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# Recent advances in focal adhesion kinase (FAK)-targeting antitumor agents

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Focal adhesion kinase (FAK) is a non-receptor intracellular tyrosine kinase that plays an important role in cell adhesion, survival, proliferation, and other processes. Research studies have shown that overexpression of FAK can promote the proliferation and migration of tumor cells. Therefore, FAK has become a promising target for small molecular anticancer drugs with great clinical potential. In recent years, research studies on small molecular FAK inhibitors have been increasing. With the rise of proteolysis-targeting chimera (PROTAC) technology, FAK PROTACs have also been developed to induce FAK degradation. This article reviews the design and biological activity of FAK-targeting antitumor agents, with a focus on their chemical structures, antitumor effects, and clinical progress.

Focal adhesion kinase (FAK) is a protein encoded and synthesized by the PTK2 gene. It plays an important role in cell adhesion, migration, survival, proliferation, and embryonic development.<sup>1</sup> FAK is a class of cytoplasmic non-receptor protein tyrosine kinases (PTKs) consisting of three domains, including an N-terminal FERM domain, a central kinase domain, and a C-terminal domain. There are multiple tyrosine phosphorylation sites (Y194, Y397, Y407, Y576, Y577, Y861, Y925, Y1007) in FAK, which play a key regulatory role in the molecular function of FAK. Their phosphorylation can provide binding sites for signal proteins and regulate the catalytic activity of FAK. FAK is widely expressed in human tissues and can regulate various cellular processes. Overexpression of FAK can be detected in many different sources of human cancer cells. Biological studies have shown that the activity of FAK is crucial for the occurrence and progression of human cancer. Therefore, targeting FAK is considered one of the effective means for development of novel antitumor drugs.<sup>2,3</sup> At present, many small molecular FAK inhibitors have been developed. Although there are no small molecular FAK inhibitors on market yet, some chemical entities such as **VS-6063** (Defactinib) and **CT-707** (Concertinib) have entered the phase III clinical research stage. In addition, with the rise of Proteolysis-Targeting Chimera (PROTAC) technology,<sup>4</sup> PROTAC targeting FAK has also been developed to induce FAK degradation. Based on a brief introduction to the structure and function of FAK protein, this review covers the design, and biological activity of

targeted FAK agents, with a focus on their chemical structures, antitumor effects, and clinical research progress.

## 1. Structure and function of FAK

The FAK protein consists of 1052 amino acids, with a molecular weight of approximately 125–130 kDa, and contains three domains: N-terminal FERM domain, central kinase domain, and C-terminal domain (Fig. 1).<sup>5,6</sup> The N-terminal FERM domain of FAK consists of three subdomains F1, F2, and F3, resembling a clover-like structure, with tyrosine residue Y397 located on it as a phosphorylation site. The FERM domain can interact with intracellular parts of many upstream membrane proteins such as growth factor receptors and c-Met, as well as with many downstream cytoplasmic proteins such as P53, MDM2, SRC kinase, *etc.*, mediating protein–lipid and protein–protein interactions through scaffold function. The FAK central kinase domain has high homology with other tyrosine kinases, and the tyrosine residues Y576 and Y577 located on it are phosphorylation sites that can mediate the activation of the PI3K/AKT/mTOR pathway. The C-terminal domain of FAK consists of a FAT (focal adhesion targeting) domain and two proline rich regions (PRRs) subdomains, on which tyrosine residues Y861 and Y925 are phosphorylation sites. Proline rich motifs can interact with proteins containing SH3 domains, while FAT domains can interact with adhesion complex proteins such as paxillin, talin, vinculin, and GRB2. In addition, the FAT domain can be combined with the F2 subdomain of the FERM domain, leading to the dimerization of FAK.

FAK is the intersection of multiple signalling pathways within cells, promoting the survival and growth of tumor cells through multiple signalling pathways, including kinase dependent and non-kinase dependent pathways, involving physiological processes such as apoptosis, drug resistance, and

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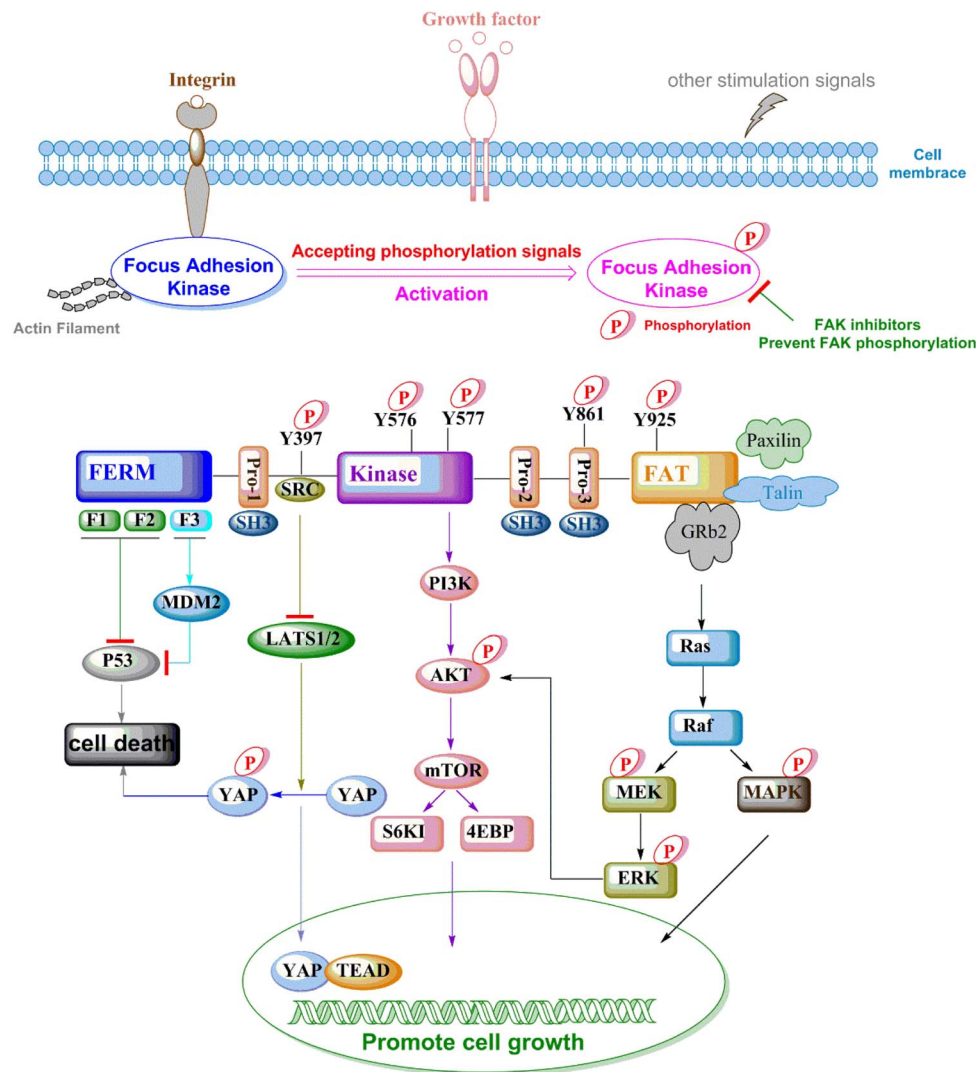


Fig. 1 FAK structure and FAK-related signaling pathways in cancer development.

cell cycle of tumor cells. After entering the cell, FAK receives signals from integrins, growth factors, receptor tyrosine kinases (RTKs), G-protein coupled receptors, and other stimuli, and undergoes phosphorylation activation, thereby mediating downstream changes in P53, MDM2, LATS1/2, PI3K, Ras, *etc.*, which have a significant impact on tumor cell growth, migration, proliferation, *etc.* (Fig. 1).

The N-terminal FERM domain of FAK protein is connected to P53 in the F1 and F2 lobes, and to the ubiquitin ligase MDM2 in the F3 lobe. It promotes the ubiquitination and inactivation of P53 through a non-kinase dependent signalling pathway. This path can slow down the rate of tumor cell apoptosis, and promote tumor cell growth and proliferation.<sup>7</sup> The key phosphorylation site Y397 is in the FERM domain of the N-terminus of FAK protein. This is also a key site for small molecular FAK inhibitors design.<sup>8</sup> The extracellular matrix (ECM) connecting to cells through the integrin receptor group results to FAK dimerization. This interaction causes autophosphorylation at the Y397 site.<sup>9</sup> It connects to the SRC family kinase to mediate the activation of the LATS1/2-YAP signaling pathway and

prevent tumor cell apoptosis.<sup>10</sup> In various tumor cells, the increase of FAK expression and activity lead to the promotion of cell antiapoptotic effects. The tyrosine residues Y576 and Y577 located on the FAK central domain are also key phosphorylation sites. Phosphorylation activates the PI3K/AKT/mTOR signaling pathway,<sup>11,12</sup> promoting tumor growth and migration. Therefore, the FAK central kinase domain has become a highly useful area for the design of FAK inhibitors. The C-terminal FAT domain of FAK protein is responsible for interacting with proteins such as talin, paxilin, and GRB2 to form focal adhesion complexes,<sup>13,14</sup> which play an important role in the localization and regulation of FAK protein. After phosphorylation of tyrosine residues Y861 and Y925 located in the FAT domain, the Ras/RAF/MEK-ERK pathway is activated through the complex, leading to tumor cell proliferation and migration. After FAK is phosphorylated and activated, it mediates multiple intracellular signalling pathways, promoting the formation and development of tumor cells. Therefore, the development of inhibitors targeting FAK can achieve the goal of treating tumors.



## 2. Development of small molecular FAK inhibitors

Nitrogen-containing heterocycles are usually used as main motif of small molecular FAK inhibitors, such as pyrimidines, triazines, and others, as well as some dual and multi-target inhibitors and inhibitors targeting FAK through protein–protein interactions (PPIs). A description of the chemical structure characteristics of small molecular FAK inhibitors is described below.

### 2.1 FAK inhibitors based on pyrimidines

FAK inhibitors containing pyrimidine structures, with 2,4-diaminopyrimidine as the most common backbone, can be divided into two categories: monocycle and fused ring. There are several reports on FAK inhibitors with 2-aminopyrimidine structure.

**2.1.1 FAK inhibitors based on monocyclic 2,4-diaminopyrimidine.** As early as 2007, Liu *et al.*<sup>15</sup> reported the role of **TAE226** as a dual inhibitor of focal adhesion kinase (FAK) and insulin-like growth factor-I receptor kinase (IGF-1R) for inhibition of glioblastoma, marking the beginning of research on small molecular inhibitors targeting FAK. Although **TAE226** has strong inhibitory activity against FAK ( $IC_{50} = 5.5$  nM), its severe toxic side effects prevented it from entering clinical studies. The chemical structure of **TAE226** is based on 2,4-diaminopyrimidine as the parent nucleus, and subsequent studies on FAK inhibitors have used **TAE226** as a positive drug. Small molecular compounds with 2,4-diaminopyrimidine skeleton play an important role in FAK inhibitors, with a large number and strong inhibitory activity against FAK. The FAK small molecular inhibitors currently in clinical research, such as **BI-853520** (Ifebemtinib), **CEP-37440**, **CT-707** (Contertinib), *etc.*, all contain 2,4-diaminopyrimidine core (Fig. 3). Research has shown that **TAE226** can significantly inhibit the autophosphorylation of Y397 in FAK, effectively block FAK mediated signaling pathways such as S6 ribosomal protein phosphorylation, ERK, and AKT. It has a broad-spectrum anti-proliferative effect on various cancer cells. The cocrystal structure of **TAE226** and FAK has been resolved (PDB ID: 2JKK).<sup>16</sup> **TAE226** is anchored to the kinase domain of FAK in a U-shaped structure (Fig. 2). The amino and carbonyl groups of Cys502 located in the hinge

region form two hydrogen bonds with the nitrogen atom on the pyrimidine ring and the amino group of 2-methoxyaniline in **TAE226**. The carbon atom on the pyrimidine ring forms a hydrophobic interaction with Ala452 and Leu553, while 2-methoxyaniline forms a hydrophobic interaction with Ile428 and Gly505. The chlorine atom at position C-5 of the pyrimidine ring penetrates into the vicinity of the gate guard amino acid Met499 residue in the ATP binding pocket. The morpholine ring in the **TAE226** structure does not interact with FAK, and its main function is to enhance the pharmacokinetic properties of **TAE226**. The interaction between **TAE226** and Asp564 and Leu567 on the FAK activation loop can stabilize the short helix structure of the DFG sequence unique to this region of FAK, explaining the selectivity of **TAE226** towards FAK. Most ATP competitive FAK inhibitors contain core structures of diaminopyridine, diaminopyrimidine, or similar N-containing rings, which are highly similar to the structure of **TAE226**. Therefore, they can bond to FAK in a similar manner. This ATP competitive binding mode has been confirmed by the cocrystal structures of various FAK inhibitors with FAK.

In 2010, A. Schultze *et al.*<sup>17</sup> reported ATP competitive FAK inhibitor **1** (**PF-573228**). Research has found that **PF-573228** exhibits a strong inhibitory effect on FAK ( $IC_{50} = 4.0$  nM), effectively reducing Y397 phosphorylation in REF52 and PC3 and inhibiting cell migration. It also dose-dependently inhibits the phosphorylation of the downstream substrate paxillin in Tyr31. **PF-573228** can affect the survival rate of OVCAR-3 cells, and its combination with metformin can enhance its cytotoxicity. Therefore, the combination of **PF-573228**, metformin and carboplatin can improve the therapeutic effect of platinum resistant ovarian cancer. By optimizing the structure of **PF-573228**, Pfizer researchers also obtained multiple FAK inhibitors, including two lead compounds **VS-6062** and **VS-6063**. Compound **2** is an analog of **TAE226**,<sup>18</sup> which differs from **TAE226** in that a carbonyl group is inserted between the morpholine ring and the benzene ring. Compared with **TAE226**, **2** exhibited higher activity in inhibiting FAK ( $IC_{50} = 5.17$  nM). Compound **2** also exhibits excellent antiproliferative activity against AsPC-1, BxPC-3, and MCF-7/ADR cells, but with very low cytotoxicity against normal human cells. In addition, the expression of MEK and ERK proteins is rarely affected by compound **2**. In the AsPC-1 cancer xenograft mouse model, compound **2** at a continuous oral dose of 60 mg kg<sup>-1</sup> for 7 days resulted in tumor regression, indicating that compound **2** has strong antitumor activity *in vivo*. Docking studies have shown that the carbonyl group introduced in compound **2** forms hydrogen bonds with the amino group of Gln438, which forms a new hydrogen bond with FAK central kinase domain, explaining that compound **2** is more potent than **TAE226**.

Molecular hybridization is one of the commonly used methods in drug design.<sup>19</sup> Thiocarbamate esters are widely used in the design of novel anticancer drugs.<sup>20–22</sup> Yin *et al.*<sup>23</sup> combined dithiocarbamate with the classical 2,4-diaminopyrimidine structure to design and synthesize a novel FAK inhibitor. Compound **3** exhibited FAK inhibition with  $IC_{50}$  value of 0.07 nM and demonstrated good anti-cancer activity in multiple cancer cell lines. Further research has shown that compound **3**

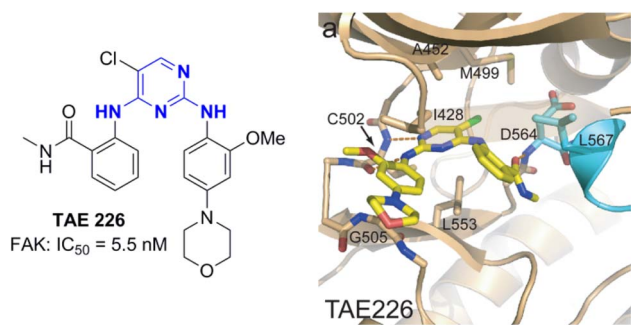


Fig. 2 Crystal structure of **TAE226** complexed with the kinase domain of FAK (PDB ID: 2JKK).<sup>16</sup>

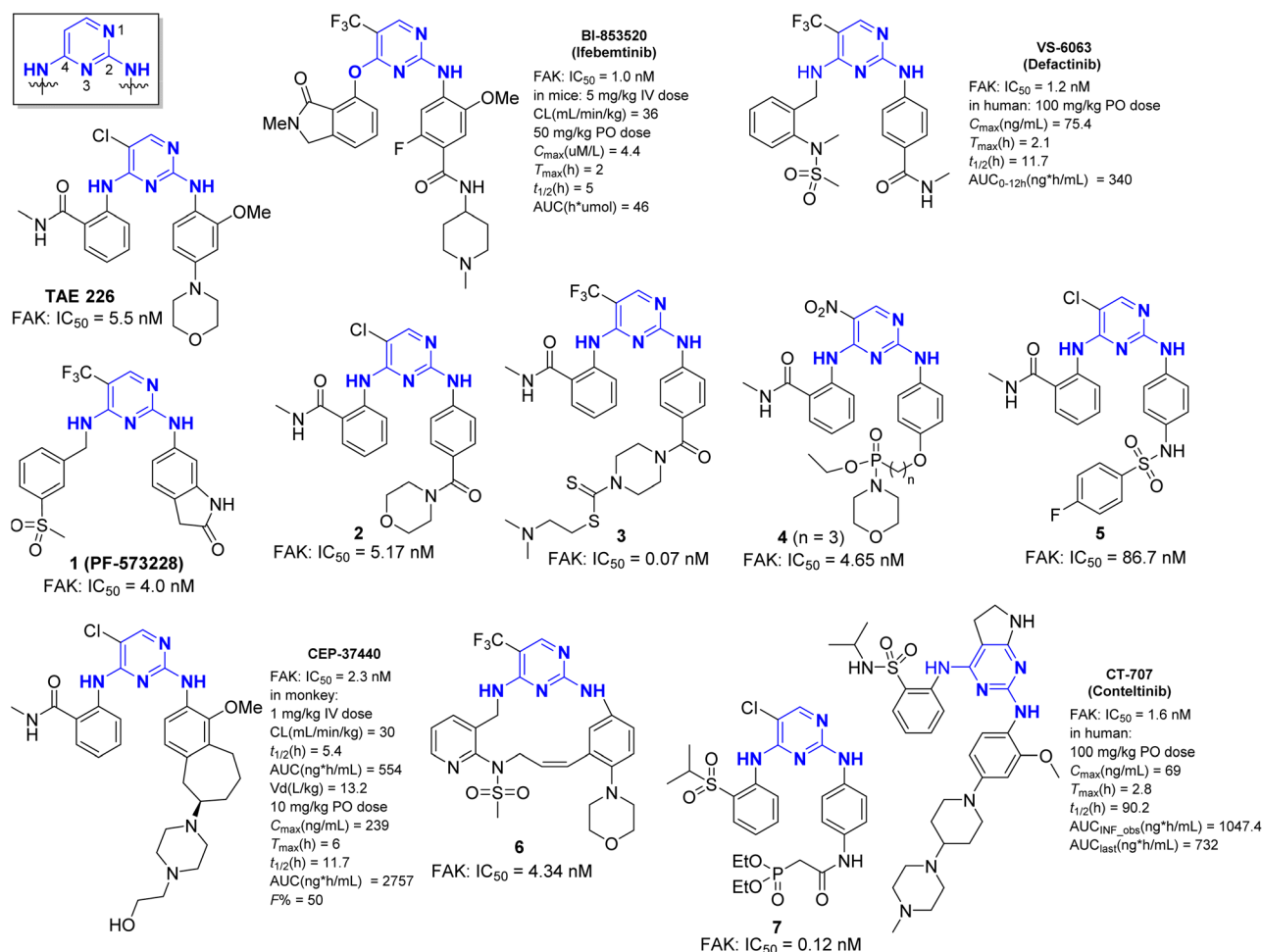


Fig. 3 FAK inhibitors based on 2,4-diaminopyrimidine core.

can induce apoptosis in MCF-7 and HCT116 cells in a dose-dependent manner, and lead to cell cycle retard in the G2/M phase. In addition, compound 3 can effectively inhibit the migration of MCF-7 and suppress microtubule formation in HUVEC cells at low concentrations, demonstrating its anti-angiogenic effect. Due to their advantages such as enhanced water solubility and improved bioavailability, phosphate and sulfonamide groups have been widely used in drug design.<sup>24,25</sup> Ma *et al.*<sup>26</sup> used fragment-based drug design (FBDD) strategy to design and synthesize a series of 2,4-diaminopyrimidine derivatives containing phosphorus amides as ATP competitive FAK inhibitors. Among them, compound 4 showed stronger FAK inhibitory activity than TAE226, effectively inhibiting the proliferation of AsPC cells, inducing apoptosis of AsPC cells in a dose-dependent and time-dependent manner, and exhibiting low cytotoxicity in HPDE6-C7 cells. Their research group also designed and synthesized a series of compounds containing sulfonamide substituted pyrimidine structures, among them, compound 5 (ref. 27) had an IC<sub>50</sub> value of 86.7 nM for FAK, which could inhibit the cell growth of AsPC-1 and Panc-1 cell lines and induce apoptosis of AsPC cells in a dose-dependent manner. Farand *et al.*<sup>28</sup> designed and synthesized a macrocyclic compound 6 containing a sulfonamide structure, which

showed high selectivity towards PYK2. The IC<sub>50</sub> values for FAK and PYK2 were 4.34 nM and 0.84 nM, respectively. The macrocyclic structure also endowed compound 6 with good metabolic stability. In 2022, Ma *et al.* replaced the formamide group and morpholine ring in the TAE226 structure with isopropyl sulfonate group and long chain phosphoryl amine group, respectively, and designed and synthesized compound 7.<sup>29</sup> Compound 7 with 0.12 nM IC<sub>50</sub> value to FAK demonstrated higher FAK inhibitory activity than TAE226, and showed significant anti-proliferation effect on six different cancer cell lines. *In vivo* model studies showed that compound 7 at a dose of 10 mg per kg per day could significantly inhibit tumor growth with an inhibition rate of up to 85%, which expected to be a candidate drug for targeted treatment of pancreatic cancer (Fig. 3).

Covalent inhibition has become one of the important strategies in drug development.<sup>30</sup> Since the discovery of the oldest covalent drug aspirin in 1895, the FDA has approved nearly 1700 small molecule drugs, of which over 120 are covalent drugs, accounting for 7%. In recent years, the development of covalent inhibitors targeting the undruggable G12C mutant KRAS protein has brought about a revival of covalent drugs.<sup>31</sup> In 2018, Chen *et al.*<sup>32,33</sup> designed and synthesized the first FAK covalent inhibitor 8 (IC<sub>50</sub> = 0.6 nM) using TAE226 as the parent structure



and introducing acrylamide covalent warheads. The inhibitor exhibited strong inhibitory activity against human glioblastoma cells U87 MG, U251, and A172 (Fig. 4). Research has shown that compound **8** can block the G2/M phase of U87 cells, thereby delaying the cell cycle progression. It has a significant inhibitory effect on the autophosphorylation of FAK and its downstream signal molecules AKT and Erk, confirming that FAK covalent inhibitors have the potential application for the treatment of malignant gliomas. The cocrystal structure reveals a strong binding affinity between **8** and FAK protein (PDB ID: 6GCX), with its acrylamide head forming a stable covalent interaction with the thiol group (–SH) of Cys427 residue in the FAK central kinase domain (Fig. 5). In 2021, Chen *et al.*<sup>34</sup> retained the pyrimidine ring and *ortho*-aminobenzamide structure in **TAE226** and replaced the morpholine ring with a piperazine ring, developing a novel covalent FAK inhibitor **9** with  $IC_{50}$  value of 35 nM. The research team replaced the covalent warhead in compound **9** with sulfonamide group<sup>35</sup> to prepare compounds **10**, which has similar inhibitory activity against FAK with  $IC_{50}$  values of 48 nM. They have also prepared compound **11** with one  $CF_3$  group to replace Cl at pyrimidine ring and connecting

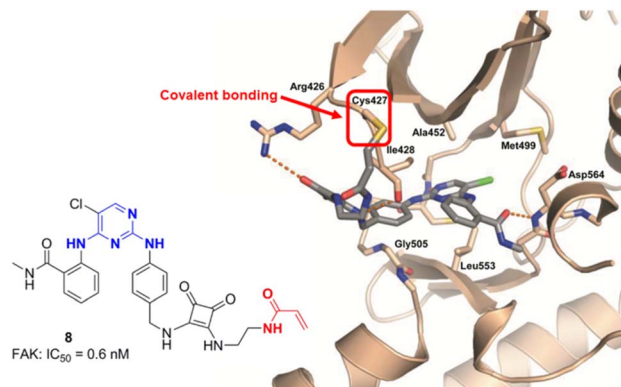


Fig. 5 Crystal structure of FAK covalent inhibitor **8** with the kinase domain of FAK (PDB ID: 6GCX).<sup>32</sup>

2,3-dihydro-1*H*-inden-1-one group on the left side. Compound **11** displayed good inhibition of FAK ( $IC_{50}$  = 45 nM) with at least 22 fold of selectivity over insulin receptor (IR,  $IC_{50}$  > 1000 nM). It also exhibited potent anticancer activity against HeLa, HCT116

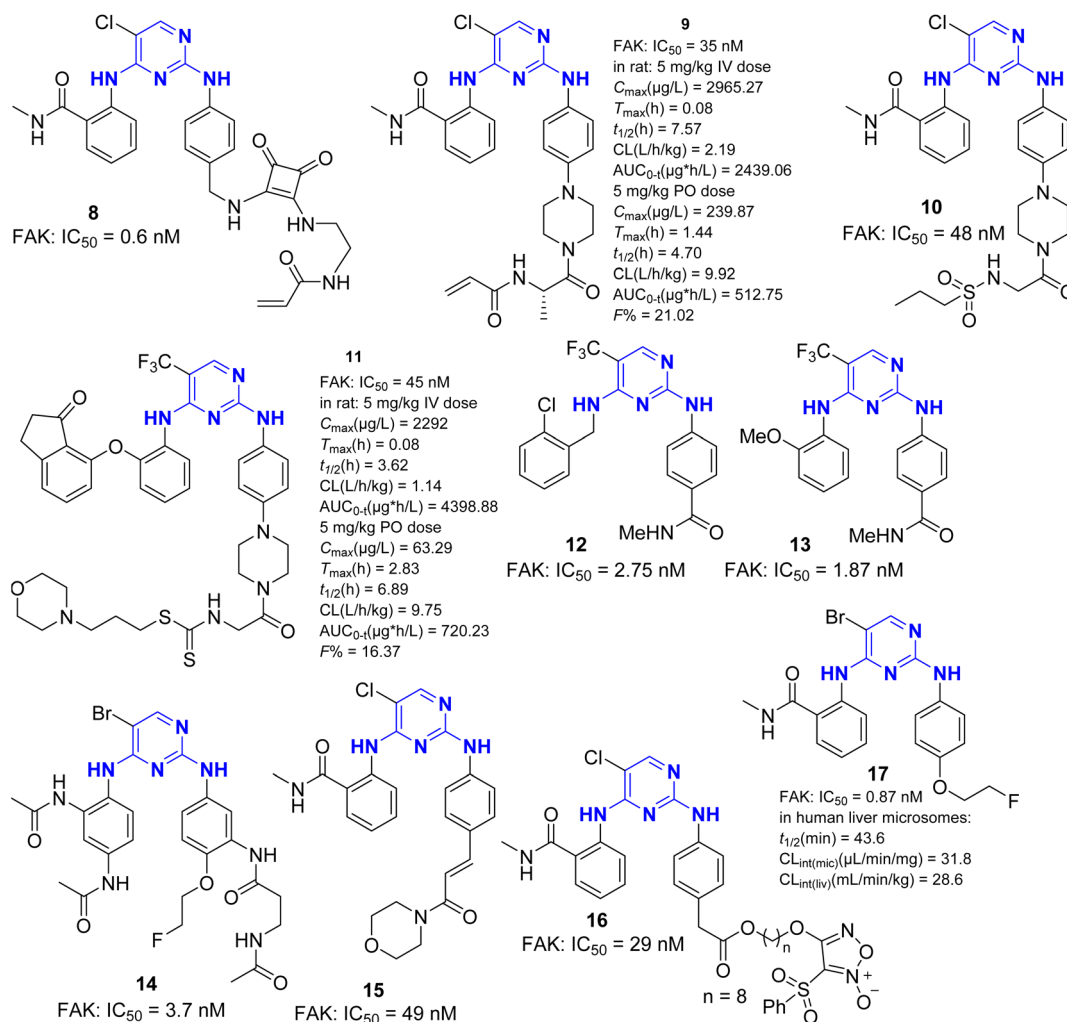


Fig. 4 FAK inhibitors based on 2,4-diaminopyrimidine core (continued).

and MDA-MB-231 cell lines with  $IC_{50}$  values of 0.27, 0.19 and 0.26  $\mu$ M respectively. Compound **11** can stimulate cell cycle arrest in the G2/M phase through the inhibition of FAK-Src-ERK signaling pathway in a dose-dependent manner. Moreover, compound **11** showed adequate oral bioavailability and good pharmacokinetic property. In 2021, Zhou *et al.*<sup>36</sup> designed and synthesized FAK inhibitors **12** and **13** based on deep understanding of the cocrystal structure of TAE226 and FAK. In this research work, they retained the pyrimidine ring to anchor the DFG short helix sequence of FAK hinge region, and oriented the 4-amino-*N*-methylbenzamide group toward the solvent region of FAK. This design made compounds **12** and **13** have extremely strong inhibitory activity against FAK, with  $IC_{50}$  value of 2.75 nM and 1.87 nM, respectively. Studies have shown that compounds **12** and **13** have potent antiproliferative activity against nine human cancer cell lines. In addition, **12** and **13** also showed good antiangiogenic effects. In 2022, Zhang *et al.*<sup>37</sup> synthesized a compound **14** targeting FAK with 2,4-diaminopyrimidine as the backbone by using bromine atom instead of the common chlorine atom or trifluoromethyl group on the pyrimidine ring. The study showed that compound **14** had significant inhibitory activity against FAK ( $IC_{50}$  = 3.7 nM), and the inhibitory effect was higher than that of the positive drug GSK-2256098 ( $IC_{50}$  = 18 nM). In addition, compound **14** could significantly inhibit the tumor growth of S180 tumor bearing mice, and the tumor volume and weight were significantly reduced compared with PF-562271 as a positive control. They also successfully prepared compound **14** containing radiolabeled  $^{18}F$ , which can specifically take up by tumor cells and can be used as a new tracer for tumor diagnosis and treatment. In 2023, Song *et al.*<sup>38</sup> introduced cinnamic acid group into TAE226 for the first time and constructed a novel FAK inhibitor **15** ( $IC_{50}$  = 49 nM) based on 2,4-diaminopyrimidine skeleton. Studies have confirmed that compound **15** can effectively inhibit FAK related signals, including AKT/mTOR and MAPK pathway in MGC-803 cells. In addition, the molecular bonding experiments between **15** and FAK exhibited favorable binding properties. The oxygen atom of the carbonyl group in the *o*-aminobenzamide group of compound **15** and the chlorine atom on the pyrimidine ring formed hydrogen bonds and halogen bonds with the Asp564 residue of the FAK central kinase domain, respectively. The 3-position nitrogen atom and 2-position amino group of the pyrimidine ring formed two hydrogen bonds with the Cys502 residue of the FAK central kinase domain.

As we all know, nitric oxide (NO) is a gas signaling molecule and has a wide range of effects in tumor biology.<sup>39,40</sup> Relevant studies have shown that NO has the potential to regulate FAK signaling function. By inducing the release of elevated NO levels, it will have a synergistic inhibitory effect on FAK kinase catalytic activity and non-kinase functions.<sup>41</sup> Phenylsulfonyl furazan is a NO release precursor. In 2023, Kang *et al.*<sup>42</sup> introduced benzenesulfonyl furazan into the molecular design of FAK inhibitors and developed a nitric oxide releasing derivative **16** based on TAE226. The pyrimidine core structure of compound **16** linked to benzenesulfonyl furazan through long-chain fatty acids, and the  $IC_{50}$  for FAK was 29 nM. Studies have confirmed that compound **16** can induce a significant increase

in the level of NO signal, exert the dual synergistic effect of NO release/FAK inhibition, and achieve potent tumor inhibition by regulating the kinase dependent and independent of FAK signaling pathway, which has made a beneficial exploration for the development of new FAK inhibitors. In 2025, Zhang *et al.* have prepared compound **17** through rational drug design strategy.<sup>43</sup> Compound **17** is a very potent FAK inhibitor with  $IC_{50}$  value of 0.83 nM, which possesses a classic 2,4-diaminopyrimidine motif with one Br to replace Cl at pyrimidine ring, and the morpholine ring was replaced by 2-fluoroethoxyl group. Both *in vitro* and *in vivo* studies showed that **17** dramatically suppressed tumor cell viability, cancer stem cell activity, and cell migration in A549 and SKOV-3 cell lines with tumor inhibition rates of 59.15% and 57.9%, respectively.

The synthesis of TAE226 is from 2,4,5-trichloropyrimidine, 2-amino-*N*-methylbenzamide and 2-methoxy-4-morpholinoaniline in two steps (Fig. 6).<sup>44,45</sup> 2-Methoxy-4-morpholinoaniline was prepared from 4-fluoro-2-methoxy-1-nitrobenzene coupling with morpholine followed the reduction of nitro group under  $H_2$  atmosphere. 2,4,5-trichloropyrimidine is usually used as one starting compound due to the different reaction activities of two Cl atoms between two nitrogen atoms and adjacent to nitrogen on the pyrimidine ring. The synthesis of the other FAK inhibitors with a 2,4-diaminopyrimidine motif is similar to the preparation of TAE226. The structure-activity relationship (SAR) of FAK inhibitors containing 2,4-diaminopyrimidine backbone is illustrated on Fig. 7 by using TAE226 as a representative. The Cl atom on pyrimidine ring can be replaced by other electron-withdrawing groups, such as  $CF_3$ , Br,  $NO_2$ , or introduce a fused ring. The amide group of the phenyl ring on the left side can be replaced by a sulfonamide group, or connect with right side to form a macrocyclic structure. The elimination of methoxyl group of the phenyl ring on the right side has no decrease of FAK inhibitory activity. The morpholine ring does not interact with FAK, and its main function is to enhance the pharmacokinetic

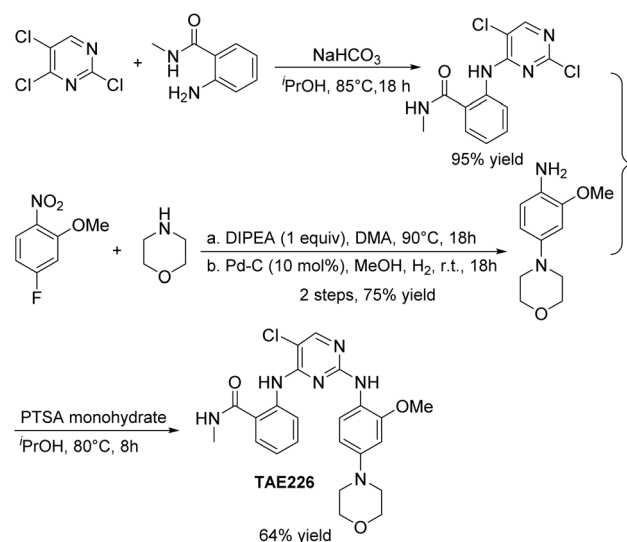


Fig. 6 The synthesis of TAE226.



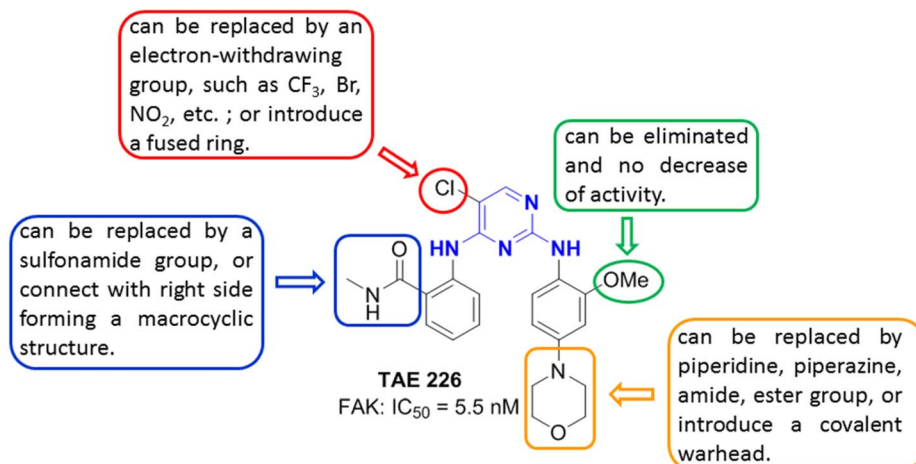


Fig. 7 The structure–activity relationship (SAR) of FAK inhibitors containing 2,4-diaminopyrimidine backbone.

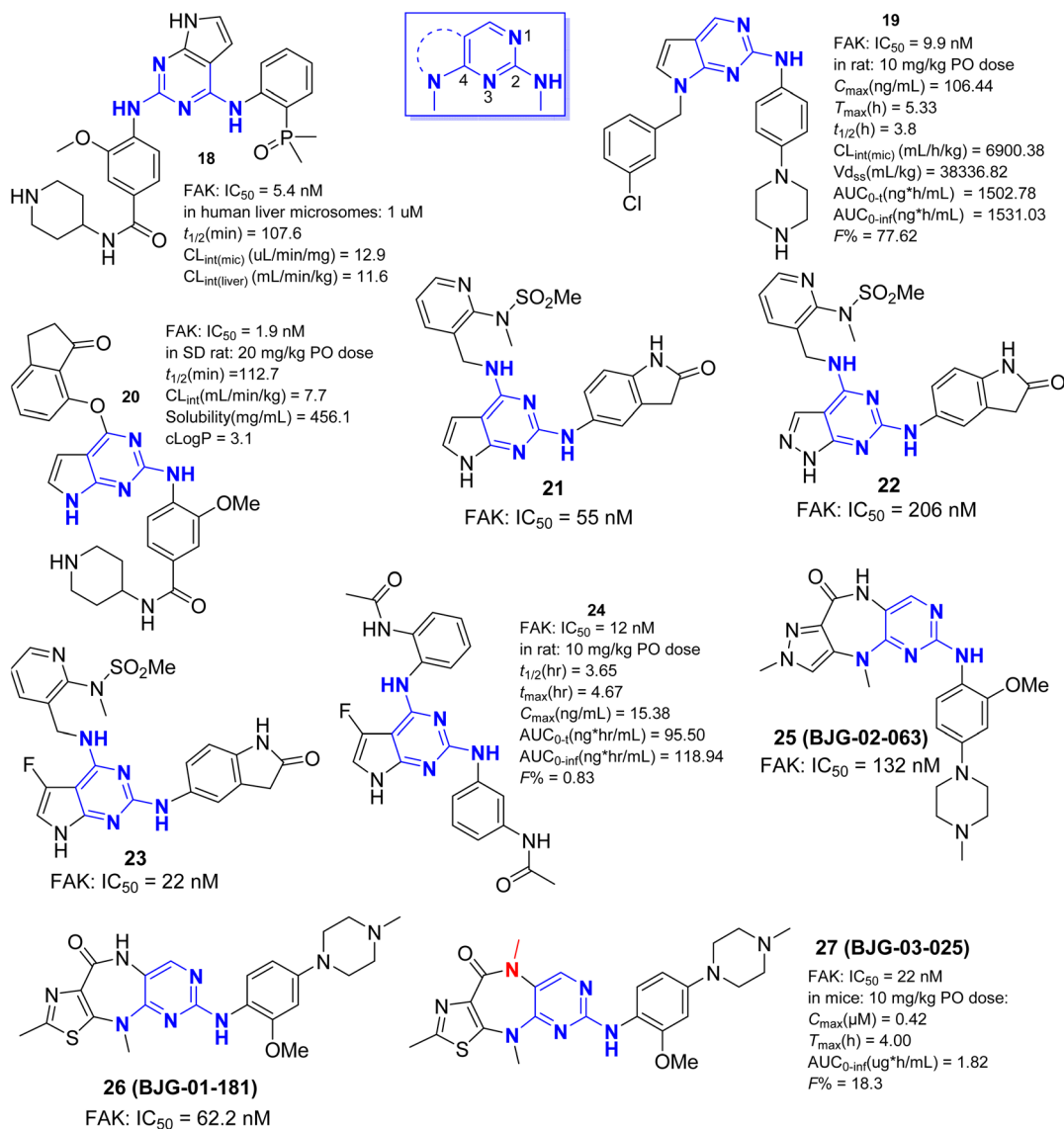


Fig. 8 FAK inhibitors based on fused ring of 2,4-diaminopyrimidine.

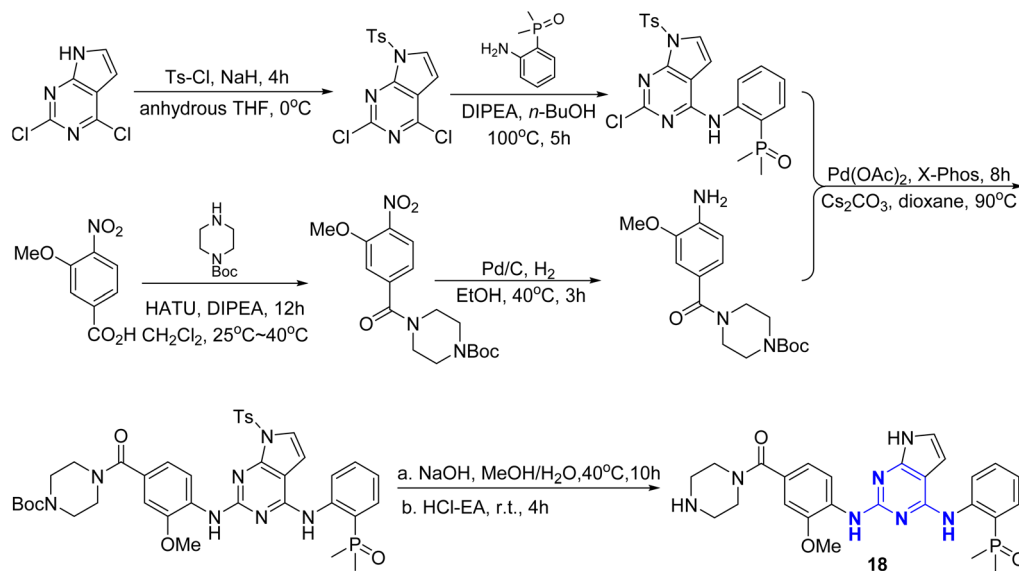


Fig. 9 The synthesis of compound 18.

properties of **TAE226**, and it can be replaced by piperidine, piperazine, amide, ester group, or introduce a covalent warhead, for example, acrylamide group, to form a covalent FAK inhibitor. It can be seen from the above description that the molecular structure of FAK inhibitors with 2,4-diaminopyrimidine monocyclus as backbone is mostly like **TAE226**. Without exception, there are halogen atoms (Cl, Br) or halogen containing groups ( $\text{CF}_3$ ) substituted at the 5-position of pyrimidine ring. The amino groups at the 2-position and 4-position of pyrimidine ring directly connect with benzene ring, ensuring that such molecules adopt a U-type structure binding to the central kinase domain of FAK.

**2.1.2 FAK inhibitors based on fused ring of 2,4-diaminopyrimidine.** FAK inhibitors with fused ring of 2,4-diaminopyrimidine are mainly the bicyclic structure of pyrrolopyrimidine, pyrazolopyrimidine, and the tricyclic structure of pyrazolo (or thiazolo) 1,4-diaza-5-cycloheptanopyrimidine (Fig. 8).

Cheng *et al.*<sup>46</sup> designed and synthesized a novel FAK inhibitor **18** containing pyrrolo[2,3-*d*]pyrimidine structure. Molecular docking studies showed that the nitrogen atom in the newly introduced pyrrole ring has an additional hydrogen bonding interaction on the Glu500 residue of FAK hinge region, thereby enhancing the interaction between compound **18** and FAK.

Compound **18** exhibited potent FAK inhibitory activity with an  $\text{IC}_{50}$  value of 5.4 nM and good FAK selectivity among 26 kinase lineages. Compound **18** can inhibit the migration of A549 cells and induce their apoptosis, showing low toxicity to normal human cell line such as HK2 cells. Animal experiments confirmed that compound **18** has metabolic stability in mouse, rat and human liver microsomes, and the inhibitory effect on human cytochrome P450 is very weak, indicating that compound **18** has good druggability. The synthesis of **18** is starting from 2,4-dichloro-7H-pyrrolo[2,3-*d*]pyrimidine by protection of NH of pyrrole with TsCl followed coupling with (2-

aminophenyl)dimethylphosphine oxide under basic conditions, and then, the Buchwald-Hartwig reaction between *tert*-butyl 4-(4-amino-3-methoxybenzoyl)piperazine-1-carboxylate and the above prepared intermediate was carried out to provide N-protected **18**. After deprotection of *N*-Ts on pyrrole and *N*-Boc on piperazine, compound **18** was obtained in good yield (Fig. 9).

Huang *et al.*<sup>47</sup> proposed a new pyrrolopyrimidine structure compound **19** ( $\text{IC}_{50} = 9.9$  nM), which is characterized by 2,4-diaminopyrimidine formed by 2,7-disubstituted secondary amine cyclization as the core skeleton, and *m*-chlorobenzyl group is substituted on the pyrrole ring nitrogen, which is used to reduce the planar rigidity and enhance the interaction with FAK. Compound **19** could effectively induce apoptosis of A549 cells and retard the cell cycle at G2/M phase. Animal experiments showed its good pharmacokinetic properties and bioavailability. Yu *et al.*<sup>48</sup> reported that the FAK inhibitor **20** with pyrrolo[2,3-*d*]pyrimidine as the core skeleton was connected to the aromatic ring by replacing the nitrogen atom at the 4-position of 2,4-diaminopyrimidine with an oxygen atom. The  $\text{IC}_{50}$  value of compound **20** for FAK was 1.9 nM, and its half-life was 4.08 hours at an oral dose of 20  $\text{mg kg}^{-1}$ , showing excellent drug metabolism parameters and good antitumor activity *in vivo*. The tumor growth inhibition rate (TGI) was 72.5% at a dose of 60  $\text{mg kg}^{-1}$ . Zhang *et al.*<sup>49</sup> used Schrodinger software to carry out extensive simulation screening of the ATP binding pocket of FAK. Based on a FAK inhibitor **PF-562271**, which has entered the clinical phase I, compounds **21** and **22** were synthesized by cyclizing pyrrolo and pyrazolo-fused pyrimidine backbone, respectively. The  $\text{IC}_{50}$  for FAK was 55 nM and 206 nM, respectively. This cyclization strategy improved the occupancy of pyrimidine ring in the ATP binding pocket to a certain extent. The introduction of a halogen group at the 5- or 6-position of the pyrrole ring can improve the activity, and the compound **23** with a fluorine atom at the 5-position has a FAK inhibitory



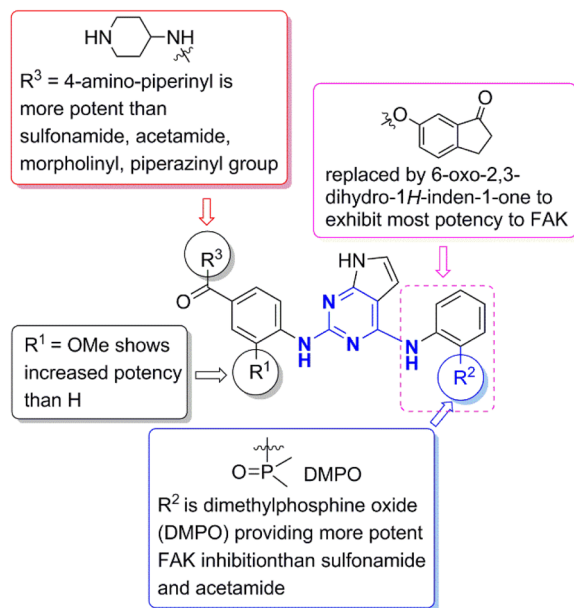


Fig. 10 The structure–activity relationship (SAR) of FAK inhibitors based on fused ring of 2,4-diaminopyrimidine.

activity of 22 nM. Subsequently, the authors returned to a similar structure as **TAE226**, retained the pyrazolopyrimidine core skeleton, still used an *o*-aminobenzamide group at the 4-position of the pyrimidine ring, and introduced an *m*-aminobenzamide group at the 2-position of the pyrimidine ring to obtain compound **24**, which showed excellent FAK inhibitory activity ( $\text{IC}_{50} = 12 \text{ nM}$ ). The  $\text{IC}_{50}$  values of compound **24** against YY8103 and SMMC7721 human hepatocellular carcinoma cells were 2.39 and 10.07  $\mu\text{M}$ , respectively, which exceeded **PF-562271**. In addition to its excellent inhibitory activity, compound **24** also has good drug metabolism parameters, including a half-life ( $t_{1/2}$ ) of 3.65 hours (10 mg per kg oral), and

showed significant *in vivo* antitumor activity (TGI = 78.6% at 30 mg per kg dose). The structure–activity relationship of FAK inhibitors containing fused pyrrole ring on 2,4-diaminopyrimidine is demonstrated on Fig. 10.

Gray *et al.*<sup>50</sup> reported a series of novel FAK inhibitors based on a pyrazolo (or thiazol)-1,4-diaza-5-cycloheptanopyrimidine tricyclic structure. In this study, they used pyrazole (or thiazole) and 1,4-diaza-5-cycloheptanone to replace the *o*-amino-benzamide of **TAE226**, and replaced the morpholine ring with 4-methylpiperazine, and synthesized compounds **25** (**BJG-02-063**) and **26** (**BJG-01-181**), with inhibitory activities against FAK of 132 nM and 62.2 nM, respectively. The structure of compound **26** was further modified to produce better inhibitory activity. The hydrogen on the 4-position nitrogen atom of 1,4-diaza-5-cycloheptanone was replaced by methyl group to obtain compound **27** (**BJG-03-025**), which enhanced its FAK inhibitory activity to 22 nM. Compound **27** could significantly inhibit the proliferation of MDA-MB-231 cells ( $\text{IC}_{50} = 3.6 \mu\text{M}$ ). The pharmacokinetics study in mice showed that the oral bioavailability of compound **27** was 18.3% (10 mg per kg dose), and the half-life of intravenous administration was 5.29 hours (2 mg per kg dose). Molecular docking studies revealed that the nitrogen atom of pyrrole ring and the oxygen atom of cycloheptanone formed hydrogen bonds with the Asp564 residue of FAK. The amino and nitrogen atoms of pyrimidine ring interacted with the oxygen atom on Cys502 residue, which was the key for this kind of tricyclic compounds to exert FAK inhibitory activity, showing its great potential in the treatment of gastric and breast cancer.

The synthesis of FAK inhibitors **25–27** with fused tricyclic structure started from ethyl 2-methylthiazole-4-carboxylate. Ethyl 2-methyl-5-(methylamino)thiazole-4-carboxylate was obtained from bromination, amination, deprotection and *N*-methylation. This above intermediate coupled with 2,4-dichloro-5-nitropyrimidine followed reductive cyclization to give tricyclic core, and then, the Buchwald–Hartwig reaction

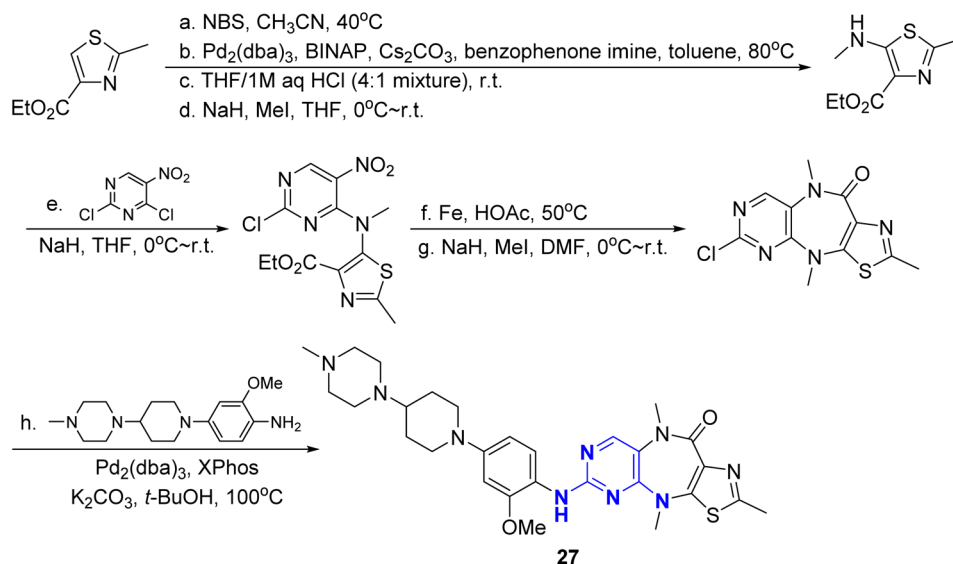


Fig. 11 The synthesis of compound **27**.



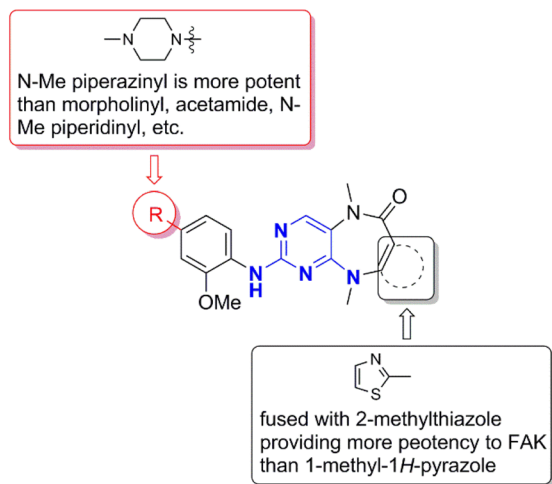


Fig. 12 The structure–activity relationship (SAR) of fused tricyclic FAK inhibitors.

between the above tricyclic intermediate and 2-methoxy-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)aniline was performed to give **27** (Fig. 11). The structure–activity relationship of these fused tricyclic FAK inhibitors is showed on Fig. 12. The fused tricyclic ring containing 2-methylthiazole is more potent than 1-methyl-1H-pyrazole, and N-Me piperazinyl is more potent than N-Me piperidinyl, morpholinyl, and acetamide on phenyl ring.

### 2.1.3 FAK inhibitors based on 2-aminopyrimidine core.

Because of the structural similarity between 2-aminopyrimidine and 2,4-diaminopyrimidine, it can also serve as an effective backbone for the development of FAK inhibitors (Fig. 13).

Kunick *et al.*<sup>51</sup> have prepared compound **28**, which has a unique 2-anilino-4-(benzimidazol-2-yl)-pyrimidine backbone. It is a multi-kinase inhibitor that can inhibit FAK, Aurora B, PLK1 and VEGFR2 ( $IC_{50}$  = 3.4, 6, 1.2, and 7.2  $\mu$ M). Compound **28** showed good antiproliferative activity against many cancer cell lines from different sources, such as renal cancer, colon cancer and central nervous system cancer. Cheng *et al.*<sup>52</sup> designed a class of thieno-2-aminopyrimidine derivatives to simulate the active conformation of 2,4-diaminopyrimidine derivatives, a classical FAK inhibitor, in which compound **29** indicated strong inhibition of FAK activity ( $IC_{50}$  = 28.2 nM).

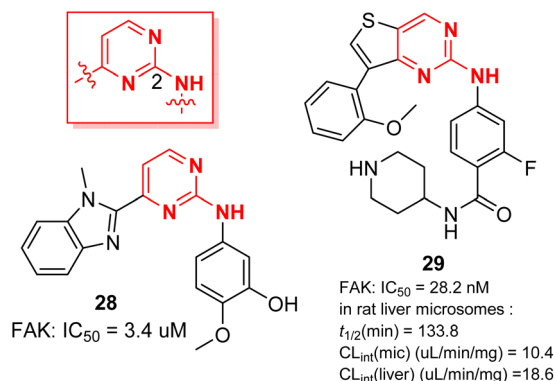


Fig. 13 FAK inhibitors based on 2-aminopyrimidine core.

Compound **29** showed better efficacy than **TAE226** in inhibiting the proliferation of U87MG, A549 and MDA-MB-231 cells. Further studies showed that compound **29** could induce apoptosis of MDA-MB-231 cells, retard the cell cycle at G0/G1 phase, and inhibit cell migration. *In vitro* studies showed that compound **29** had good metabolic stability in rat liver microsomes ( $t_{1/2}$  = 133.8 min).

## 2.2 FAK inhibitors based on triazine core

As bioelectronic isosteres of pyrimidines, 1,3,5-triazine and 1,2,4-triazine have also been used in the design and development of FAK inhibitors (Fig. 14).

Chen *et al.*<sup>53</sup> designed and synthesized a new class of FAK inhibitors of diarylamino-1,3,5-triazine derivatives. The representative compound **30** showed moderate FAK inhibitory activity ( $IC_{50}$  = 0.4  $\mu$ M) and could inhibit the expression of Y397 in HUVEC cells at low concentrations. The compound can effectively inhibit the generation of fibroblast growth factor receptor 2 (FGFR2) in blood vessels. Compared with **TAE226**, compound **30** has no 5-position chlorine atom on the triazinering, so it reduces the van der Waals interaction with Met499 on FAK to some extent. In addition, the 1,3,5-triazine ring in **30** has lower electron density and weaker ability to form hydrogen bonds with FAK than the 1,3-pyrimidine ring in **TAE226**, which may be the reason for the unsatisfactory inhibitory activity. In order to improve the inhibitory activity of compound **30**, Chen *et al.*<sup>54</sup> designed and synthesized imidazo [1,2-a]-[1,3,5]triazine derivative **31** which is a more selective inhibitor of FAK. It has no inhibitory activity against IGF-IR and Pyk2 at 1  $\mu$ M, but its  $IC_{50}$  for FAK is 50 nM, and its selectivity for FAK is more than that of other 30 kinases. Compound **31** strongly inhibited FAK mediated autophosphorylation and cell proliferation in U87 MG, HCT-116, MDA-MB-231 and PC-3 cell

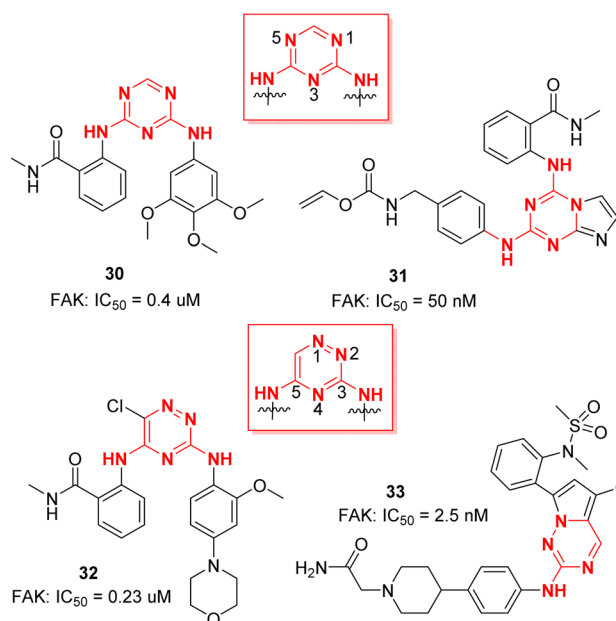


Fig. 14 FAK inhibitors based on triazine core.



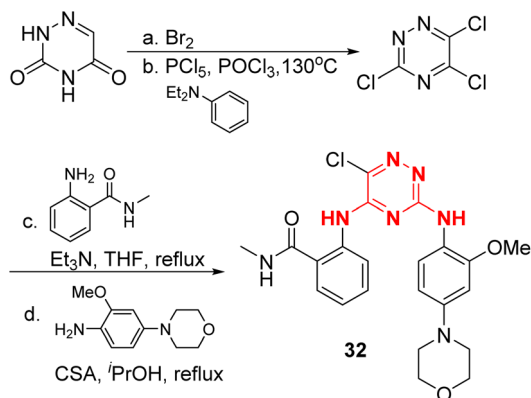


Fig. 15 The synthesis of compound 32.

lines, significantly induced apoptosis in HCT-116 cells at low concentrations, and retarded cell progression at the G2/M phase. Further studies indicated that 31 could inhibit the adhesion, migration and invasion of U87-MG cells to the matrix. Considering the importance of the pyrimidine ring and the chlorine atom at the 5-position of TAE226 to inhibit FAK, Chen *et al.*<sup>55</sup> designed and synthesized a series of new compounds with 1,2,4-triazine skeleton. Among these compounds, the chlorine atom at the 6-position remained unchanged, compound 32 had weak inhibitory activity against FAK ( $\text{IC}_{50} = 0.23 \mu\text{M}$ ). Molecule docking studies released that the van der Waals force between the 6-position chlorine atom in compound 32 and Met499 of FAK may not contribute much to its binding with FAK, and the hydrogen bonding between the triazine ring and its amino group and FAK hinge region is weak, affecting the

inhibitory activity of 32 on FAK. Based on the previously identified ALK inhibitors and JAK2 (Janus kinase 2) inhibitors, scientists from Cephalon company developed a class of JAK2/FAK dual inhibitors based on pyrrolo[2,1-*f*][1,2,4] triazine skeleton, and compound 33 (ref. 56) can potently inhibit JAK2 ( $\text{IC}_{50} = 2.5 \text{ nM}$ ) and FAK ( $\text{IC}_{50} = 5 \text{ nM}$ ). Studies have shown that compound 33 has ideal pharmacokinetic characteristics and oral bioavailability. It can strongly inhibit pStat3 and reduce the phosphorylation level of FAK *in vitro*, and the inhibitory activity of 33 is not limited to JAK2 and FAK. At  $1 \mu\text{M}$  concentration, it can inhibit 19 of 53 tumor related kinases with an inhibition rate of  $>90\%$ .

The preparation of compound 32 is listed on Fig. 15. 3,5,6-Trichloro-1,2,4-triazine was obtained from 1,2,4-triazine-3,5(2*H*,4*H*)-dione through chlorination, and then coupling with the corresponding substituted anilines to provide compound 32, these two coupling steps are similar to the preparation of TAE226.

### 2.3 FAK inhibitors with other skeletons

In addition to the above FAK inhibitors with six membered heterocycles, such as pyrimidine and triazine as the core skeleton, some five membered N-containing heterocycles also appear in the structure of FAK inhibitors including 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,2,4-triazole, imidazole, pyrazole, *etc.* Compared with six membered N-containing heterocycles, these FAK inhibitors with five membered N-containing heterocycles generally have lower activity and the inhibition rate is generally at the  $\mu\text{M}$  level (Fig. 16).

Zhu *et al.*<sup>57,58</sup> found a class of compounds 34 and 35 containing 1,2,4-thiadiazole, which can be used as FAK inhibitors.

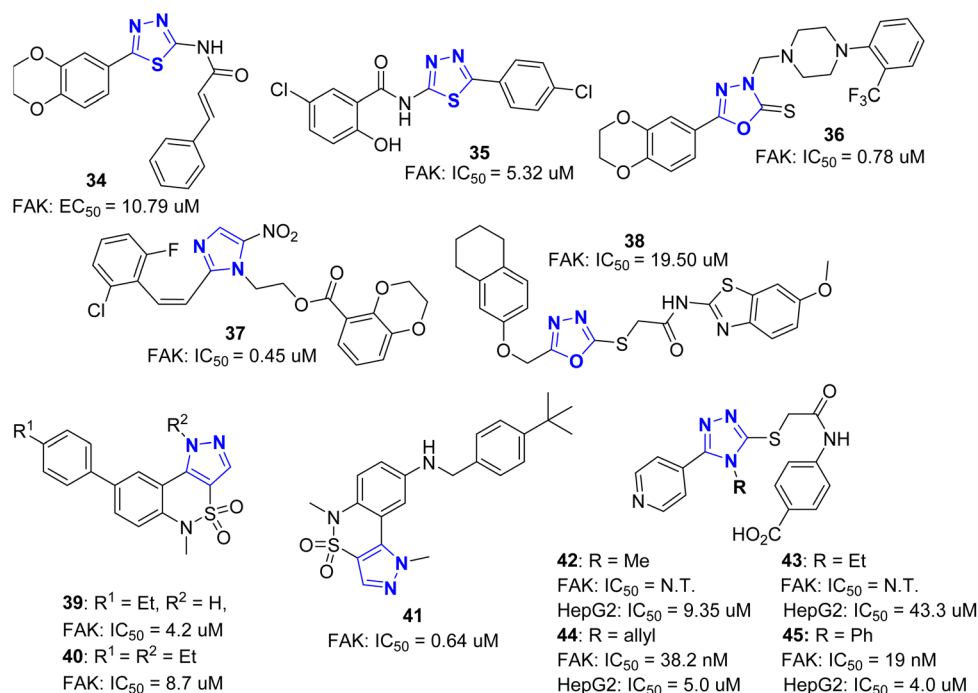


Fig. 16 FAK inhibitors based on other N-containing five-member rings.



Docking studies proved that these two compounds extended into the ATP binding pocket through hydrogen bond  $\pi$ - $\sigma$  interaction and  $\pi$ -cation interaction. Compound **34** inhibited FAK with an  $EC_{50}$  value of 10.79  $\mu$ M and could induce apoptosis of HepG2 cells in a dose-dependent manner. The  $IC_{50}$  of compound **35** for FAK was 5.32  $\mu$ M. Compounds **34** and **35** could effectively inhibit the growth of MCF-7 and B16-F10 cells with  $IC_{50}$  values of 0.45 and 0.31  $\mu$ M, respectively. By replacing 1,2,4-thiadiazole in **34** and **35** with 1,2,4-oxadiazole-2(3H)-thione, they designed and synthesized a class of FAK inhibitors represented by compound **36**.<sup>59</sup> The  $IC_{50}$  of compound **36** for inhibition of FAK was 0.78  $\mu$ M, and the  $IC_{50}$  for inhibition of the proliferation of HepG2 cells and SM1116 cells was 5.78  $\mu$ M and 47.15  $\mu$ M, respectively. They also reported a class of FAK inhibitors containing 2-styrene-5-nitroimidazole.<sup>60</sup> The  $IC_{50}$  of representative compound **37** for inhibition of FAK was 0.45  $\mu$ M, and it induced HeLa cell apoptosis in a dose-dependent manner. Similar to the research work of Zhu *et al.*,<sup>57,58</sup> Altintop *et al.*<sup>61</sup> designed and synthesized compound **38** with 1,2,4-oxadiazole as the framework of FAK inhibitor. Its  $IC_{50}$  for A549 and C6 cells were 9.33  $\mu$ M and 4.63  $\mu$ M, respectively. It also caused significant morphological changes in the above two types of cells and inhibited the expression of Caspase-3 in these two cell lines. The mechanism study revealed that it could effectively inhibit the activity of FAK and AKT, with  $IC_{50}$  of 19.50  $\mu$ M and 2.60  $\mu$ M, respectively. Docking studies showed that compound **38** could bind to the kinase domain in AKT and FAK. When bound to the FAK kinase domain, it can form  $\pi$ - $\pi$  stacking and salt bridges with the Phe568 residue and  $\pi$ -cation interactions with the Lys457 residue. It is worth noting that the 6-methoxybenzothiazole group of **38** has a close relationship with the tight binding of FAK. These studies showed that compound **38** represents a new class of ATP competitive FAK inhibitors.

In addition to ATP competition for type I and type II kinase inhibitors, the development of allosteric kinase inhibitors<sup>62,63</sup> has attracted more attention to medicinal chemists. Allosteric kinase inhibitors do not compete with ATP, so it is possible to overcome the side effects of poor selectivity of ATP competition and reduce drug resistance. Through high-throughput screening, Miki *et al.*<sup>64</sup> found a new class of FAK inhibitors **39** and **40** containing 1,5-dihydropyrazolo[4,3-c][2,1] benzothiazine

backbone, with  $IC_{50}$  of 8.7  $\mu$ M and 4.2  $\mu$ M for FAK, respectively. Compound **39** was pre-incubated with ATP for a long time, and no competitive binding with ATP was found. The crystal structure of compound **39** with the kinase domain of FAK (PDB ID: 4EBV) showed that the allosteric site involved in the induction of **39** was in the kinase domain and had polar and hydrophobic interactions with FAK. The pyrazole ring has  $\pi$ -cation interaction with the Arg550 side chain, one nitrogen atom in the pyrazole ring has hydrogen bonding with water molecules, and the other nitrogen atom has weak hydrogen bonding with the carboxylic acid group in the Asp604 side chain (Fig. 17). The introduction of ethyl on the pyrazole nitrogen of compound **39** produced compound **40**, which was only two times weaker than **39** in inhibiting FAK, indicating that hydrogen bonding with water molecules is not important. Biological studies have shown that both **39** and **40** can bind to unphosphorylated FAK allosteric sites, but only **39** can target phosphorylated FAK. Docking studies showed that when bound to phosphorylated FAK, the nitrogen atom in the pyrazole ring of **39** has a hydrogen bonding interaction with Glu500, but in compound **40**, the hydrogen on this nitrogen atom was replaced by ethyl, so phosphorylated FAK could not be formed. Interestingly, **40** showed higher FAK selectivity compared with compound **39**, indicating that the pyrazole N-substitution of **39** significantly improved kinase selectivity. Based on the studies of **39** and **40**, this research group synthesized N-substituted pyrazolo [4,3-c] [2,1] benzothiazine derivative **41**, which showed potent inhibitory activity against FAK ( $IC_{50}$  = 0.64  $\mu$ M). The crystal structure shows that (PDB ID: 414F), the core structure of tricyclic compound **41** binds to FAK in the same way as compound **38** (Fig. 18). The amino group connected with 4-*tert*-butylbenzyl group in the core structure of compound **41** has hydrogen bonding with Gly563, while 4-*tert*-butyl group occupies the hydrophobic cavity that formed by Met475, Leu486, Met499 and Val484 residues of FAK.<sup>65</sup>

In 2021, Hayallah *et al.*<sup>66</sup> reported novel FAK inhibitors (**42**–**45**) with 1,2,4-triazole structure. The structure–activity relationship (SAR) study of the substituents on the triazole ring showed that the 4-phenyl substituted compound **45** had higher FAK inhibitory activity ( $IC_{50}$  = 19.0 nM) than GSK-2256098 ( $IC_{50}$  = 22.1 nM). Compounds **44** and **45** showed significant inhibitory effects on Hep G2 and Hep 3B cells ( $IC_{50}$  of 4.72 and 3.78  $\mu$ M for Hep G2 and 2.88 and 4.83  $\mu$ M for Hep 3B).

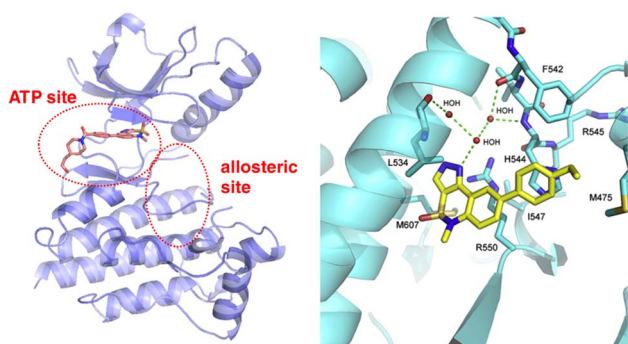


Fig. 17 Crystal structure of allosteric FAK inhibitor **39** complexed with the kinase domain of FAK (PDB ID: 4EBV).<sup>64</sup>

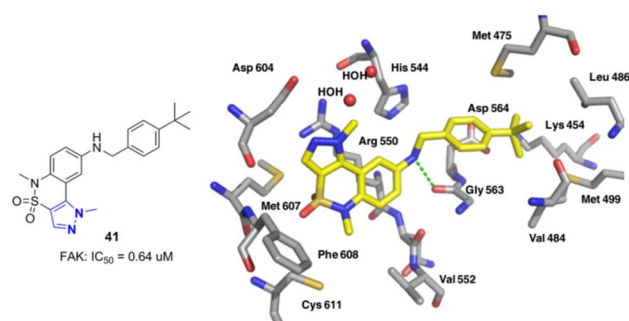


Fig. 18 Crystal structure of allosteric FAK inhibitor **41** complexed with the kinase domain of FAK (PDB ID: 414F).<sup>65</sup>



## 2.4 FAK based dual inhibitors

Compared with traditional single target inhibitors, dual target or multi-target inhibitors have the following advantages.<sup>67</sup> Firstly, dual target or multi-target drugs can simultaneously regulate multiple tumor pathways to achieve the best therapeutic effect.<sup>68</sup> Secondly, these drugs usually show lower side effects than drugs with two different targets at the same time.<sup>69</sup> Studies have confirmed that dual target drugs can significantly reduce the generation of drug resistance in the treatment of fungal diseases.<sup>70,71</sup> Therefore, the design and development of dual target inhibitors based on FAK is expected to become a new research trend in the field of cancer therapy.<sup>72</sup>

FLT3 (FMS like tyrosine kinase 3, FMS like tyrosine kinase 3) belongs to the receptor tyrosine kinase III (RTK III) family. FLT3 can regulate the differentiation, proliferation and survival of hematopoietic progenitor cells and dendritic cells, and can activate the phosphorylation of downstream SHC1 and AKT1, involving the signaling cascade of mTOR, RAS and MAP kinases. In recent years, studies have confirmed that the activating mutation of FLT3 plays an important role in the occurrence and disease progression of acute myeloid leukemia (AML).<sup>73</sup> In 2021, Sim *et al.*<sup>74</sup> reported a novel dual target inhibitor **46** based on FAK, targeting both FAK and FLT3. Compound **46** was derived from the first fused ring FAK inhibitor reported by this research group.<sup>75,76</sup> At the beginning of the study, they tried to use the benzenesulfonamide of PF-562271 (VS-6062) as a functional group entering the ATP binding pocket inside FAK. Subsequent SAR studies showed that the compound connected with the thiophene ring and the *m*-benzenesulfonamide group exhibited excellent inhibitory activity against FAK ( $IC_{50} = 7$  nM). Compound **46** with 4-ethylpiperazine phenyl core finally screened and showed the best activity against FAK, even exceeding TAE226 and PF-562271. Kinase selectivity studies showed that compound **46** was highly specific among 334 kinases, with  $IC_{50}$  values of less than 0.5 nM for 15 of them including FLT3, and showed strong inhibitory effects on Ba/F3 cells carrying four FLT3 mutations. The *in vivo* activity study showed that **46** had significantly inhibitory effect on MV4-11 xenograft mice. This finding not only provides a new way for the study of FAK inhibitors and FLT3 mutation inhibitors, but also has potential in the change of AML treatment.

Histone deacetylase (HDAC) is a kind of protease, which plays an important role in the structural modification of chromosomes and the regulation of gene expression. Abnormal histone acetylation level is closely related to cancer and immune diseases, so HDAC is an important target for cancer treatment.<sup>77</sup> HDAC inhibitors can inhibit the invasion and metastasis of tumor cells and antitumor angiogenesis, and play an important role in the field of antitumor drug research and development. Studies have confirmed that the combination of FAK inhibitors and HDAC inhibitors can show a synergistic effect, and they have a common regulatory function on the Hippo pathway. At the same time, targeting FAK and HDACs may synergistically improve the efficacy of cancer treatment. Generally, the structure of dual target inhibitors of FAK and HDACs contains three parts, the group interacting with the ATP binding pocket of FAK,

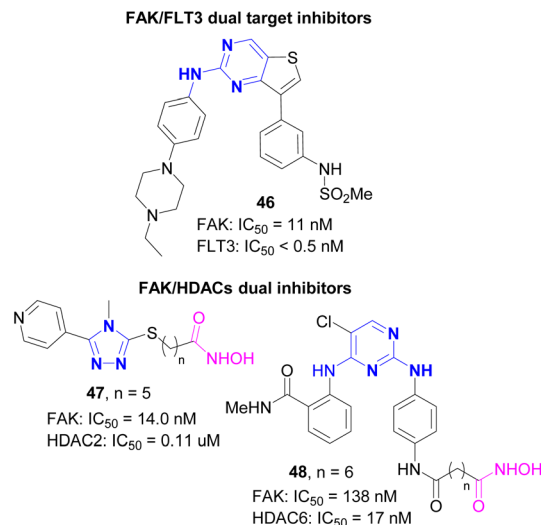


Fig. 19 FAK/FLT3 and FAK/HDAC2 dual inhibitors.

the linker with a specific length, and the group chelating with zinc ions in HDAC (carboxylic acid, hydroxamic acid, 2-amino-benzamide are commonly used). In 2021, Mustafa *et al.*<sup>78</sup> reported the first HDAC2 and FAK dual inhibitor **47**. In this study, Mustafa used 5-pyridyl-1,2,4-triazole as the binding part with FAK, and introduced various substituents (methyl, ethyl, phenyl, allyl, *etc.*) on the N atom at the 4-position of the triazole ring. The inhibitory activities of representative compound **47** on HDAC2 and FAK were 0.09  $\mu$ M and 12.59 nM, respectively, and it had significant inhibitory effects on a variety of tumor cells. In 2023, Song *et al.*<sup>79</sup> reported a dual FAK and HDAC6 inhibitor **48** (MY-1259). Starting from TAE226, they used long-chain hydroxamic acid to replace the morpholine group of TAE226 to obtain compound **48**. The results indicated that hydroxamic acid linked with six carbon atoms bearing the highest activity, with  $IC_{50}$  of 16 nM and 132 nM for HDAC6 and FAK, respectively. Compound **48** showed strong inhibitory effect on multiple tumor cells including gastric cancer, breast cancer and lung cancer. Compound **48**, administered by intraperitoneal injection at a dose of 20 mg  $kg^{-1}$  for 21 days, had a tumor inhibitory effect of 53.54% on MGC-803 tumor bearing mice, which was significantly better than the combination of TAE226 and SAHA (Fig. 19).

Epidermal growth factor receptor (EGFR) is a member of tyrosine kinase family and a key factor regulating intracellular signaling pathways such as PI3K, AKT and mTOR. EGFR plays a key role in tumor cell proliferation, migration, invasion and angiogenesis. EGFR expression increases in gastric cancer, breast cancer, bladder cancer, head and neck squamous cell carcinoma, so EGFR is a key target for anticancer drug development.<sup>80–82</sup> Targeting FAK and EGFR can achieve dual inhibition of downstream signal transduction.<sup>83–85</sup> In 2021, Abe *et al.*<sup>86</sup> reported FAK/EGFR dual target inhibitors **50–53** with 2-arylquinoline as the core skeleton (Fig. 20). Starting from the lead compound **49**, they carried out various substitutions on the substituents of the quinoline ring to obtain compounds **50–53**. They found that when  $CF_3$  or Cl were present at the *para*-

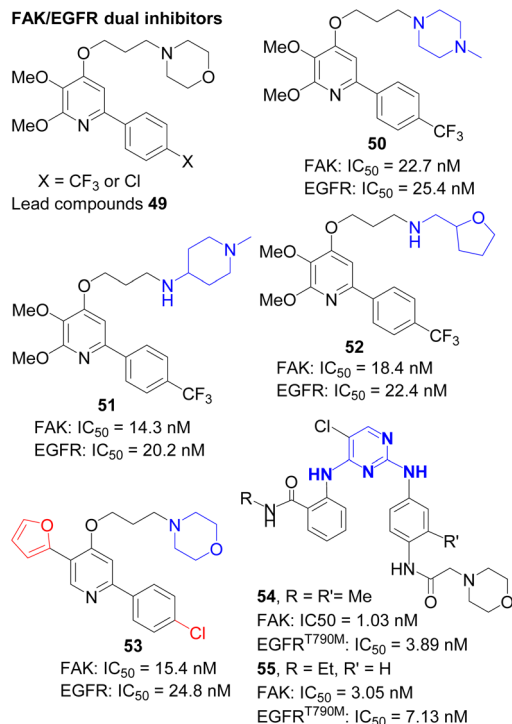


Fig. 20 FAK/EGFR dual inhibitors.

position of the benzene ring at the 2-position of quinoline, they had high inhibitory activity against FAK and EGFR, and compound 51 was the best, with IC<sub>50</sub> of 14.25 and 20.15 nM for FAK and EGFR, respectively. Chen and co-workers<sup>87</sup> have developed a new class of pyrimidine derivatives as potential dual FAK and EGFR<sup>T790M</sup> inhibitors based on a fragment-based drug design strategy. Among them, compounds 54 and 55 displayed strong inhibitory activities against FAK kinase (IC<sub>50</sub> = 1.03, 3.05 nM) and EGFR<sup>T790M</sup> mutants (IC<sub>50</sub> = 3.89, 7.13 nM), respectively. These compounds also exhibited strong inhibitory activity toward the three evaluated FAK-overexpressing PC cells (AsPC-1, BxPC-3, Panc-1) and two drug-resistant cancer cell lines (breast cancer MCF-7/adr cells and lung cancer H1975 cells) at concentrations below 6.94 μM. These compounds showed potent dual FAK and EGFR<sup>T790M</sup> inhibitors with a great potential for the treatment of hard to treat cancers.

PLK1 (polo like kinase 1), a member of the polo like kinase family, is a crucial protein kinase that regulates cell mitosis.<sup>88,89</sup> It can promote nuclear division and chromosome segregation in G2/M phase,<sup>90</sup> and is closely related to tumorigenesis and progression. Recent studies have shown that simultaneously targeting FAK and PLK1 has a synergistic effect, probably by affecting p53 through affecting CDK2 in the MAPK pathway. Previous studies have also reported the importance of inhibiting FAK during PLK1 degradation.<sup>91,92</sup> In 2023, Wu *et al.* reported a dual target inhibitor of FAK/PLK1 based on quinazolinone backbone through computer-aided drug design and structure-activity relationship (SAR) study.<sup>93</sup> The results showed that compound 56 had a significant inhibitory effect on MCF-7, HepG2, SGC7901 and A375 cells. The IC<sub>50</sub> for FAK and

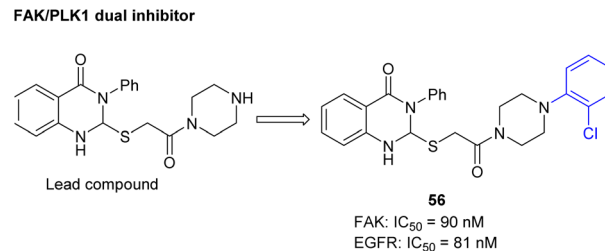


Fig. 21 FAK/PLK1 dual inhibitors.

PLK1 were 90 and 81 nM, respectively, showing that quinazolinone can be used as an important framework for the design of FAK inhibitors (Fig. 21).

## 2.5 FAK-targeting protein-protein interactions (PPIs)

Protein-protein interaction (PPI) can regulate many physiological processes in organisms and can be used as a key point for the treatment of various diseases.<sup>94,95</sup> Important physiological activities of life, such as cell signal transduction and regulation of material metabolism, protein synthesis and transport, DNA replication and transcription, are realized through PPI network. Changes in cellular microenvironment, epigenetic changes, gene mutations, *etc.*, can interfere with PPI patterns or directly induce protein binding, forming tumor specific interactions, which can lead to the occurrence, development, invasion and metastasis of tumors. In recent years, significant progress has been achieved in the research and development of antitumor drugs targeting PPIs. Many drugs are in clinical trials. Venetoclax (ABT-199) has been approved to market for the treatment of p17 deficient chronic lymphocytic leukemia (CLL).<sup>96</sup> More and more evidence shows that drugs targeting specific PPIs may have higher specificity and better efficacy than traditional anticancer drugs, providing new strategies and opportunities for treatment of specific tumors. As mentioned earlier, FAK protein interacts with MDM2, p53, IGF-1R, VEGFR-3 and other proteins, and plays an important role in the growth, proliferation, invasion and migration of tumor cells. Therefore,

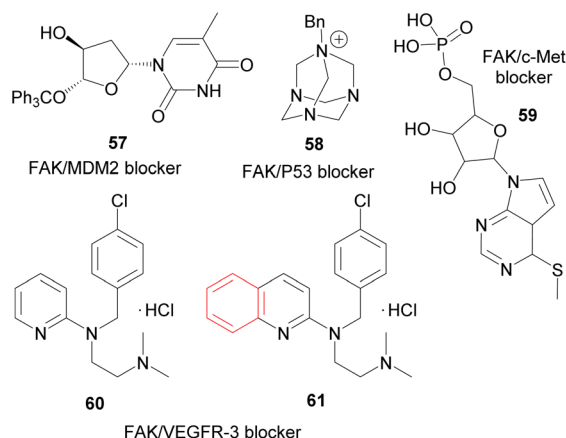


Fig. 22 Targeting FAK PPI blockers.



the development of blockers targeting the interaction between FAK and the above proteins can achieve the purpose of tumor inhibition (Fig. 22).

MDM2 is an E3 ligase that plays a key role in mediating p53 degradation.<sup>97</sup> There is an interaction between FERM domain of FAK protein and MDM2, which inactivates p53 ubiquitination through a kinase independent signaling pathway, resulting in slower apoptosis of tumor cells and promoting tumor cell growth and proliferation. Therefore, it is necessary to develop blockers targeting FAK/MDM2 interaction. Based on crystal structures of FAK and MDM2 proteins, Cance *et al.*<sup>98</sup> first reported that FAK/MDM2 interaction blocker **57** can activate p53 in a dose-dependent manner. It induced apoptosis of liver, breast and colon cancer cells through molecular modeling and high-throughput virtual screening, confirming that simultaneous inhibition of FAK/MDM2 can effectively combat the growth and proliferation of cancer cells.

The FAK FERM domain can also directly interact with p53 and disrupt its pro-apoptotic function.<sup>99</sup> Disrupting the binding of FAK to p53 may reactivate p53 to play a tumor suppressor role. Cance *et al.*<sup>100</sup> found that compound **58** had potent inhibitory activity on colon cancer cell HCT116 by disrupting the scaffold function of FAK and blocking the interaction between FAK and p53 in cells, and its inhibitory activity was significantly enhanced when combined with doxorubicin or 5-fluorouracil. Studies have shown that FAK interacts with insulin-like growth factor receptor-1 (IGF-1R) and c-Met to promote the survival and growth of cancer cells, and blocking the interaction between FAK and c-Met or IGF-1R may be a new tumor treatment strategy.<sup>101,102</sup> Compound **59** was obtained by Hochwald *et al.*<sup>103</sup> through molecular modeling and high-throughput virtual screening. This compound can disrupt the interaction between FAK and IGF-1R and c-Met, reduce the phosphorylation of FAK and AKT in adenocarcinoma cells, inhibit the growth of a variety of cancer cells, and have no effect on normal cells. Compound **59** combined with gemcitabine can significantly enhance cancer cell apoptosis and significantly inhibit the growth of pancreatic tumor *in vivo*. In addition to the FERM domain, the FAT domain of FAK can also interact with a series of proteins, including vascular endothelial growth factor receptor-3 (VEGFR-3) and paxillin, which can promote cancer cell survival. Cance *et al.*<sup>104</sup> found compound **60** by virtual docking using the FAK protein FAT domain crystal structure. Compound **60** decreased the phosphorylation level of FAK/VEGFR3 in a concentration-dependent manner, and had a significant inhibitory effect on some cancer cell lines. **60** could induce VEGFR3-dependent apoptosis of breast cancer cells. *In vivo* experiments showed that **60** effectively inhibited the over-expression of VEGFR-3 in tumor bearing mice and had a significant synergistic effect with doxorubicin. Compound **61** derived from structural modification of **60** had higher selectivity for FAK and VEGFR-3 overexpressing cancer cells than normal expressing cells.<sup>105</sup>

### 3. FAK inhibitors combined with other drugs in the treatment of tumors

Drug combination is very common in the treatment of tumor, diabetes and other aspects, and can play a good synergistic effect.<sup>106</sup> Similarly, the combination of FAK inhibitors and other drugs can also play a synergistic role in tumor inhibition.

In July 2019, Yang and others<sup>107</sup> published a patent to disclose the method of combining FAK/ALK/ROS1 inhibitors with EGFR inhibitors to treat cancer. They combined one or more of FAK inhibitors (**APG-2449**), ALK inhibitors and ROS1 inhibitors with EGFR inhibitors (such as Osimertinib) and showed synergistic inhibitory effects on a variety of cancer cells *in vitro* and *in vivo*. In May 2021, **VS-6766** broke the limitation of KRAS mutation status in patients.<sup>108</sup> The results of the phase 1/2 frame trial showed that the ORR of the combination was 52%, that of KRAS mutant patients was 70%, and that of KRAS wild-type patients was 44%, showing a good therapeutic effect. In June 2021, Li and others<sup>109</sup> applied for a patent for the combination of FAK inhibitor and KRAS inhibitor in the treatment of solid tumors. They verified the synergistic inhibitory effect of FAK inhibitor Ifebemtinib combined with KRAS G12C inhibitor (**AMG510** or **MRTX849**) on a variety of cancer cells, especially on cancer cell lines carrying KRAS G12C mutation. They confirmed that the therapeutic effect of the combination was achieved through the synergistic anticancer effect of FAK-YAP signaling pathway.<sup>110</sup> In August 2021, Inxmed Co. Ltd announced that FAK inhibitor Ifebemtinib (**IN10018**) combined with liposomal doxorubicin (PLD) for the treatment of platinum-resistant recurrent ovarian cancer. This combination had obtained the fast-track certification of the US FDA,<sup>111</sup> and was recognized as a breakthrough therapeutic drug by the China National Drug Administration (NMPA) in April 2022. Studies have shown that Ifebemtinib can break the tumor defense mechanism and effectively overcome drug resistance and metastasis by overcoming the tumor stromal fibrosis barrier and regulating the tumor immunosuppressive microenvironment. At present, this combination treatment is being used for a variety of solid tumor indications that lack effective methods, including platinum-resistant ovarian cancer, melanoma, triple negative breast cancer, head and neck cancer, pancreatic cancer and so on. In October 2023, Inxmed Co. Ltd announced that Ifebemtinib combined with MEK inhibitor (Cobimetinib), PD-1 antibody (Toripalimab), KRAS G12C inhibitor (**D-1553**) and EGFR TKI inhibitor (Furmonertinib), respectively. These combinations showed great potential antitumor efficacy in clinical research to give significant survival benefit trend to patients.<sup>112</sup> In May 2024, Chai *et al.*<sup>113</sup> disclosed the use of FAK inhibitor **GSK-2256098** or **PF-573228** combined with autophagy inhibitor hydroxychloroquine to treat drug-resistant pancreatic cancer. Through cell and animal experiments, it was found that these combinations can significantly reduce the viability of pancreatic cancer cells and inhibit the growth of pancreatic tumors. FAK inhibitors can promote the efficacy of hydroxychloroquine chemotherapy and enhance the antitumor effect by reducing the density of matrix around pancreatic cancer cells. In



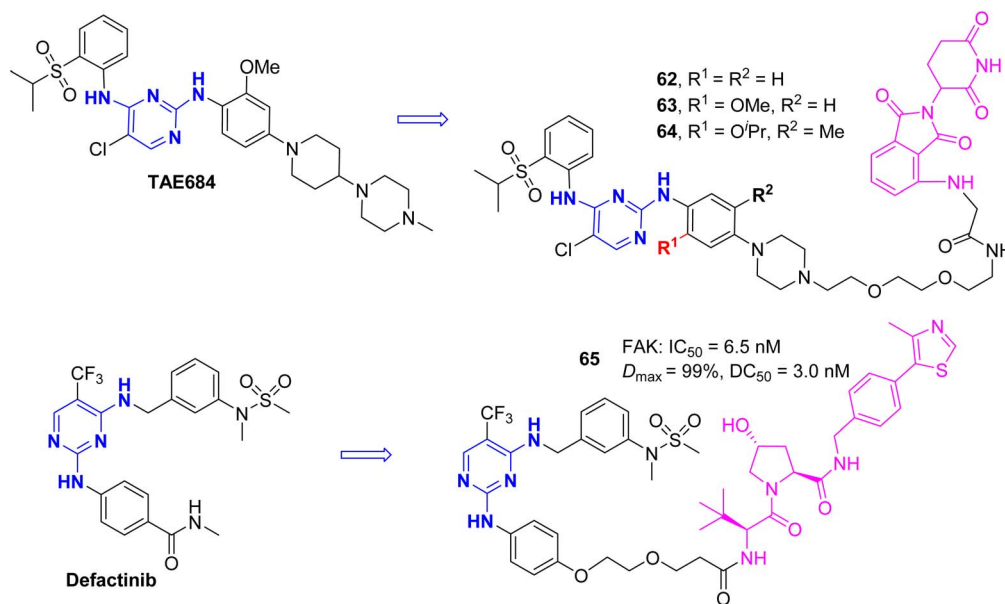


Fig. 23 FAK protacs 62–65.

September 2024, the US FDA granted Narmafotinib with Gemcitabine and Apatinib as a fast-track treatment for advanced pancreatic cancer.<sup>114</sup> Among the 14 patients who received Narmafotinib combined with chemotherapy, the tumor of 6 patients significantly shrank, indicating that the combination had good efficacy in some patients. In the phase I clinical study, it showed good tolerance and safety. The strategy of small molecule FAK inhibitors combined with other targeted drugs in the treatment of cancer has been recognized by clinical

research, providing new therapeutic opportunities and ways for patients with multidrug-resistant tumors.

#### 4. FAK-targeting protacs

Protac (proteolysis targeting chimera, Protac), which is a protein degradation targeting chimera technology, has made great progress in the past 20 years. It is a method of targeted degradation of specific pathogenic proteins by using natural

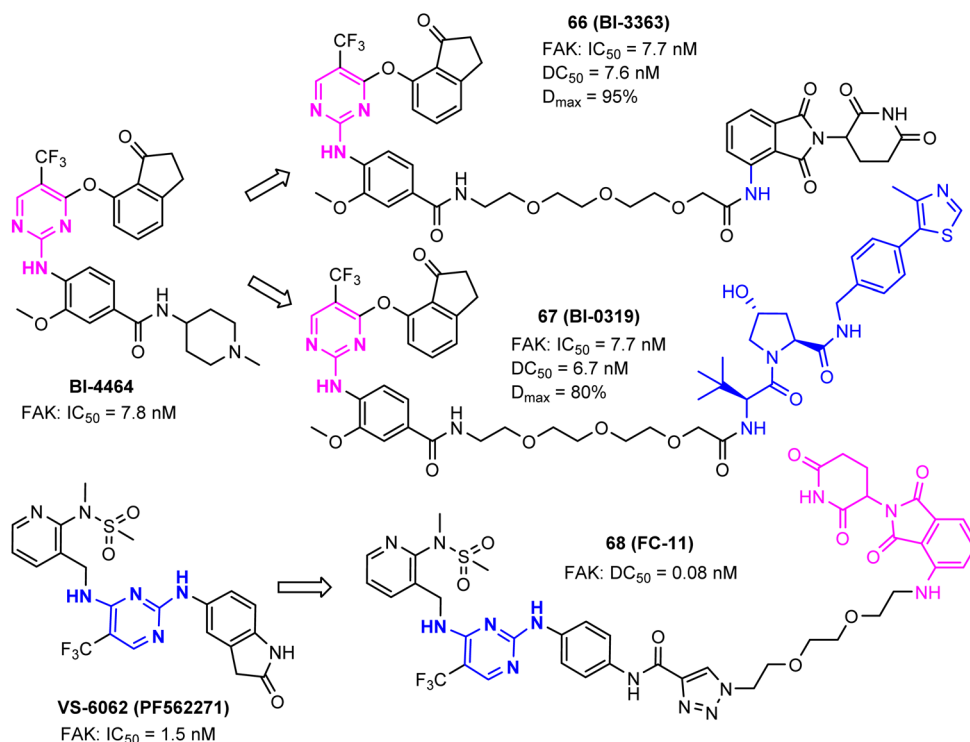
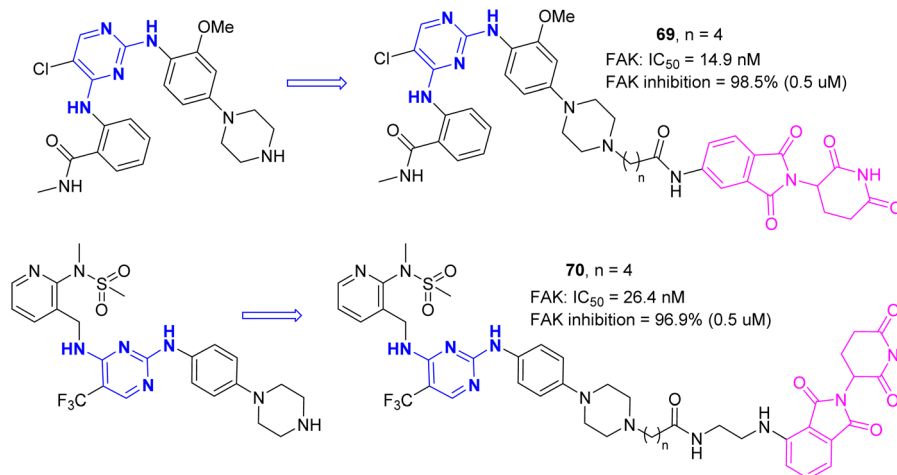


Fig. 24 FAK protacs 66–68.

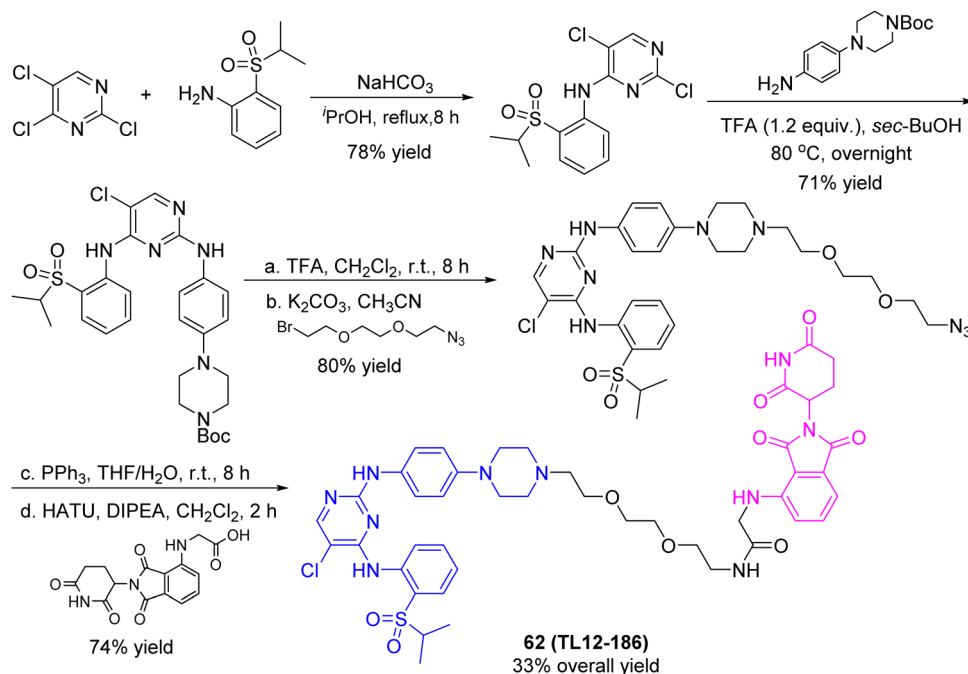


Fig. 25 FAK proteas **69** and **70**.

ubiquitin protease system with synthetic molecules.<sup>115</sup> Protac molecule is heterobifunctional compound composed of E3 ligand, linker, and protein of interest ligand (POI). The most used E3 ligands are CRBN and VHL. The linkers are generally long-chain alkanes, ethers, *etc.*, and POIs are usually small molecule kinase inhibitors. Due to its special targeting selectivity and anti-drug-resistance, protac has become a drug development pathway with great clinical application prospects.<sup>116,117</sup> At present, the research of proteas targeting FAK has entered the clinical research stage.

In 2018, Gray *et al.*<sup>118</sup> designed and synthesized a multi kinase degradation compound **62** (TL12-186) by coupling FAK inhibitor with pomalidomide through ethylene glycol ether linker. The study found that 28 kinases including BTK, PTK2,

FLT3, AurkA, AurkB, TEC, ULK1, ITK, CDK can be degraded by **62**. Later, they prepared ALK degraders **63** and **64** based on the pyrimidine ALK inhibitor **TAE684**, and found that these compounds could not only induce ALK degradation, but also FAK, Aurora A, FER, rSK1 degradation.<sup>119</sup> These studies demonstrate the flexibility of the development of FAK degraders. Also in 2018, Crews *et al.*<sup>120</sup> reported that FAK selective degraders **65**. They coupled the FAK inhibitor Defactinib with VHL ligand through ether linker to obtain compound **65**. Its half degradation concentration  $DC_{50}$  of FAK was 3 nM, and the degradation rate of FAK was more than 99% at the concentration of 10 nM, reaching almost complete degradation of FAK. Compound **65** was more effective than Defactinib in

Fig. 26 The synthesis of FAK proteas **62**.

inhibiting the migration and invasion of MDA-MB-231 cells (Fig. 23).

In 2019, scientists from Boehringer Ingelheim designed and synthesized FAK degraders **66** (BI-3663) and **67** (BI-0319).<sup>121</sup> Studies have confirmed that **66** ( $D_{\max} = 95\%$ ) and **67** ( $D_{\max} = 80\%$ ) can specifically degrade FAK in 12 cell lines. However, **66** and **67** did not show higher antiproliferative activity than FAK inhibitors. Rao *et al.*<sup>122</sup> connected the CRBN ligand pomalidomide through “click reaction” of FAK inhibitors **VS-6062** or **VS-6063** to prepare compound **68**, which has a very potent degradation ability for FAK of five different cell lines, and the half degradation concentration  $DC_{50}$  is as low as 0.08 nM. It is worth noting that compound **68** could inhibit FAK autophosphorylation more effectively than **VS-6062**. Consistent with the findings of Boehringer Ingelheim scientists, FAK degraders did not show more potent antiproliferative activity than FAK inhibitors (Fig. 24).

In 2022, Cheng *et al.*<sup>123</sup> reported that FAK degrader **69** based on **TAE226** structure had significant effect in combating non-small cell lung cancer (NSCLC). They retained the pyrimidine backbone and *o*-aminobenzamide moiety of **TAE226**, only replaced the morpholine ring with a piperazine ring, and sequentially installed a linker and pomalidomide on the piperazine ring for the recruitment of E3. According to the structure–activity relationship study, compound **69** containing a linker of five carbon atoms showed excellent activity, reaching 86.4% of the degradation activity of FAK in A549 cells, and the  $IC_{50}$  for FAK was 14.9 nM. Cheng *et al.*<sup>124</sup> also reported a FAK degrader **70** based on **PF562271** (**VS-6062**). Compound **70**, with

an amide chain of 10 atoms as the linker, showed better anti-proliferative activity and anti-invasion ability in A549 cells, with a degradation activity of 85% and an  $IC_{50}$  of 26.4 nM at a concentration of 10 nM. In addition, compound **70** has excellent stability with a plasma half-life  $t_{1/2}$  greater than 194.8 min (Fig. 25).

The synthesis of FAK protacs is listed on Fig. 26 by using **62** (**TL12-186**) as an example. The first two steps are similar to the preparation of **TAE226**. Following the deprotection of *N*-Boc group at piperazine, the linker was installed by alkylation with 1-azido-2-(2-(2-bromoethoxy)ethoxy)ethane. After then, the azide group was reduced by  $PPh_3$  followed coupling with E3 ligand to give **62** in 33% overall yield.<sup>118</sup> The synthesis of the other FAK-targeting protacs are similar to the preparation of **62** with different small molecular FAK inhibitors, linkers with proper length and E3 ligands.

## 5. Clinical trials of FAK inhibitors

The research on FAK inhibitors and degraders is very active, and some small molecular FAK inhibitors and protacs targeting FAK have entered the clinical research stage.

### 5.1 Clinical trials of small molecular FAK inhibitors

At present, there are nine small molecular FAK inhibitors to enter clinical research (Fig. 27)<sup>125</sup> including **CEP-37440**, **APG2449**, *etc.* Among them, **VS-6063** (Defactinib) and **CT-707** (Conteltinib) have entered clinical trials at phase III stage.

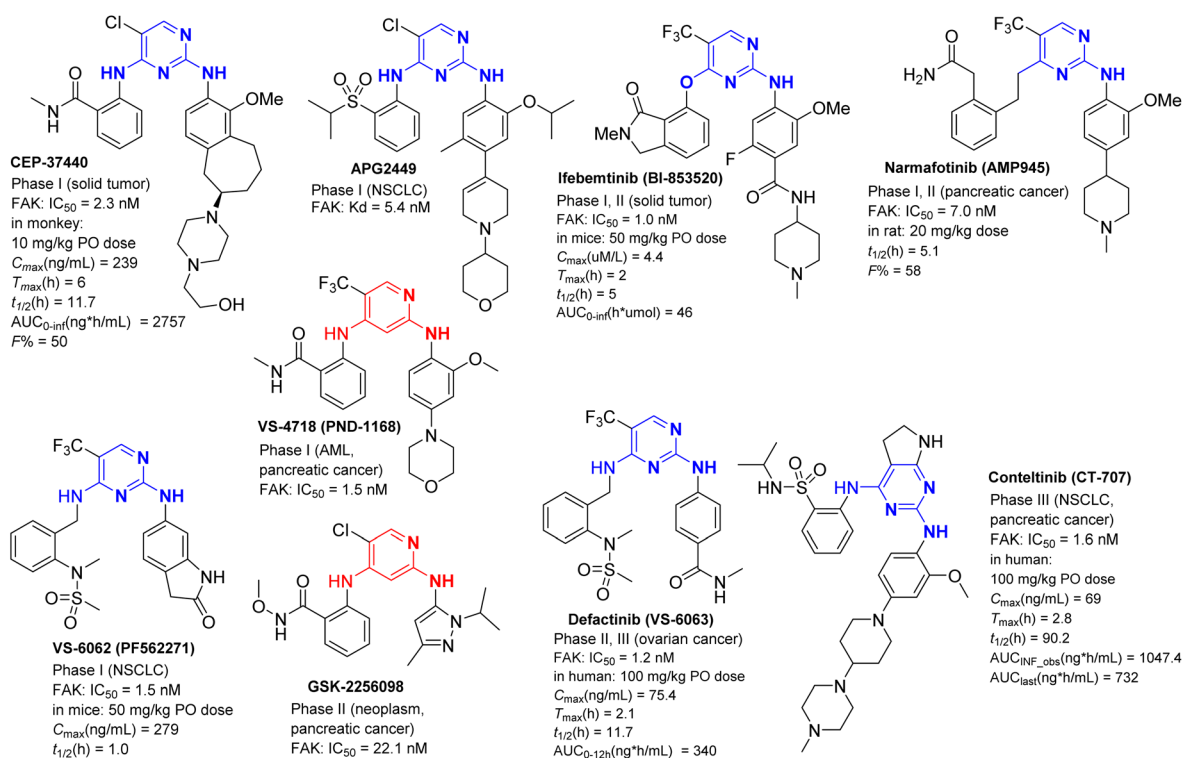


Fig. 27 Small molecular FAK inhibitors in clinical trial.



**CEP-37440** is an oral effective dual inhibitor of FAK/ALK developed by Teva pharmaceutical company.<sup>126</sup> The  $IC_{50}$  of FAK and ALK inhibition is 2.3 nM and 3.5 nM, respectively. It exerts the function of inhibiting tumor cell proliferation by blocking Tyr397 autophosphorylation of FAK. At present, it has completed clinical phase I research for the treatment of ALK positive non-small cell lung cancer (NSCLC) and inflammatory breast cancer (IBC). **APG2449** is a new small molecule FAK/ALK/ROS1 triple tyrosine kinase inhibitor (TKI) with oral activity independently developed by Ascentage pharmaceutical.<sup>127</sup> It is the first third-generation ALK inhibitor that has entered the clinical stage. It has excellent antitumor activity in a mouse model of non-small cell lung cancer (NSCLC) and is in clinical stage I. It shows potent inhibitory activity against NSCLC carrying ALK/ROS1 double mutations, providing a new treatment strategy for NSCLC patients resistant to the second-generation ALK inhibitor. Ifembemtinib (**BI-853520** or **IN10018**),<sup>128</sup> a FAK inhibitor with oral activity ( $IC_{50}$  = 1 nM) jointly developed by Boehringer Ingelheim and Inxmed, shows strong antiproliferative activity against a variety of solid tumors, including prostate cancer, and is currently in clinical phase I/II. Narmafotinib (**AMP945**)<sup>129</sup> is a potent FAK inhibitor ( $IC_{50}$  = 7.0 nM) developed by Australian Amplia pharmaceutical company, which can inhibit the autophosphorylation of FAK protein Y397 in MDA-MB-231 cells and has low cytotoxicity. On September 25, 2024, the FDA of the United States granted it the fast-track qualification of the leading drug for the treatment of advanced pancreatic cancer. The clinical trial of Narmafotinib for the treatment of advanced pancreatic cancer is being carried out in Australia and South Korea, and is currently in clinical phase I/II. **VS-4718 (PND-1168)**, which entered phase I clinical research, is a highly specific reversible FAK inhibitor with an  $IC_{50}$  of 1.5 nM, which can selectively promote tumor cell apoptosis and is used for the treatment of acute myeloid leukemia (AML) and pancreatic cancer. The structure of **GSK-2256098** is very similar to **TAE226**, except that the CL on the pyrimidine ring of **TAE226** is replaced by  $CF_3$ .<sup>130</sup> It is a selective FAK inhibitor that can inhibit the growth and proliferation of pancreatic cancer cells. It is currently in phase II clinical research for the treatment of pancreatic cancer and progressive meningioma.

**VS-6062 (PF562271)**,<sup>131</sup> **VS-6063 (Defactinib)**<sup>132</sup> and **VS-4718 (PND-1168)**<sup>133</sup> were FAK inhibitors developed by Pfizer in the early stage, and then Verastem was responsible for clinical research. **VS-6062** is an effective and reversible ATP competitive FAK and PYK2 kinase inhibitor with  $IC_{50}$  of 1.5 nM and 13 nM, respectively. At present, phase I clinical research has ended for the treatment of non-small cell lung cancer (NSCLC). **VS-6063 (Defactinib)**, which inhibits Tyr397 phosphorylation of FAK in a time- and dose-dependent manner, can also reduce the levels of AKT and YB-1 in taxane-resistant cell lines, and is now in clinical phase III. In March 2024, the US Food and Drug Administration (FDA) granted Avutometinib (**VS-6766**) alone or in combination with the FAK inhibitor **VS-6063 (Defactinib)** orphan drug qualification for the treatment of patients with KRAS mutated recurrent low-grade serous ovarian cancer, bringing new hope for the treatment of this refractory disease.

In clinical trials, the efficacy of the combination of Defactinib and Avutometinib was better, 45% of patients had significantly reduced tumors, and the disease control rate was at least 90%. In KRAS mutant patients, the disease control rate of dual drug combination also reached 100%. In terms of safety, the most common treatment-related adverse events (occurring in more than 20% of patients) included nausea, diarrhea, elevated CPK, peripheral edema, vomiting, blurred vision, acne like dermatitis, fatigue, rash, dry skin, and anemia.

**CT-707 (Conteltinib)**<sup>134</sup> is a first-in-class drug from China's Shouyao holdings. It is a multi-kinase inhibitor targeting FAK, ALK and Pyk2. The  $IC_{50}$  of FAK was 1.6 nM, which was used to treat ALK positive non-small cell lung cancer, including newly treated and Crizotinib resistant patients. The phase I clinical trial results of **CT-707** for ALK positive non-small cell lung cancer patients showed that for newly treated patients, the objective remission rate of patients in the 450 mg dose group was 87.5%, and the disease control rate was as high as 100%. For Crizotinib resistant patients, the overall remission rate of patients in the 300 mg dose group was 83.3%, and the disease control rate was 100%. Among patients in the dose group above 450 mg, the median progression free survival was 13 months, and 58% of patients had remission lasting more than 11 months. The most common adverse reactions of **CT-707** were gastrointestinal reactions and elevated transaminases, mostly grade 1–2, which showed good tolerability and safety. Multiple phase II and phase III clinical trials of **CT-707** (ctr20200770,

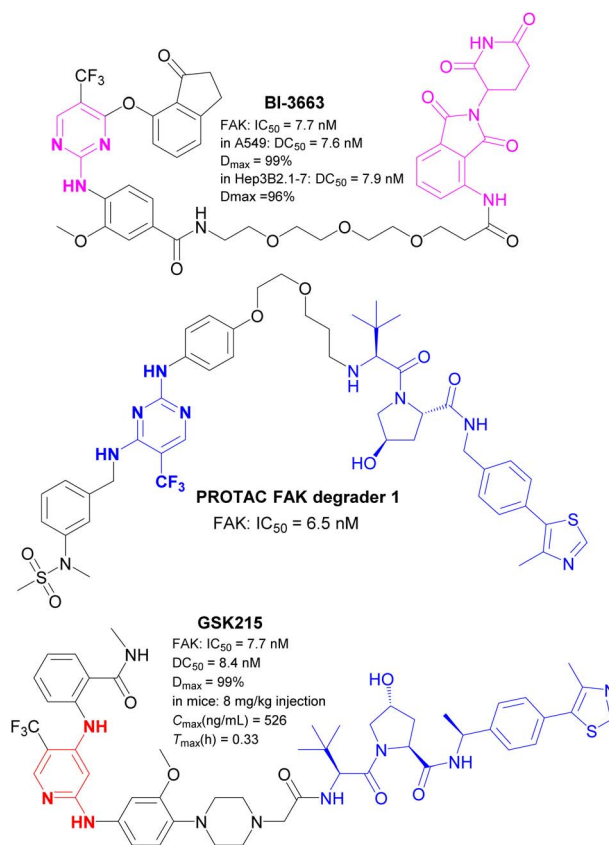


Fig. 28 FAK PROTACs in clinical trial.

ctr20181770) are in progress. On October 22, 2024, CT-707 granules was accepted as a new drug by the State Drug Administration for the treatment of anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).

## 5.2 Clinical trials of FAK protacs

Although the research of protacs is in full swing, no protac molecule has yet been approved for clinical use, as have the protacs targeting FAK. Up to now, three FAK protac molecules have entered clinical research, namely BI-3663, FAK degrader 1 and GSK215 (Fig. 28). BI-3663 is a highly selective protac molecule of PTK2/FAK ( $DC_{50} = 30$  nM), which can degrade PTK2 with an  $IC_{50}$  of 18 nM. It is formed by linking PTK2/FAK inhibitor BI-4464 and CRBN E3 ligase ligand through long-chain ether. Protac FAK degrader 1 is a selective FAK degrader based on VHL E3 ligase ligand, with  $IC_{50}$  of 6.5 nM and  $DC_{50}$  of 3 nM. GSK215 is a protac molecule targeting FAK,<sup>135</sup> which can induce rapid and persistent degradation of FAK and have a long-term effect on FAK levels, with a half degradation concentration of  $DC_{50}$  of 8.4 nM. GSK215 is designed with VS-4718 as a ligand targeting FAK protein and VHL as an E3 ligase ligand. The above three protacs targeting FAK are currently in phase I clinical research, and there are few published reports on their clinical experimental data.

## 6. Outlook and perspectives

FAK is a protein closely related to the proliferation, invasion and metastasis of tumor cells. Since its discovery in the 1990s, it has become one of the widely concerned and potential targets for antitumor drugs.<sup>136</sup> Because of an important role of FAK in the proliferation and metabolism of normal cells, targeted FAK drugs may affect normal cells and even lead to serious adverse reactions. To enhance the curative effect and reduce the toxic and side effects, optimizing the design of FAK targeted drugs and achieving its excellent tumor targeting are essential for its clinical application. We outline the structural composition of FAK protein and highlight its key phosphorylation sites. We also summarize the drugs targeting FAK and highlight its backbone structure and molecular design.

First, in the design of targeted FAK drugs, it is urgent to break through the classical 2,4-diaminopyrimidine core skeleton. 2,4-diaminopyrimidine is the traditional backbone of small molecule targeted drugs on the market and well developed. It competitively binds with ATP at most kinase sites. This backbone is bound to cause target mutations, multidrug resistance and off target effects. Therefore, it is necessary to search for small molecule FAK inhibitors with skeletal diversity. At present, five membered azole rings, fused heterocycles and linear frameworks also appear in the structure of FAK inhibitors,<sup>137</sup> which is worthy of further exploration and development.

Second, the synergistic effect based on dual target or multi-target inhibitors of FAK can effectively improve the antitumor activity. Dual target or multi-target drugs located in the same signaling pathway or parallel pathways have attracted much

attention in recent years. The dual- or multi-target small molecule drugs play a synergistic role, reduce the generation of drug resistance, and improve the therapeutic effect.<sup>138–141</sup> However, there are few studies on dual target or multi-target inhibitors of FAK/SRC, FAK/FGFR, FAK/HER2/EGFR, FAK/ALK/ROS, FAK/AKT/mTOR. This situation leaves a broad space for the development of dual- or multi-target drugs based on FAK.

Third, the introduction of covalent structure in drug design has become a new direction for the development of FAK inhibitors.<sup>142</sup> The antitumor drugs listed in recent years, such as Zanubrutinib targeting BTK, Sotorasib, Adagrasib, Garsorasib, and Fulzerasib targeting KRAS G12C mutation, are all covalent inhibitors. They have excellent performance in the treatment of refractory tumors such as drug resistance and easy relapse, which has inspired the “gold rush” wave of medicinal chemists to develop covalent drugs. The design and synthesis of FAK covalent inhibitors are also not lagging. Since the first irreversible covalent FAK inhibitor<sup>32</sup> was reported in 2018, many FAK covalent inhibitors have been reported, but most of them use mature acrylamide as covalent warheads, and it is urgent to develop FAK inhibitors containing covalent warheads with other structures such as nitrile group.<sup>143,144</sup>

Fourth, the combination of FAK inhibitors and other anti-tumor drugs has great clinical application prospects. Many clinical trials have confirmed that the combination of FAK inhibitor and other antitumor drugs can play a synergistic effect. For example, the combination of Ifebeamtinib (IN10018) and MEK inhibitor (Cobimetinib), PD-1 antibody (Toripalimab), KRAS G12C inhibitor (D-1553) and EGFR TKI inhibitor (Furmonertinib) described previously has shown excellent anti-tumor efficacy in clinical research and significantly increased the survival of patients.

Finally, the development of proximity induction strategy<sup>145,146</sup> injects fresh vitality into the development of FAK targeted drugs. Proximity inducing strategy refers to the emerging drug design technology that drug molecules destroy the pathogenic target by using the ubiquitin proteasome system (UPS), autophagy, lysosomal degradation and other pathways possessed by the cell itself, or achieve the functional regulation of the target by narrowing the distance between the target and other functional bodies. Protac belongs to the proximity inducing strategy. FAK inhibitors bind to E3 ligase ligands such as CRBN or VHL through the linker to form protacs that target FAK for degradation, which has certain advantages. However, the inherent characteristics of protac molecules, such as difficulties in druggability, limit further application. This is also the main reason why no protac drug has been listed so far. Medicinal chemists are overcoming the lack of protac, and the first protac is likely to be approved in the very near future.

To sum up, although no drug targeting FAK has been approved for marketing, FAK inhibitors that have entered clinical research have achieved significant effects. For example, Defactinib (VS-6063) and Conteltinib (CT-707) have progressed to phase III clinical trials and have been used in the treatment of non-small cell lung cancer (NSCLC), ovarian cancer and pancreatic cancer, showing the great potential of FAK inhibitors in the fight against malignant tumors. It is believed that soon,



targeted FAK drugs will become a breakthrough method for the treatment of human cancer.

## Data availability

No primary research results, software or code has been included and no new data were generated or analysed as part of this review.

## Author contributions

S. K. Zhu and Q. Wu are the drafters of the overall framework of the article and are responsible for the content writing; G. X. Liu and X. Y. Wang were responsible for literature collation; P. G. Wang and A. Q. Geng directed the writing of the paper, checked and revised it.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

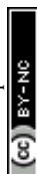
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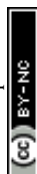
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