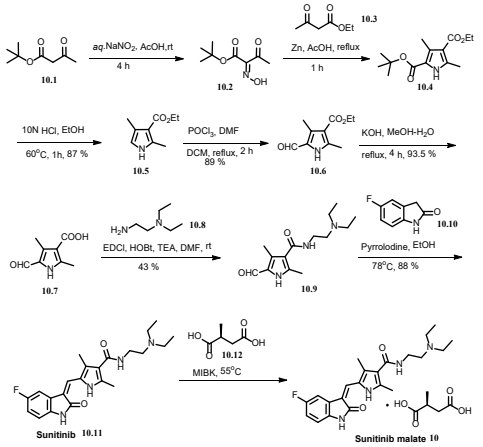
## 10. Sunitinib

Sunitinib (Sutent Capsules, Pfizer, Inc) is one of the widely studied anticancer drugs.It was approved by FDA on May 2011 to cure pancreatic neuroendocrine tumors (pNET). Though it got first approval in 2006 for treating renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumour (GIST) in 2011 it was approved for pNET. This drug targets receptor tyrosine kinase including platelet-derived growth factor (PDGF-Rs), vascular endothelial growth factor receptors (VEGFRs) and CD117.Since its discovery by SUGEN several other molecules have been also synthesised based on the concept of mimicking their structures with ATP to compete with binding on tyrosine kinases. There are controllable side effects shown by this drug.[48]



The synthetic route for the synthesis of **Sunitinib** is depicted in **scheme 10**. The synthesis is originated with nitrosation of tert-butyl acetoacetate **10.1** which reacts with sodium nitrite to produce 2-oxime compound **10.2***in situ*, and consecutive addition of zinc to this intermediate transformed the 2-oxime group to the amino group.[49]

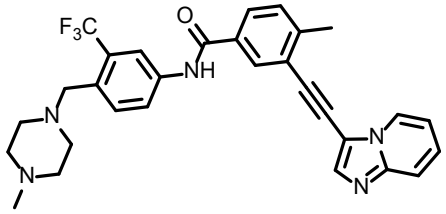
Subsequently, *tert*-butyl 2-aminoacetoacetate intermediate was then condensed with ethyl acetoacetate **10.3** to generate 3,5-dimethylpyrrole **10.4** with *tert*-butyl ester and ethyl ester securing at the 2- and 4-positions, correspondingly. Selective hydrolytic decarboxylation of the *tert*-butyl ester group of **10.4** takes place in the presence of hydrochloride and ethanol leads to the formation of intermediate **10.5** which is followed by Vilsmeier–Haack formylation at the C(2)-position giving the 2-formyl compound **10.6**. The carboxylic acid **10.7** was obtained through basic hydrolysis. Reaction of **10.7** with amine analogous in the presence of EDCl, HOBtanf triethyl amine afford compound **10.8** which is followed by Knoevenagel condensation reaction with 5-F-oxindole in the presence of pyrrolidine and ethanol resulting in the formation of **Sunitinib10**.




**Scheme 10: Synthesis of Sunitinib**

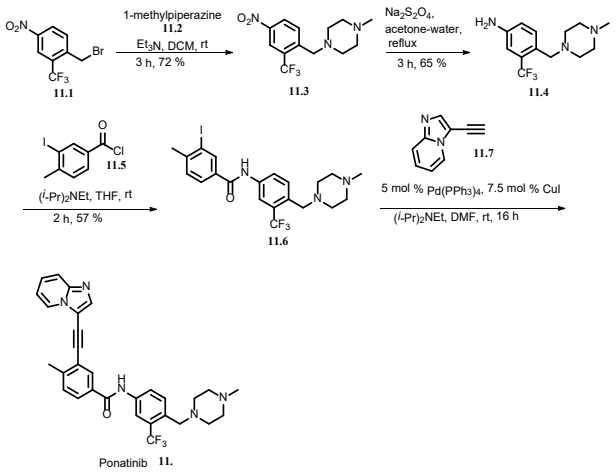
## 11. Ponatinib

Ponatinib (Iclusig tablets, ARIAD Pharmaceuticals, Inc) was approved by FDA to treat chronic myeloid leukaemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ALL) which is actually resistant to previous tyrosine inhibitor therapy in 2012.



It inhibits BCR-ABL which is an abnormal tyrosine kinase and causes CML and Ph+ ALL.[50] It was temporarily kept on hold in 2012 as it forms blood clots and again approved in 2013 with black boxed warning.[51] The common side effect shown by it are hypertension, rash, abdominal pain and headache.[52]

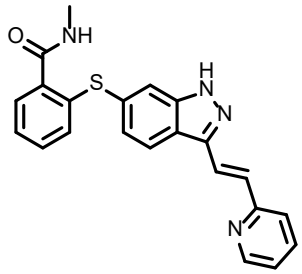
The synthetic route of **Ponatinib** is shown in **scheme 11**. Firstly, the synthesis of compound **11.3**is executed by $S_N2$ reaction with 4-nitro-2-(trifluoromethyl) benzylbromide and 1-methylpiperazine in the presence of triethylamine. Then the reduction of compound **11.3**occurs with $Na_2S_2O_4$ in actone water afford compound **11.4** which further reacts with 3-iodo-4-methylbenzoyl chloride**11.5** by using DIPEA to give compound **11.6.** Subsequent Sonogashira coupling of **11.6** with **11.7** was done by $Pd(PPh_3)_4$, CuI and DIPEA to give **Ponatinib 11**.[53]



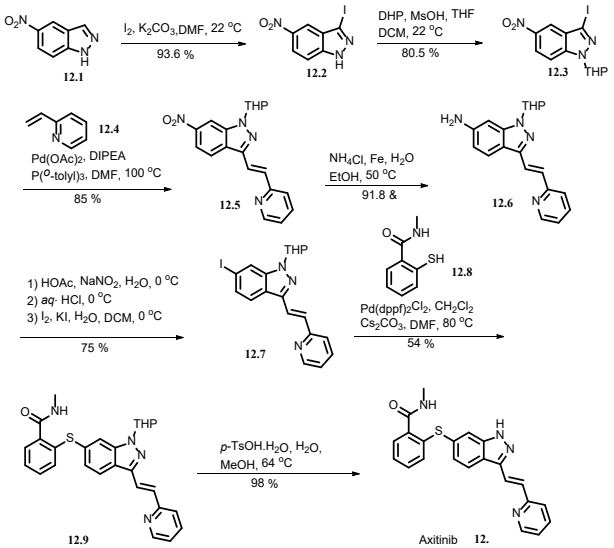

**Scheme 11: Synthesis of Ponatinib**

## 12. Axitinib

Axitinib (Inlyta, Pfizer, Inc.)got FDA approval in 2012 to cure advanced renal cell carcinoma especially in cases where systemic therapy has been shown to be failed. It targets vascular endothelial growth factor receptor 1-3, c-KIT and PDGFR.[54] It is also reported to cause autophagy (programmed cell death) to inhibit tumour growth.[55] Some of the usual adverse effects include dysphonia, hypertension, diarrhoea, nausea, fatigue, hand-foot syndrome and decrease in weight.



**Axitinib** was synthesized as shown in **Scheme 12**. Fictionalized C-3 position of indazole ring by treated with 6-nitroindazole **12.1** reacts with iodine in the presence of potassium carbonate and DMF to produce 3-iodo-6-nitro-indazole **12.2** which is followed by reaction with 3,4-dihydro-2*H*-pyran and methane sulfonic acid to give 3-iodo-6-nitro-1-(tetrahydropyran-2-yl) **12.3**. Furthermore, heck reaction is accomplished between 3-iodo-6-nitro-1-(tetrahydropyran-2-yl) **12.3**and 2-vinyl pyridine **12.4** in the presence of palladium



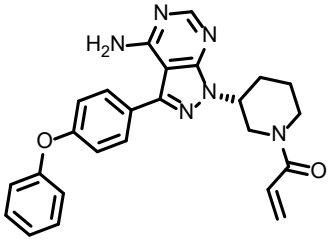

**Scheme 12: Synthesis of Axitinib**

and a ligand tri-o-totylphosphine to provide compound **12.5**whichisreduced to 6-amino compound **12.6** by treatment with iron and ammonium chloride. In the next step, treatment of **12.6** with a diazotization reagent, like sodium nitrite in hydrochloride to produce intermediatediazonium salt which was treated with KI and iodine to give 6-iodo-3-(E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole **12.7.** Compound **12.7** reacts with 2-mercapto-N-methylbenzamide **12.8** in presence of a catalytic amount of $Pd(dppf)_2Cl_2$ and cesium carbonate in DMF to generate compound **12.9.** Finally,

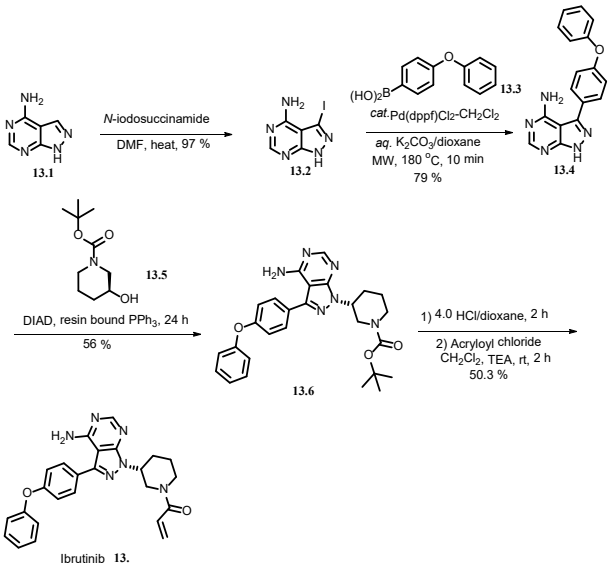
deprotection of compound **12.9**using p-TsOH in methanol/water is performed to produce **Axitinib 12.**[56]

## 13. Ibrutinib

Ibrutinib (IMBRUVICA, Pharmacyclics, Inc) was approved by FDA on November 2013 for treating mantle cell lymphoma (MCL) and later for treating chronic lymphocytic leukemia (CLL) in 2014 and for Waldenstrom's macroglobulinemia in 2015. Its mechanism of action is based on covalent binding with Bruton's tyrosine kinase (BTK) which is important for B-cells. It has reported to impede signalling through BCR (B cell receptor) leading to apoptosis and hence tumour inhibition. It exhibits very common side effects like low platelet counts, neutrophil count, headache, diarrhea, vomiting, nausea and inflammation of mouth and lips.[57-585960]



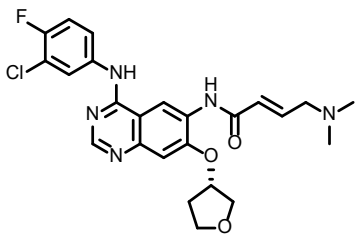
The synthesis of **Ibrutinib** is dysplayed in **Scheme 13**. Initial step is halogenation of commercially available 1H-pyrazolo[3,4-d]pyrimidin-4-amine**13.1** with the NIS and DMF as a solvent to provide 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine**13.2**. Then the metal catalysis cross coupling reaction is performed on compound **13.2** with phenyl boronic acid **13.3** in presence of palladium and a base potassium carbonate to build intermediate **13.4** which is coupled with *N*-Boc-hydroxypiperidine 13.5 *via*Mitsunobu reaction to construct protected intermediate **13.6**. After that, deprotection with hydrochloride of intermediate **13.6** acryloyl chloride is completed in the synthesis of **Ibrutinib 13.7**.[61]



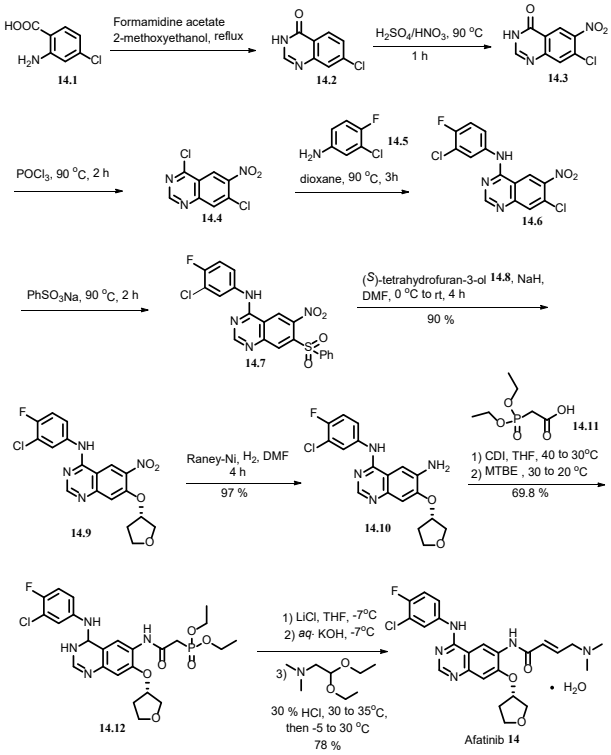

**Scheme 13: Synthesis of Ibrutinib**

## 14.Afatinib

Afatinib (Gilotrif tablets, Boehringer Ingelheim Pharmaceuticals, Inc)got FDA approval in 2013 for the treatment of metastatic non-small cell lung cancer (NSCLC) as first line treatment especially for those having mutation in epidermal growth factor receptor (EGFR). It interferes with the production of new blood vessels (angiogenesis) and thereby inhibiting growth of cancer. It is an oral medication which is an inhibitor of tyrosine kinase. standard



In addition, it acts against mutation like T970M which does not show susceptibility to otherinhibitors.[62-6364]

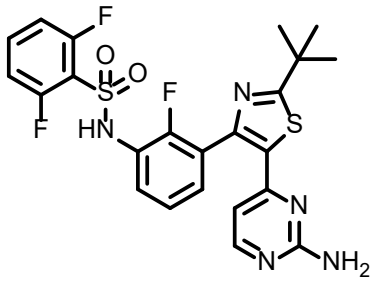


**Scheme 14: Synthesis of Afatinib**

The synthesis of Afatinib is discussed in Scheme 14. First step starts with cyclization of commercially available 2-amino-4-chlorobenzoic acid 14.1 with the formamidine acid and 2-methoxyethanol to give 7-chloroquinazolinone 14.2. Then nitrationof **14.2** takes place in the presence of nitric acid and sulphuric acid to generate the 7-chloro-6-nitroquinazolinone**14.3**which is heated with $POCl_3$ succeeded by addition of aniline analogous **14.5** to construct intermediate **14.6.** The next step is sulfonylation which takes place with the sulfinic acid sodium salt to give intermediate **14.7** which is treated with (S)-3-hydroxytetrahydrofuran **14.8** and sodium hydride to provide compound **14.9**. Thereafter, the reduction of compound **14.9** occurs in the presence of Raney-Ni to give compound **14.10**which is subsequently is reacted with 2-(diethoxyphosphoryl) acetic acid to generate compound **14.11** which finally react with 2,2-diethoxy-N,N-dimethylethan-1-amine and hydrochloride leading to the formation of **Afatinib 14.**[65]

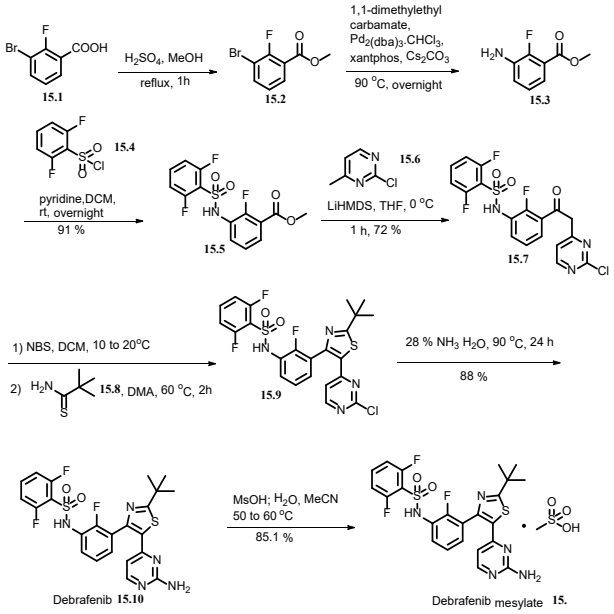
## 15. Dabrafenib

On May 2013, Dabrafenib (TAFINLAR capsule, GlaxoSmithKline, LLC)got FDA approval to treat patients having metastatic melanoma with BRAF mutated at V600E. Further, on 2014 FDA approved its use in combination with trametinib, an inhibitor or MEK for treating metastatic melanomaBRAF V600E or V600K mutation. Moreover, Dabrafenib/ trametinib combination therapy was approved by FDA in 2018 for adjuvant therapy to treat metastatic melanomaBRAF V600E or V600K mutation and also for treating hyroid cancer with BRAF V600E mutation.[66-6768]



**Debrafenib** described herein were generally prepared according to **Scheme 15**. It starts with esterification of 3-bromo-2-fluorobenzoic acid**15.1** with the $H_2SO_4$ and methanol to build **15.2**. Consequently, palladium-catalyzed amination reacts with *t*-butyl carbamate afforded anilino esters **15.3**. The anilino

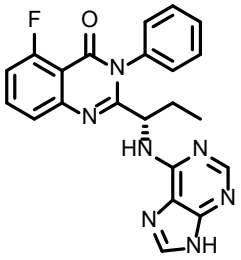
ester **15.3**istreated with an arylsulfonyl chloride **15.4** in presence of pyridine to give the compound **15.5** which is then condensed with the lithium anion of 2-chloro-4-methylpyrimidine**15.6** to create ketone intermediate **15.7**. Next step, bromination of intermediate **15.7** with NBS occurs with subsequently cyclization with isopropyl thioamide **15.8**afforded the thiazole core **15.9**. Next step is $S_NAr$ displacement at the chloropyrimidinein **15.9** with ammonia to generate the **Debrafenib 15.10** which is treated with MsOH to give **Debrafinb mesylate 15.**[69]



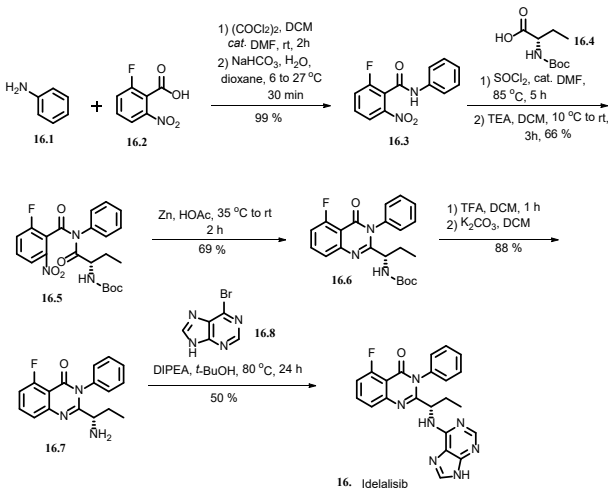

**Scheme 15: Synthesis of Debrafenib**

## 16. Idelalisib

Idelalisib (Zydelig tablets, GileadSciences, Inc) was approved by FDA on July 2014 to cure patients with relapsed chronic lymphocytic leukaemia (CLL) sometimes combined with rituximab. It causes great effects on lymphadenopathy and splenomegaly. Interestingly, it is effective for patients having p53 mutation in CLL which generally is cured by first in drug fludarabine. Later, it was also approved for follicular and small lymphocytic lymphoma (SLL) and B-cell non-Hodgkin lymphoma (FL).It inhibits PI3Kδ kinase which is found in normal as well as malignant B-cells. In addition, it also inhibits signalling of B cell receptor.[70,71]



**Idelalisib** was synthesized as shown in **Scheme 16**. First step is chlorination of 2-fluoro-6-nitrobenzoic acid**16.2** with the $(COCl_2)_2$ and DCM followed by addition of aniline **16.1** in the presence of sodiumbicarbonate afforded 2-fluoro-6-nitro-N-phenylbenzamide**16.3**. After that acetylation of 2-(*N*-Boc-amino) butanoic acid**16.4**with $SOCl_2$ and DCM occurs to



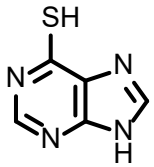

**Scheme 16: Synthesis of Idelalisib**

generate the *tert*-butyl (1-chloro-1-

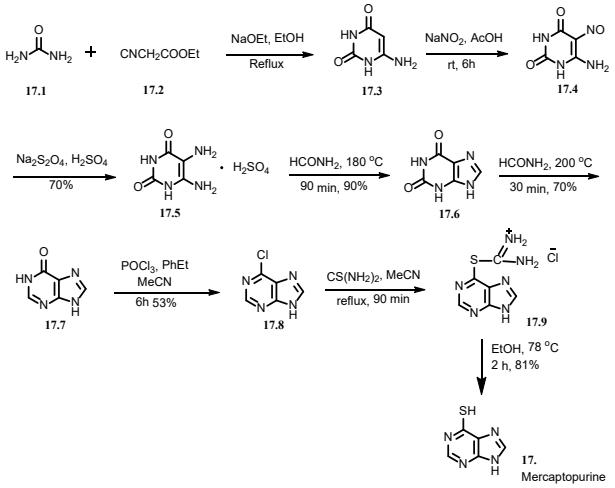
oxobutan-2-yl)carbamate which reacts with 16.3 in presence of triethylamine to construct intermediate **16.5**. The next step is reduction of **16.5** followed by cyclization to produced compound **16.6**. Then deprotection of 16.6 with triethylamine and DCM subsequently treated with base potassium carbonate to generate compound **16.7**. As a final point, the substitution reaction with 6-bromo-9H-purine**16.8** in presence of DIPEA and *t*-BuOH furnished the synthesis of **Idelalisib16.9**.[72]

## 17. Mercaptopurine

Mercaptopurine (Purixan, NOVA Laboratories Limited)was approved by FDA in 2014 to treat acute lymphoblastic leukaemia (ALL) and used as oral suspension. Additionally, it is also used for ulcerative colitis and crohn's disease. As it is a type of purine so competes with hypoxanthine and guanine for Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) and interferes with nucleotide synthesis. The common side effects caused by it include nausea, diarrhoea, fatigue, vomiting, bone marrow suppression and liver toxicity.[73]



The synthesis of Mercaptopurine was shown in **Scheme 1**7. Initially, urea **17.1** treated with ethylcyano acetate **17.2** to produced 6-Aminopyrimidine-2,4(1*H*, 3*H*)-dione**17.3**in 95%

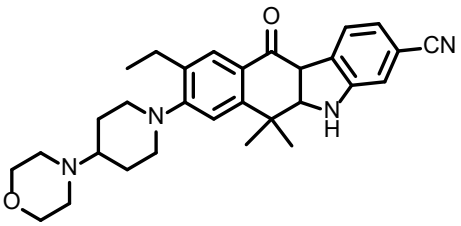



**Scheme 17: Synthesis of Mercaptopurine**

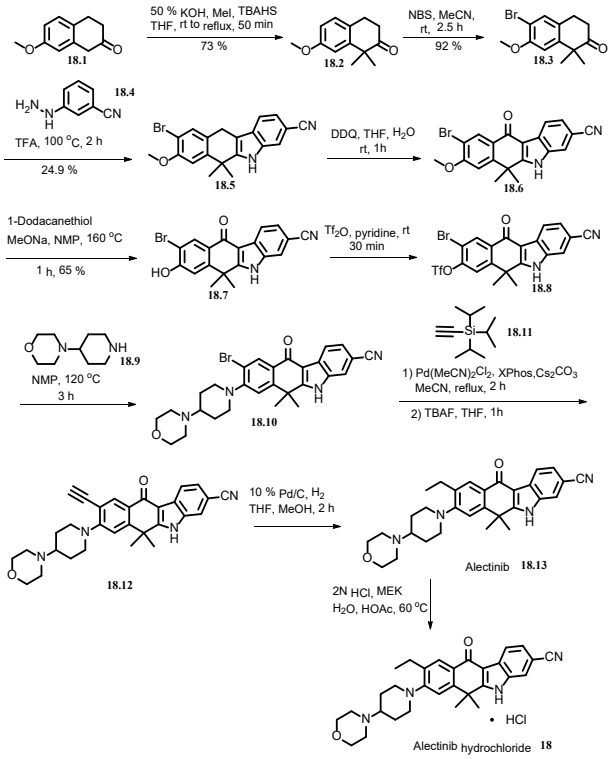
yield. After this nitration reaction of **17.3** with sodium nitrite and acetic acid was afforded 6-Amino-5-nitrosopyrimidine-2,4(1H,3H)-dione**17.4**which further reduced to **17.5** in the presence of $Na_2S_2O_4$. In the next step, cyclization reaction of **17.5** in presence of formamide was afforded **17.6** then again for the dehydration reaction **17.6** react with formamide to produced hypoxanthine **17.7.**Chlorination reaction of **17.7** in presence of phosphoryl chloride was delivered 6-chloropurine **17.8**. The compound **17.8** react with thiourea to afford salt **17.9.** In the final step, **17.9** were refluxed in ethanol to produce **Mercaptopurine17**.[74]

## 18. Alectinib

Alectinib (ALECENSA capsules, Hoffmann-La Roche Inc) got FDA approval in 2015 to treat patients with metastatic non-small cell lung cancer (NSCLC) associated with anaplastic lymphoma kinase.



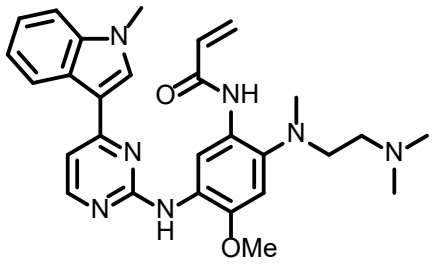
It acts by blocking two receptor tyrosine kinases- one is anaplastic lymphoma kinase (ALK) and the other is RET proto-oncogene. It causes side effects like constipation, nausea, myalgia, oedema and anaemia.[75]The synthesis of **Alectinib** is summarized in **Scheme 18**. Methylation of 7-methoxy-3,4-dihydronaphthalen-2(1H)-one**18.1**with the methyl iodide occurs in presence of KOH and TBAHS to produce **18.2**. Bromination of compound **18.2** with N-bromo-succinimide is followed to generate intermediate **18.3**. The Fischer indole ring formation of **18.3** with cyanohydrazine**18.4** produce (1-CN-derivatives)**18.5**. The oxidation of **18.5** is conducted with DDQ and THF to give compound **18.6** which further **18.6** treated with 1-Dodacanethiolafford the desired ketone **18.7**. Then the protection of hydroxygroup on **18.7** with trifluoromethanesulfonic anhydride and pyridine occur which leads to the formation of compound **18.8**. The triflate **18.8** reacts with piperazine in NMP to provide 8-piperazinyl compound **18.9**.The intermediate**18.9**treats with resultant building blocks under conservative Pd-catalyzed cross-coupling conditions to give compounds 9-TIPS-acetylene derivative **18.11.** This 18.11 is deprotected with TBAF to provide compound **18.12**. Hydrogenation of**18.12**with catalytic palladium on charcoal affords the Alectinib**18.13** which is treated with hydrochloride to give **Alectinib hydrochloride18.**[76]



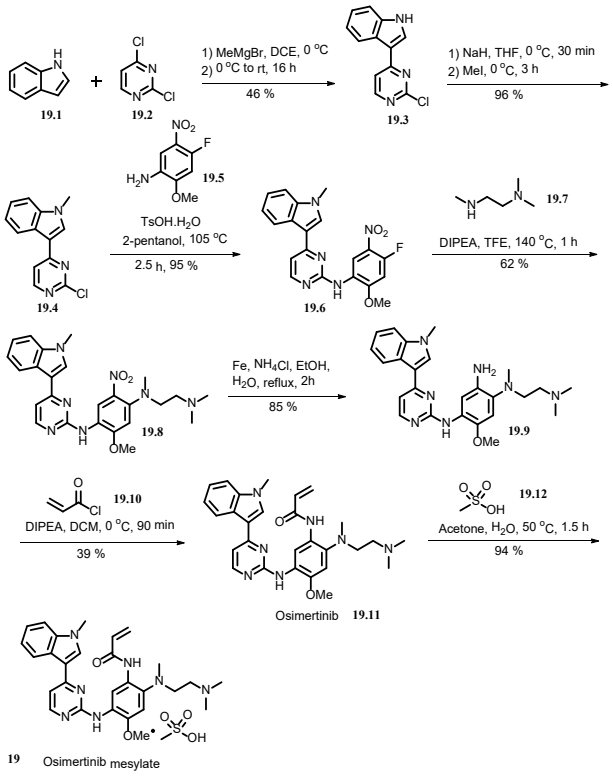

**Scheme 18: Synthesis of Mercaptopurine**

## 19. Osimertinib

On November 2015, Osimertinib (TAGRISSO, AstraZeneca Pharmaceuticals LP) was approved by FDA for the treatment of non-small cell lung cancer (NSCLC) positive for T790M mutation on epidermal growth factor receptor (EGFR). However, resistance has been shown to be developed for Osimertinib within 10 months of treatment. As mentioned above it



is an inhibitor of EGFR. This drug causes common adverse effects like diarrhoea, stomatitis, rashes, dry skin and interstitial lung disease.[77-7879]

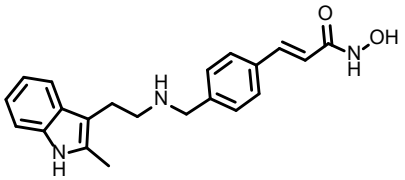



**Scheme 19: Synthesis of Osmertinib**

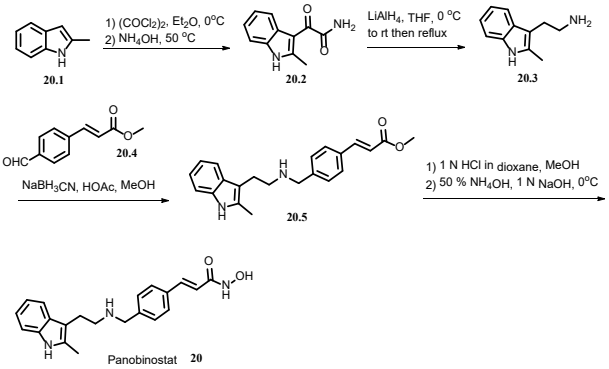
The 7-step synthesis of **Osimertinib** is shown in **Scheme 19.** It starts with the deprotonation of indole **19.1** with MeMgBr followed by addition of the anion to 2, 4-dichloropyrimidine**19.2**; produce compound **19.3** in 46% yields. Methylation of compound **19.3** with NaH/MeI delivers indole **19.4** in 96% yields. The substitution of the chloride of the pyrimidine **19.4** is accompanied under acidic conditions in dioxane with 4-fluoro-3-nitroaniline **19.5**generating intermediate **19.6**.$S_NAr$ reaction of compound **19.6** with the diamine **19.7** and DIPEA afford **19.8** in 62% yields. Reduction with iron in aq. ammonium chloride delivers next to last compound**19.9** in 85% yields. Acylation with acryloyl chloride **19.10** gives **Osimertinib19.11** in 39% yields which reacts with MSA to generate the **Osimertinib mesylate19**.[80]

## 20. Panobinostat

Panobinostat (FARYDAK capsules, Novartis Pharmaceuticals)was approved by FDA to cure multiple myeloma on February 2015. Generally, it is used in combination with bortezomib and dexamethasone.



It's mode of action is based on inhibition of histone deacetylase enzyme results in apoptosis of malignant cells. The patients treated with this drug experience some common side effects like fatigue diarrhoea, nausea and low blood cell counts.[81,82]



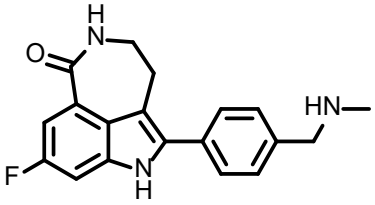

**Scheme 20: Synthesis of Panobinostat**

The synthesis of Panobinostat was initiated from commercially available

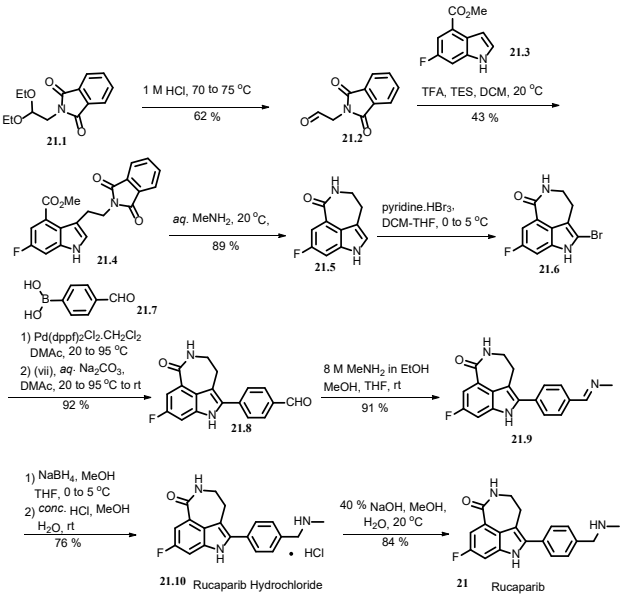
2-methyl-indole as described **20.1** (**Scheme 20**). Acetylation of **20.1** with the $(COCl_2)_2$ and diethyl ether occurs which subsequently reacts with hydroxylamine to construct 2-(2-methyl-1H-indol-3-yl)-2-oxoacetamide **20.2.** The reduction of **20.2** with the lithium aluminium hydride and THF happens to provide 1-(2-methyl-1H-indol-3-yl) propan-2-amine 20.3 which treats with methyl (E)-3-(4-formylphenyl)acrylate **20.4** in presence of cyanoborohydride and acetic acid to generate the compound **20.5.** Finally**,** ester group of **20.5** is changed to oxime group in presence of hydrochloride in dioxane which is followed by reaction with hydroxyl amine and sodium hydroxide to provide **Panobinostat20**.[83,84]

## 21. Rucaparib

On December 2016, Rucaparib (RUBRACA, Clovis Oncology, Inc.) got approval from FDA for treating ovarian cancer caused by mutation in BRCA (a tumour suppressor gene). It is known to inhibit PARP (poly ADP ribose polymerase) thereby impairing contraction of smooth muscle. It also impedes migration of cancer cells in culture hence prevents metastasis.[85,86]



The synthesis of **Rucaparib** is outlined in **Scheme 21**. Phthalimidoacetaldehyde diethyl acetal **21.1** converts into deprotected aldehyde **21.2** using hydrochloride furthermore reaction between 21.2 and methyl 6-fluoro-1H-indole-4-carboxylate **21.3** in the presence of TFA and triethylsilane in DCM which further gives intermediate **21.4** in 43% yield. Then the cyclization is taken place using methyl amine to produce compound **21.5.** Subsequently, bromination reaction is carried out with pyridine tribromide to generate intermediate **21.6.** Suzuki coupling of **21.6** and 4-formylbenzene boronic acid **21.7** affords **21.8** in 92% which is then treated with methyl amine in methanol THF to produce compound **21.9.**Thereafter, the reduction of **21.9** by using $NaBH_4$ in methanol produces compound **21.10** which is treated with sodium hydroxide in methanol to afford **Rucaparib21**.

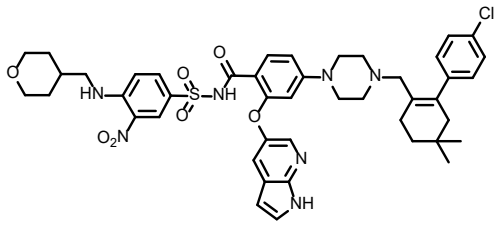



**Scheme 21: Synthesis of Rucaparib**

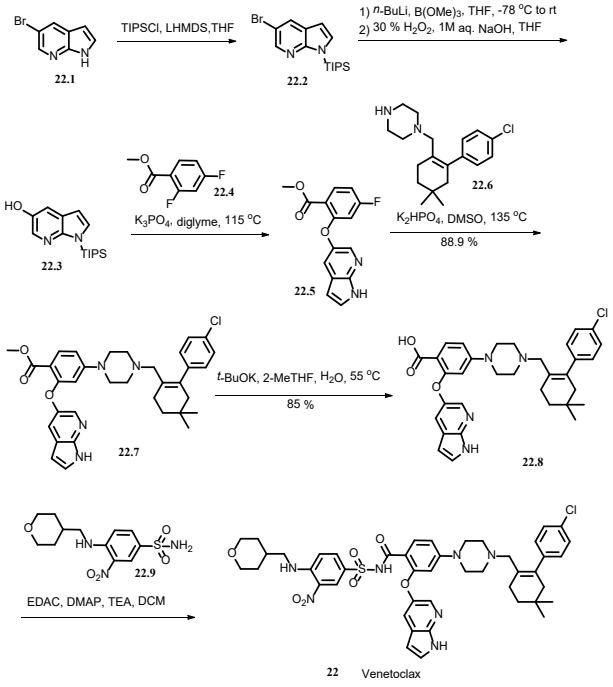
## 22. Venetoclax

Venetoclax (VENCLEXTA tablets, marketed by AbbVie, Inc. and Genentech USA, Inc)was approved by FDA on April 2016 to treat chronic lymphocytic leukaemia (CLL) patients having 17p deletion mutation (FDA approved test).

It inhibits B-cell lymphoma-2 (Bcl-2) which results in apoptosis of CLL cells. In some cases, it has shown resistance where overexpression of Bcl-2 gene has detected. Some of the common side effects include nausea, neutropenia, anaemia, thrombocytopenia, diarrhoea and upper respiratory tract infection.[87,88]



The preparation of Venetoclax (**Scheme 22**) starts with TIPS protection of 5-bromoindole 22.1 followed by conversion of the bromo substituent to hydroxyl via the construction of the boronate ester and oxidation using hydrogen peroxide, producing **22.3**. ArSN reaction with

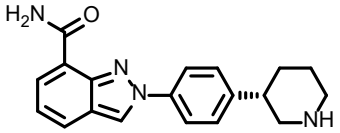


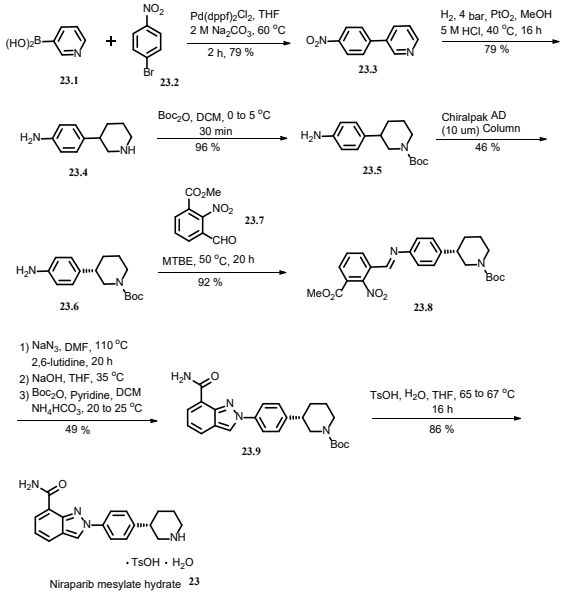

**Scheme 22: Synthesis of Venetoclax**

methyl 2,4-difluorobenzoate 22.4 and K3PO4 gives intermediate 22.5. Another SNAr reaction is between 22.5 and piperazine fragment 22.6 leading to the formation of compound 22.7.The ester group of **22.7** is converted to acid group by using a base *t*-BuOk in 2-MeTHF deliver compound **22.8** which reacts with sulfonamide analogous **22.9** and EDAC, DMAP and a base triethylamine afford **Venetoclax22.**[89]

## 23. Niraparib

Niraparib (ZEJULA, Tesaro, Inc.)was approved on March 2017 for patients having recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer generally for those giving complete or partial response to platinum-based chemotherapy.






**Scheme 23: Synthesis of Niraparib**

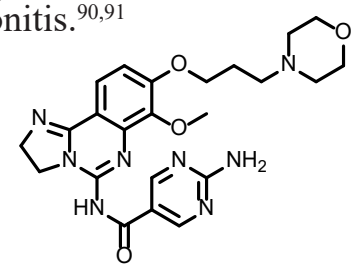
This drug blocks action of PARP 1 and

PRAP 2. In addition to inhibit PARP it also traps PARP on damaged DNA. Like other anticancer drugs it also exhibits common side effects such as constipation, neutropenia, anaemia and thrombocytopenia. ,

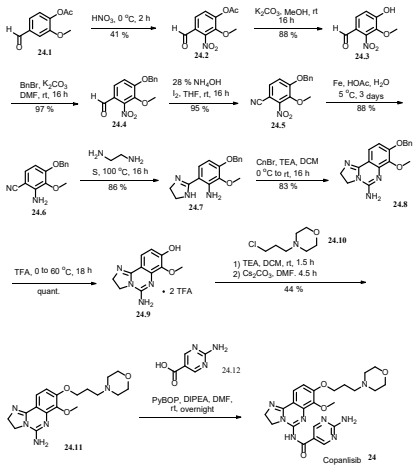
Niraparib was synthesized as shown in **Scheme 23**. In the first step, 3-pyridineboronic acid **23.1** couples with 1-bromo-4-nitrobenzene **23.2** by using palladium as a catalyst and a base sodium carbonate in THF give3-(4-Nitrophenyl) pyridine **23.3** which after hydrogenation by $H_2/PtO_2$ and hydrochloride produce 4-(Piperidin-3-yl)aniline **23.4**. Then the protection of compound **23.4** is done by using $Boc_2O$ in DCM to construct intermediate **23.5**.

## 24.Copanlisib

On September 2017, Copanlisib (ALIQOPA, Bayer HealthCare Pharmaceuticals Inc.) received approval for the treatment of patients having follicular lymphoma with at least two prior systemic therapies. It inhibits phosphatidylinositol-3-kinase (PI3K) particularly PI3K-α and PI3K-δ. Its administration is not oral but intravenous. Its common side effects are hypertension, hyperglycaemia, skin rashes and Pneumonitis.[90,91]



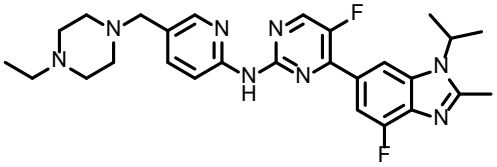
The synthesis of Copanlisib is described in **Scheme 24**. In the first step the nitration reaction is performed between 6-nitrovanilline **24.1** and nitric acid to generate compound **24.2**.Furthermore, deacetylation of compound **24.2** occurs with a base potassium carbonate in methanol to afford **24.3**. Protection of hydroxyl group on **24.3** is performed by using benzyl bromide and potassium carbonate in DMF which produces intermediate **24.4**. By using hydroxyl amine and iodine the aldehyde group on **24.4** converts into cyano group to build **24.5**. Reduction of **24.5** is performed by the reaction with iron and acetic acid to form compound **24.6**. Conversion of compound **24.6**to the imidazoline **24.7** is accomplished using ethylenediamine in the presence of a catalyst such as elemental sulphur. Then the cyclization of compound **24.7** is achieved using cyanogen bromide in presence oftriethylamine to afford compound **24.8.** Afterwards, the removal of protected group in compound **24.8**isaccomplishedin the presence of TFA to generate **24.9**. Then, the alkylation of **24.9** is achieved using a base such as cesium carbonate in DMF with introduction of a side chain **24.10** to give compound **24.11** which after reaction with 2-aminopyrimidine-5-carboxylic acid**24.12** leads to the formation of **Copanlisib 24.**[92]



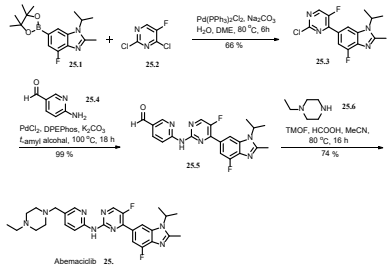
**Scheme 24: Synthesis of Coaanlisib**

## 25.Abemaciclib

Abemaciclib (VERZENIO, Eli Lilly and Company)got approval for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with fulvestrantby FDA on September 2017. It is also known to inhibit CDK 4/6 like other related palbociclib and ribociclib. Side effects caused by it are nausea, fatigue, anaemia and low blood count.[93,94]



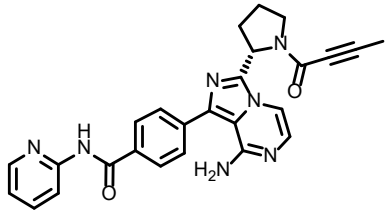
The synthesis of Abemaciclib is explained in **Scheme 25**. In first step, Suzuki coupling reaction between boronic ester **25.1** and 2,4-dichloro-5-fluoropyrimidine**25.2** takes place by using of $PdCl_2(PPh_3)_2$ with $Na_2CO_3$ in DME providing the biaryl compound **25.3** in 66% yield. The Buchwald–Hartwig amination is accomplished with 6-aminonicotinaldehyde**25.4** in presence of palladium and base potassium carbonate in *t*-amyl alcohol producing compound **25.5**which after reaction with*N*-ethylpiperazine generates **25.6** (reductive amination) in presence of trimethyl orthoformate and formic acid in acetonitrile to generate **Abemaciclib25.**[95]



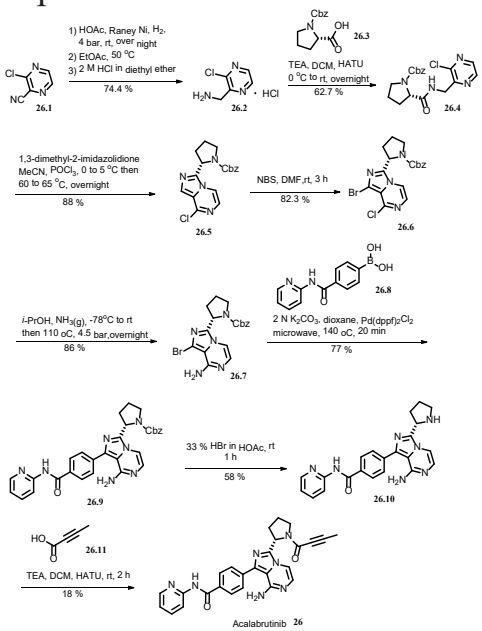

**Scheme 25: Synthesis of Abemaciclib**

## 26. Acalabrutinib

Acalabrutinib (Calquence, AstraZeneca Pharmaceuticals Inc. under license of Acerta Pharma BV)was approved for the treatment of mantle cell lymphoma (MCL) by FDA on October 2017 usually for cases already received prior therapy. It has been shown to inhibit Bruton's tyrosine kinase (BTK). Interestingly, it is more active anticancer drug than ibrutinib, first BTK inhibitor.[96,97]



The synthesis of Acalabrutinib initiates from reduction of 3-chloropyrazine-2-carbonitrile **26.1** in the presence of Raney-Ni and acetic acid as shown in **Scheme** 26. Subsequently, addition of ethyl acetate and hydrochloride affords (3-chloropyrazin-2-yl)methanamine hydrochloride **26.2** which is reacted with amine protected



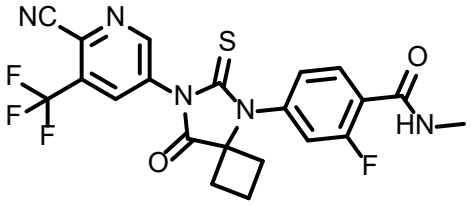

**Scheme 26: Synthesis of Acalabrutinib**

amino acid **26.3** in presence of

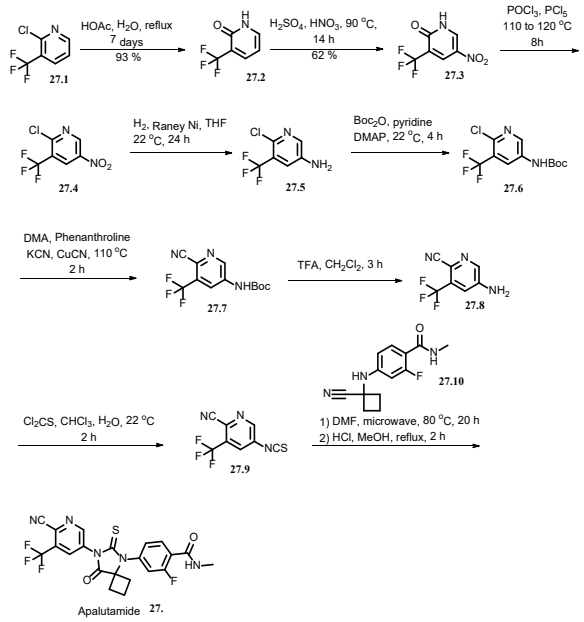
triethylamine in DCM to provide intermediate **26.4**. Cyclization of **26.4** is performed by using condensation reagent phosphorousoxychloride under heating condition to generate compound **26.5**. Thereafter, bromination is completed using NBS in DMF provide intermediate **26.6**. Compound **26.7** is prepared by using ammonia in *i*-PrOH and then coupling reaction between **26.8** and **26.7** compounds by using palladium and a base potassium carbonate resulting in the production of compound **26.9**. Furthermore, deprotection of **26.9** takes place in the presence of hydrogen bromide in acetic acid to afford **26.10** which after treatment with but-2-ynoic acid **26.11** by using triethylamine in DCM affords **Acalabrutinib 26.**[98]

## 27. Apalutamide

Apalutamide (Erleada™, Janssen Biotech, Inc) was approved by FDA on February 2018 to cure patients having non-metastatic castration-resistant prostate cancer (NM-CRPC). It is an anti-androgen which competitively binds with androgen receptor using ligand binding domain. Though it is well tolerated yet shows some common side effects like nausea, fatigue, abdominal pain and diarrhoea.[99-100101]



The synthesis of Apalutamide is elaborated in **Scheme 27**. It starts with oxidation of 2-chloro-3-(trifluoromethyl) pyridine**27.1** by using acetic acid under heating condition producing 3-(trifluoromethyl)pyridin-2(1H)-one **27.2**.Nitration of **27.2** by using nitric acid and sufuric acid to generate 5-nitro-3-(trifluoromethyl)pyridin-2 (1H)-one**27.3**. Chlorination of **27.3** in presence of $POCl_3$ to produce2 -chloro-5-nitro-3-(trifluoromethyl)pyridine**27.4**.The reduction of **27.4** by using Raney-Ni in THF affords **27.5** which after protection of amine group on **27.5** by using $Boc_2O$, pyridine and DMAP produces compound **27.6**. Substitution reaction of **27.6** is accomplished by using KCN and CuCN under heating condition to afford **27.7**.The deprotection of amino group on **27.7** is achieved by using TFA in DCM to produce compound **27.8** which reacts with thiophosgene and affords compound **27.9**. Finally, compound **27.9** treats with **27.10** in the presence of DMF followed by reaction hydrochloride in methanol to synthesise **Apalutamide27.**[102]

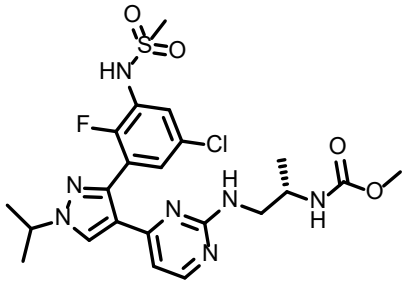



**Scheme 27: Synthesis of Apalutamide**

## 28.Encorafenib

Encorafenib (BRAFTOVI and MEKTOVI, Array BioPharma Inc.) was approved on June 2018 by FDA for

the treatment of metastatic melanoma associated with a BRAF V600E or V600K mutation in combination with binimetinib.



It is an inhibitor of RAF kinase with reduction in ERK phosphorylation. It also downregulates cyclin D1 which thereby causing arrest of cell cycle in G1 phase of cancer cells. It is associated with common adverse effects like diarrhoea, nausea, vomiting, fatigue and arthralgia.

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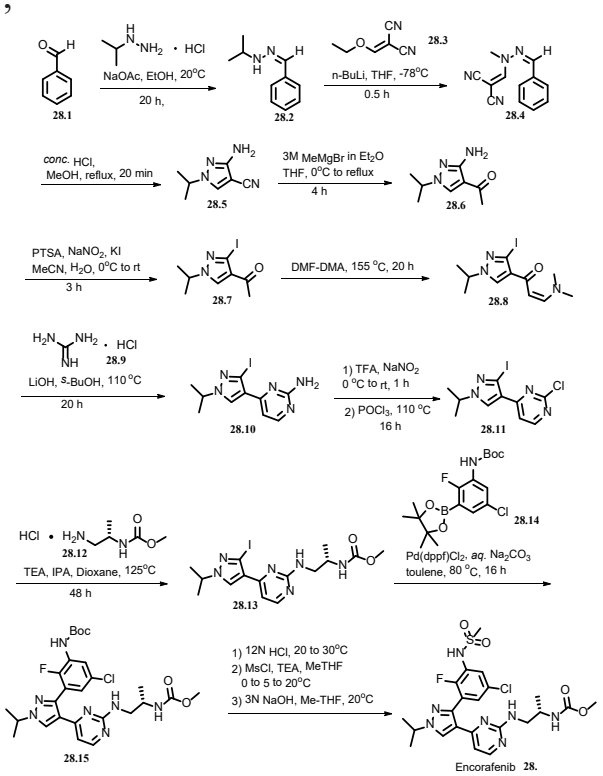



**Scheme 28: Synthesis of Encorafenib**

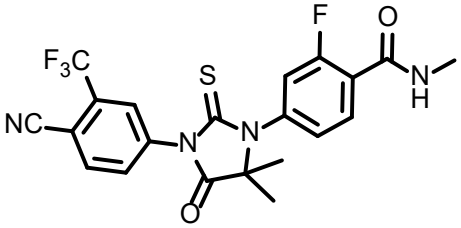
The synthesis of Encorafenib is shown in **Scheme 28**. Benzoldehyde**28.1** is treated with isopropylhydrazine by using base sodium acetate in ethanol to generate **28.2** which is reacted with **28.3** in presence of n-BuLi in THF to afford **28.4**. This **28.4** was cyclized and remove phenyl group is removed by using hydrochloride in methanol to produce 3-amino-1-isopropyl-1H-pyrazole-4-carbonitrile **28.5**.For generation the ketone group on intermediate

**28.5** are treated with MeMgBr in diethylether to afford **28.6**. Iodonization of **28.6** is accomplished by using PTSA, sodium nitrite and potassium iodide in acetonitrile producing **28.7.** Condensation reaction was performed by using DMF-DMA under heating condition to give intermediate **28.8** which is cyclized with guanidine hydrochloride **28.9** in presence of lithium hydroxide in secondry-butanol to produce intermediate **28.10**. Diazotization reaction of **28.10** is performed in presence of sodium nitrite and trifilic acid. Subsequently chlorination is accomplished with the $POCl_3$ to generate compound **28.11** which then is treated with **28.12** by using a base triethyl amine to give **28.13**. Then the coupling reaction is completed between **28.13** and boronic analogous **28.14** by using palladium and sodium carbonate to afford **28.15** which firstreacts with hydrochloride followed by MsCl and triethylamine in 2-MeTHF and then is treated with sodium hydroxide resulting in the formation of **Encorafenib 28.**[103]

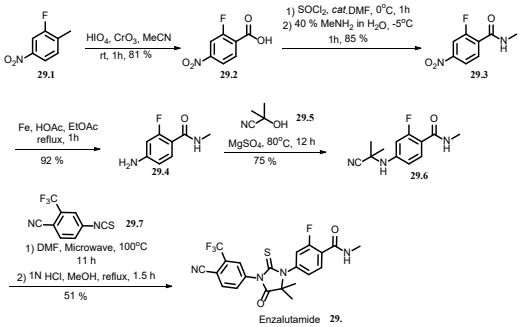
## 29.Enzalutamide

Enzalutamide (XTANDI, Astellas Pharma US, Inc)received FDA approval on July 2018 to cure patients having castration-resistant prostate cancer (CRPC). It is also an antiandrogen

like apalutamide and thereby targets testosterone and dihydrotestosterone and prevents the effect on prostate gland produced by these hormones. The usual adverse effects of it are nausea, diarrhoea, gynecomastia and breast pain.[104-105106]



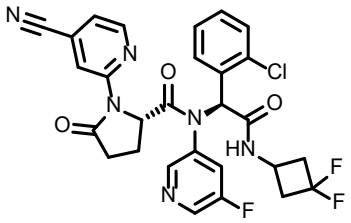
The synthesis of Enzalutamide is displayed in **Scheme 29**. Oxidation reaction of 2-fluoro-1-methyl-4-nitrobenzene **29.1** is performed by using $HIO_4$ and chromium (VI) oxide in acetonitrile producing 2-fluoro-4-nitrobenzoic acid **29.2**.Chlorination of **29.2** is executed by using $SOCl_2$, DCM and catalytic amount of DMF simultaneously, treats with methylamine in water generates 2-fluoro-4-nitrobenzamide **29.3**. Reduction of **29.3** is performed in presence iron and acetic acid in ethyl acetate to produce 4-amino-2-fluorobenzamide **29.4** which is treated with 2-hydroxy-2-methylpropanenitrile **29.5** by using magnesium sulfate to afford intermediate **29.6**. Finally, reaction between **29.6** and **29.7** is accomplished in DMF followed by hydrochloride in methanol leading to the formation of **Enzalutamide 29.8**.[107]



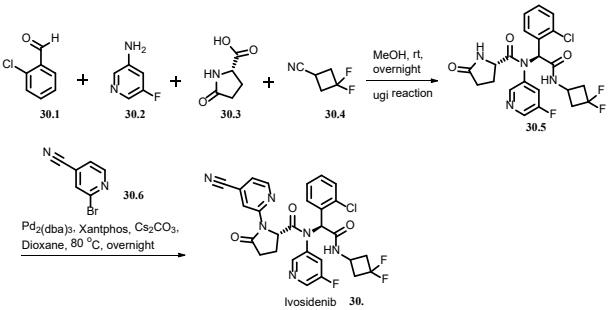

**Scheme 29: Synthesis of Enzalutamide**

**30. Ivosidenib**

On July 2018, Ivosidenib (Tibsovo, Agios Pharmaceuticals, Inc.)was approved to treat acute myeloid leukaemia (AML) generally relapsed or refractory and associated with a susceptible IDH1 mutation. It is an inhibitor of IDH1 (isocitrate dehydrogenase 1) which is mutated in cancer. This drug is first in IDH inhibitor class of drug. It does not inhibit IDH2 at micromolar range suggesting selective binding with IDH1.[108,109]



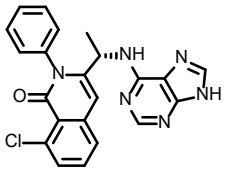
The synthesis of Ivosidenib is shown in **Scheme 30**. In the first step Ugi reaction is executed among 2-chloro-benzaldehyde **30.1**, 5-fluoropyridin-3-amine **30.2**, 5-oxopyrrolidine-2-carboxylic acid **30.3** and 3,3-difluorocyclobutane-1-carbonitrile in methanol to produce compound **30.5**. Suzuki coupling reaction is accomplished between **30.5** and 5-bromonicotinonitrile **30.6** by using palladium and a base caesium carbonate in dioxane to afford **Ivosidenib 30.7**.[110]




**Scheme 30: Synthesis of Ivosidenib**

**31.Duvelisib**

Duvelisib (COPIKTRA, Verastem, Inc.) was approved on or September 24, 2018 to cure patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). Moreover, this drug got accelerated approval for adult patients with relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies. Its mode of action is based on inhibition of Phosphoinositide 3-kinaseresulted in malfunctioning of apoptosis, senescence, cell cycle regulation, DNA repair, angiogenesis and cell metabolism.[111,112]



The synthesis of Duvelisib is designated in Scheme 31. The first step is hydrolysis reaction accomplished between amine protected amino **31.1** acid and hydroxyl amine hydrochloride **31.2** to produce **31.3** then C-H functionalization of **31.4** was taken place with **31.3** in presence of HMPA and n-BuLi to afford compound **31.5**. Deprotection of **31.5** is performed by using hydrochloride in methnol under heating condition to produce compound **31.6**. Substitution reaction was accomplished between 31.6 and 31.7 by using DIPEA in n-BuOH to afford compound **31.8** which was treated with hydrochloride in methanol to produce **Duvelisib 31.9**.[113]

**Scheme 31: Synthesis of Duvelisib**

## Conclusion

In conclusion, this review presents the excellent contribution of anti-cancer five-membered *N*-heterocyclic in FDA approved drugs. The unique properties connected with five-membered *N*-heterocycles made them privileged structures for anti-cancer drugs. Our analysis exposed the comparative frequency by which the several nitrogen heterocycles have been incorporated into FDA approved drug architectures. We have also defined chemical and pharmacokinetic data and their synthetic routes.

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