



Exploring DNA-targeted cytotoxic mechanisms of Novel *N*-Phenyl pyridopyrimidine analogs through experimental and computational studies

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Highlights

- Novel *N*-phenyl pyridopyrimidines (L1–L18) were synthesized and characterized.
- Third of the ligands showed strong selectivity toward prostate cancer (PC3) cells.
- L17 exhibited best anticancer activity with no fibroblast toxicity.
- Docking revealed para-substituted ligands bound DNA minor groove strongly.
- MD confirmed L17 stable DNA binding with highest binding energy (–126.5 kJ/mol).

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Abstract

Over the last two decades, pyridopyrimidine analogs have captivated many enthusiasts due to their potent anticancer potential. Bearing this in mind, in this study, a novel series of *N*-phenyl pyridopyrimidine analogs (**L1–L18**) were generated and characterized *via* FT-IR, ¹H-NMR, ¹³C-NMR, MASS, and elemental analysis. The *N*-phenyl pyridodipyrimidine analogs were then introduced to *in vitro* studies to assess their cytotoxicity potential against prostate cancer (PC3), cervical cancer (HeLa) cell lines, breast cancer (MCF7), as well as on normal fibroblast cells, demonstrating that the third (six out of thirteen) of the synthetic ligands had higher selectivity against PC3 cell lines. Also, compound **L17** selectively targeted cancer cell lines, and showing the most anticancer potential with IC₅₀ magnitudes of 14.01 μM, 12.5 μM, and 45 μM, respectively. SAR results also indicated that the *para*-substituted compounds enhanced PC3 selectivity, and the presence of –N(Me)₂ moiety in this position (like **L17**) showed the strongest cytotoxicity and no fibroblast inhibition, making it a promising therapeutic candidate with high selectivity. Interestingly, docking results showed that the *para*-substituted ligands (**L3**, **L6**, **L9**, **L14**, and **L17**) showed the lowest binding energies with DNA and bound to DNA minor groove by polar interactions. Then, **L3** and **L17** were chosen for 100 ns molecular dynamics simulations. MD simulations confirmed stable DNA binding for **L17** and **L3**, with **L17** inducing greater structural instability. **L17** showed the strongest binding energy (–126.5 kJ/mol), mainly governed by Van der Waals forces, aligning with docking results. To sum,

compound **L17** as a promising anticancer agent is nominated for further studies to prove its efficacy.

Keywords

Pyridopyrimidine derivatives; Cancer; DNA interaction; Molecular dynamics simulation

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Introduction

Cancer stands as one of the most widespread and significant threat to global health. Cervical, breast, lung, and prostate cancers are among the most predominant types of cancers [1]. The most common cancer in males is prostate cancer worldwide [2]. The most prevalent and widespread approaches for treating cancers are radiotherapy, surgery, and chemotherapy [3]. Apart from their widespread use, these conventional therapies suffer from notable limitations and challenges. Some of the major concerns associated with these therapeutic approaches are inadequate drug delivery to tumor sites, severe toxicity to healthy cells, and the emergence of drug resistance [4]. Although various medications and treatments are currently available, their limitations and challenges have led researchers to prioritize the development of novel pharmacologically active compounds.

Heterocyclic rings are crucial in medicinal chemistry, drug design, and chemical biology, acting as a vital link between life sciences and biochemical research [5,6]. Among these chemical architectures, pyridopyrimidine is a nitrogen-containing heterocyclic structure formed by fusing pyrimidine and pyridine. This unique combination enhances biological activity and has a wide range of applications [7]. Pyridopyrimidines bear various pharmacological peculiarities, including antiviral, anticonvulsant, analgesic, and anticancer effects [[8], [9], [10]], making them highly valuable in drug discovery and development. Interestingly, the fascinating pyridopyrimidines have aroused many enthusiasts due to their potent anticancer potential against different cancer cell lines, e.g. Khalid B. Selim and coworkers developed pyrido[2,3-*d*]pyrimidine derivatives to assess their antitumor effects on HePG2, MCF-7, PC3, HCT-116, and HeLa cells. Among them, compound 11 (Fig. 1) showed the highest dihydrofolate reductase inhibition ($IC_{50} = 6.5 \mu M$), nearing methotrexate's efficacy ($IC_{50} = 5.57 \mu M$), inducing apoptosis and G2/M cell-cycle arrest, supported by molecular docking analyses [11]. In another job, Lou et al. fabricated a novel series of pyrido[1,2-*a*]pyrimidin-4-ones to investigate their anticancer potential against several cancer cell lines, showing superior cytotoxicity versus Hep G2 cell line [6]. In 2019, a novel set of pyrido[2,3-*d*]pyrimidines were developed to investigate their antitumor potential against few cancer cell lines such as HCT-116, PC3, MCF-7, HeLa, and HePG2. The compound with the highest antitumor activity showed a good IC_{50} value of $6.5 \mu M$ against dihydrofolate reductase enzyme, which was comparable to that of the control drug methotrexate ($IC_{50} = 5.57 \mu M$). To the best of their knowledge, the most potent molecule was revealed to pose apoptosis induction at Pre-G phase and cell cycle arrest at G2/M phase in MCF-7 cells [11]. In 2022, a series of pyrido[2,3-*d*:6,5-*d'*]dipyrimidines has been prepared to shed light on their anticancer effects on MCF-7, HCT-116, and HEPG-2, cell lines, and compound 6b (Fig. 1) revealed a strong anticancer activities against HCT-116, HEPG-2, MCF-7 cell lines with the IC_{50} magnitudes of $7.8 \mu M$, $6.9 \mu M$, and $4.5 \mu M$, respectively [12]. In 2023, a novel derivatives of 2*H*-pyrido[1,2-*a*]pyrimidine-2,4(3*H*)-dione were fabricated to test their anticancer potential against HeLa cell line, showing good IC_{50}

values between 270 and 400 μM [13]. Recently in 2024, Nafie et al. have reported the production of pyrido[2,3-*d*]pyrimidine analogs, demonstrating strong cytotoxicity against HepG2 and MCF-7 cell lines with the IC_{50} magnitudes of 1.13 μM and 0.57 μM , correspondingly [14].

The free radicals induce oxidative stress and pose cellular damages, causing serious health issues such as cancer, degenerative disorders, etc. Thus, antioxidants, as a significant shield against free radicals, can protect cells against reactive oxygen species. Therefore, discovery novel heterocyclic compounds, such as pyrido-dipyrimidine, as strong antioxidants has caught serious attention in the field of cancer therapy [15]. In another work, pyrido-dipyrimidine analogs were prepared through a environmentally-friendly condition, thanks to their green approach [15,16], to study the free radical scavenging potential of vanillin-based pyrido-dipyrimidines. All of the synthetic ligands indicated promising antioxidant potential, and suggested as promising cases in antioxidant therapy [15].

Since the current cancer therapy face the challenges and limitations, discovery of novel active compounds become a hot research spot for research community. In this line, armed with the potent anticancer/antioxidant activities of pyridopyrimidine analogs, in this research, a novel series of *N*-phenyl pyridopyrimidine analogs (**L1-L18**) has been fabricated *via* a multicomponent and green reaction to study their cytotoxicity potential against four various cancer cell lines (Scheme 1). These compounds underwent preliminary characterization through methods like FT-IR, ^1H -NMR, ^{13}C -NMR, MASS, and elemental analysis. Then, their anticancer potential was tested *via* MTT-based assay. Afterward, their interactions with DNA were assessed by molecular docking, and the compounds with the highest binding affinities and the most strong cytotoxicity activities were introduced to 100 ns molecular dynamics (MD) simulations to investigate their effects on DNA structure.

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Chemicals and apparatus

The starting materials were purchased from Sigma-Aldrich and Merck, with double-distilled water utilized in all experimental processes. To monitor the course of the reactions, TLC was carried out on Merck silica gel 60 F254 plates. Melting points determined *via* a calibrated Kofler hot stage apparatus, while FT-IR spectra were acquired with a Shimadzu 470 spectrophotometer, employing KBr disks. NMR data were collected on Bruker AVANCE 250 MHz spectrometers. A Thermo Finnegan Flash EA 1112 ...

Chemistry

We have fabricated a new analogs of pyridopyrimidine (**L1-L18**) by an eco-friendly multicomponent reaction between benzaldehydes, 2-aminotoluene, and barbituric acid in the vicinity of borax and EtOH as catalyst and solvent under reflux (Scheme 1). According to our preparation technique, barbituric acid and 2-aminotoluene participate in reaction with the bezaldehydes in EtOH through a trustworthy multicomponent reaction, leading to the generation of eighteen ligands in 77–92% yield. Ultimately, ...

Conclusion

Over the past two decades, pyridopyrimidine analogs have gained significant attention for their strong anticancer properties. In the present work, a new set of *N*-phenyl pyridopyrimidine analogs (**L1-L18**) were prepared and identified correspondingly (¹³C-NMR, ¹H-NMR, MASS, FT-IR, and elemental analyses. Their cytotoxic effects were evaluated through *in vitro* studies against PC3, MCF7, and HeLa cancer cell lines, along with normal fibroblast cells. MTT test and SAR studies indicated that third ...

CRedit authorship contribution statement

Parisa Pourgoodarzi: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Armin Zarei:** Writing – review & editing, Writing – original draft, Visualization, Software, Investigation, Formal analysis, Data curation. **Leila Hosseinzadeh:** Supervision, Formal analysis, Data curation. **Seyyed Abolghasem Ghadami:** Supervision, Methodology, Formal analysis, Data curation. **Zahra Samadi:** Methodology, Data curation. **Fereshteh Jalilian:** Methodology, Formal analysis, Data ...

Declaration of competing interest

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

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