



Discovery of antiproliferative and anti-FAK inhibitory activity of 1,2,4-triazole derivatives containing acetamido carboxylic acid skeleton

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ABSTRACT

Small molecule inhibitors of the focal adhesion kinase are regarded as promising tools in our armamentarium for treating cancer. Here, we identified four 1,2,4-triazole derivatives that inhibit FAK kinase significantly and evaluated their therapeutic potential. Most tested compounds revealed potent antiproliferative activity in HepG2 and Hep3B liver cancer cells, in which **3c** and **3d** were the most potent (IC₅₀ range; 2.88 ~ 4.83 μM). Compound **3d** possessed significant FAK inhibitory activity with IC₅₀ value of 18.10 nM better than the reference GSK-2256098 (IC₅₀ = 22.14 nM). The preliminary mechanism investigation by Western blot analysis showed that both **3c** and **3d** repressed FAK phosphorylation comparable to GSK-2256098 in HepG2 cells. As a result of FAK inhibition, **3c** and **3d** inhibited the pro-survival pathways by decreasing the phosphorylation levels of PI3K, Akt, JNK, and STAT3 proteins. This effect led to apoptosis induction and cell cycle arrest. Taken together, these results indicate that **3d** could serve as a potent preclinical candidate for the treatment of cancers.

Focal adhesion kinase (FAK), a non-receptor tyrosine kinase, is a critical enzyme in the signaling pathway and is overexpressed in different solid tumors such as liver cancer, breast cancer, colon cancer, etc.¹ FAK plays a prominent role in cell survival, migration, adhesion, and proliferation.² Also, FAK consists of three different domains, including an N terminal FERM (four-point-one, ezrin, radixin, moesin) domain, a catalytic kinase domain (central), and a C-terminal focal adhesion targeting (FAT) domain. These domains contain tyrosine phosphorylation sites that regulate the molecular functions and the catalytic activity of FAK.³ Ample evidence indicates that FAK potentiates cancer progression and that inhibiting the kinase is a promising therapeutic strategy.^{3,4} Consequently, FAK is recognized as an important therapeutic target for the treatment of cancer.

FAK inhibition influences other essential proteins such as Akt and Signal transducer and activator of transcription 3 (STAT3).^{5,6} Akt plays a

fundamental role in regulating numerous cellular functions such as proliferation, survival, metabolism, and growth, while STAT3 is crucial for cell growth and is activated mostly in solid tumors (the same as FAK). In this respect, the inhibition of Akt and STAT3 phosphorylation leads to remarkable anticancer activity. Interestingly, the FAK inhibition results in suppressing the phosphorylation of both Akt and STAT3.^{5,7,8}

Recently, numerous efforts devoted to developing potent FAK inhibitors to treat cancers.^{4,9,10} Most of the developed inhibitors targeted the ATP binding site of FAK and were designed to bind to the essential amino acids in the active site, such as Cys502 in the kinase hinge and Asp564 of the DFG motif. TAE226 is one of the earliest discovered FAK inhibitors with potent antiproliferative activity (Fig. 1).¹¹ Despite its superior potency, TAE226 did not enter clinical trials due to its effect on glucose metabolism.¹² Four FAK inhibitors; PND-1186, PF-562271, CEP37440, and GSK-2256098, finished phase I clinical trials, whereas

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defactinib is the only compound that completed phase II clinical trials (Fig. 1).⁴ The main pharmacophore of FAK inhibitors comprises diphenyl five/six-membered nitrogenous heterocyclic rings. Several five-membered heterocyclic FAK inhibitors, such as oxadiazoles (VII, VIII),^{13,14} triazoles (IX, X),^{15,16} and thiadiazoles (XI, XII)^{17,18} revealed potent FAK inhibitory and antiproliferative activity (Fig. 2). The structural features analysis displayed that the diphenyl substitution at ring A and ring B on the five-membered heterocyclic ring is fundamental for the activity. Several compounds bearing diphenyl dioxine, substituted phenyl, or pyridinyl in ring A possessed significant anti-FAK and antiproliferative activity, whereas ring B was separated from the heterocyclic ring by a linker containing thioacetamide, butanamide, thioacetohydrazide, or amide.

The 1,2,4-triazole and pyridine rings are well-known moieties present in several anticancer agents.^{13,19–21} The 1,2,4-triazole is an important bioisostere to various bonds and heterocyclic ring and possesses H-bond accepting properties, strong dipole moment, and pi electron-deficient aromaticity.²² Besides, both 1,2,4-triazole and pyridine moieties display considerable stability towards chemical and metabolic degradation.

Based on the abovementioned findings and as a probe for the investigation of more potent FAK inhibitors, we report herein the synthesis and biological investigation of 5-pyridinyl-1,2,4-triazole derivatives as potential FAK inhibitors. Pyridine and benzoic acid were investigated as ring A and ring B, respectively. The 1,2,4-triazole (five-membered ring) was connected to ring B via thioacetamide moiety.

The synthesis of derivatives **3a–d** was accomplished by treating isonicotinic acid hydrazide with the appropriate isothiocyanate (methyl, ethyl, allyl, or phenyl) at 70 °C (Scheme 1). The resulting thiosemicarbazide was then reacted with 2 N NaOH and acidified with HCl to yield the 1,2,4-triazole-3-thiol derivatives **1a–d**, whereas 4-(2-bromoacetamido) benzoic acid **2** was obtained by reacting *p*-aminobenzoic

acid with bromoacetyl bromide. The target compounds **3a–d** were obtained through reacting **1a–d** with **2** in the presence of triethylamine in 93–96% yield at 70 °C. The structures of the target compounds were checked by ¹HNMR, ¹³CNMR, mass spectroscopy, and further confirmed by elemental analyses. The purity of compound **3d** was further checked by HPLC analysis using a linear gradient of methanol: water mixture at a rate of 1.0 mL/min leading to elution of hybrid **3d** as a single peak after 4.79 min at λ_{max} of 220 nm (Supporting information).²³

The synthesized carboxylic acid derivatives **3a–d** were evaluated for their antiproliferative activity on HepG2 and Hep3B liver cancer cell lines. These cells were selected deliberately because they profoundly express FAK protein.^{24,25} Doxorubicin and GSK2256098 were used as a positive control. As illustrated in Table 1, the derivatives **3a–d** possessed a distinctive potency on both tested cells; compounds **3c** and **3d** showed potent antiproliferative activity in HepG2 cells with IC₅₀ values of 4.72 and 3.78 μ M, respectively. Besides, **3a** revealed moderate antiproliferative activity in HepG2 cells (IC₅₀ = 8.83 μ M). Despite this promising activity of the prepared compounds on HepG2 cells, the derivative **3b** did not possess notable activity and showed 20-folds lower antiproliferative activity than Doxorubicin. On Hep3B cells, compounds **3a**, **3c**, and **3d** showed more potent antiproliferative activity than Doxorubicin and GSK2256098. The most active derivatives **3c** and **3d** were tested for their FAK inhibitory activity, using GSK2256098 as a positive control. Interestingly, both tested compounds revealed strong FAK inhibitory activity in low nanomolar concentrations (Table 1). It is worth mentioning that **3d** possessed comparable FAK inhibitory activity to the reference GSK2256098 with IC₅₀ value of 18.10 nM.

Moreover, the immunoblotting analysis was performed in HepG2 cells for compounds **3c** and **3d**, whereas GSK-2256098 was used as a positive control. The obtained results revealed that both **3c** and **3d** displayed a substantial ability to repress FAK phosphorylation comparable to the reference GSK-2256098 at 4 μ M concentration (Fig. 3A and

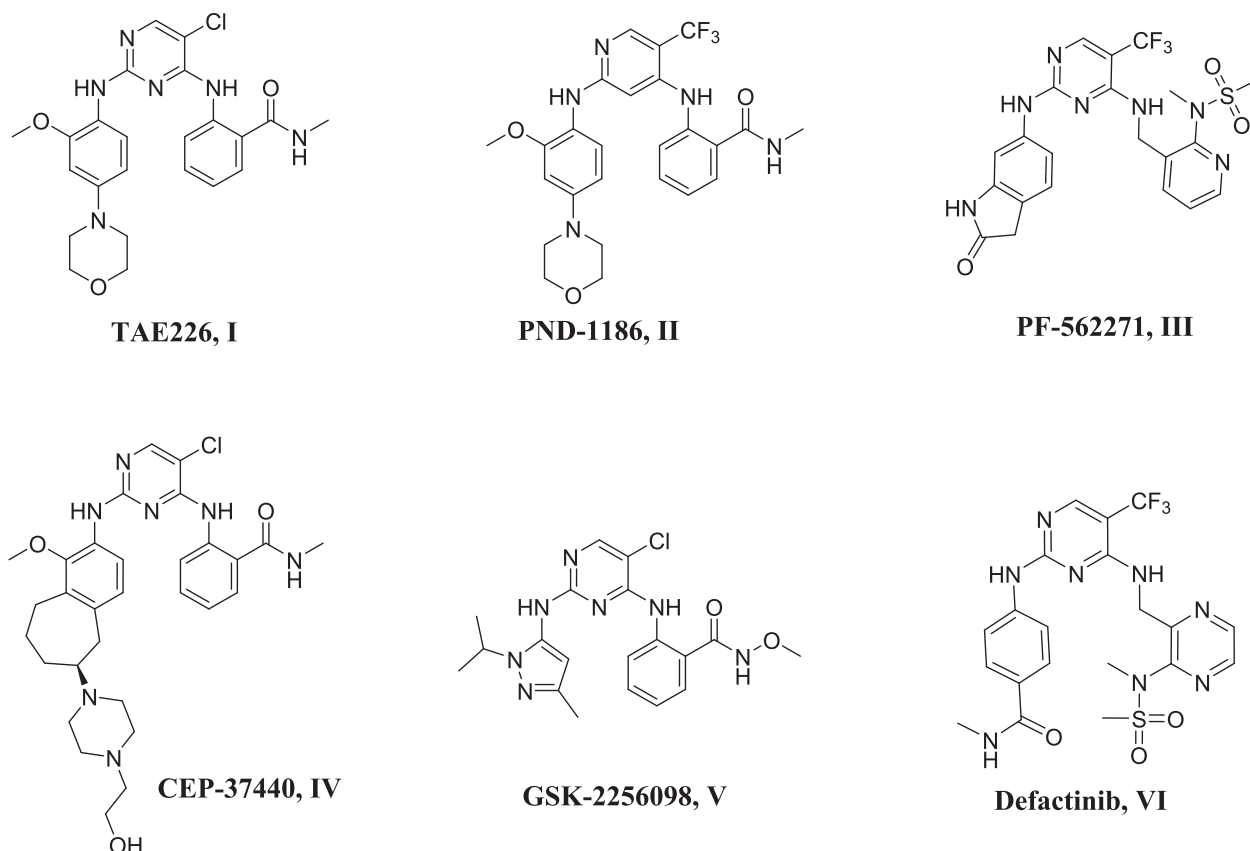


Fig. 1. Chemical structures of different six-membered FAK inhibitors.

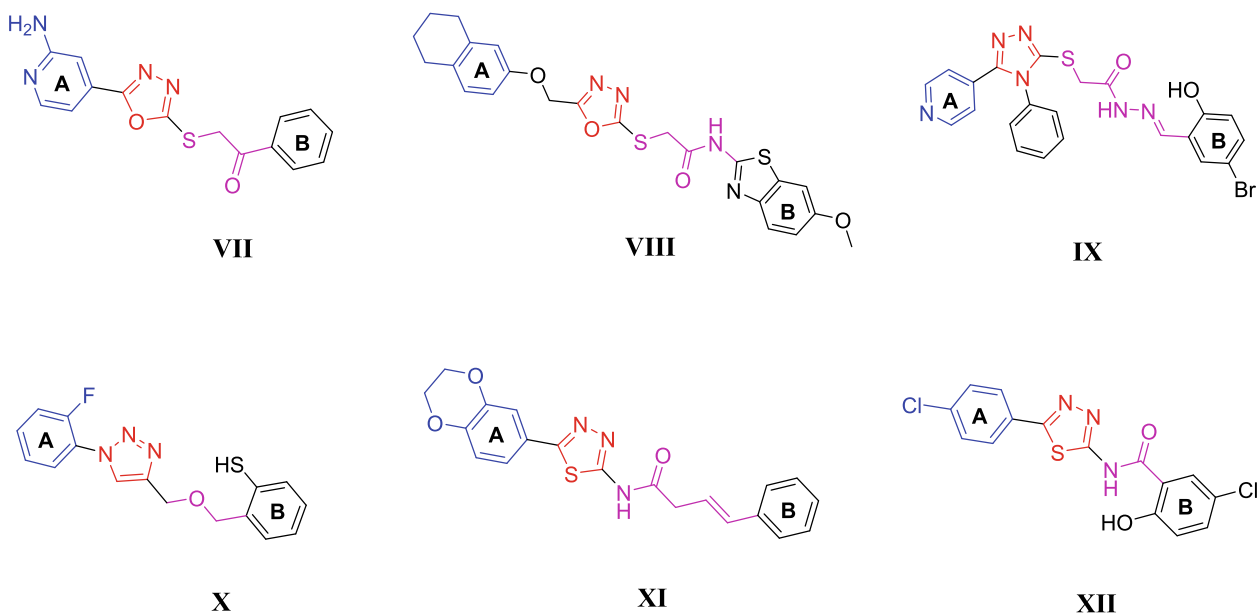
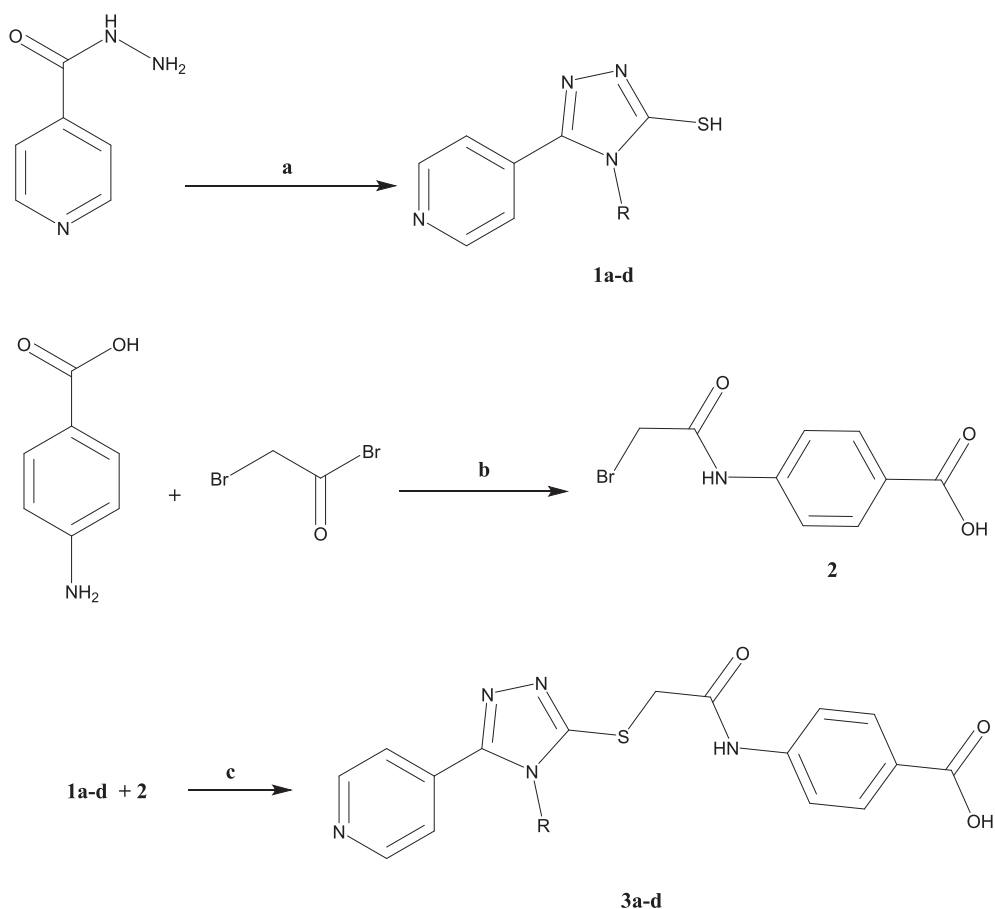


Fig. 2. Chemical structures of various five-membered FAK inhibitors.



Scheme 1. Synthetic approach of the target 1,2,4-triazole derivatives **3a-d**. a) (i) RNCS, EtOH, 70 °C, 4 h, (ii) 2 N NaOH, 3 h, (iii) HCl; b) K₂CO₃, 24 h; c) TEA, DMF, 70 °C, 10 h.

B). As FAK plays an important role in the activation of different pro-survival mechanisms, including PI3K/Akt and JNK/STAT3 in the liver cancer cells, we tested the effect of **3c** and **3d** on the PI3K/Akt and JNK/STAT3 pathways using western blotting.²⁶ We found that **3c** and **3d**

significantly repressed the phosphorylated PI3K, Akt, JNK, and STAT3 (Fig. 3A, C–F) in HepG2 cell line. These degrees of suppression of the signaling pathways were positively correlated with the observed anti-proliferative activity. We hypothesized that such suppression of the

Table 1

Concentration producing 50% growth inhibition (IC_{50} , $\mu M \pm SEM$) of the carboxylic acid derivatives **3a-d** on HepG2 and Hep3B liver cancer cells.

Cpd	R	Antiproliferative activity, μM		FAK inhibitory activity, nM
		HepG2	Hep3B	
3a	Methyl	8.83 ± 0.52	3.87 ± 0.23	N.T.
3b	Ethyl	40.97 ± 2.4	17.94 ± 1.05	N.T.
3c	Allyl	4.72 ± 0.28	2.88 ± 0.17	36.37 ± 1.8
3d	Phenyl	3.78 ± 0.22	4.83 ± 0.28	18.10 ± 0.92
Doxorubicin	–	1.99 ± 0.12	7.21 ± 0.42	N.T.
GSK2256098	–	3.24 ± 0.57	6.91 ± 1.02	22.14 ± 1.12

PI3K/Akt and JNK/STAT3 signaling pathways might alter cell survival and lead to apoptosis. Therefore, we examined the effect of **3d** on cell cycle progression in HepG2 cells using its IC_{50} concentration ($3.78 \mu M$), we observed that compound **3d** was able to arrest the cell cycle at sub G_1 and S phases (41.61% and 54.11%, respectively), (Fig. 4). Meanwhile, **3d** revealed a substantial ability to induce apoptosis by dissipating and dispersing cellular integrity leading to increasing the early and late apoptotic cells by 4.98% and 23.62%, respectively (Fig. 5).

Compound **3d** was docked into the ATP binding site of FAK kinase (PDB code: 2JJK) to elucidate its binding mode.¹¹ The native ligand (TAE226) was re-docked into the active site to validate the docking study (RMDS = 1.3813). Compound **3d** showed two possible binding modes inside the ATP binding site of FAK, and both modes revealed essential interactions inside the active site. Regarding the 1st mode, N1 of the 1,2,4-triazole made a hydrogen bond with Cys502 of the kinase hinge (Fig. 6A). Meanwhile, the oxygen of the amide group showed two hydrogen bonds with Asp564 of the DFG motif of the activation loop and

Gly563 amino acids. The sulfur atom formed a hydrogen bond with Glu506 amino acid and the 1,2,4-triazole-3-thiol moiety pointed toward the gatekeeper amino acid Met499. Also, the pyridine ring formed H... π interaction with Ile428 amino acid. On the other hand, the 2nd mode revealed an essential hydrogen bond between the nitrogen of the pyridine moiety and Cys502 of the kinase hinge (Fig. 6B). Also, both pyridine and 1,2,4-triazole rings formed H... π contacts with Leu501 and Leu567 amino acids, respectively, whereas N2 of the latter ring showed a hydrogen bond with Gly429 amino acid. The presence of the phenyl group helped in the formation of several π interactions and was in high proximity to Asp564 of the DFG motif. Moreover, the carboxylic acid formed a hydrogen bond with Ser568. Both obtained poses are reasonable and showed several essential interactions. However, the 2nd pose might be more realistic because it rationalized the role of both the nitrogen in the pyridine moiety and the phenyl group through the formation of different electrostatic interactions.

The prediction of Lipinski and ADME properties is one of the significant and widely identified parameters used to predict the oral bioavailability of active therapeutics.^{27,28} Compounds that obey all or three of these parameters: molecular weight (MW) ≤ 500 , number of hydrogen bond acceptors (HBA) ≤ 10 , number of hydrogen bond donors (HBD) ≤ 5 , and octanol–water partition coefficient (iLogP) ≤ 5 , will most probably have acceptable oral bioavailability. Therefore, Lipinski violations and drug-likeness properties of the synthesized 1,2,4-triazoles were calculated using the SwissADME online predictor. All the prepared derivatives showed no Lipinski violations and showed acceptable topological polar surface area (TPSA) and bioavailability scores (F). Fortunately, none of the prepared derivatives was classified as Pan-Assay Interference Compounds (PAINS). In other words, these compounds are predicted to interact specifically with the ATP binding site of FAK instead of binding to random targets, and hence, likely to have fewer off-target effects.

In conclusion, the 5-pyridinyl-1,2,4-triazole derivatives **3a-d** were synthesized and evaluated for their antiproliferative activity in two hepatic cancer cell lines (HepG2 and Hep3B). Compounds **3c** and **3d**

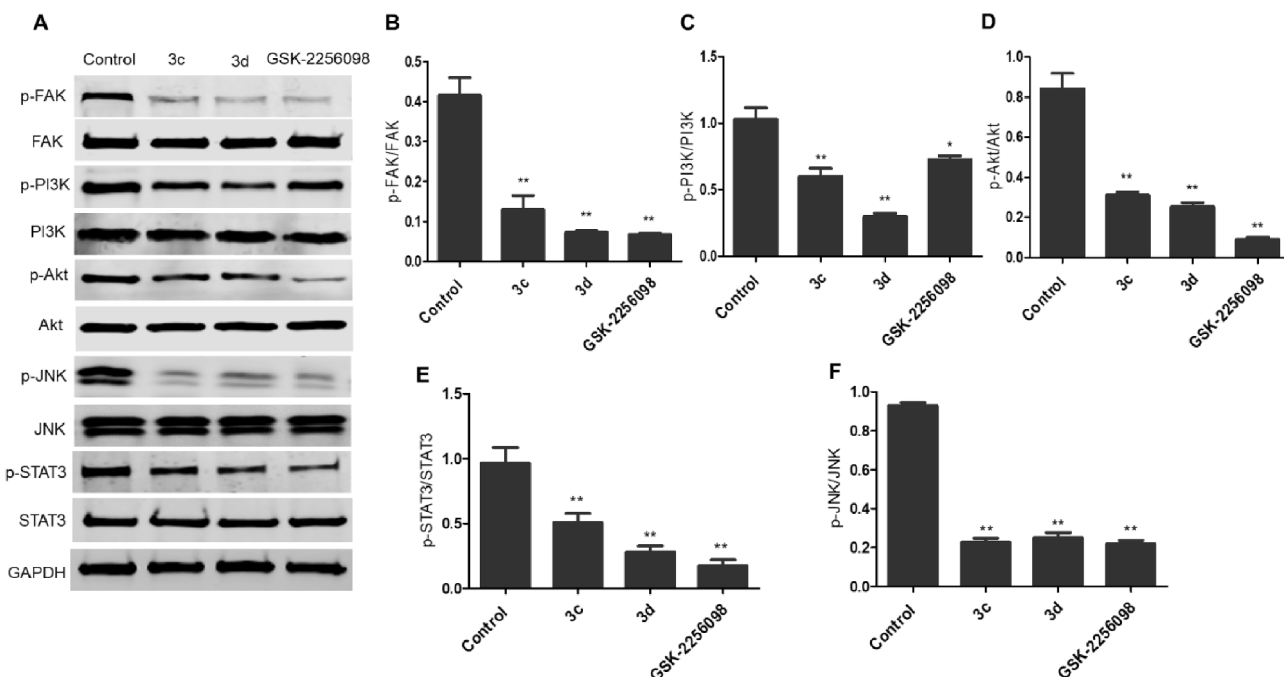


Fig. 3. The 1,2,4-triazole derivatives **3c** and **3d** inhibited FAK phosphorylation and its downstream cascades. A) Western blotting analysis showed that levels of p-FAK, p-PI3K, p-Akt, p-JNK, and p-STAT3 were downregulated in HepG2 cells treated with **3c** and **3d**, DMSO served as a negative control, and GAPDH served as a loading control; B-F) The relative protein expression levels of p-FAK, p-PI3K, p-Akt, p-JNK, and p-STAT3, compared to their total form FAK, PI3K, Akt, JNK, and STAT3, respectively, were quantified by Image J. The values are the means \pm SEM of three different experiments. *, $P < 0.05$, ** and $P < 0.01$ indicate a significant difference compared with DMSO negative control treatment.

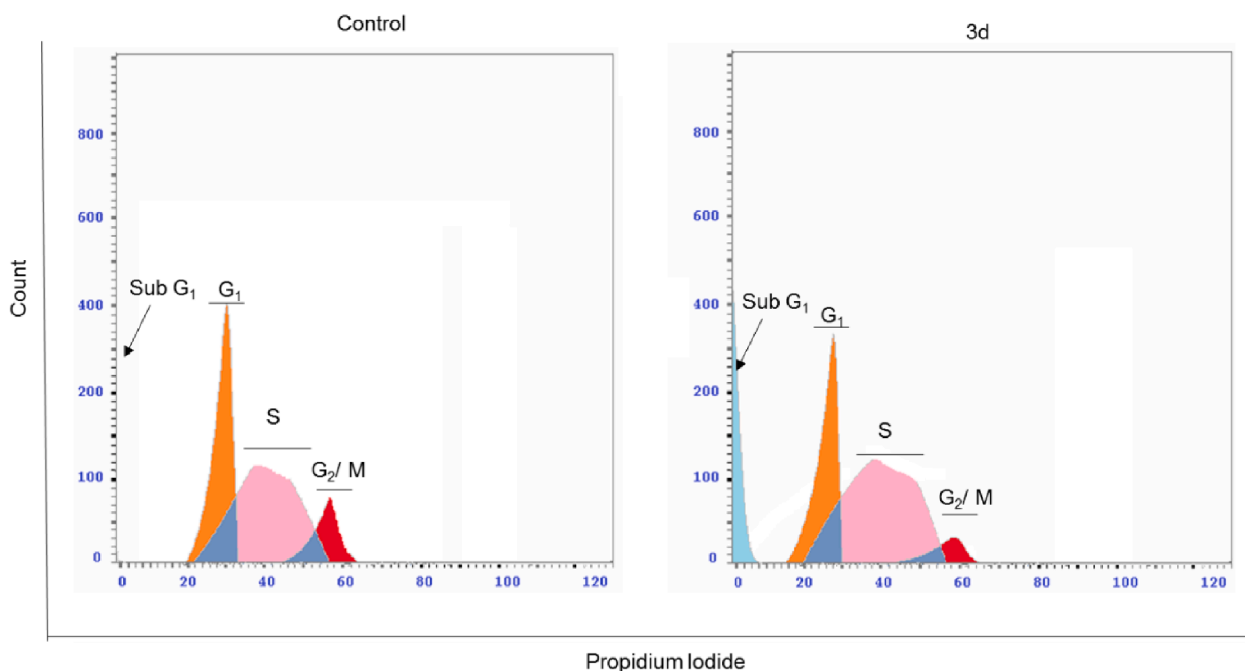


Fig. 4. Compound **3d** arrested the cell cycle at sub G₁ and S phases in HepG2 cells. Representative cell cycle distribution data are shown by flow cytometric analysis upon incubation with **3d** or DMSO as a negative control for 24 h.

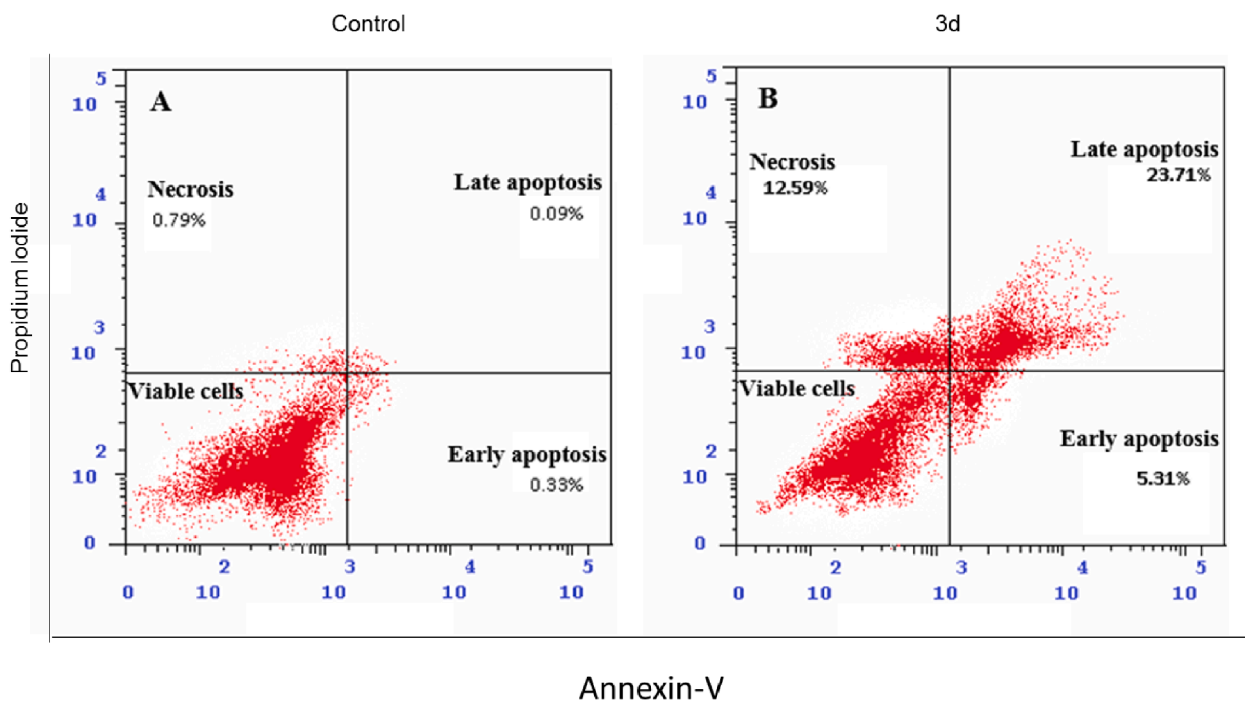


Fig. 5. Apoptotic effect of compound **3d** on HepG2 cells. Representative cytograms of apoptotic HepG2 cells stimulated with **3d** or DMSO as a negative control for 24 h.

emerged as potent antiproliferative agents against both cell lines tested. The top potent derivatives **3c** and **3d** were assessed for their anti-FAK activity and revealed remarkable potency at nanomolar concentrations. Furthermore, the study of FAK phosphorylation inhibition in HepG2 cells revealed that both **3c** and **3d** repress the phosphorylation of FAK significantly. Preferably, compound **3d** decreased the phosphorylation of PI3K, Akt, JNK, and STAT3. Moreover, **3d** induced apoptosis and arrested preG₁ and S phases of the cell cycle. In support of this study, molecular docking analysis revealed that **3d** showed good fitting

within the ATP binding site of FAK. Also, the obtained ADME properties were in an acceptable range. From the above data, it could be assumed that the synthesized 5-pyridinyl-1,2,4-triazole carboxylic acid derivatives (**3a-d**) are a set of promising compounds for the development of potent antiproliferative agents as well as FAK inhibitors.

Declaration of Competing Interest

The authors declare that they have no known competing financial

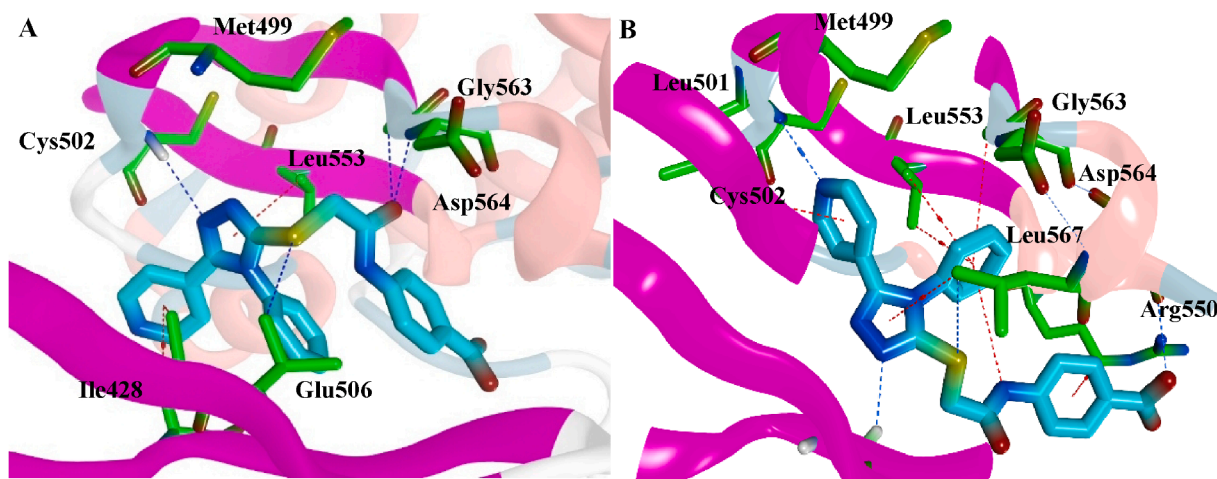


Fig. 6. 3D representation of **3d B** (cyan) within the ATP binding site of FAK. A) Proposed binding mode 1; B) Proposed binding mode 2 (PDB code: 2JKK).

interests or personal relationships that could have influenced the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bmcl.2021.127965>.

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- Compound **3d**: Yellow powder (0.62 g ym-CHM, CDCl₃) (ppm): 4.24(s, 2H, S-CH₂), 7.25(d, 2H, J=4.81 Hz, Ar-H), 7.47(d, 2H, J=7.21 Hz, Ar-H), 7.54-7.60(m, 3H, Ar-H), 7.65(d, 2H, J=8.81 Hz, Ar-H), 7.87(d, 2H, J=8.81 Hz, Ar-H), 8.52(d, 2H, J=5.61 Hz, Ar-H), 10.67(s, 1H, NH), 12.74(s, 1H, OH); ¹³CNMR (100 MHz, CDCl₃, δ ppm): 37.36, 118.94, 122.05, 125.97, 128.08, 130.79, 131.04, 131.14, 133.81, 134.32, 143.31, 150.66, 152.84, 153.50, 166.50, 167.42; Anal. Calcd for C₂₂H₁₇N₅O₃S: C, 61.24; H, 3.97; N, 16.23; S, 7.43. Found: C, 61.32; H, 4.12; N, 16.45; S, 7.61; ESI-MS: [M-H]⁻, 430.4, found: 430.3; HPLC-analysis: linear gradient of water-methanol (20: 80) for 10 min, followed by linear gradient to 50% methanol within 30 min, at a flow rate of 1 ml/min, Rt = 3.26 min.
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