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Azaindole Therapeutic Agents

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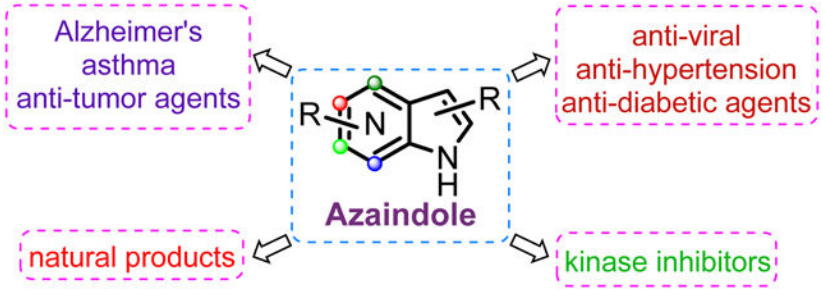
Abstract

Azaindole structural framework is an integral part of several biologically active natural and synthetic organic molecules; and several FDA approved drugs for various diseases. In the last decade, quite a number of literature reports appeared describing the pharmacology, biological activity and therapeutic applications of a variety of azaindole molecules. This prompted the organic and medicinal chemistry community to develop novel synthetic methods for various azaindoles and test them for a bioactivity against a variety of biological targets. Herein, we have summarized the biological activity of therapeutically advanced clinical candidates and several preclinical candidate drugs that contain azaindole structural moiety.

Graphical Abstract



Keywords

Guitarrins; PLX4720; Pexidartinib; BMS626529; Fevipiprant and HIV treatment

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CONFLICTS OF INTEREST

There are no conflicts to declare.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1. INTRODUCTION

Azaindoles are structurally bioisosteric chemical structures to ubiquitously appeared indoles in biological materials, natural products and pharmaceuticals.[1–12] There are four structural isomers of azaindoles, named as 4-, 5-, 6-, and 7- azaindoles (Fig. 1). Interestingly, these four structural isomers show distinct physicochemical properties such as Log P (partition coefficient between octanol and water), total polar surface area (*t*PSA), and aqueous solubility (Log S) due to the presence of extra nitrogen atom within the six membered ring in comparison to indole structure (Fig. 1). Therefore, these azaindoles attracted medicinal chemistry community for the last decade to derive a number of pharmacological agents that showed enhancements in medicinal chemistry properties.[13–15] Among these, 7-azaindole moiety has appeared in a plethora of biologically active molecules, relatively more in comparison to other three structural isomers, although all four seems to be represented as biologically active and important moieties. Notably, a majority of azaindole molecules appear to target a variety of kinases as inhibitors, in comparison to other targets.[16] The biostructural analysis of azaindoles with kinase inhibitors revealed that two nitrogen atoms of azaindole form hydrogen bonds with the hinge region of the protein kinase, which is similar to the bonding pattern of adenine moiety of natural substrate ATP. Moreover, the introduction of *N*-atom in place of CH group in the molecules increases the aqueous solubility, results in favorable physicochemical, and adsorption, distribution, metabolism and excretion (DMPK), and pharmacokinetic (PK) properties, and molecular interactions as described in detail by Pennington and Moustakas.[17] Moreover, their ultimate biological/ pharmacological actions are beneficial to treat a variety of diseases, including but not limited to cancer, Alzheimer's disease, diabetes, allergen-induced asthma, HIV, influenza infections and other diseases as detailed in below sections.[18–31] Because of the biological significance witnessed by these azaindoles, various synthetic methods have also been developed to produce derivatives around these chemical structures.[32, 33] While number of derivatives have been synthesized by the reported methods thus far, challenges remain to develop additional derivatives around these azaindoles as described elsewhere.[31–33] As a part of our research on developing lead candidates towards Alzheimer's disease, we have made several indole[34–36] and azaindole derivatives. The literature survey of azaindoles offered significant therapeutic potential, which attracted us to review the recent developments in azaindole motifs. Herein, we have highlighted the pharmacological, biological properties of various isomeric azaindoles. The literature on these azaindoles biological activity appeared vast; therefore, we only surveyed and cited the literature from 2011-till now in this review article to stay focused on current developments.

1.1 Therapeutically advanced naturally occurring and synthetic azaindoles

Azaindoles are widely represented in natural products, biologically active molecules and FDA approved drugs. For example, Guitarrins A-D (**1**–**4**, Fig. 2) are isolated from marine sponge Guitarra fimbriata, which exhibited a weak inhibition activity against alkaline phosphatase from the marine bacterium *Cobetia marina*. Variolin B (**5**) and deoxyvariolin B (**6**, aka, PM01218) were isolated from the rare access Antarctic sponge, *Kirkpatrickis variolosa*. Variolins **5** and **6** displayed potent cytotoxic activity against number of cancer cell lines including P388 murine leukemia cells.[37] These derivatives are reported to inhibit

various kinases such as cyclin dependent kinases (CDKs), glycogen synthase kinase-3 (GSK-3), cyclic nucleotide-dependent kinases, and casein kinase 1 (CK1), and subsequently show anti-proliferative effects. From these, deoxyvariolin **6** has been investigated in clinical trials as an anti-tumor agent. These natural products inspired the development of synthetic derivatives, Meriolin 1 (**7**) and Meriolin 3 (**8**), which showed improved potency, selectivity toward CDKs and exhibited better anti-proliferative and pro-apoptotic properties in cell cultures than their parent molecules. In particular, Meriolin 3 significantly inhibited tumor growth in two mouse xenograft models.[37]

Inspired by the above natural products, several biologically active azaindole clinical candidates and drugs have been developed thus far. For example, 7-azaindole derivative vemurafenib (**9**) (aka., PLX4720 and Zelboraf®) (Fig. 3), a potent protein kinase inhibitor that delays tumor growth, has received an FDA approval for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation.[38] Likewise, a 7-azaindole derivative pexidartinib (**10**, Fig. 3) (Turalio®), a tyrosine kinase inhibitor, received a FDA approval for the treatment of adult patients with symptomatic tenosynovial giant cell tumors associated with severe morbidity.[27, 39] A 6-azaindole derivative named Temsavir (aka, BMS-626529) (**11a**, Fig. 3) and its prodrug known as Fostemsavir **11b** (aka., BMS-663068 (Fig. 3) have been shown to inhibit the attachment of viral gp120 thus preventing HIV entry. After 96 weeks of treatment, Fostemsavir has shown HIV viral suppression in 60% of the clinical study participants with HIV; therefore, it has been recently approved by the FDA for HIV treatment.[26, 28] Another 7-azaindole clinical candidate named Fevipiprant (**12**, Fig. 3) is a prostanoid receptor DP2 antagonist, has been promoted for the treatment of asthma, however, it failed to meet clinical endpoints in the phase III trial, thus dropped from the clinic.[22, 29]

1.2 Azaindole's biological activities

The above clinical candidates and drugs inspired many pharmaceutical companies and academic laboratories to develop various other azaindoles and investigate their biochemical and pharmacological properties in vitro and therapeutic efficacy in vivo models. For example, it has been reported that 7-azaindole derivative JNJ-63623872 (**13**, Fig. 4) as a potent influenza polymerase-B2 inhibitor with activity against multiple influenza strains such as H1N1 and H5N1.[18,19, 40] Similarly, 7-azaindole **14** (Fig. 4) inhibit PI3K at molecular and cellular level and tumor cell proliferation,[23] it is noteworthy to mention that the two nitrogen atoms of 7-azaindole form two hydrogen bonds with Val882 of PI3Kγ. Several compounds belongs to 7-azaindole represented by compound **15** are looking promising as anti-cancer agents via PIM2 (proviral integration site for moloney murine-2 Leukemia virus) kinase inhibition.[21] Interestingly, 2-substituted-6-azaindoles represented by compounds **16** and **17** have shown promising glucocorticoid receptor agonist activity in vitro and they reduced collagen-induced arthritis, and prevented bone loss in mouse compared with traditional steroidal glucocorticoid agonists.[20, 41] Another, 6-azaindole derivative named GNF2133 (**18**, Fig. 4) has been developed as DYRK1A inhibitor and has been shown to promote β-cell proliferation, glucose disposal capacity and insulin secretion in response to glucose potentiated arginine-induced insulin secretion challenged rats and mice, therefore they can be used for treatment of type 1 diabetes.[15]

Several other 7-azaindole derivatives that show promising biological activities are worth highlighting here. For example, 2-,5-disubstituted-7-azindole **19** has shown inhibition activity against multiple kinases (34 out of 104 kinases tested) and broad anti-proliferative activity against various cancer cells including PC-3, Caki-2, MDA-MB-231 and NCI-H1975.[42] A study reports that substitution of one of the amino groups in anti-mitotic drug cisplatin with 1-methyl-7-azaindole moiety to afford compound **20** (*cis*-[$PtCl_2(NH_3)$(1-methyl-7-azaindole)], Fig. 5), increased efficiency and selectivity for tumor cells in cisplatin resistant cancer cells, and this was associated with increased level of cellular DNA platination by azaindole moiety.[43] DYRK kinases, DYRK1A, DYRK1B and DYRK2, are implicated in progression of various cancers including glioblastoma. A number of 7-azaindole derivatives represented by compound **21** have shown to inhibit viability, survival, migration and invasion of glioblastoma with nanomolar potency against DYRK1B and DYRK2 kinases.[44] Likewise, 7-azaindole sulfonamide **22** showed anti-proliferative activity against various cancer cell lines, anti-tumor activity in colorectal HCT116 xenografts via inhibition of HDAC6 enzyme with good selectivity against HDAC1 and HDAC2.[8] A 7-azaindole clinical candidate AZD6738 (**23**, Fig. 5) is shown to inhibit growth of ataxia telangiectasia mutation (ATM) deficient xenografts via ataxia telangiectasia mutated and Rad3 related (ATR) kinase inhibition mechanism.[6] Similarly, 7-azaindole **24** (Fig. 5) has shown promising activities against dengue virus both in vitro and in human primary dendritic cells and Ebola virus via adaptor-associated kinase 1 (AAK1) that functions as a key regulator of the trafficking of multiple unrelated RNA viruses.[45] Likewise, 7-azaindole molecule named URMC-099 (**25**, Fig. 5) has been shown to display neuroprotective and anti-neuroinflammatory properties in vitro and in vivo models of HIV-1 associated neurocognitive disorders (HAND) via inhibition of mixed lineage kinase 3 (MLK3) and leucine-rich repeat kinase 2 (LRRK2).[46] Similarly, 3,5-disubstituted-7-azaindoles such as **26** (Fig. 5) have shown anti-tumor activity in triple negative breast cancer mouse model, via inhibition of activity against cyclin-dependent kinases (CDK2 and CDK9).[47]

Several compounds belongs to 1,3-disubstituted-4-azaindole such as PF-06764427 (**27**) and **28** (Fig. 6) have shown as M1 mAChR PAM agonists and potential treatment for Alzheimer's disease.[48] 1,3-disubstituted-4-azaindoles (e.g. **29**) kills *Mycobacterium tuberculosis* in vitro and efficacious in mouse TB model via non-covalent inhibition of decaprenylphosporyl-β-D-ribose2'-epimerase (DprE1), which plays a key role in synthesis of mycobacterial cell wall arabinan.[10]

Likewise, several 2-,5-disubstituted-4-azaindoles such as **30** (Fig. 6) have been shown as promising anti-proliferative agents against human cancer cell lines, via selective inhibition of Aurora A kinase with significant selectivity against CHK1, CDK2, and MEK1, GSK3β, BRAF, IKKβ and PKC.[49] 7-Azaindole-1-carboxamide named as ST7710AA1 (**31**, Fig. 6) displayed anti-proliferative activity against cancer cell lines in vitro, and antitumor activity against MX1 human breast cancer growth in nude mice via inhibition of poly(ADP-ribose)polymerase protein-1 (PARP-1), which is involved in DNA integrity and regulation of programmed cell death.[24] Moreover, a 7- azaindole derivative NVP-QAV680 (**32**) has emerged as a clinical candidate for the treatment of allergic diseases such as Asthma via selective antagonism of CRTh2 receptor (also known as prostanoid receptor DP2).[50] Several

7-azaindoles **33–36** (Fig. 6) are discovered as ROCK (Rho Kinase) inhibitors, which will find useful for the development of therapeutic agents for variety of disorders including hypertension, glaucoma, and erectile dysfunction.[25, 51, 52]

Likewise, 3,4-disubstituted-7-azaindole such as NPS-1034 (**37**, Fig. 7) was found to inhibit AXL (a receptor tyrosine kinase), which plays a key role in growth and proliferation of cancer cells.[53] Other 7-azaindoles such as **38** has shown anti-HIV properties via non-nucleoside reverse transcriptase (NNRT) inhibition activity,[54] and, **39** and **40** (Fig. 7) have been shown to inhibit CC-chemokine receptor-2 (CCR2), which is heavily implicated in various inflammatory pathological conditions such as asthma, atherosclerosis, rheumatoid arthritis and multiple sclerosis.[55, 56] Additionally, tropomyosin-related kinase (Trk) is one of the important targets for development of therapeutics for the treatment of cancer and pain. A novel 7-azaindole derivative **41** was identified as Trk inhibitor through the structure-based design strategy and found to be selective inhibitor for TrkA over a panel of 30 other kinases (Fig. 7).[57, 58] Finally, 7-azaindole derivative **42** (Fig. 7) showed anti-inflammatory activity, and inhibition of airway cell infiltration in bronchoalveolar lavage fluid (BALF) in ovalbumin induced rat model of allergic inflammation, via inhibition of Orai calcium channel.[59] Furthermore, not only as therapeutic agents, azaindole moiety is appeared in unnatural amino acids such a 7-azatryptophan (**43**, Fig. 7), which is found to show pH sensitive vibrational frequencies and can be used as sensitive proton transfer markers in gated proton transfer reactions in photosystem II and other enzymes.[60]

The above listed compounds in Figures 4, 5, 6 and 7 are not comprehensive of various azaindole-containing biologically active molecules, however, these are the molecules reported with clear understanding on the molecular target, mechanism of action and animal proof-of-concept study; therefore, these may be useful for further development into therapeutically useful drugs.

2. CONCLUSIONS

From the above discussion, it is clear that azaindoles with a wide range of pharmacological and biological activities continue to attract and entice the medicinal chemistry community to develop them for therapeutic use. Interestingly, the biophysical and metabolic properties of azaindole framework are modulated by functionalization pattern and position of nitrogen atom in a six-membered ring (Fig. 1). Due to high biological significance, several laboratories have investigated syntheses for these isomeric azaindoles in the recent years, by many unconventional methods using simple building blocks and novel metal catalytic and metal-free conditions, which will further aid in design of diversely substituted novel azaindole therapeutics.

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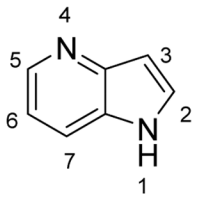
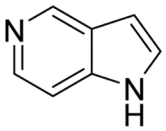
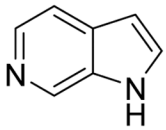


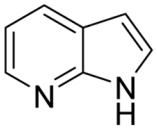
4-Azaindole:
1*H*-pyrrolo[3,2-*b*]pyridine
Log P: 0.66
*t*PSA: 24.39
CLogP: 1.385
LogS: -1.464



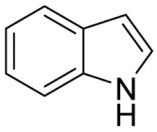
5-Azaindole:
1*H*-pyrrolo[3,2-*c*]pyridine
Log P: 0.24
*t*PSA: 24.39
CLogP: 1.175
LogS: -1.4



6-Azaindole:
1*H*-pyrrolo[2,3-*c*]pyridine
Log P: 0.24
*t*PSA: 24.39
CLogP: 1.175
LogS: -1.389



7-Azaindole:
1*H*-pyrrolo[2,3-*b*]pyridine
Log P: 0.98
*t*PSA: 24.39
CLogP: 1.175
LogS: -1.897



Indole:
1*H*-indole
Log P: 1.57
*t*PSA: 12.03
CLogP: 2.132
LogS: -2.275

Fig. 1:
Azaindoles and their chemical names and biophysical properties (calculated using ChemDraw software 16.0).

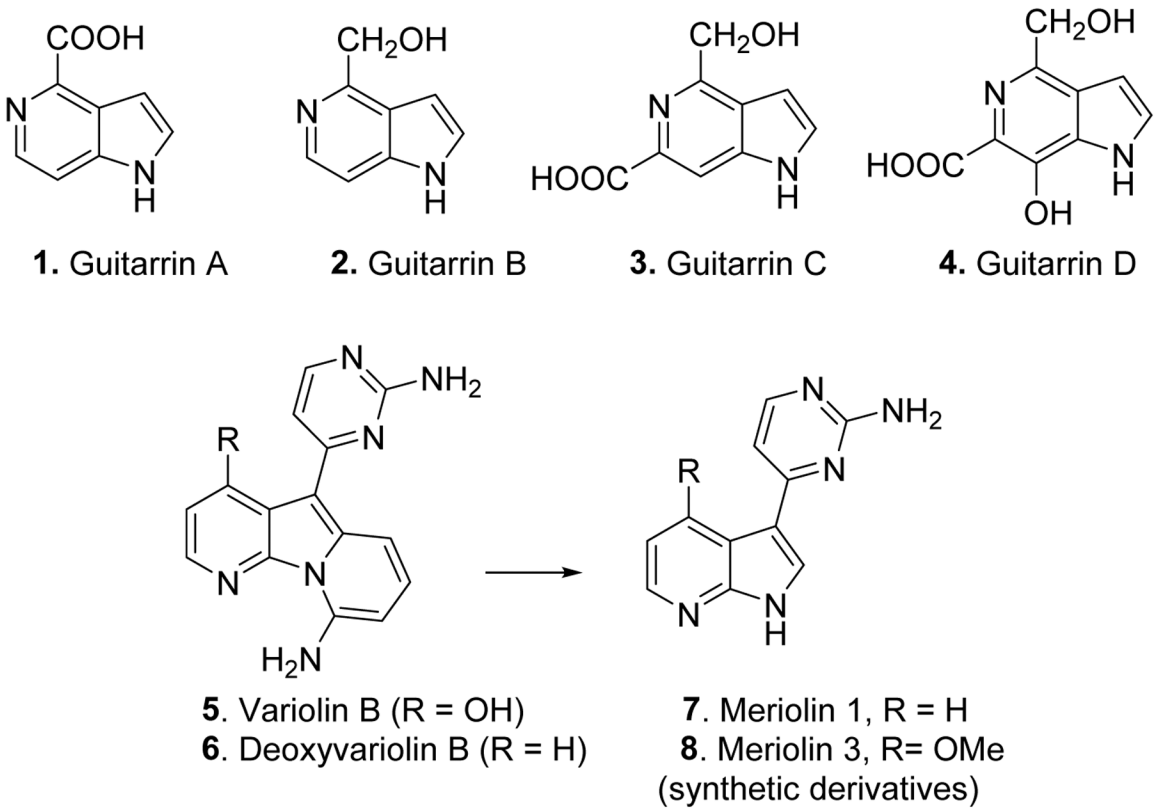


Fig. 2:
Azaindole natural products and synthetic derivatives.

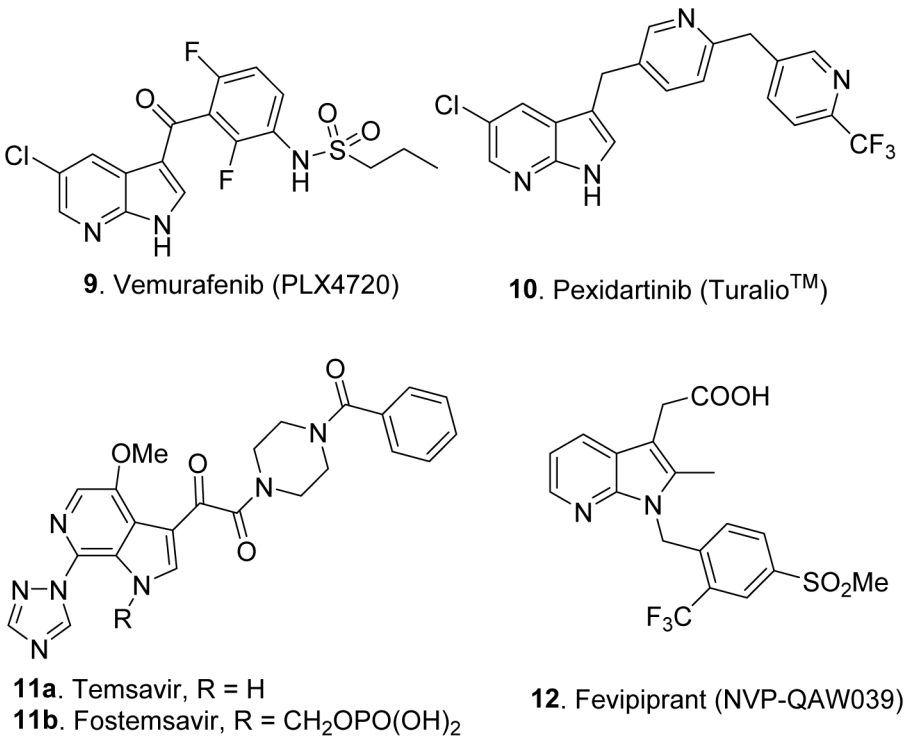


Fig. 3:
FDA approved drugs and clinical candidates with the azaindole core unit.

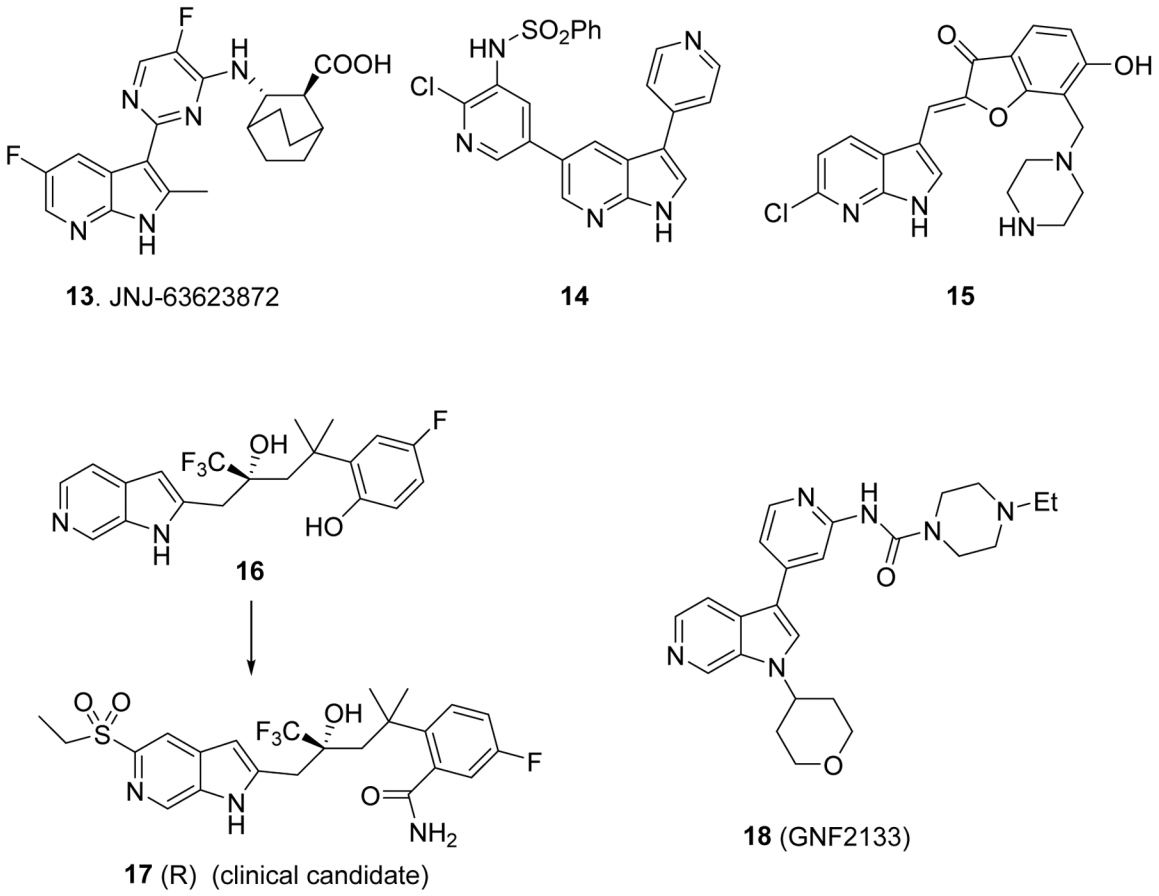


Fig. 4:
Clinical candidates and promising molecules of azaindole derivatives.

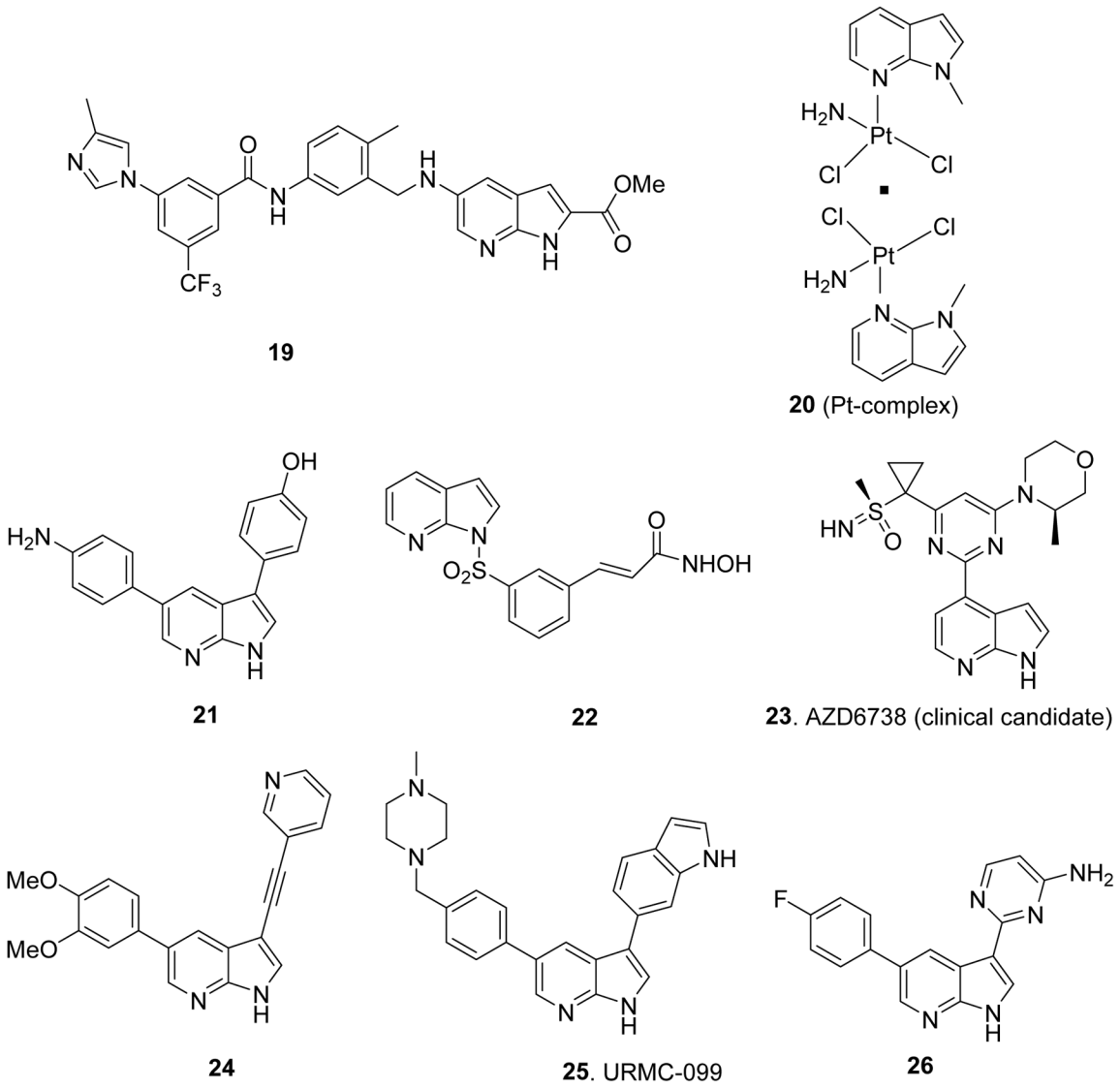


Fig. 5:
Azaindole derivatives that displayed promising biological activity.

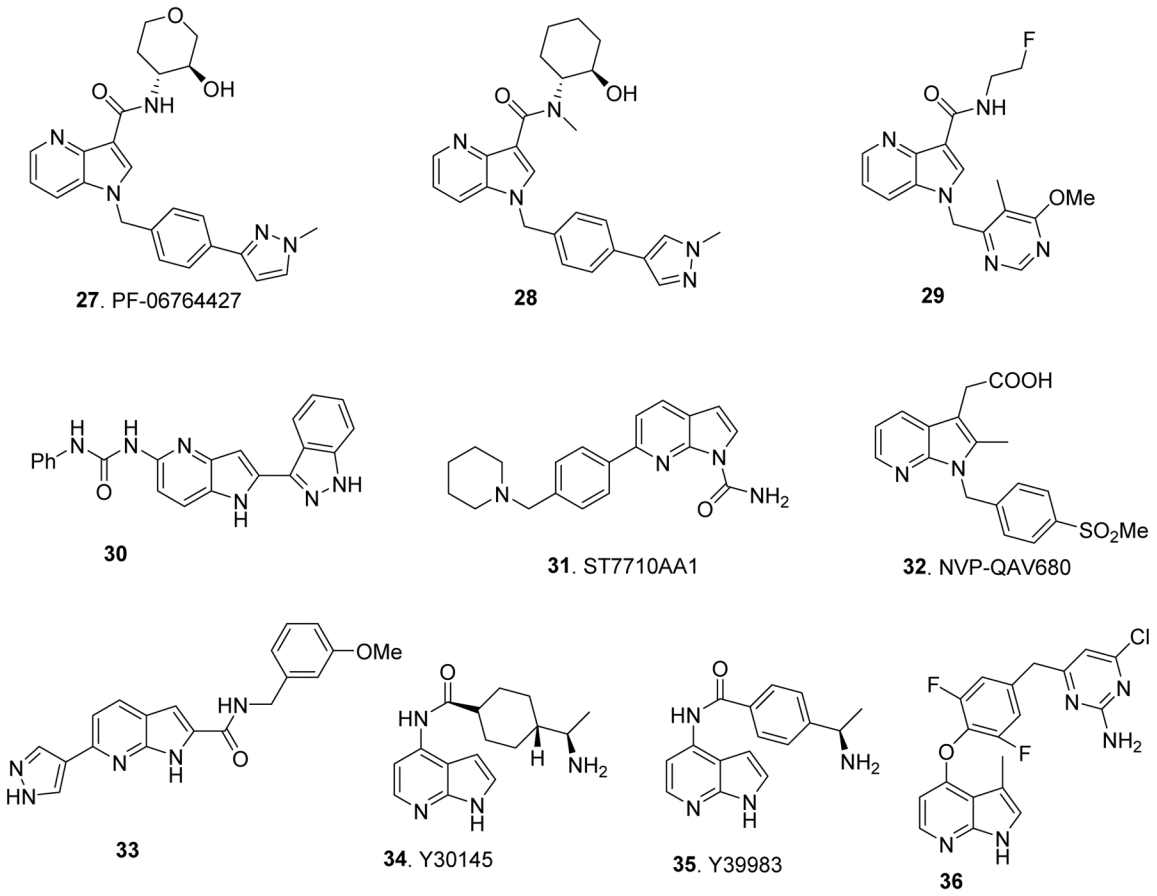


Fig. 6:
Bioactive azaindole derivatives.

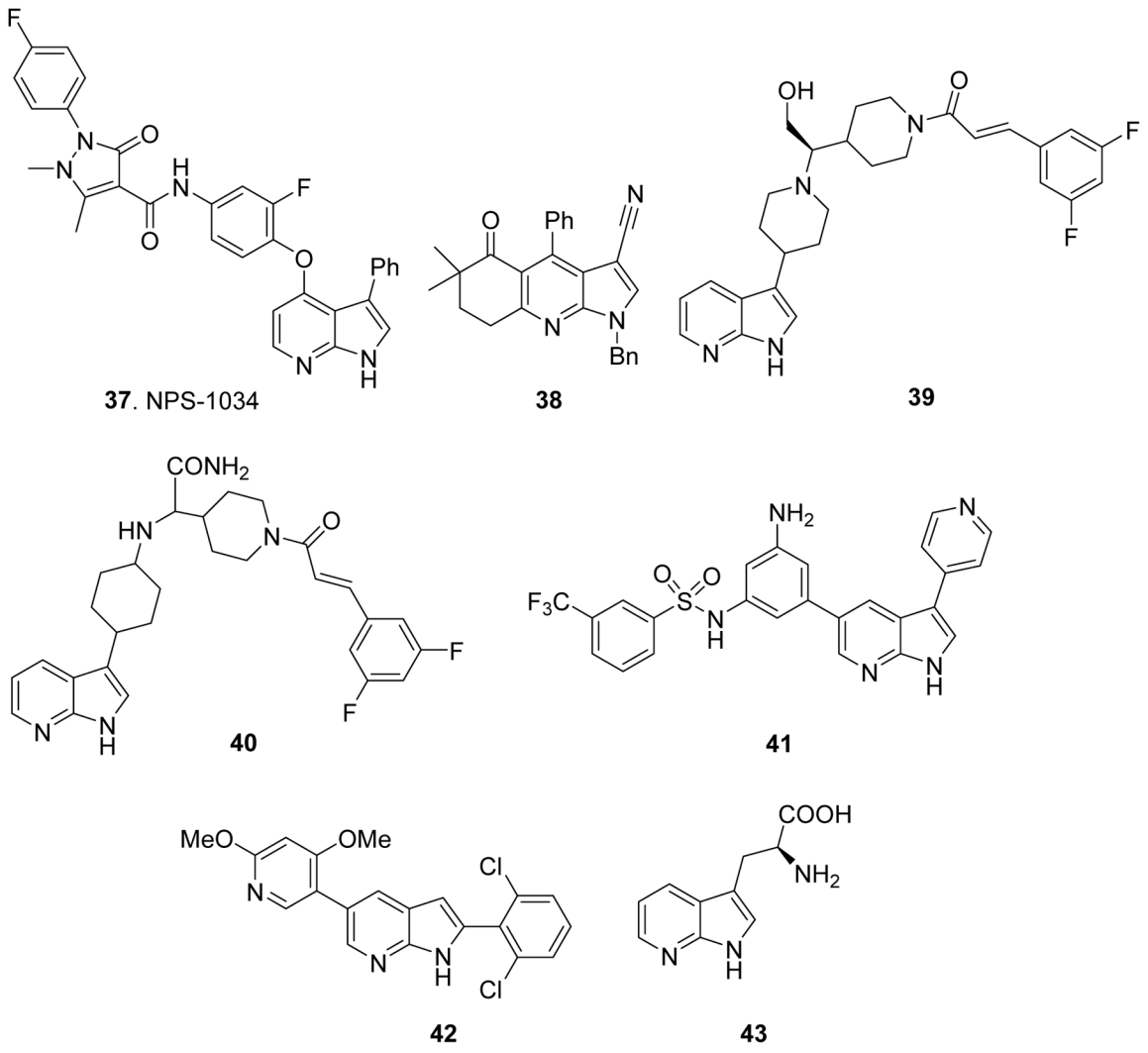


Fig. 7:
Additional biologically interesting azaindole derivatives.