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Synthesis of indole-tethered [1,3,4]thiadiazolo and [1,3,4]oxadiazolo[3,2-*a*]pyrimidin-5-one hybrids as anti-pancreatic cancer agents

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ABSTRACT

New indole-tethered [1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one (**8a-j**) and [1,3,4]oxadiazolo[3,2-*a*]pyrimidin-5-one hybrids (**9a-e**) were synthesized using [4+2] cycloaddition reactions of functionalized 1,3-diazabuta-1,3-dienes with indole-ketenes. All molecular hybrids were structurally characterized by spectroscopic techniques (IR, NMR, and HRMS) and screened for their anti-pancreatic cancer activity *in vitro*. The [1,3,4]oxadiazolo[3,2-*a*]pyrimidin-5-one hybrids (**9a-e**) showed stronger anti-pancreatic cancer activity than the [1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one hybrids (**8a-j**) against the PANC-1 cell line. Compound **9d** bearing an *ortho*-chlorophenyl moiety emerged as the most potent anti-pancreatic cancer agent with an IC_{50} value of 7.7 ± 0.4 μM, much superior to the standard drug Gemcitabine (IC_{50} > 500 μM). The discovery of these [1,3,4]thiadiazolo and [1,3,4]oxadiazolo[3,2-*a*]pyrimidin-5-one hybrids elicits their potentials as pursuable candidates for pancreatic cancer chemotherapy.

Pancreatic cancer (PC) persists as one of the seven leading causes of cancer-related deaths worldwide.[1] The mortality rate is estimated at 2.5% and 14.8% per 0.1 million people in developing and developed countries, respectively.[2] This indicates that PC is more frequent and fatal in developed countries. The death related to PC has increased by 0.3% per year since 1975. In the year 2019 alone in the United States, approximately 56,770 people were newly diagnosed with PC.[3] Many patients with PC are diagnosed at a metastatic and advanced stage, missing the chance for curative surgical resection. Although surgical resection remains the primary curative option for this disease, the suitability is compromised when the cancer is advanced due to poor prognosis.[4] Moreover, radiotherapy and chemotherapy are also not remarkably effective for the treatment of metastatic PC.[5] Thus, there is an urgent demand for the development of new, effective and safe chemotherapeutic agents against PC.

Over the years, medicinal chemistry has provided access to chemical libraries bearing privileged structures, which have received increased attention due to their proven therapeutic relevance. Pyrimidinone, the most important skeleton of diazine heterocycles has attracted great interest in this regard due to its broad range of pharmacological applications. For instance, the pyrimidinone-based marine natural alkaloids batzelladine A and B inhibited the binding of HIV gp-120 to CD4 cells,[6] while the synthetic derivative monastrol, a promising anticancer compound as mitotic kinesin inhibitor, can cross the cell membrane.[7,8] Functionalized pyrimidinones substituted at C-5 or C-6 positions have also exhibited diverse biological activities such as antimicrobial, and EGFR T790M inhibition for lung cancer treatment.[9–11] Whereas fused bicyclic pyrimidinones are promising anti-HIV, antiviral, anti-inflammatory and anticancer agents.[12–17] The therapeutic value of this scaffold is also evidenced by the different pyrimidinone-containing drugs approved by the US Food and Drug Administration (FDA) for PC chemotherapy such as gemcitabine, capecitabine, folinic acid and fluorouracil (Fig. 1).[18] However, despite the wide availability of drugs for PC treatment, acquired drug resistance remains a major hurdle for effective therapy. Besides, the undesirable side effects of existing drugs due to poor selectivity necessitates the quest for new anti-PC agents.

On the other hand, indole is a prolific scaffold that is both widely distributed in pharmacologically important natural products and recruited as an organic synthon. The indole nucleus has also been endorsed by the unique ability to mimic peptide derivatives and reversibly bind to proteins.[19] Indole-based synthetics have also found enormous applications as dyes, agrochemicals, antiproliferative, anti-HIV, anti-inflammatory and antibacterial agents.[20–26] Precisely, in anticancer drug discovery, indole and its derivatives have attracted considerable

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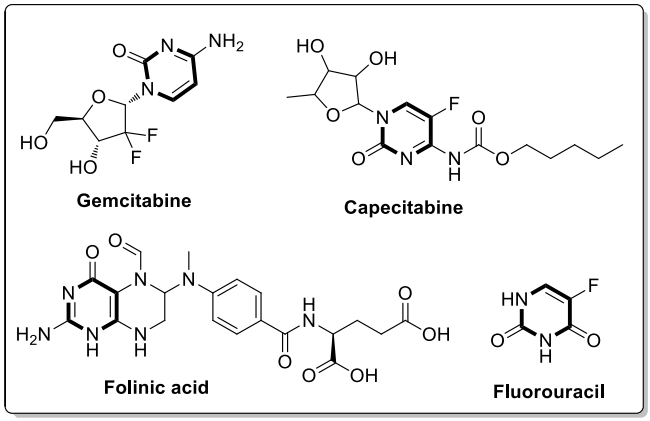


Fig. 1. Pyrimidinone-containing drugs.

interest not only as cytotoxins but also as bio-reductively activated prodrugs which effectively inhibits the growth of human pancreatic cancer cells.[27–30]

On this backdrop, this study adopted the molecular hybridization (MH) strategy to synthesize conjugates of fused-pyrimidinone and indole as potential anti-pancreatic cancer agents. MH has evolved as a preferred strategy in drug discovery, because of its proficiency to combine two or more biologically active moieties with a unique or novel mechanism of action.[31] This endorses our research rationale, in combining the pharmacophores; fused-pyrimidinone and indole into a single framework using [4 + 2] cycloaddition reaction. The literature survey clearly shows that the most effective route to functionalized pyrimidinones is *via* the [4 + 2] cycloaddition reaction of conjugated 1,3-diazabuta-1,3-dienes with appropriate ketene precursors.[32,33] As part of our ongoing interest to find novel bioactive heterocyclic molecules,[34,35] herein, we report an efficient route for the synthesis of functionalized pyrimidinone-indole molecular hybrids (**8a-j** and **9a-e**) by [4 + 2] cycloaddition reactions of different functionalized 1,3-diaza-1,3-butadienes with indole-ketene. Subsequently, the synthesized molecular hybrids were evaluated *in vitro* for their anti-pancreatic cancer activity.

The reaction protocol employed for the preparation of the two series of indole tethered pyrimidinone molecular hybrids (**8a-j** and **9a-e**) is depicted in Scheme 1. Firstly, the reaction was carried out between the appropriate substituted benzoic acids (**1a-g**) with semicarbazide or thiosemicarbazide (**2a-b**) in the presence of phosphorus oxychloride ($POCl_3$) and aqueous NaOH at 90°C to afford the amine derivatives (**3a-j** and **4a-d**).[36] Their subsequent condensation with *N,N*-dimethylformamide dimethyl acetal (DMF-Acetal) at room temperature resulted in the key precursors 1,3-diazabuta-1,3-dienes (**5a-j** and **6a-d**).[37] Separately the other precursors indoloylglycines (**7a-b**) were prepared by a base-promoted condensation of indole or 2-methyl indole with bromoacetic acid following our recently reported method.[38] Finally, the desired pyrimidinone hybrids (**8a-j** and **9a-e**) were synthesized from the [4 + 2] cycloaddition reaction between 1,3,4-thiadiazole/oxadiazole substituted 1,3-diazabutadienes (**5a-j** and **6a-d**) and indole-ketene (generated *in situ* from the corresponding indole acids **7a-b**) in the presence of *p*-toluene sulphonyl chloride and triethylamine in dry dichloromethane. Different substituents placed on both the thiadiazole- and oxadiazole-1,3-diazabutadienes did not have any remarkable effect on the overall yields of desired products.

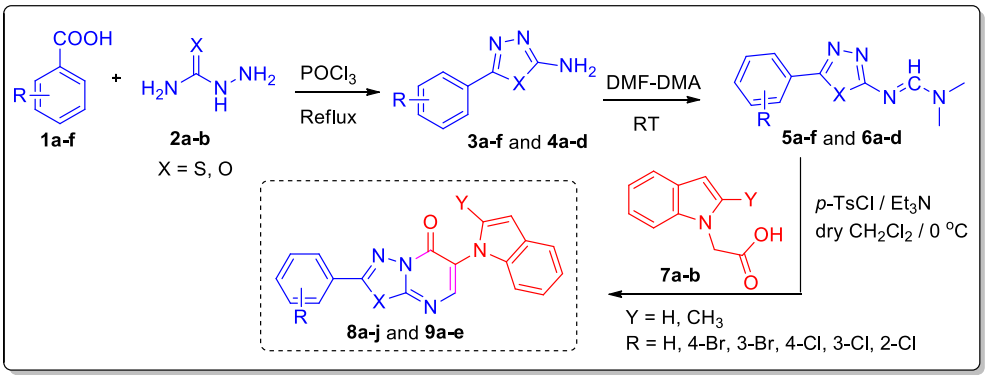
The structures of synthesized hybrids were fully established by their spectral data (IR, NMR, and HRMS). For instance, in the ^{1}H NMR spectrum of compound **8b**, the pyrimidinone ring proton resonated as a characteristic singlet peak at δ 8.30 ppm while the two doublet signals at δ 7.41 (J = 3.3 Hz) and 6.75 (J = 3.0 Hz) ppm correspond to the CH protons of indole moiety. Other aromatic ring protons appeared at their respective aromatic region; the proton peak assignment was further supported by COSY (details in the experimental section). Furthermore, the appearance of a carbonyl carbon signal at δ 159.6 ppm in the ^{13}C NMR spectrum (Fig. 2**a**) and a strong absorption peak at 1686 cm^{-1} in the IR spectrum validated the formation of the pyrimidinone core. These structural elucidations were further supported by HSQC and HMBC experiments; the selected HMBC correlations of **8b** are shown in Fig. 2**b**. High-resolution mass spectrometry (HRMS) showed a molecular ion peak at (M + Na) *m/z* 444.9732.

Based on the empirical evidence,[39] the [4 + 2] cycloaddition reaction of 1,3-diazabuta-1,3-dienes (4π component) with indole-ketene (2π component) proceeds *via* the nucleophilic addition of *N*1 in 1,3-diazabuta-1,3-dienes (**5a-f** and **6a-d**) to the carbonyl group of ketene (**7a-b**), which leads to a zwitterionic intermediate (**I**) (Scheme 2). The intermediate **I** then rearranges to dipolar intermediate (**II**), which after ring closure and elimination of *N,N*-dimethyl amine ($HN(CH_3)_2$) afforded the desired products (**8a-j** and **9a-e**) in good yields.

The potentials of compounds **8a-j** and **9a-e** as anti-pancreatic cancer agents were evaluated using the PANC-1 cell line. The cells were treated with various doses of the test compounds for 48 h, and cell survival was determined. The results are illustrated in Fig. 3 and Table 1.

Based on the MTS cell viability data, the [1,3,4]oxadiazolo[3,2-*a*] pyrimidin-5-ones (**9a-e**) were stronger cytotoxic agents than the [1,3,4] thiadiazolo[3,2-*a*]pyrimidin-5-ones (**8a-j**) against PANC-1 cell line. The cytotoxicity of compounds **8a-j** and **9a-e** was dependent on the type of substitutions at different positions on the phenyl ring of [1,3,4]thiadiazolo and [1,3,4]oxadiazolo[3,2-*a*]pyrimidin-5-one moieties. The [1,3,4]oxadiazolo[3,2-*a*]pyrimidin-5-one derivatives **9a**, **9b**, **9c**, **9d** and **9e** showed moderate to potent anticancer activity with IC_{50} values of 21.1 ± 0.5, 94.9 ± 1.3, 90.5 ± 2.0, 7.7 ± 0.4 and 40.0 ± 1.1 μM, respectively (Table 1).

Overall, the *ortho*-chlorophenyl analogue (**9d**) emerged as the most promising anti-pancreatic cancer agent with an IC_{50} value of 7.7 ± 0.4 μM and was several-folds more potent as compared to the



Scheme 1. Synthesis of pyrimidinones *via* [4 + 2] cycloaddition reaction.

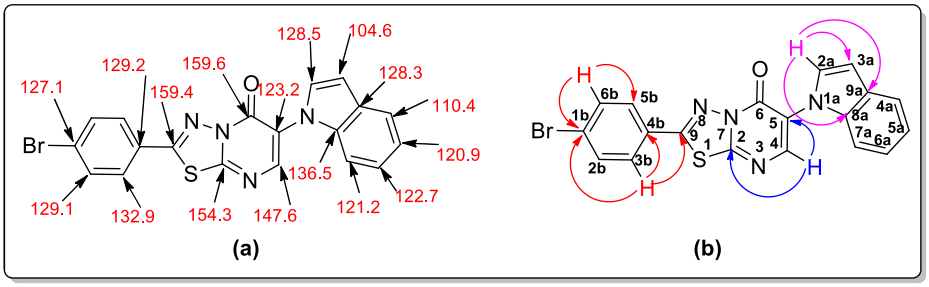
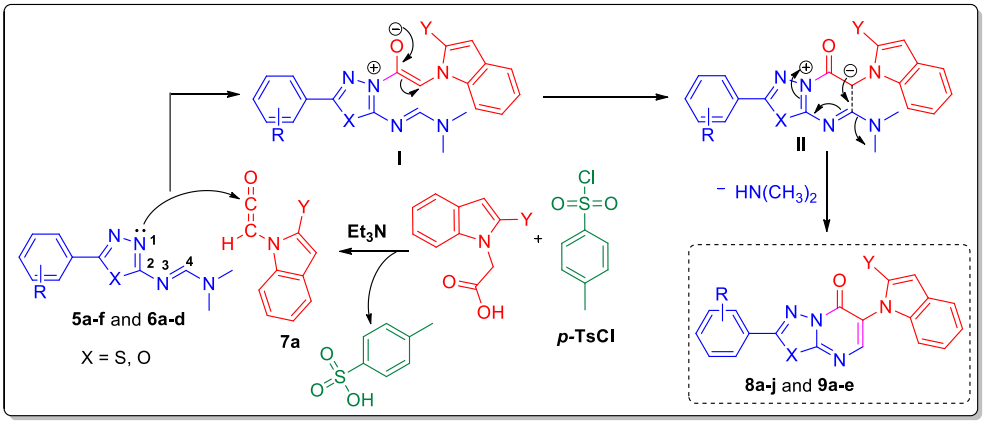


Fig. 2. (a) ^{13}C NMR and (b) HMBC correlation of **8b**.



Scheme 2. A plausible mechanism of [4 + 2] cycloaddition reaction for the formation of pyrimidinone hybrids.

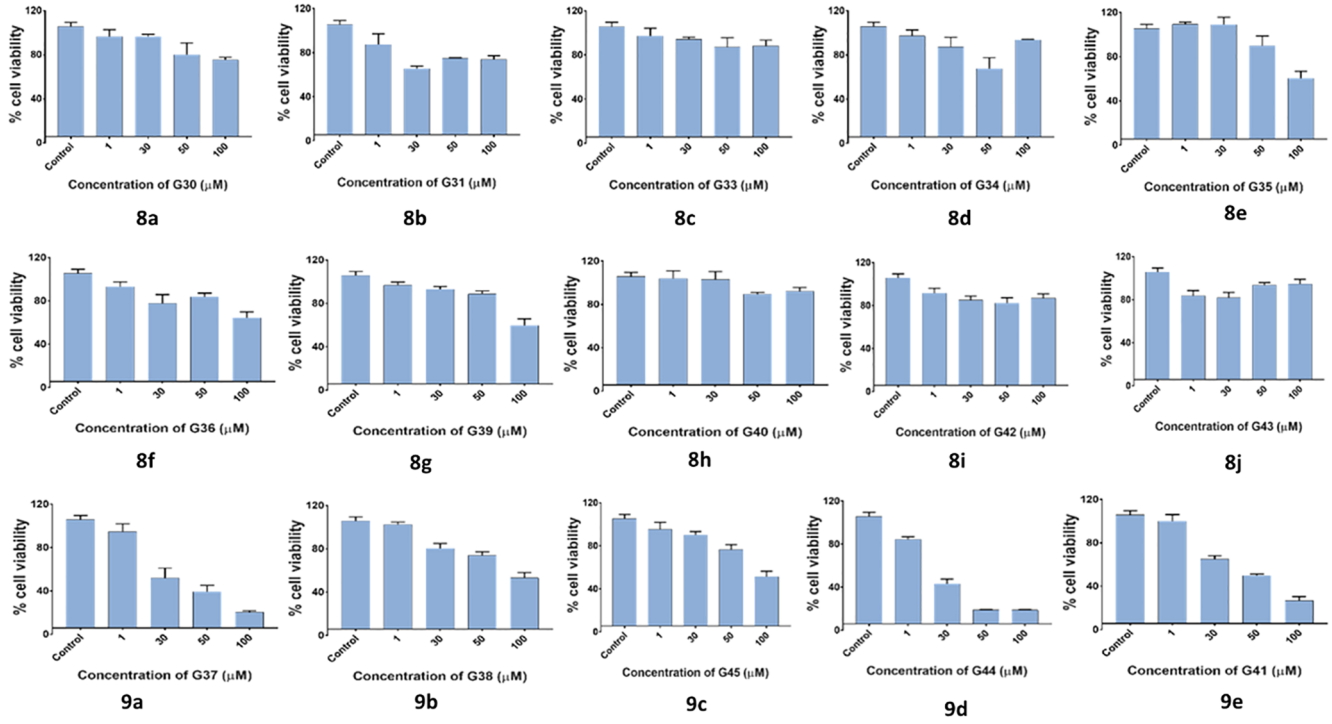
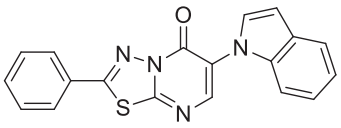
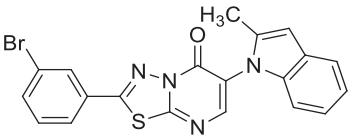
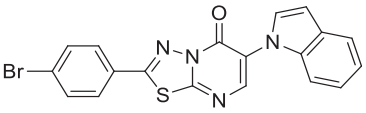
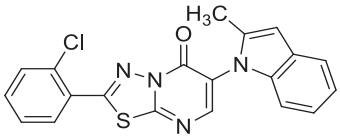
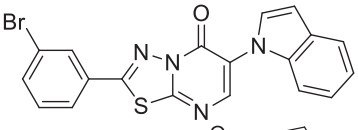
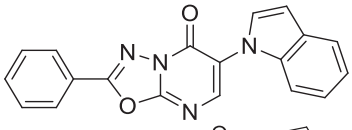
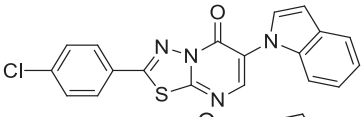
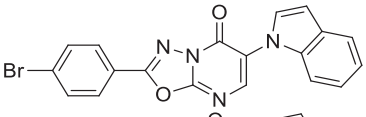
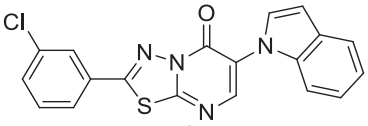
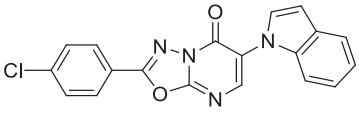
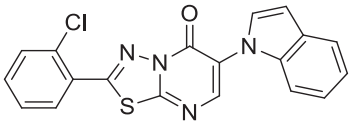
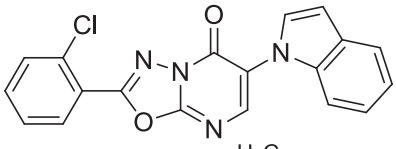
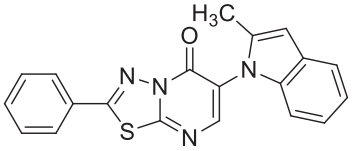
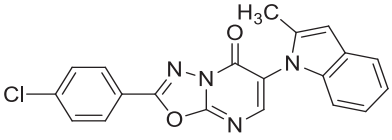
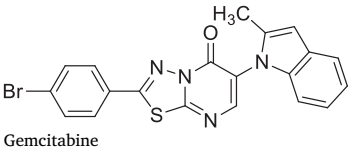


Fig. 3. Dose-dependent cell viability inhibitory effects of pyrimidinone compounds **8a-j** and **9a-e** on PANC-1 cells. The cells were treated with the respective compounds for 48 h at different doses. Then, cell viability was measured using MTS assay, and the data were analyzed using GraphPad Prism software.

standard drug gemcitabine (IC_{50} > 500 μM). Whereas compounds **9b** and **9c** with *para*-chloro and bromophenyl units, respectively, showed mild activities with IC_{50} values of 94.9 ± 1.3 and 90.5 ± 2.0 μM, respectively. The unsubstituted compound **9a** also exhibited good cytotoxicity (IC_{50} = 21.1 ± 0.5 μM) while 2-methylindole compound **9e** had relatively lower potency (IC_{50} = 40.0 ± 1.1 μM), albeit more potent than gemcitabine. Surprisingly, no significant activity (IC_{50} = > 100 μM) was observed for [1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one hybrids (**8a-j**) against PANC-1 cell line. These results clearly show that the presence of 1,3,4-oxadiazole core is crucial for potent

Table 1
IC_{50} values of screened compounds (**8a-j** and **9a-e**) against PANC-1 cancer cell line.

Code	Structure	IC_{50} (μM)	Code	Structure	IC_{50} (μM)
8a		> 100	**8i**		> 100
8b		> 100	**8j**		> 100
8c		> 100	**9a**		21.1 ± 0.5
8d		> 100	**9b**		94.9 ± 1.3
8e		> 100	**9c**		90.5 ± 2.0
8f		> 100	**9d**		7.7 ± 0.4
8g		> 100	**9e**		40.0 ± 1.1
8h		> 100			
Standard drug	Gemcitabine	> 500			

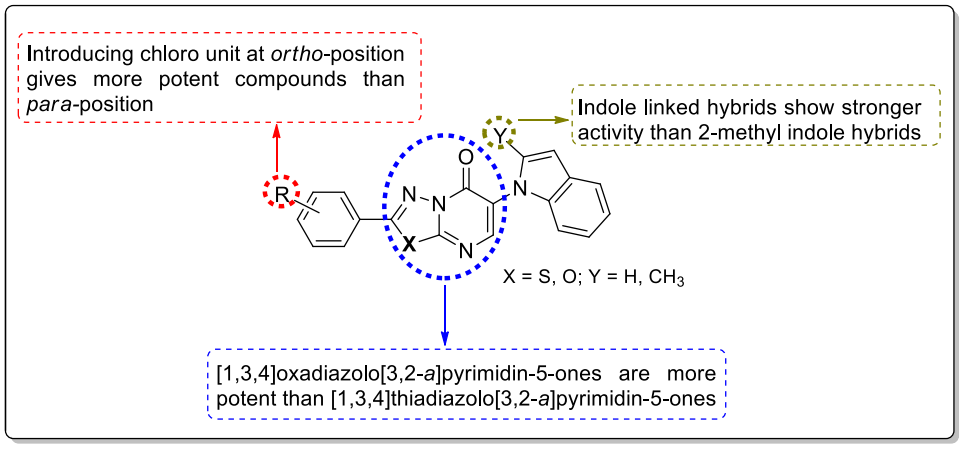


Fig. 4. SAR analysis of fused pyrimidinone hybrids as potent anti-pancreatic cancer agents.

cytotoxicity against the PANC-1 cell line as compared to 1,3,4-thiadiazole core. The structure–activity relationship (SAR) analysis of the test compounds is summarized in Fig. 4.

To sum up, the synthesis of indole linked [1,3,4]thiadiazolo and [1,3,4]oxadiazolo[3,2-*a*]pyrimidin-5-one hybrids (**8a-j** and **9a-e**) from [4 + 2] cycloaddition reaction has been described. All the novel

molecular hybrids were evaluated for their cytotoxicity against the PANC-1 pancreatic cancer cell line. [1,3,4]oxadiazolo[3,2-*a*]pyrimidin-5-one hybrids showed stronger anti-pancreatic cancer activity compared to [1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one hybrids. Compound **9d** bearing *ortho*-chlorophenyl substituent on [1,3,4]oxadiazolo[3,2-*a*] pyrimidin-5-one core displayed the most potent anti-pancreatic cancer activity with an IC_{50} value of 7.7 ± 0.4 μM superior to the *para*-substituted analogue **9c** (IC_{50} = 90.5 ± 2.0 μM) and standard drug gemcitabine (IC_{50} > 500 μM). As a result, further structural derivatization of these compounds is necessary to deliver compounds with increased efficacy and selectivity against PANC-1 and presumably, other pancreatic cancer cell lines which will be valuable for pancreatic cancer chemotherapy.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2020.127544.

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