Pyrrolo[2,1-f][1,2,4]triazine: a promising fused heterocycle to target kinases in cancer therapy

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Abstract
Cancer is the second leading cause of death worldwide responsible for about 10 million deaths per year. To date several approaches have been developed to treat this deadly disease including surgery, chemotherapy, radiation therapy, hormonal therapy, targeted therapy, and synthetic lethality. The targeted therapy refers to targeting only specific proteins or enzymes that are dysregulated in cancer rather than killing all rapidly dividing cells, has gained much attention in the recent past. Kinase inhibition is one of the most successful approaches in targeted therapy. As of 30 March 2021, FDA has approved 65 small molecule protein kinase inhibitors and most of them are for cancer therapy. Interestingly, several kinase inhibitors contain one or more fused heterocycles as part of their structures. Pyrrolo[2,1-f][1,2,4]triazine is one the most interesting fused heterocycle that is an integral part of several kinase inhibitors and nucleoside drugs viz. avapritinib and remdesivir. This review articles focus on the recent advances made in the development of kinase inhibitors containing pyrrolo[2,1-f][1,2,4]triazine scaffold.

Keywords Pyrrolo[2,1-f][1,2,4]triazine · Kinase inhibition · Fused heterocycles · Cancer · Targeted therapy

Introduction
Cancer is the second leading cause of death worldwide responsible for about 10 million deaths per year [1]. On average, one in six deaths is due to cancer. To date, several approaches have been developed to treat this deadly disease viz. surgery [2], chemotherapy [3–6], radiation therapy [7], hormonal therapy [8, 9], targeted therapy [10].
therapy [10–13], and synthetic lethality [14]. The choice of treatment depends upon the type, location, and stage of cancer. The use of surgery, hormone therapy, chemotherapy, and radiation therapy are being in use since the 19th century whereas immunotherapy and targeted therapies were developed in the 20th century. If detected early, surgery is the best choice of treatment; however, in most cases cancer is metastasized to other parts of the body prior to detection so requires combination of other therapies prior or after surgery. Radiation therapy involves the use of ionizing radiations (X-ray) to kill cancer cells and shrink tumors. Radiation therapy is not preferred if cancer is diagnosed in late stages or if the tumor is located on vulnerable places. Chemotherapy involves the use of single or combination of cytotoxic drugs which affect rapidly dividing cells. The major drawback of chemotherapy is its specificity, the cytotoxic drugs also kill healthy cells especially those which are fast growing e.g., cells on intestinal lining. Several combinations of cytotoxic drugs have been developed to treat various forms of cancers e.g., combination of cyclophosphamide, methotrexate, 5-fluorouracil, vinorelbine is given to patients with breast cancer [15], the combination of Doxorubicin, bleomycin, vinblastine, dacarbazine is optimized for Hodgkin’s lymphoma [16]. Immunotherapy refers to use of therapeutic strategies that involve the use of patient’s own immune system to fight cancer. Examples include the use of interferons and other cytokines [17, 18] to induce an immune response in patients with renal cell carcinoma and melanoma [19, 20]. Hormonal therapy refers to the blocking or administration of certain hormones to treat cancer. For example, the blocking of estrogen or testosterone is beneficial in some patients suffering from breast or prostate cancers [21, 22]. However, in most cases the patients develop resistance to hormone therapy demanding the use of next-generation drugs [23]. Synthetic lethality is an approach used to explore those cancers in which a combination of deficiencies in the expression of two or more genes leads to cell death but one of these genes does not. Examples include the use of PARP inhibitors Olaparib, Rucaparib, Niraparib for ovarian cancer patients with mutated BRCA1 [24, 25].

Targeted therapy refers to the use of those drugs that target only specific proteins or enzymes that are dysregulated in cancer rather than killing all rapidly dividing cells [10, 26, 27]. Various small organic molecules and monoclonal antibodies are in clinical use that targets such enzymes or proteins. Examples include the use of tyrosine kinase inhibitors imatinib (for chronic myelogenous leukemia and acute lymphocytic leukemia) and gefitinib (for certain breast and lung cancers) [28, 29]. Rituximab is a monoclonal antibody used to treat non-Hodgkin lymphoma, chronic lymphocytic leukemia, and certain autoimmune diseases [30–32]. Although all approaches are used to treat various forms of cancer, the use of targeted therapy is an active and most advanced area of cancer research these days.

Kinases are the enzymes that catalyze the transfer of phosphate groups from high-energy, phosphate-donating molecules to specific substrates viz. proteins, lipids, and carbohydrates through a process known as phosphorylation [33–36]. Kinases have been classified into different categories depending upon the substrate they phosphorylate. Protein kinases are kinases that phosphorylate amino acids residues of proteins either on serine/threonine and/or tyrosine or histidine residues. Approximately 30% of the current R&D budget in pharmaceutical companies is focused on developing kinase inhibitors to treat cancer, inflammatory disorders, and other diseases. After the approval of Imatinib, a tyrosine kinase inhibitor, in 2001, FDA has approved 65 small molecule protein kinase inhibitors as of 30 March 2021 [37].

Fused heterocycles are the organic compounds in which two heterocycles are fused and the π-electrons move on both heterocyclic rings by resonance thus providing a unique set of electrons donors and acceptors. Fused heterocycles are of high interest in designing drugs targeting kinases due to their ability to provide selectivity for a specific kinase or its isoform [38–41]. The presence of multiple heteroatoms at specific positions on fused heterocycles allows them to form hydrogen bonds and other interactions with surrounding amino acid residues that are sometimes not possible with monocyclic heterocycles [42] or heterocycles fused with phenyl rings [43]. Most of the FDA-approved kinases inhibitors contain one or more heterocyclic rings and 29 among them (Table 1) possess fused heterocycles with two or more nitrogen atoms. Pyrrolo[2,1-f][1,2,4]triazine is one of the most interesting fused heterocycles that is an integral part of several kinase inhibitors and nucleoside drugs [44]. It is an integral part of avapritinib recently approved for adults with unresectable or metastatic gastrointestinal stromal tumor harboring a platelet-derived growth factor receptor alpha exon 18 mutation, including D842V mutations [45]. Pyrrolo[2,1-f][1,2,4]triazine is also a part of nucleoside [46, 47] drug remdesivir used to treat broad-spectrum viral infections including SARS COVID-19 [48]. Various synthetic strategies have been developed to synthesize pyrrolo[2,1-f][1,2,4]triazine either starting from triazine or pyrrole [48]. Scheme 1 depicts the general methods of synthesis of pyrrolo[2,1-f][1,2,4]triazine. The focus of this review is to cover the recent advances made in the development of various kinase inhibitors possessing pyrrolo[2,1-f][1,2,4]triazine scaffold.
Table 1 List of FDA-approved kinase inhibitors with fused heterocyclic rings

| Name           | Structure | Target                          | Fused heterocycle           | References |
|----------------|-----------|---------------------------------|-----------------------------|------------|
| Abemaciclib    | ![Abemaciclib](image1) | CDK4/6                          | benzimidazole               | [157]      |
| Acalabrutinib  | ![Acalabrutinib](image2) | Bruton tyrosine kinase          | dihydroimidazo[1,5-a] pyrazine | [158]      |
| Afatinib       | ![Afatinib](image3) | EGFR, ErbB2, ErbB4              | quinazoline                 | [159]      |
| Avapritinib    | ![Avapritinib](image4) | GIST with PDGFR exon 18 mutations | pyrrolo[2,1-f][1,2,4] triazine | [45]       |
| Axitinib       | ![Axitinib](image5) | VEGFR1/2/3, PDGFRβ              | indazole                    | [160]      |
| Baricitinib    | ![Baricitinib](image6) | JAK1/2                          | pyrrolo[2,3-d]pyrimidine     | [161]      |
| Benimetinib    | ![Benimetinib](image7) | MEK1/2                          | benzimidazole               | [162]      |
| Name          | Structure | Target                      | Fused heterocycle          | References |
|---------------|-----------|-----------------------------|----------------------------|------------|
| Capmatinib    | ![Capmatinib Structure](image1) | MET                         | imidazo[1,2-b][1,2,4]triazine | [86]       |
| Dacomitinib   | ![Dacomitinib Structure](image2) | FR/ErbB2/ErbB4              | quinazoline                | [163]      |
| Erdafitinib   | ![Erdafitinib Structure](image3) | FGFR1/2/3/4                 | quinazoline                | [164]      |
| Erlotinib     | ![Erlotinib Structure](image4) | EGFR                        | quinazoline                | [165]      |
| Gefitinib     | ![Gefitinib Structure](image5) | EGFR                        | quinazoline                | [163]      |
| Ibrutinib     | ![Ibrutinib Structure](image6) | Bruton tyrosine kinase      | pyrazolo[5,4-d]pyrimidine  | [166]      |
| Lapatinib     | ![Lapatinib Structure](image7) | EGFR, ErbB2                | quinazoline                | [167]      |
| Larotrectinib | ![Larotrectinib Structure](image8) | NTRK                        | pyrazolo[1,5-a]pyrimidine  | [168]      |
| Name     | Structure | Target                          | Fused heterocycle                  | References |
|----------|-----------|---------------------------------|------------------------------------|------------|
| Palbociclib | ![Image](image1) | CDK4/6                          | pyrido[2,3-d]pyrimidin-7-one       | [169]      |
| Pazopanib   | ![Image](image2) | VEGFR1/2/3, PDGFRα/β, FGFR1/3, Kit, Lck, Fms, Itk | indazole                       | [170]      |
| Pemigatinib | ![Image](image3) | FGFR2                           | pyrrolo[2,3-b]pyridine            | [171]      |
| Pexidartinib | ![Image](image4) | CSFR1/Kit                       | pyrrolo[2,3-b]pyridine            | [172]      |
| Ponatinib   | ![Image](image5) | BCR-Abl, BCR-Abl T315I, VEGFR, PDGFR, FGFR, EphR, Src family kinases, Kit, RET, Tie2, Flt | Imidazo[1,2-b]pyridazine         | [173]      |
| Ribociclib  | ![Image](image6) | CDK4/6                          | pyrrolo[2,3-d]pyrimidine          | [169]      |
| Name        | Structure | Target          | Fused heterocycle | References |
|-------------|-----------|-----------------|-------------------|------------|
| Ruxolitinib | ![Ruxolitinib](image1) | JAK1/2          | pyrrolo[2,3-d]pyrimidine | [174]       |
| Selpercatinib | ![Selpercatinib](image2) | RET            | pyrazolo[1,5-a]pyridine | [175]       |
| Selumetinib | ![Selumetinib](image3) | MEK1/2         | benzo[d]imidazole   | [176]       |
| Tofacitinib | ![Tofacitinib](image4) | JAK1/3         | pyrrolo[2,3-d]pyrimidine | [177]       |
| Trilaciclib | ![Trilaciclib](image5) | CDK4/6         | pyrrolo[2,3-d]pyrimidine | [178]       |
| Tucatinib  | ![Tucatinib](image6) | ErbB2/HER2     | quinazoline and [1,2,4]triazolo[1,5-a]pyridine | [179]       |
| Vandetanib | ![Vandetanib](image7) | EGFRs, VEGFRs, RET, Brk, Tie2, EphRs, Src family kinases | quinazoline | [180]       |
| Vemurafenib | ![Vemurafenib](image8) | A/B/C-Raf, B-Raf (V600E), SRMS, ACK1, MAP4K5, FGR | pyrrolo[2,3-b]pyridine | [181]       |
Tyrosine kinase inhibitors

Receptor tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKI) are the largest class of kinase inhibitors. 48 among 62 FDA-approved kinases inhibitors target tyrosine kinases [49, 50]. 13 among 48 are non-receptor tyrosine kinase inhibitors whereas 35 target receptor protein tyrosine kinases [37]. In 2020 FDA approved 10 TKI viz. Tepotinib, Capmatinib, Pemigatinib, Ripertinib, Avapritinib, Tucatinib, Selumetinib, Pralsetinib, and Seppercatinib [51]. The epidermal growth factor receptor (EGFR, ErbB-1, HER1) is a transmembrane tyrosine kinase receptor that belongs to the ERBB family of proteins [52]. EGFR regulates several cell signaling pathways, proliferation, differentiation, and division. EGFR family consists of four closely related proteins EGFR (HER1/ErbB1), ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4) [53]. The activation and auto-phosphorylation of the intracellular tyrosine kinase domain of receptors trigger several signaling pathways such as PI3K/AKT/mTOR, RAS/RAF/MEK, and STAT. Over-expression of EGFR results in the development of various cancers. Blocking of EGFR signaling has developed as a promising therapeutic strategy to prevent the growth of EGFR-expressing tumors. Several small organic molecules developed as EGFR TKIs are either in clinical use or clinical/preclinical trials [54]. Gefitinib and erlotinib are the first-generation EGFR inhibitors approved for the treatment of NSCLC patients in 2003 and 2004, respectively [55, 56].

Scheme 1 Reagents and conditions: a Tetracyanoethylene oxide, THF; b Phenyl vinyl sulfoxide, 1,4-dioxane, Reflux; c NaH, DMF, NH₂Cl, rt; d KOH, H₂O, rt; e pyridine, CICO₂Et, dioxane, 110°C; f EtOH, EtONa, reflux; g POCl₃, DIPEA, 120 °C; h NH₃, H₂O, 80 °C; i (1) Chloramine, KO-t-Bu, THF, 10 °C; (2) Benzoyl isothiocyanate, THF; j (1) 2 M NaOH, H₂O, 85 °C, (2) MeI, THF, 45 °C; k CCl₂NMe₂Cl, ClCH₂CH₂Cl, Reflux; l HCl; m POCl₃, PCl₅, 110 °C [143, 151–156]
VEGF are receptors for vascular endothelial growth factors (VEGF). These are of three main types, VEGF1, VEGF2, and VEGF3 [57, 58]. Overexpression of VEGF receptors is linked to soft tissue sarcomas, renal cell carcinomas, colorectal cancers, thyroid cancer, and several other cancers. Axitinib (VEGF1 inhibitor) [59], Cabozantinib (VEGF2 inhibitor) [60], Lenvatinib (VEGF2 inhibitor) [61], Pazopanib (VEGF1/2/3 inhibitor) [62], Sorafenib (VEGF1/2/3 inhibitor) [63], pazopanib (VEGF1/2/3 inhibitor) [64], Sunitinib (VEGF2 inhibitor) [65], and Vandetanib (VEGF2 inhibitor) [66] are in clinical use for the treatment of various cancers [67].

Fig. 1 Structures of compounds 1–3

VEGF2, and VEGF3 [57, 58]. Overexpression of VEGF receptors is linked to soft tissue sarcomas, renal cell carcinomas, colorectal cancers, thyroid cancer, and several other cancers. Axitinib (VEGF1 inhibitor) [59], Cabozantinib (VEGF2 inhibitor) [60], Lenvatinib (VEGF2 inhibitor) [61], Pazopanib (VEGF1/2/3 inhibitor) [62], Sorafenib (VEGF1/2/3 inhibitor) [63], pazopanib (VEGF1/2/3 inhibitor) [64], Sunitinib (VEGF2 inhibitor) [65], and Vandetanib (VEGF2 inhibitor) [66] are in clinical use for the treatment of various cancers [67].

Hunt et al. synthesized a series of compounds possessing pyrrolo[2,1-f][1,2,4]triazine nucleus and evaluated their activity on VEGF-2 and EGFR kinases [68]. Compounds 2 (IC_{50} = 0.066 μM) and 3 (IC_{50} = 0.023 μM) displayed most potent activities against VEGF-2, whereas compound 1 (IC_{50} = 0.100 μM) was more selective for EFGR (Fig. 1). Compounds were also tested for their activities on DiFi cell lines (cells sensitive to EGFR inhibitors) and human umbilical vein endothelial cells (HUVECs). However, the cellular behaviors of these compounds were somewhat inconsistent.

The same group also synthesized another series of pyrrolotriazine derivatives as VEGFR-2 inhibitors [69]. Compounds 4 and 5 (Fig. 2) displayed the most potent cellular activity and VEGFR-2 inhibition. Low rates of glucuronidation (an indication of higher metabolic stability) were observed with both compounds.

The fibroblast growth factor receptors (FGFR) are the family of tyrosine receptor kinases that bind to members of the fibroblast growth factor (FGF) family of proteins and regulate the fundamental process of cell development [70]. These are of four main types, FGFR 1, FGFR2, FGFR3, and FGFR4. FGFR5 (also known as FGFRL1) is a closely related receptor that can bind FGFs but has no tyrosine kinase domain. FGFRs are over-expressed in several cancers [71]. Erlotinib (EGFR1/2/3/4 inhibitor), Nintedanib (FGFR1/2/3) are the only two FGFR inhibitors currently in clinical use for the treatment of Urothelial bladder cancers and Idiopathic pulmonary fibrosis [72–74].

Borzilleri et al. reported some substituted 4-(2,4-difluoro-5-(methoxy carbamoyl)phenylamino)pyrrolo[2,1-f][1,2,4]triazines as inhibitors of VEGF-2 and FGFR-1 [75]. Compounds 6, 7, and 8 displayed the most potent activities among all compounds screened (Fig. 2). Table 2 shows the VEGF-2, FGFR-1, and cellular activities of compounds 6–8. Docking studies revealed 8 to be an ATP competitive inhibitor of VEGF-2. Hydrogen-bond interactions between amide-NH of Cys919 and the N1 of the pyrrolo[2,1-f][1,2,4]triazine ring anchored 8 to the hinge region of the adenine binding pocket (Fig. 2). In kinase profiling, compound 8 showed a good selectivity over a panel of kinases including HER-1, HER-2, Pdgfr-α, IGF-1R, Pkcr, and CDK2. Compound 8 also showed well in vitro metabolic stability and PK profile. In the L2987 cells-driven human lung carcinoma xenograft model, 8 showed robust in vivo efficacy at multiple dosing with no observation of morbidity or weight loss.

Fink Lab discovered compound 9 as potent and selective inhibitor of EGFR (IC_{50} = 0.04 μM) and HER2 (IC_{50} = 0.04 μM) [76]. It exhibited IC_{50} values of 0.86 and 0.46 μM, respectively on BT474 (breast carcinoma) and Sal2 (saliary gland carcinoma) cell lines. Notably, both cell lines overexpress HER-2. In kinome screening, 9 showed up to 200-fold selectivity over FAK, p38, MAPKAP kinase 2, and IGF-1R (Fig. 3).

Mastalerz and co-workers discovered compounds 10 and 12 as dual inhibitors of EGFR and HER2 [77]. The methyl group on the pyrrolo ring was crucial for the activity of 10 and 12. Replacing the methyl group of 10 by OMe (compound 11) resulted in deterioration of activity against both kinases. Compound 10 was slightly more active than 12 against both kinases (Fig. 4).

In another report, the same group developed compound 13 containing a morpholine side chain on the pyrrolo ring of pyrrolotriazine [78]. A significant improvement of activity against EGFR (IC_{50} = 0.061 μM) and HER (IC_{50} = 0.055 μM) was observed compared to 10 and 12 (Fig. 4). Compound 13 also displayed good selectivity over a panel of kinases. In vitro cellular assay on N87 cells showed a dose-dependent inhibition of HER2 phosphorylation. Compound 13 showed a significant reduction of tumor in GEO and N87 xenografts mice model when dosed subcutaneously and orally. Docking studies revealed that 13 occupied ATP binding sites of EGFR whereas pyrrolotriazine N-1 formed hydrogen bonding with Met769 NH in the hinge region whereas benzyl indazole group was deeply
inserted in a hydrophobic pocket formed partially by the C-helix (Fig. 5).

Mastalerz lab developed 14 and 15 as dual inhibitors of EGFR and HER2 by modifications of earlier compound 13 in two different reports. In one report, 14 was shown as a lead [79] whereas 15 was reported as a lead in the second report [80] (Fig. 4). Both compounds showed comparable activities for both kinases but in cellular assay 15 was more potent than 14 on N87 cells. In N87 human gastric carcinoma and GEO human colon carcinoma athymic mouse xenograft models 15 showed TGI of 180 and 85% at dose loading of 180 mg/kg and 240 mg/kg, respectively.

Fink et al. reported compound 16 as a dual inhibitor of HER2 and EGFR [81]. It inhibited both HER2 and EEFAR with IC50 values of 0.01 and 0.006 µM, respectively. 16 was also active in cell assays carried out on N87 cells (IC50 = 0.12 µM). A significant tumor growth inhibition was noticed in EGFR driven GEO colon tumor xenograft mice model. The in vivo and in vitro activities of 16 were much better than 17, a lead compound discovered by the same group previously [82] (Fig. 6).

Cai et al. designed and synthesized some pyrrolo-triazine derivatives containing N-cyclopropylamides as VEGFR-2 kinase inhibitors which led to the discovery of 18 as a nanomolar inhibitor of VEGFR-2 (IC50 = 11 nM). Compound 18 was highly selective over CYP3A4, human cytochrome CYP450 isozyme (Fig. 6) [83]. Compound 18 also showed potent activity in VEGF-stimulated HUVEC proliferation assay. In the L2987 human lung carcinoma xenograft model in athymic mice, 18 showed 66% TGI at dose loading of 90 mg/kg with no adverse effects.

c-Mesenchymal-epithelial transition factor (c-Met also known as hepatocyte growth factor receptor is a protein tyrosine kinase that in humans is encoded by the MET gene [84]. c-Met involvement is crucial for the formation, metastasis, and invasion of various malignant tumors thus emerged as an attractive therapeutic target for cancer treatment [85]. Last year FDA approved Tabrecta (capmatinib), a c-Met inhibitor for the treatment of adult patients with non-small cell lung cancer (NSCLC) [86]. Shi et al. synthesized some pyrrolo[1,2-f][1,2,4]triazine derivatives as inhibitors of c-Met and VEGFR-2 [87]. Compound 19 showed micromolar activities against c-Met and VEGFR-2 with IC50 values of 2.3 ± 0.1 nM and 5.0 ± 0.5 nM, respectively. The kinase activity of 19 was not better than Foretinib (Fig. 7). IC50 values of 0.71 ± 0.16 nM and 37.4 ± 0.311 nM were observed against BaF3-TPR-Met and

Table 2 VEGFR-2 and FGFR-1 biochemical and cellular potencies of compounds 6, 7, and 8

| Entry | IC50 (nM) | Growth inhibition of HUVECs |
|-------|----------|---------------------------|
|       |          | VEGF | FGF |
| Kinase inhibition |
| VEGFR-2 | FGFR-1 |
| 6      | 57       | 100  | 17  | 21 |
| 7      | 16       | 16   | 2.1 | 4.6 |
| 8      | 53       | 220  | 27  | 130 |

Fig. 2 A Structures and activities of compounds 4-8; B Binding of 8 in the ATP binding sites of VEGFR-2 kinase (Figure reproduced with the permission of the original publisher)
HUVEC-VEGFR2 cells treated with 19. The docking study showed 19 occupied the same binding sites as Foretinib on c-Met and VEGFR-2. Compound 19 also showed good pharmacokinetic profile in SD rats after oral and intravenous injection (iv).

Schroeder et al. designed and synthesized some C-5 and C-6 substituted pyrrolotriazine derivatives and evaluated their activity against Met kinase [88]. Among them, compound 20 displayed good inhibitory activity against Met kinase (IC$_{50}$ = 0.045 μM) along with acceptable stability in mouse-liver microsome but with a poor clearance and oral bioavailability in PK studies. Compound 20 also showed poor cell permeability in Caco-2 assay (Pc < 15 nm/s). An X-ray crystal structure of 20 complexes with the Met kinase suggested binding in ATP-binding sites (Fig. 8). The pyrrolotriazine scaffold formed the H-bonding with Met1160 and Pro1158 in the hinge region whereas the NH$_2$ group attached to the piperidine ring formed H-bonding with Asp1164.

Anaplastic lymphoma kinase (ALK) also known as cluster of differentiation 246 (CD246), discovered in 1994 is a tyrosine receptor kinase encoded by the ALK gene [89–91]. It has two main domains, intracellular (tyrosine kinase domain) and extracellular (ligand-binding domain). The intracellular tyrosine kinase domain shares a high degree of similarity with insulin-like growth factor-1 receptor (IR) [92]. Axitinib, Brigatinib, Ceritinib, Crizotinib, Lorlatinib are the FDA-approved ALK inhibitors currently in clinical use for the treatment of NSCLC [37]. Ott et al. synthesized 2,7-disubstituted-pyrrolo[2,1-f][1,2,4]triazine 25(BMS-754807) as an inhibitor of IGF-1R (IC$_{50}$ = 2 nM) (Fig. 11). 25 showed high selectivity over CDK2E (inhibition of CDK2E also inhibits IGF-Sal cell lines) and showed nanomolar potency on IGF-Sal cell lines (IC$_{50}$ = 7 nM) [103]. 25 was also evaluated for in vivo efficacy in the transgenic-derived IGF-Sal tumor model. Complete tumor growth inhibition was observed in mice at a dosing of 6.25 mg/kg. The crystal structure of 25 co-crystallized with the kinase domain of IGF-1R revealed that the cyclopropyl group occupied the shallow “gate-keeper” region of the kinase, whereas fluoropyridyl amide was extended into the sugar pocket (Fig. 11). H-bonding with Met1052 and Glu1050 in the hinge region was crucial for high activity.

ALK-negative K562 cells at concentrations up to 3000 nM, indicating 21 inhibited ALK-positive ALCL cells primarily through inhibiting NPM-ALK activity. Compound 21 also showed good oral bioavailability in mice (F = 0.38). Oral dosing of 21 in SCID mice in a xenograft model (SUP-M2) inhibited tumor growth at 10, 30, and 55 mg/kg dose loading with no observable toxicity or body-weight loss.

Mesaros and co-workers discovered compound 22 as a potent ALK inhibitor displaying IC$_{50}$ of 6 nM along with high selectivity over IR (Fig. 9) [94]. In PK studies, 22 showed good iv half-life ($t_{1/2}$ = 3.4 h), low clearance (12 mL/min/kg) and good stability in rat liver microsomes. Compound 22 inhibited tumor growth in ALK-driven tumor xenograft dose-dependently in mice.

Mesaros et al. discovered isomeric compounds 23 and 24 (Fig. 10) as potent inhibitors of ALK displaying ALK enzyme inhibitory activities with IC$_{50}$ values of 3 and 5 nM, respectively [95]. Both compounds also displayed good activity on ALK cell lines. Change of cis (23) to trans (24) geometry did not deteriorate selectivity over IR or other kinases. When tested for in vivo efficacy in ALK-driven Sup-M2 tumor xenografts in SCID mice, 24 (trans-isomer) showed better tumor growth inhibition (75–87% at 30 mg/kg) than 23 (cis isomer) at the same dosing.

The insulin-like growth factor 1 (IGF-1) receptor is a transmembrane tyrosine receptor kinase found on the surface of human cells [96–98]. It is activated by insulin-like growth factor 1 (IGF-1) and related hormone IGF-2. IGF-1 induces hypertrophy of skeletal muscle and other target tissues and plays an important role in cell growth. The IGF-1R is implicated in several cancers including breast, prostate, and lung [99]. The similar ATP binding sites of IGF-1R and the insulin receptor (IR) are hurdles in designing IGF-1R specific inhibitors. So far, no drug has been approved by FDA as an inhibitor of IGF-1. AG538, AG1024, and NVP-AEW541 are the potent IGF-1 inhibitors currently under clinical trials [100–102].
Non-receptor tyrosine kinase inhibitors

Janus kinase (JAK) is a family of non-receptor tyrosine kinases that transduce cytokine-mediated signals through the JAK-STAT signaling pathway [104, 105]. The JAK family of proteins has four members, JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). JAKs are involved in different inflammatory, autoimmune diseases, and malignancies. Baricitinib (JAK1/2 inhibitor for Rheumatoid arthritis) [106], Fedratinib (JAK2 inhibitor for Myelofibrosis) [107], Ruxolitinib (JAK 1/2/3 inhibitor for Myelofibrosis, polycythemia vera), and Tofacitinib (JAK3 inhibitor for Rheumatoid arthritis) [108] are the JAK inhibitors currently in clinical use. Harikrishnan et al. synthesized some pyrrolo[1,2-f]triazines and evaluated them against different isoforms of JAK [109]. Compounds 26, 27, and 28 displayed potent activities against JAK2 over JAK1 and JAK3 (Fig. 12). Although compound 26 showed the most potent activity and selectivity for JAK2 27 was the most active compound in cellular assay when tested on SET-2 cell lines. X-ray crystal structure of pyrrolotriazine 28 docked on JAK2 showed that the pyrazole basic nitrogen accepts a hydrogen bond from Leu932 amidic NH whereas pyrazole NH donates a hydrogen bond to the carbonyl of Glu930 in the hinge region. Unfortunately, all compounds displayed poor metabolic stability.
Weinberg Lab developed some 2,7-Pyrrolo[2,1-f][1,2,4]triazines as JAK2 inhibitors [110]. Lead compounds were also checked for liver microsome stability by measuring their ability to form Glutathione (GSH) adduct. Compound 29 exhibited JAK2 inhibition with an IC₅₀ value of 0.17 ± 0.03 nM along with significantly low glutathione adduct formation (Fig. 12) [111].

Serine/threonine kinase inhibitors

The Aurora kinases are serine/threonine kinases that are crucial for cell proliferation [112]. Aurora kinases regulate cell cycle transit from G2 through cytokinesis. In humans three classes of aurora kinases are found namely, aurora kinase A, aurora kinase B, and aurora kinase C [113].
The former two types play a central role in mitosis, whereas the last one plays an important role in meiosis. Overexpression or gene amplification of aurora kinases is observed in several cancers. ZM447439 [114], Hesperadin [115], and Tozasertib [116] are the three potent aurora kinase inhibitors under clinical trials. Abraham et al. synthesized pyrrolotriazine 31, 32, 33, and 34 (Fig. 13) as potent pan-Aurora kinase inhibitors by structural modifications of their lead molecule 30 [117]. Compounds 31 ($K_d = 7$ nM) and 32 ($K_d = 9$ nM) were better than 30 against aurora kinase A whereas 34 showed better aurora kinase B inhibition ($K_d = 20$ nM) than 1 ($K_d = 20$ nM) along with high activity on HCT-116 cells (Table 3). The new analogs also showed an improved PK profile when
compared to 30. In vivo studies carried out with 34 in a flank-tumor xenograft model in nude mice using the HCT-116 cells resulted in a dose-dependent tumor growth inhibition but along with severe body loss at high dosing.

The same research group also discovered 35 and 36 as potent aurora kinase inhibitors (Fig. 14) [118]. Both compounds inhibited Aurora kinase A and B in nanomolar potency but with high selectivity for aurora B. Both compounds were also active at cellular levels when evaluated on HCT-116 cells either by measuring the inhibition of histone H3 phosphorylation mediated by aurora kinase B14 or the inhibition of cell proliferation. Both compounds showed high efficacy in the in vivo studies carried out in nude rats in a xenograft model with no significant body weight loss or lethality. Both compounds also showed good selectivity over a panel of 359 kinases.

Mitogen-activated protein kinase kinase kinase kinase 4 (MAP4K4) also known as hepatocyte progenitor kinase-like/germinal center kinase-like kinase and Nck-interacting kinase is a serine/threonine kinase that is involved in cell proliferation, migration, and adhesion [119]. MAP4K4 activity is implicated in systemic inflammation, metabolic disorders, cardiovascular diseases, and cancer. There is very limited information on the role of MAP4K4 in cancer [120]. Wand et al. discovered compounds 37 and 38 (Fig. 15) as potent inhibitors of MAP4K4 [121]. Both compounds inhibited MAP4K4 effectively with IC_{50} values of 4 and 5 nM, respectively. In PK studies, 37 showed much higher oral bioavailability (F = 0.72) than 38 (F = 0.12).

Phosphoinositide 3-kinases (PI3Ks) discovered by Lewis Cantley et al. are the family of enzymes involved in cellular functions viz. cell growth, proliferation, survival, differentiation, motility, and intracellular trafficking [122–124]. Based upon a primary structure, regulation, and in vitro lipid substrate specificity, the PI3K family is divided into four main classes. PI3Ks are activated by various factors and cytokines that result in the activation of serine/threonine kinase AKT and other downstream effector pathways. The early clinical trials with pan-PI3K inhibitors were halted due to high toxicities and modest antitumor effects but there have been continued efforts to develop safer and isoform-selective inhibitors to improve the therapeutic index. Recently three PI3K inhibitors namely, idelalisib, copanlisib, and duvelisib) are approved by FDA [125–127].

Dugar and co-workers discovered compound 39 as an inhibitor of PI3Kα (IC_{50} = 0.02 µM) (Fig. 16) [128]. When evaluated for in vitro metabolic stability in liver microsomal enzymes of three species (mouse, dog, and human) it showed more stability in human liver microsomes compared to other species. In the cellular assay, it inhibited human
ovarian cancer cell lines, A2780, SKOV3 (ovarian carcinoma cell line), and PC3 (human prostate cancer cell line) with EC50 values of 1.10, 3.2, 2.4 µM, respectively. It showed good selectivity over a panel of 23 kinases at 1 µM concentration except for homologous PI3 kinases and mTOR.

Erra et al. discovered 40 (LAS191954) as a selective nanomolar inhibitor of PI3Kδ (IC50 = 2 nM) for the treatment of inflammatory diseases (Fig. 16)[129]. 40 also inhibited human B-cell proliferation (hu B-cell prolif) and human whole blood assay measuring suppression of CD86 expression (hu WB CD86) with IC50 of 6 and 118 nM, respectively [130]. The selectivity of 41 against other isoforms (α, β, and γ) was 666, 800, and 130-fold, respectively. Compound 41 showed a good PK profile with clearance of 82.1 mL/min/kg, 6.2 L/kg volume of distribution, 0.46 of fraction (F), and a half-life of 1 h. The efficacy of 41 in a mouse collagen-induced arthritis was found to be superior to methotrexate.

From the same team of researchers, another PI3Kδ inhibitor, 42, with higher activity and selectivity over β isoform than 41 was reported (Fig. 17) [131]. The cellular activity (B-cells) of 42 (IC50 = 5.8 nM) was slightly better than 41. Compound 42 exhibited good efficacy in a mouse KLH model at dose loading of 3 mg/kg (twice a day). Compound 42 was well tolerated after day-4 at a dose loading of 300 mg/kg (QD) in mice with no sign of morbidity or mortality indicating its high selectivity index.

| Entry | Compd | Aurora Kd (nM) | Cell IC50 (nM) | pHH3 (HCT-116) | Proliferation (HCT-116) |
|-------|-------|----------------|----------------|----------------|------------------------|
| 1     | 30    | 12 20 4        | 55             | 28             |
| 2     | 31    | 7 4 5          | 190            | 75             |
| 3     | 32    | 9 8 2          | 15             | 8              |
| 4     | 33    | 12 5 nd        | 16             | 4              |
| 5     | 34    | 15 8 nd        | 44             | 5              |

Table 3 The activities of compounds 30–34 on aurora kinase and HCT-116 cells

Bhide and co-workers discovered another pyrrolo[2,1-f][1,2,4]triazine based compound 41 as a nanomolar inhibitor of PI3Kδ (IC50 = 2 nM) (Fig. 17). 41 also inhibited human B-cell proliferation (hu B-cell prolif) and human whole blood assay measuring suppression of CD86 expression (hu WB CD86) with IC50 of 6 and 118 nM, respectively [130]. The selectivity of 41 against other isoforms (α, β, and γ) was 666, 800, and 130-fold, respectively. Compound 41 showed a good PK profile with clearance of 82.1 mL/min/kg, 6.2 L/kg volume of distribution, 0.46 of fraction (F), and a half-life of 1 h. The efficacy of 41 in a mouse collagen-induced arthritis was found to be superior to methotrexate.

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Marcoux et al. discovered selective PI3Kδ inhibitor 44 by structural modification of their early hit 43 which was a potent and dual inhibitor of PI3Kδ and γ but selective for PI3Kα and PI3Kβ. 43 showed weak inhibition in a T cell hWB IFNγX assay as well as in a B cell hWB CD69 assay probably due to low cell permeability [132]. Compound 44 exhibited high potency compared to 43 and showed an outstanding kinome selectivity profile (Fig. 18). In human B cell proliferation assay it displayed an IC50 of 1 nM. Despite showing high potency and selectivity, compound 44 exhibited poor stability in liver microsomes.

Xiang et al. synthesized a series of 6-aminocarbonyl pyrrolo[2,1-f][1,2,4]triazine derivatives and evaluated their activity against all isoforms of PI3K. Initially compounds 45 was synthesized which exhibited potent activity against p110α and p110δ with IC50 of 122 nM and 119 nM, respectively while requiring higher dose for p110β and p110γ inhibition (IC50 = 1293 and 663 nM, respectively) (Fig. 19) [133]. 45 displayed good efficacy against human rhabdomyosarcoma Rh30 cells. By performing further SAR study compounds, 46 and 47 were developed (Fig. 19). Both compounds showed good efficacy in cellular assay when tested against a panel of cell lines, Rh30, BT-474, SK-BR-3, SKOV-3, and T47D LO2. The poor PK profile of 47 halted its further development.

Fig. 14 Structures, activities, and PK profile of compounds 35 and 36

Fig. 15 Structures, activity, and PK profiles of compounds 37 and 38

Fig. 16 Structure and PI3K inhibition of compounds 39 and 40 (LAS191954)

Fig. 17 Structures and activities of compounds 41 and 42
Jia et al. used a combination of electronic density model and molecular docking and discovered pyrrolotriazinone containing compound 48 as a potent and selective PI3K$\gamma$ - PI3K$\delta$ dual inhibitor (Fig. 20) [134]. 48 exhibited potent inhibitory effects on basophil and B cell activation. In PK studies 48 displayed moderate clearance in rats and low clearance in dogs but high oral bioavailability ($F=1.08$ and 0.82) in rats and dogs, respectively).

Interleukin-1 receptor-associated kinase 4 (IRAK4) is a threonine-serine protein kinase that belongs to the IRAK family of proteins [135, 136]. IRAK4 is the most upstream kinase in Toll/Interleukin-1 receptor signaling. IRAK4 possesses two main domains, a kinase domain, and a death domain. IRAK4 overactivation is linked with several autoimmune diseases and cancers. CA-4948, an IRAK4 inhibitor in the early stages of clinical trials [137]. Degorce and co-workers discovered compounds 49 (IRAK4 IC$_{50}$ = 0.022 $\mu$M) and 50 (IRAK4 IC$_{50}$ = 0.094 $\mu$M) as potent IRAK4 inhibitors using a scaffold hopping strategy (Fig. 21) [138]. Both compounds displayed good selectivity over a panel of 126 kinases at 1 $\mu$M concentration. Anti-tumor activity of 49 was evaluated in female SCID mice bearing OCILY10 tumors. Daily oral treatments with 49 (200 mg/kg) and ibrutinib (12 mg/kg) resulted in TGI of 92% and 52%, respectively. A combination of 49 and ibrutinib showed synergistic effects with TGI>100% after 43 days.

### Non-kinase inhibitors

The hedgehog signaling pathway transmits information to embryonic cells required for proper cell differentiation [139, 140]. Different concentrations of hedgehog signaling proteins are found in different parts of the embryo. The Hedgehog (Hh) signaling pathway was first identified in the common fruit fly. Mammals have three Hedgehog homologs, Desert (DHH), Indian (IHH), and Sonic (SHH). Among these SHH is the most studied. Several Hh signaling pathway inhibitors have been discovered for cancer therapy [141]. Vismodegib, (for basal cell carcinoma), Sonidegib FDA (basal cell carcinoma), and Itraconazole are the Hh signaling pathway inhibitory currently under clinical use [142]. Xin et al. synthesized some pyrrolo[2,1-f][1,2,4]triazine framework containing molecules and evaluated their Hh signaling pathway inhibitory activity using a luciferase reporter in NIH3T3 cell carrying a stably transfectedGli-reporter construct (Gli-
luciferase reporter cell lines) [143]. Compound 51 was developed as the lead after a detailed SAR study. It showed an IC50 value of 0.83 nM in the in vitro Gli-luciferase reporter assay. An area-under-curve of 2230.32 ng.h/mL and clearance of 414.07 mL/h/kg were observed with 51 in PK studies (Fig. 22).

Kim et al. synthesized few compounds containing pyrrolotriazine-4-one scaffold and assessed their activities against Eg5 (also known as K1F11 or kinesin-5) [144]. Compound 52 (Fig. 22) was emerged as a lead which displayed potent activity in Eg5 ATPase (IC50 = 0.06 µM) and A2780 cell proliferation assays (IC50 = 0.05 µM). Clearance and t1/2 values of 16 ± 2.7 mL/min/kg and 4.5 ± 1.6 h respectively were observed in pharmacokinetic studies performed in mice. In the in vivo studies, a T/C (treated/control) value of 163% was observed at iv dosing of 20 mg/kg in mice with P388 murine leukemia.

Kinase design and SAR study

It has been seen from several examples that the bulky group’s substitution at C-4 and C-6 positions of pyrrolo[2,1-f][1,2,4]triazine is crucial to develop selective VEGFR2, EGFR, and c-Met inhibitors (Figs. 1–8, 23). Both positions (C-4 and C-6) can accommodate moderate to large substituents and their structural changes alter the activity/selectivity of the inhibitor. In addition, there is a small room to adapt smaller substituents at the C-5 position for improving the selectivity further (Fig. 23). The C-2 and C-7 positions of pyrrolo[2,1-f][1,2,4]triazine have not been explored yet for VEGFR2, EGFR, or c-Met selectivity. In contrast, the substitution at C-2 and C-7 positions of pyrrolo[2,1-f][1,2,4]triazine plays an important role to develop ALK selective inhibitors (Figs. 9, 10, 23). In general, large groups could be accommodated at the C-2 position compared to C-7. There is a single example of an IGF-1R inhibitor that contains pyrrolo[2,1-f][1,2,4]triazine scaffold, the results indicate that both C-2 and C-4 substitution lead to higher selectivity for IGF-1R (Figs. 11 and 23). In the case of non-receptor tyrosine kinase, the substitution at C-2 and C-4 is the key for higher JAKs selectivity. In general, most of the modifications are done on the C-2 position of pyrrolo[2,1-f][1,2,4]triazine whereas small groups such as amino pyrazole are placed at the C-4 position (Figs. 12 and 23). Putting substituents at the C-7 position (e.g., compound 29, Fig. 12) improves the selectivity of an inhibitor for JAK2 over the other isoforms. In the case of serine/threonine kinase inhibitors, the substitution at C-2 and C-4 makes the inhibitor more selective for aurora kinase. Interestingly, the substituents preference of inhibitors for aurora kinases is like JAKs). The substitution at C-6 further improves the activity (Table 3). The substitution at C-4 and C-6 is important to achieve higher MAP4K4 selectivity (Figs. 15 and 23). Interestingly, all the carbons of pyrrolo[2,1-f][1,2,4]triazine have been explored to get PI3K selective inhibitors (Figs. 16–21, 23). In general, most of the substituents used are small to moderate. Future design to develop more selective kinase inhibitors should focus on substituting the unexplored sites of pyrrolo[2,1-f][1,2,4]triazine for a specific kinase and also the modifications of groups at the appropriate positions.

Conclusions and outlook

The use of targeted therapy to treat cancer by targeting specific proteins or enzymes has gained much attention in the recent past when compared to other therapies. Several drugs are approved every year as kinase inhibitors to treat cancer. Most the kinase inhibitors contain one or more fused heterocycles, and pyrrolo[2,1-f][1,2,4]triazine is one among them. We have seen that several small organic molecules containing pyrrolo[2,1-f][1,2,4]triazine scaffold have shown potent in vitro and in vivo activities against a variety of cancer cells and tumors. The compounds have potently...
inhibited receptor tyrosine kinase inhibitors viz. EGFR, VEGF, FGR, c-Met, ALK, IGF-1 as well as non-receptor tyrosine kinase such as JAK. This class of compound is also active against serine/threonine kinases including aurora kinases, MAP4K4, PI3Ks, and IRAK4. Most of the compounds are ATP-competitive inhibitors. A few compounds containing pyrrolo[2,1-f][1,2,4]triazine scaffold have also inhibited the Eg5 and hedgehog signaling pathway that is dysregulated in some cancers.

Future studies should also focus on developing irreversible or covalent inhibitors to target kinases [145]. All the examples discussed in this review article are of reversible inhibitors which means these inhibitors follow occupancy-driven pharmacology wherein the efficacy of the inhibitor correlates with
its off constant thus requiring a higher dose of a drug to maximally inhibit the kinase [146]. In contrast, the efficacy of a covalent or irreversible inhibitor depends upon its inhibitor constant as well as the proximity of its electrophilic component viz. Michael acceptor and the nucleophilic component of the protein such as sulphhydryl group of the surface exposed cysteine residue. A Bruton’s tyrosine kinase inhibitor, Ibrutinib is an excellent example of a covalent kinase inhibitor that has been approved by the FDA for the treatment of mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenström’s macroglobulinemia [147]. Future studies should also focus on converting the kinase inhibitor into a kinase selective degrader. The PROTAC [148] and molecular Glue [149] approaches rely on artificially inducing the degradation of a targeted protein by hijacking cellular quality control machinery. To develop a selective kinase degrader, the solvent-exposed sites of pyrrolo[2,1-f][1,2,4]triazine could be extended and connected to E3 ligase recruiting ligands such as VHL or thalidomide through a linker of an appropriate length [150]. We believe that this review article will be useful to medicinal chemists in designing better kinase inhibitors/degraders containing pyrrolo[2,1-f][1,2,4]triazine scaffold for cancer therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest, financial or otherwise.

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