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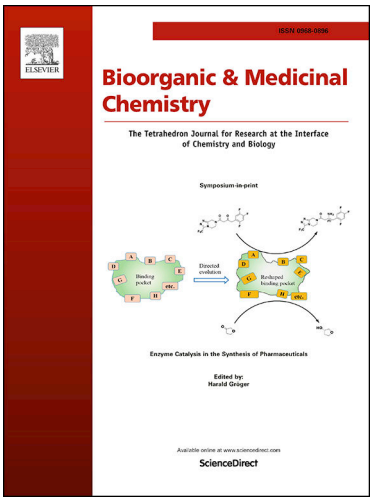

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Investigations of Antiproliferative and Antioxidant Activity of β-Lactam Morpholino-1,3,5-Triazine Hybrids

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Abstract:

This article reports for the first time the synthesis of some novel β-lactam morpholino-1,3,5-triazine hybrids by a [2+2]-cycloaddition reaction of imines **7a-c**, **9a-c** and **11** with ketenes derived from substituted acetic acids. The reaction was totally diastereoselective, leading exclusively to the formation of *cis*-β-lactams **8a-l, 10a-f** and **12a-c**. The synthesized compounds were tested for activity towards SW1116, MCF-7 and HepG2 cancer cell lines and non-cancerous HEK-293 cell line by MTT assay. None of the compounds exert an observable effect on HepG2, MCF-7 and HEK-293 cells, but compounds **7b**, **8f**, **8g**, **8l**, **10c**, and **10e** exhibited excellent growth inhibitory activity (IC_{50} < 5 μM) against SW 1116 cells, comparable to that of doxorubicin (IC_{50} = 6.9 μM). An evaluation of the antioxidant potential of each of the compounds, performed by diphenylpicrylhydrazyl (DPPH) assay, indicated that **7b, 9a, 9b** and **9c** have strong free radical scavenging activity. UV absorption titration studies reveal that **7b**, **8l**, **8g** and **8f** interact strongly

with calf-thymus DNA (CT-DNA) in the order of **8l** > **7b** > **8f** > **8g**. Collectively, the in vitro capabilities of some of these morpholino-triazine imines and β-lactams suggest possible applications to development of new antioxidants and DNA binding therapeutics.

Keywords: β-lactams, morpholino-1,3,5-triazines, diastereoselective, Staudinger reaction, DNA-binding, antioxidants.

1. Introduction

Molecular hybridization is a promising drug discovery method in which two (or more) bioactive molecules having orthogonal, complementary pharmacophoric properties are covalently linked.[1,2] These dual- or sometimes multi-drug hybrids often improve therapeutic activity and synergism, and a decrease in the incidence of drug-resistance versus the individual molecules.[3-9] In this current study, we further examine an additional aspect in which we combine two important families of biologically-active compounds, namely, β-lactams (azetidine-2-ones) and 1,3,5-triazines (s-triazines), into single molecular hybrids for biological exploration. β-Lactams are an important class of compounds because of their broad biological properties (Fig. 1).[10,11] While the most prominent β-lactams are the antibacterial agents that include the penicillins, cephalosporins, carbapenems, nocardicins, monobactams, clavulanic acid, sulbactams and tazobactams, many other β-lactams have antifungal,[12] antiviral/anti-HIV,[13,14] anti-inflammatory,[9,15] antimalarial,[16,17] or anticancer activities,[15,18-26] and inhibit activity of human leukocyte elastases and human cytomegalovirus proteases.[27-29] Steadily increasing levels of antibiotic resistance remains one of the important challenges in the continuing clinical utility of β-lactams.[30,31]

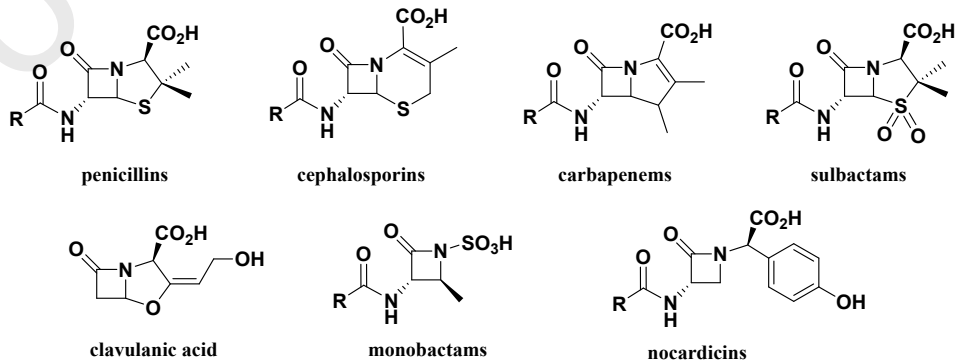


Figure 1: Structures of common β-lactam compounds.

Substituted s-triazines[32-34] also have antimicrobial,[35] antiviral,[36] anti-inflammatory,[37] or anticancer activities.[38] Examples include the anticancer agents tretamine, furazil and dioxadet.[39] Bis(arylamino)-s-triazines are reported to be small-molecule inhibitors of anaplastic lymphoma kinase (ALK),[40] and may offer an effective treatment for anaplastic large cell lymphoma (a rare form of non-Hodgkin lymphoma), non-small cell lung cancers, and neuroblastomas in patients whose tumors contain genetic variations of ALK.[41] Additionally, morpholino triazine derivatives have been reported to be inhibitors of histone deacetylases and dihydrofolate reductases,[42,43] acting as antileukemic,[44] anticancer[45,46] and antiproliferative agents (Fig. 2). It is widely accepted that DNA is an important target for cancer chemotherapy, and as such, the interaction of triazine compounds with DNA induces electronic perturbations that can be detected by UV-vis spectroscopy as a means to assess the strength and mode of interaction.[43,47-53]

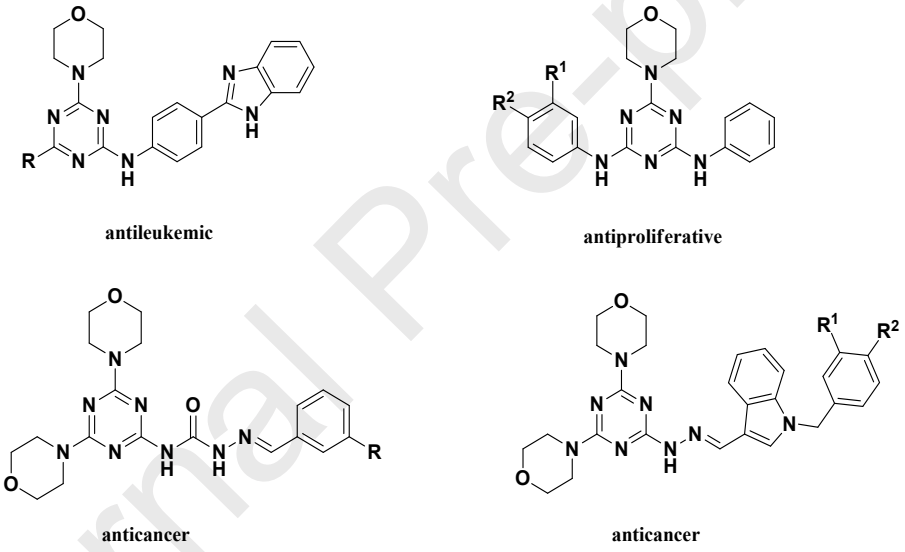


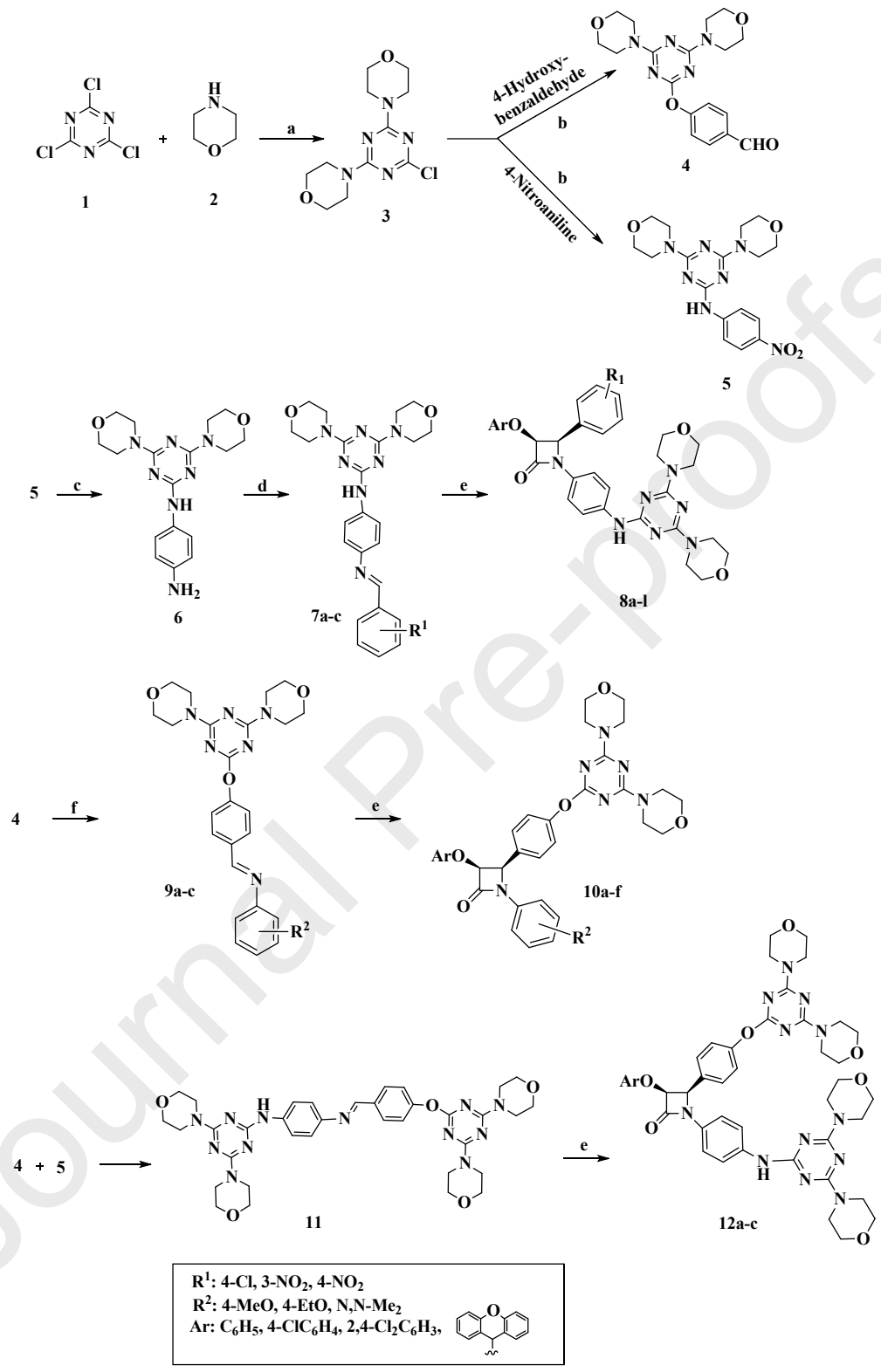
Figure 2: Structures of morpholino-s-triazine derivatives with diverse biological activities.

2. Results and discussion

2.1. Chemistry

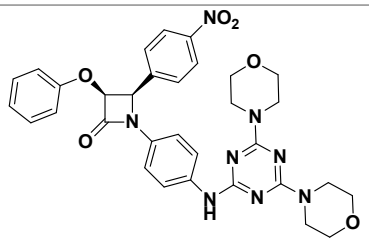
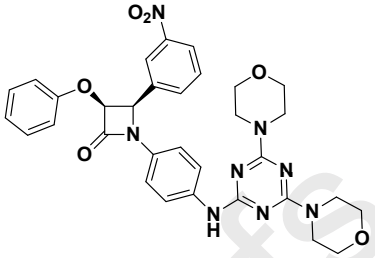
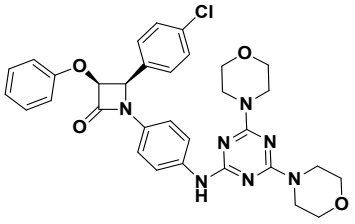
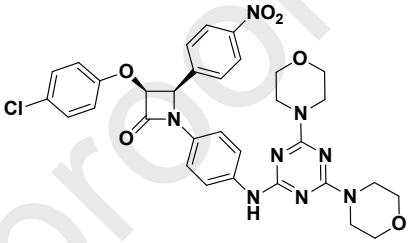
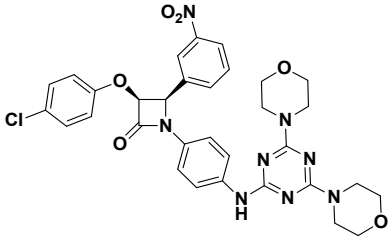
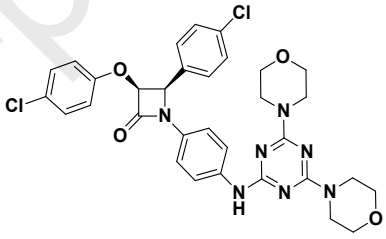
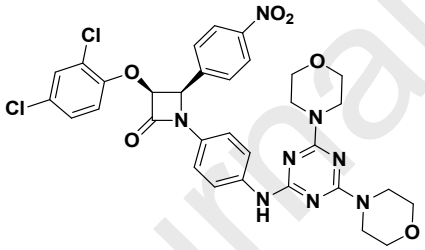
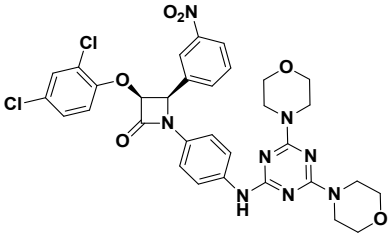
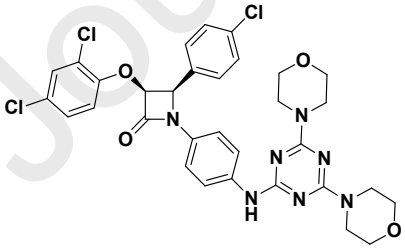
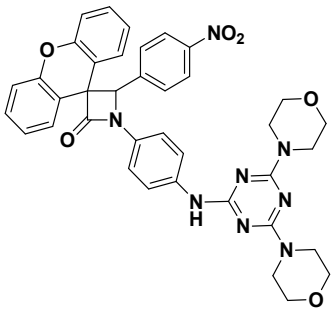
In this study we have synthesized twenty-one new morpholino triazine β-lactam hybrids for preliminary biological evaluation (Table 1).[54] These are divided into three series. The first group consists of β-lactams **8a–l** in which the dimorpholino triazine moiety is attached to the N-1 of the β-lactams ring. The second group consists of β-lactams **10a-f** in which the dimorpholino triazine moiety is attached to the C-4 of the β-lactams ring. The third group consists of β-lactams **12a-c** in

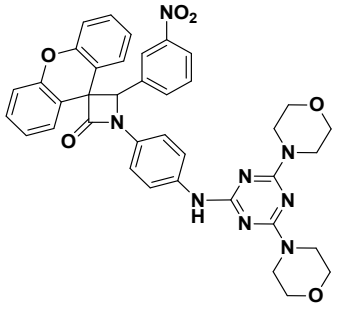
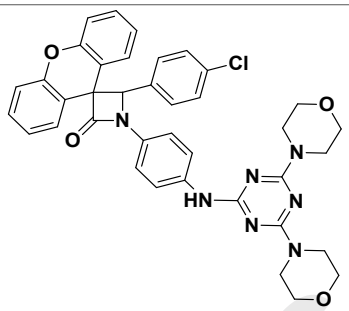
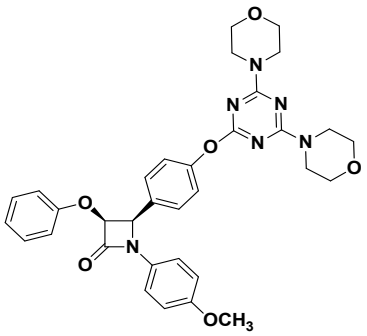
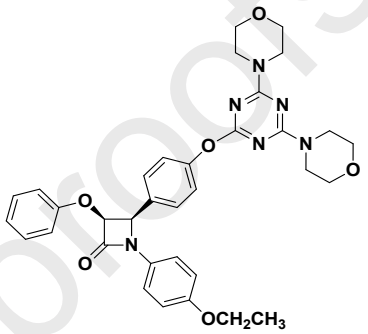
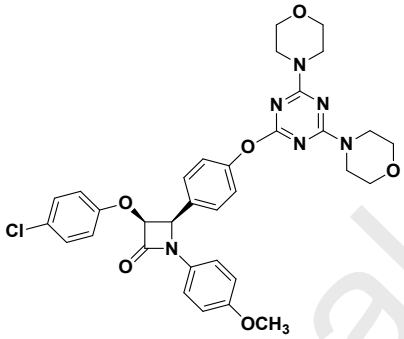
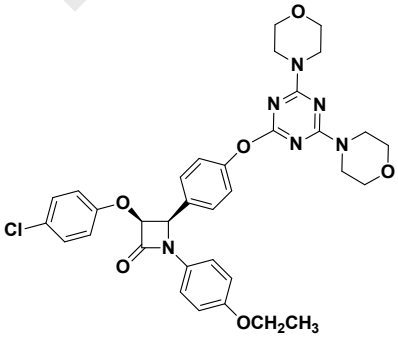
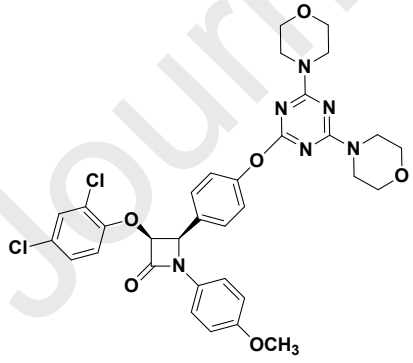
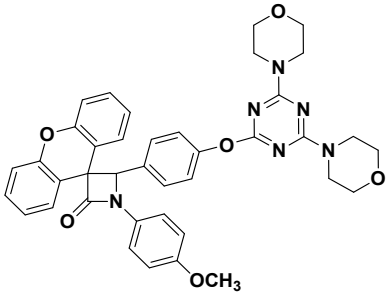
which the dimorpholino triazine moiety is attached to both the N-1 and the C-4 centers of the β-lactam ring. The synthesis of these three groups of target compounds is outlined in (Scheme 1). The starting compound, 4,4'-(6-chloro-1,3,5-triazine-2,4-diyl) dimorpholine (**3**), was synthesized from cyanuric chloride (**1**) by a previously reported procedure.[55] A solution of cyanuric chloride in acetone and crushed ice was treated with a mixture of triethylamine and morpholine at -10°C in molar ratios of 1:4:2 to afford adduct **3**. Subsequent reaction of **3** with 4-hydroxybenzaldehyde or 4-nitroaniline in the presence of potassium carbonate and *N*,*N*-dimethylformamide (DMF) provided 4-((4,6-dimorpholino-1,3,5-triazin-2-yl) oxy)benzaldehyde (**4**) and 4,6-dimorpholino-*N*-(4-nitrophenyl)-1,3,5-triazin-2-amine (**5**), respectively. The aryl nitro substituent of triazine **5** was reduced with Raney Ni/N_2H_4 in aqueous EtOH to give 4-aminoaniline derivative **6**,[56] which reacted with various aldehydes to generate N-arylimines **7a-c**. Conversely, benzaldehyde **4** was reacted with various aniline derivatives to afford N-arylimines **9a-c**. Schiff bases **7a-c** and **9a-c** were then each combined with substituted acetic acids in the presence of triethylamine and tosyl chloride, in molar ratios of 1:1.5:5:1.5, to afford the *cis*-β-lactams **8a–l** and **10a-f** in yields of 75-90% (Scheme 1). Amine **6** and aldehyde **4** were then reacted together to prepare the Schiff base **11**, which was used to prepare *cis*-β-lactams **12a-c**.

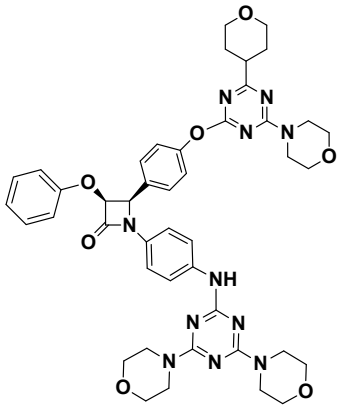
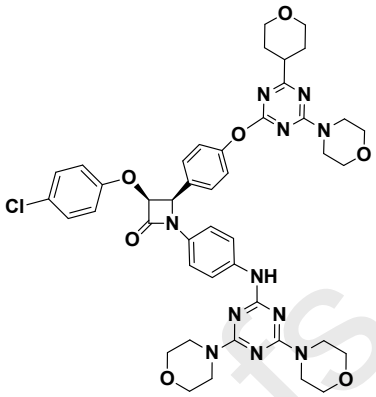
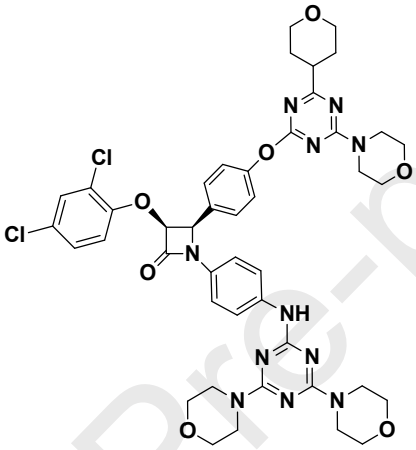


Scheme 1: Synthesis of novel *cis*-β-lactam morpholino-1,3,5-triazine hybrids **8a-l**, **10a-f** and **12a-c**. Reagents and conditions: (a) Et_3N, acetone; (b) K_2CO_3, reflux, DMF; (c) Raney nickel, N_2H_4, EtOH, H_2O (d) R^1PhCHO, EtOH, reflux; (e) $ArCH_2CO_2H$, Et_3N, CH_2Cl_2, TsCl; (f) R^2PhNH_2, EtOH, reflux

Table 1. Structures of *cis*-β-lactam morpholino-1,3,5-triazines **8a-f, 10a-l**, and **12a-c**.

β-lactam	Structure	Yield[a](%)	β-lactam	Structure	Yield[a](%)
8a		80	**8f**		85
8b		90	**8g**		80
8c		85	**8h**		80
8d		85	**8i**		80
8e		85	**8j**		75

8k		75	**8l**		75
10a		90	**10d**		87
10b		85	**10e**		85
10c		90	**10f**		75

12a		70	**12b**		45
12c		40			

[a] Isolated yield

The structures of the products were confirmed by elemental analysis and from their spectral data (IR, ^{1}H NMR, ^{13}C NMR and mass spectra). The IR spectra of imines **7a-c**, **9a-c** and **11** showed absorption peaks at 1573-1612 cm^{-1} due to CH=N stretching vibrations. The stretching vibration at 1735-1759 cm^{-1} confirmed the formation of β-lactams **8a–l**, **10a-f** and **12a-c**. The *cis* stereochemistry of the β-lactam ring substituents was assigned from the proton NMR coupling constants of the β-lactam ring hydrogens H-3 and H-4 ($J_{3,4}$ > 4.0 Hz for the *cis* versus < 3.0 Hz for the *trans* stereoisomer).[57-68] The ^{1}H NMR spectra of compounds **7a-c** and **9a-c** showed a singlet at δ 9.25 and 8.50 for the –NH and –N=CH, respectively. The disappearance of the –N=CH singlet for the imine **11**, and the presence of new doublets at δ 5.20-6.06 for H_3 and H_4 on the β-lactam ring, confirmed the structures of products **10a–l**, **8a-f** and **12a-c**. The ^{13}C NMR spectra of each of these adducts exhibited signals at δ 43.2 and 66.7 for the two distinct CH_2 carbons of the morpholine ring, δ 55.5-62.8 for the C_3 carbon and δ 80.4-81.6 for the C_4 carbon in β-lactams **10a–l**, **8a-f** and **12a-c**. The aromatic carbons also gave signals at the appropriate chemical shifts, and

the β-lactam carbonyl carbon resonated at δ 161.0-162.5. Elemental and mass spectral data further confirmed the assigned product structures. Single crystal X-ray analysis on **10f** corroborated the *cis* stereochemistry and the high planarity of the β-lactam ring (Fig. 3). The mean plane of the xanthene ring system forms dihedral angles of 90°, 102° and 125°, respectively, with the β-lactam ring and the two phenyl rings. The ORTEP image of **10f** (Figure 3) indicates the presence of spatially-close C-H···O contacts (the C6-H6 to O2 contact is 2.4 angstroms, the C7-H7 to O2 contact is 2.48 angstroms, and the C27-H27 to O3 contact is 2.63 angstroms, listed in Table 2). [60-64]

Table 2: Hydrogen bond contact distances and geometries (Å, º) in the ORTEP structure of **10f**

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C6—H6···O2	0.93	2.40	3.019 (2)	124 º
C7—H7···O2	0.93	2.48	3.207 (2)	135 º
C27—H27···O3	0.93	2.63	3.548 (3)	167 º

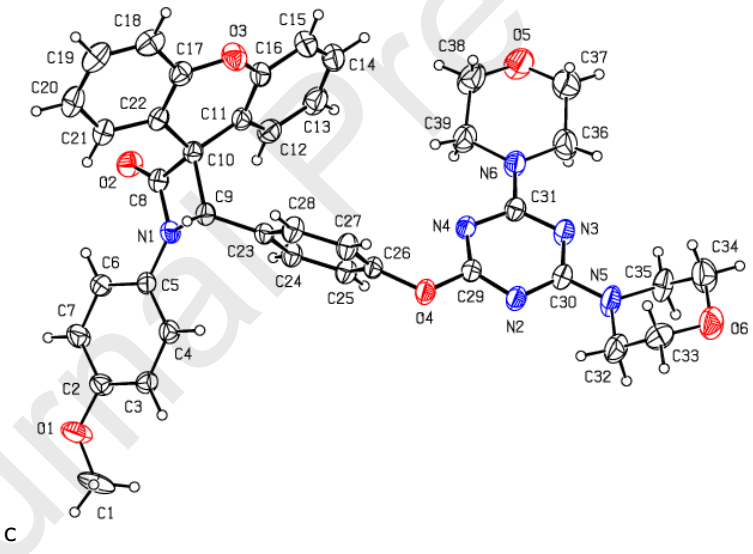


Figure 3: ORTEP diagram of **10f**.

2.2 Antioxidant Activity Assay:

The electron richness of s-triazines makes them suitable for use as potential antioxidants. Consequently, the antioxidant properties of the synthesized β-lactam-s-triazine hybrids were evaluated using DPPH radical scavenging assay.[65-67] The inhibitory IC_{50} values are displayed in Table 3. Lactams **8b** and **8d** were the best among the various hybrids, with IC_{50} values of about 5 mg/ml. Lactams **10b** and **10d** were slightly less active, with IC_{50} values of about 6 mg/ml. We next

examined the precursor compounds, imines **7** and **9**, and found surprisingly, that **9c** and **9b** were far more potent, with IC_{50} values of 30 and 50 μg/ml, respectively, about four times more effective than the positive control standard, vitamin C (IC_{50} of 195 μg/ml). Compounds **9a** and **7b** showed the same IC_{50} value as vitamin C, while imines **7a** and **7c** have moderate IC_{50} values of 275 and 445 μg/ml, respectively. The structure-activity profile for the imines **7** and **9** suggests that the compounds with an electron-releasing group offer better antioxidant properties.

Table 3: Antioxidant activity measured as % scavenging of DPPH radical

Compounds	**IC_{50} (μg/ml)**	**Compounds**	**IC_{50} (μg/ml)**
8a	>10000	**10c**	9600
8b	4800	**10d**	5900
8c	>10000	**10e**	>10000
8d	5800	**10f**	>10000
8e	>10000	**12a**	>10000
8f	>10000	**12b**	>10000
8g	>10000	**12c**	>10000
8h	>10000	**7a**	275
8i	>10000	**7b**	**195**
8j	>10000	**7c**	445
8k	>10000	**9a**	**195**
8l	>10000	**9b**	**50**
10a	>10000	**9c**	**30**
10b	6200	**11**	>10000
Vitamin C	**195**	Blank	-

2.3 Antiproliferative Activity Assays

As noted earlier, some s-triazine derivatives have anticancer properties, and thus, we next set out to examine the behavior of the β-lactam-triazine hybrids versus the normal HEK-293 (human embryonic kidney cell line by MTT assay as well as three different cancer cell lines: SW 1116 (colon), HepG2 (liver), and MCF-7 (breast).[68] Our results are tabulated in Table 4. It is noteworthy that no inhibitory growth activity was observed for any of the 21 tested compounds towards the normal HEK-293 cells, or against the HepG2 (liver) and MCF-7 (breast) cancer cell lines at the tested concentrations (5, 10, 50, 100 and 200 μM). This is in stark contrast to the potent activity of doxorubicin against the normal healthy (HEK-293) and cancerous (HepG2 and MCF-7) cells (IC_{50} of 6.1, 7.3 and 5.5 μM, respectively). On the other hand, compounds **7b, 8f, 8g, 8l, 10c** and **10e** demonstrated excellent inhibitory activity towards the colon cancer cells, with IC_{50} values below 5 μM, in comparison to the clinically-used anticancer agent, doxorubicin (IC_{50} of 6.9 μM). The

underlying basis for the selective antiproliferative activity the synthetic compounds have towards colon cancer cells over liver or breast is unclear, but might be causally related to production of intracellular free radicals in the colon cells that induce apoptosis.

Table 4: Cell growth inhibitory activity against different cancer and normal cell lines

Compound	IC_{50} (μM)			
	SW1116	HepG2	MCF-7	HEK-293
8a	17.52	> 100	> 100	> 100
8b	> 100	> 100	> 100	> 100
8c	99.97	> 100	> 100	> 100
8d	35.71	> 100	> 100	> 100
8e	86.23	> 100	> 100	> 100
8f	**1.98**	> 100	> 100	> 100
8g	**4.88**	> 100	> 100	> 100
8h	> 100	> 100	> 100	> 100
8i	> 100	> 100	> 100	> 100
8j	> 100	> 100	> 100	> 100
8k	> 100	> 100	> 100	> 100
8l	**2.06**	> 100	> 100	> 100
10a	> 100	> 100	> 100	> 100
10b	30	> 100	> 100	> 100
10c	**2.70**	> 100	> 100	> 100
10d	> 100	> 100	> 100	> 100
10e	**1.53**	> 100	> 100	> 100
10f	38.43	> 100	> 100	> 100
12a	> 100	> 100	> 100	> 100
12b	> 100	> 100	> 100	> 100
12c	> 100	> 100	> 100	> 100
7a	93.44	> 100	> 100	> 100
7b	**3.32**	> 100	> 100	> 100
7c	15.1	> 100	> 100	> 100
9a	> 100	> 100	> 100	> 100
9b	> 100	> 100	> 100	> 100
9c	15.64	> 100	> 100	> 100
11	> 100	> 100	> 100	> 100
Doxorubicin (positive control)	**6.9**	7.3	5.5	6.1

The IC_{50} value is defined as the concentration of a compound at which 50% cell growth inhibition is observed.
Cancer cell line: SW 1116 (colon), HepG2 (liver), MCF-7 (breast).
Normal cell line: HEK-293 (embryonic kidney).

Structure-activity profiles of the β-lactams reveals that the placement of dimorpholino triazine moiety on N-1 and C-4 of the β-lactam ring enhances the antiproliferative properties. A common

feature in the most active compounds is the presence of at least one chlorine atom on the phenyl rings at C-3 and C-4 of the β-lactam ring. For compounds **7b, 8f**, **8g, 8l**, **10c** and **10e** the substituents on the aryl substituent on N-1, C-2 and C-3 of the β-lactam ring further modulate bioactivity.

2.4 UV/Vis Titration Studies

UV-vis absorption spectroscopy is one of the most effective techniques available to evaluate the interaction of compounds with duplex DNA. Changes in the absorbance and/or shift in wavelength position upon addition of DNA to a solution containing a fixed concentration of a test compound can give valuable information about the presence and even the type of intermolecular interaction.[69] Namely, compounds that intercalate into duplex DNA usually cause hypochromism with or without a blue or red shift. Conversely, hyperchromism in UV-vis absorption bands indicate minor groove binding, or unwinding of the DNA double helix.[70-71] UV-vis absorption studies have been used to investigate the binding mode and strength of interaction of triazine compounds with DNA.[43,47-53] Accordingly, UV-vis absorption titration studies were used to study the binding of complexes **7b**, **8l**, **8g** and **8f** with various concentrations of calf-thymus DNA (Fig. 4).

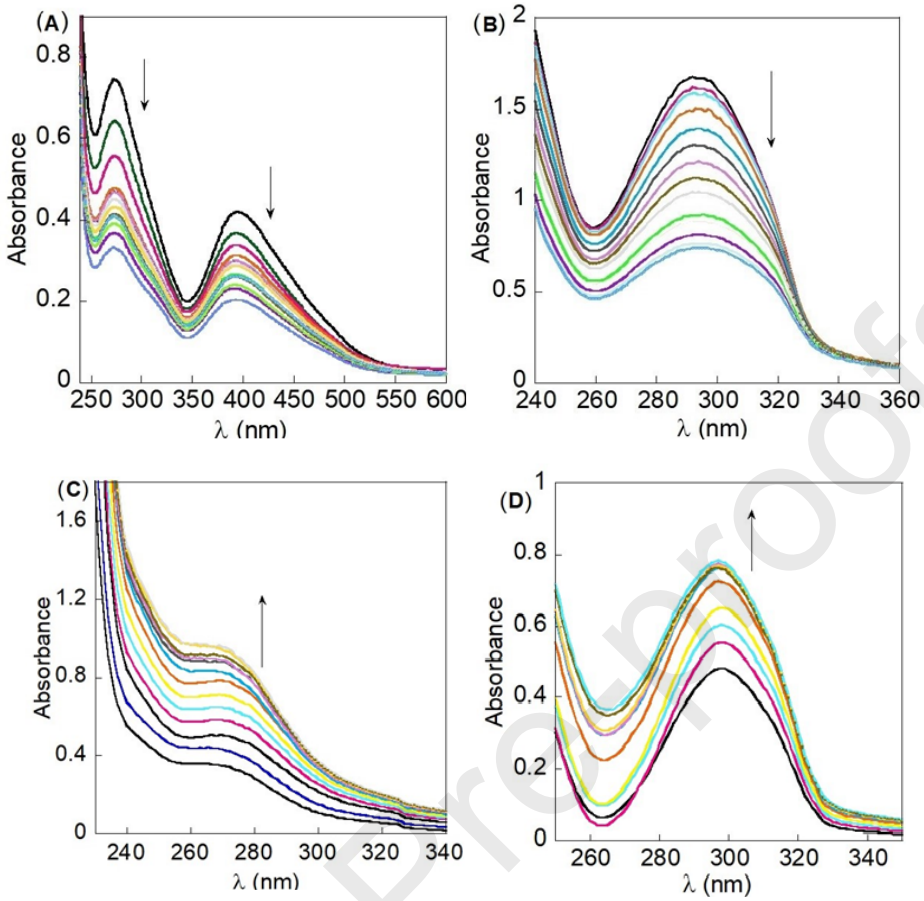


Figure 4. Absorption titration spectra of **7b (A)**, **8g (B)**, **8l (C)**, and **8f (D)** in 50 mM Tris HCl buffer at pH 7.4, in the absence versus presence of increasing amounts of DNA (0-22 μM **7b**-**8g** and 0-180 μM **8l**-**8f**).

In the absence of CT-DNA, compounds **7b** shows absorbances at 393 and 273 nm, and **8g** has an absorbance band at 293 nm. Upon subsequent addition of CT-DNA, hypochromism was observed for both compounds, with a slight red shift of ~4 nm (λ = 293 nm) for complex **7b** and a slight blue shift of ~5 nm (λ = 393 nm) for **8g**. These observations indicate the formation of an adduct between **7b** or **8g** with CT-DNA via an intercalative mode rather than electrostatic or groove binding.[53] Notably, **8l** and **8f** show quite different behavior in CT-DNA titration studies. Addition of **8l** to a solution of CT-DNA produced a hyperchromic shift of the absorption band (λ = 297 nm) along with a slight blue shift of ~2 nm. Complex **8f** exhibits similar behavior under similar conditions with a blue shift of ~2 nm (λ = 268 nm). The observed hypochromism in **8l** and **8f** with a blue shift suggested that these bind to CT-DNA by external contact, possibly electrostatic binding.[71] Overall, the results suggested that although these compounds interact with CT-DNA, the mode of interaction is different for **7b** and **8g** relative to **8l** and **8f**. To compare the binding

affinities of complexes with CT-DNA, quantitatively, the intrinsic binding constant K_b was calculated by monitoring the changes in their absorbance of compounds with increasing concentration of CT-DNA (see Fig. 5 and Table 5) using equation 1,

$$DNA] / (\varepsilon_a-\varepsilon_f) = [DNA] / (\varepsilon_b-\varepsilon_f) + 1 / K_b(\varepsilon_b-\varepsilon_f) \quad (1)$$

where [DNA] is the concentration of DNA in base pairs, ε_a stands for apparent extinction coefficient obtained by calculating A_{obs}/[compound], ε_f is the extinction coefficient of each compound in theirs free form, and ε_b corresponds to the extinction coefficient of compounds in the fully bound form. The values of K_b were obtained from the ratio of the slope to intercept in the plot of [DNA]/ (ε_a - ε_f) versus [DNA]. The intrinsic binding constant values suggest a relatively strong binding to CT-DNA, and the K_b values are in the range for those of other previously reported triazine compounds. For example, Singla et al, reported the synthesis of a new series of triazine–benzimidazole analogues with different substitutions, having the intrinsic DNA binding constant K_b in the range of our compounds.[43,44,47,48]

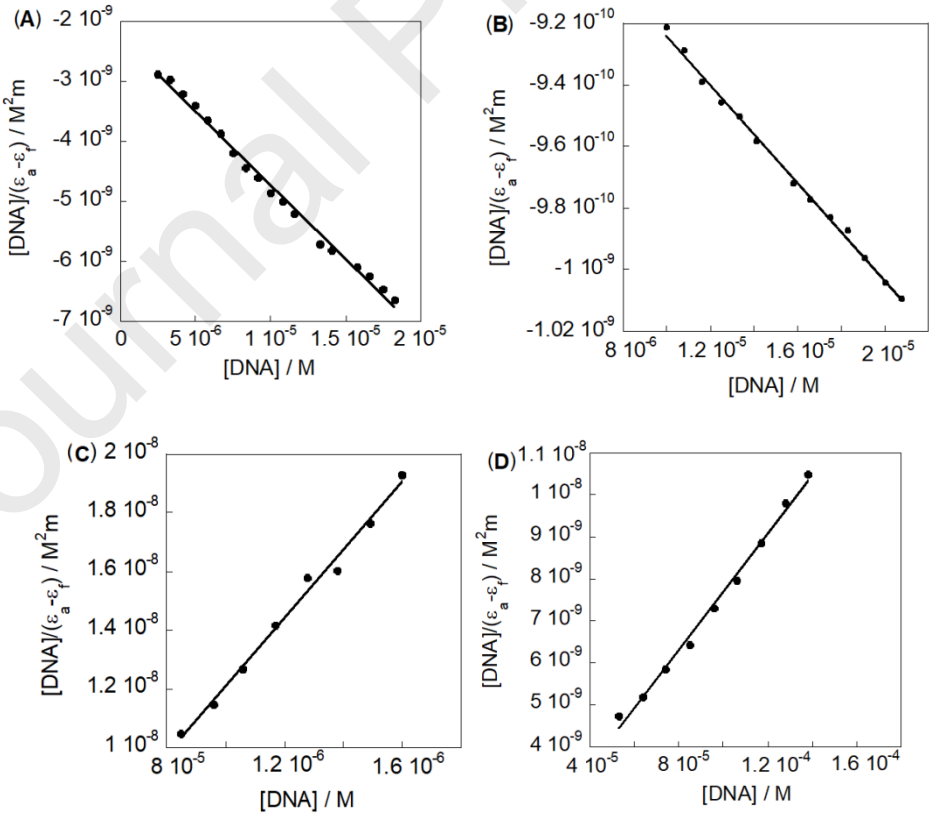


Figure 5. Plots of [DNA] / (ε_a − ε_f) vs. [DNA] for **7b (A)**, **8g (B)**, **8l (C)** and **8f (D)**.

Table 5. Binding constants for the interaction of **7b, 8g, 8l** and **8f** with CT-DNA at 25ºC in 50 mM Tris HCl buffer at pH 7.4.

Compound	λ (nm)	K_b (M^{-1})	R^2 [a]
7b	393	$1.0781 \times 10^{+5}$	0.9936
8g	294	$0.9427 \times 10^{+4}$	0.9964
8l	296	$2.6000 \times 10^{+5}$	0.9942
8f	270	$0.9351 \times 10^{+5}$	0.9938

[a] R^2 is the linear correlated coefficient.

3. Conclusion

In summary, a series of novel triazine-containing β-lactams hybrids were synthesized via the [2+2] ketene imine cycloaddition reaction of morpholino-1,3,5-triazine imine derivatives and different phenoxyacetic acids in the presence of trimethylamine and *p*-toluenesulfonyl chloride. These cycloadditions were completely stereoselective for producing only the *cis* stereoisomers, as confirmed by proton NMR spectroscopy and X-ray crystallography. The products **7a-c, 9a-c, 11, 8a-l, 10a-f** and **12a-c** were evaluated for antioxidant and antiproliferative activity. The compounds **9b** and **9c** showed the most potent radical scavenging activity. In the cell assays, compounds **7b**, **8f, 8g, 8l, 10c,** and **10e** exhibited selective inhibitory activity towards the SW1116 colon cancer cell, with *in vitro* IC_{50} values below 5 μM, which is comparable to that of the clinically used anticancer agent doxorubicin (IC_{50} of 6.9 μM). Structure-activity considerations of these β-lactam-triazine hybrids suggest that the chlorophenyl group enhances *in vitro* inhibitory activity towards the colon cancer cells. UV-vis titration studies also indicated that the **7b** and **8g** are potential DNA intercalating agents, while **8f** and **8l** may bind to duplex DNA through electrostatic interactions. Additional studies are underway to further improve the biological activity as well as to determine a better-defined mechanism of action.

4. Experimental Section

4.1: General:

All chemicals were purchased from Merck, Fluka and Acros chemical companies and used without further purification. Reagents and solvents such as CH_2Cl_2 and Et_3N were dried before use by

distillation over CaH_2 under a nitrogen atmosphere. All known reaction products were identified by comparison of their spectral data. Infrared spectra were run on a Shimadzu FT-IR 8300 spectrophotometer using potassium bromide pellets (υ in cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or dimethylsulfoxide-d_6 (DMSO-d_6) using a Bruker Avance DPX instrument (^1H NMR at 250 MHz or 400 MHz; ^{13}C NMR at 100 MHz). Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Coupling constants (*J*) are reported in hertz (Hz). Proton signal splitting patterns are indicated as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, dd: doublet of doublet. The mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument. Elemental analyses were run on a Thermo Finnigan Flash EA=1112 series instrument. Melting points were determined on a Buchi 510 melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was carried out on silica gel 254. The crystallographic data were solved and refined by using SHELXS97 (Sheldrick, 2008) and SHELXL2018 (Sheldrick, 2015), respectively.

4.2: Preparation of 4,4'-(6-chloro-1,3,5-triazine-2,4-diyl) dimorpholine (**3**):

To a stirred solution of cyanuric chloride (**1**) (5.0 g, 27.1 mmol) in acetone (30 ml) and crushed ice, a mixture of triethylamine (8.15 ml, 111 mmol) and morpholine (**2**) (4.72 ml, 54.2 mmol) was added at -10°C. After the addition, the reaction mixture was stirred at room temperature for 1 h and diluted with 50 ml of water. The white solid generated was filtered and washed with water and acetone. The white solid was dried under reduced pressure (5.79 g, 74.9% yield).

4.3: Preparation of 4,6-Dimorpholino-*N*-(4-nitrophenyl)-1,3,5-triazin-2-amine (**5**)

A suspension of 4,4'-(6-chloro-1,3,5-triazine-2,4-diyl) dimorpholine (300 mg, 1.05 mmol), 4-nitroaniline (159.5 mg,1.15 mmol), and potassium carbonate (159.5 mg, 1.15 mmol), *N, N*-dimethylformamide (2 ml) was refluxed for 5 h. The precipitates generated were filtered through a Buchner funnel and washed sequentially with methanol and water. After being dried under reduced pressure, the title product (258.6 mg, 64%) was obtained as a pale yellow solid.[55]

4.4: Preparation of *N*-1-(4,6-dimorpholino-1,3,5-triazin-2-yl) benzene-1,4-diamine (**6**)

4,6-Dimorpholino-*N*-(4-nitrophenyl)-1,3,5-triazin-2-amine (**5**) (710 mg, 2.2 mmol) was dissolved in 200 ml of EtOH: H_2O (9:1) by heating to reflux. The temperature was reduced to 60°C and

hydrazine hydrate (250 µl, 5.15 mmol) and ca. 0.5 ml of Raney-Ni suspension were added. [56] Reflux was then maintained for 15 min. The cold mixture was filtered through a compressed pad of celite and the solvent was then evaporated. The crude product was purified by silica gel chromatography (eluent was 4–7% MeOH in CH_2Cl_2) to yield pure **6** in 83% yield.

4.4.1 *N*1-(4,6-dimorpholino-1,3,5-triazin-2-yl) benzene-1,4-diamine (**6**)

White solid; Mp. 265-267 °C; IR (KBr, cm^{-1}) 3371 (NH_2), 1573, 1504; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.73-3.75 (16H, m, 8×CH_2), 6.50 (1H, s, N-H), 6.64-6.68 (2H, m, NH_2), 7.26-7.32 (4H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 67.0, 115.3, 121.9, 130.3, 141.5, 164.5, 165.3; GC-MS m/z 357.19 [M^+]; Analysis calculated for $C_{17}H_{23}N_7O_2$: C, 57.13; H, 6.49; N, 27.43%. Found: C, 57.46; H, 6.12; N, 27.21%.

4.5: General procedure for the preparation of 4-((4,6-dimorpholino-1,3,5-triazin-2 yl) oxy)benzaldehyde (**4**)

A suspension of 4,4'-(6-chloro-1,3,5-triazine-2,4-diyl) dimorpholine (300 mg, 1.05 mmol), 4-hydroxybenzaldhyde (159.5 mg, 1.15 mmol), and potassium carbonate (159.5 mg, 1.15 mmol) in N*, N*-dimethylformamide (2 ml) was refluxed for 8 h. The precipitates generated were filtered and washed sequentially with methanol and water. After being dried under reduced pressure, the title product (75%) was obtained as a pale white solid.

4.5.1 4-((4,6-dimorpholino-1,3,5-triazin-2-yl) oxy)benzaldehyde (**4**)

White solid; Mp. 253-255 °C; IR (KBr, cm^{-1}) 2869, 1705 (CHO), 1581, 1496; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.42-3.58 (16H, m, 8×CH_2), 7.42 (2H, d, *J* =7.5 Hz, ArH), 7.96 (2H, d, *J* =7.5 Hz, ArH), 9.99 (1H, CHO) ,^{13}C NMR (100 MHz, DMSO-d_6) δ 43.3,65.7, 122.4, 130.8, 133.0, 156.8, 165.4, 169.9, 191.9; GC-MS m/z 371.16 [M^+]; Analysis calculated for $C_{18}H_{21}N_5O_4$: C, 58.21; H, 5.70; N, 18.86 %. Found: C, 57.93; H, 5.32; N, 18.23%.

4.6: General procedure for preparation of Schiff bases **7a-c**

A stirred mixture of amine **6** (1.00 mmol) and one of the aromatic aldehydes (1.00 mmol) was refluxed in ethanol containing 2-3 small drops of glacial AcOH for an appropriate time. The

mixture was then cooled to room temperature, and the precipitate was filtered and recrystallized from ethanol to give Schiff bases **7a-c**.

4.6.1 (E)-N-(4-((4-chlorobenzylidene) amino) phenyl)-4,6-dimorpholino-1,3,5-triazin-2-amine (**7a**)

Cream solid; Mp. 273-275 °C; IR (KBr, cm^{-1}) 3417,2854,1612 (CH=N) 1542,1504; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.60-3.69 (16H, m, 8×CH_2), 7.26 (2H, d, *J* = 10.0 Hz, ArH), 7.55 (2H, d, *J* = 7.5 Hz, ArH), 7.71 (2H, d, *J* = 7.5 Hz, ArH), 7.90 (2H, d, *J* = 7.5 Hz, ArH), 8.66 (1H, s, CH=N), 9.24(1H, s, NH), ^{13}C NMR (100 MHz, DMSO) δ 43.4, 66.1, 119.9, 121.5, 128.8, 129.8, 135.1, 135.5, 139.1, 144.2, 156.8, 163.9, 164.6; GC-MS m/z 479.18 [M^+]; Analysis calculated for $C_{24}H_{26}ClN_7O_2$: C, 60.06; H, 5.46; N, 20.43%. Found: C, 60.36; H, 5.13; N, 20.23%.

4.6.2 (E)-4,6-dimorpholino-N-(4-((4-nitrobenzylidene) amino) phenyl)-1,3,5-triazin-2-amine (**7b**)

Orang solid; Mp. 283-285 °C; IR (KBr, cm^{-1}):3417,2854, 1612 (CH=N),1504; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.61-3.69 (16H, m, 8×CH_2), 7.35 (2H, d, *J* = 10.0 Hz, ArH), 7.75 (2H, d, *J* = 10.0 Hz, ArH), 8.13 (2H, d, *J* = 10.0 Hz, ArH), 8.33 (2H, d, *J* = 10.0 Hz, ArH), 8.83 (1H, s, CH=N), 9.30 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.3, 66.0, 119.7, 121.9, 123.9, 129.3, 139.6, 142.0, 143.8, 148.4, 156.0, 163.9, 164.6; GC-MS m/z 490.21 [M^+]; Analysis calculated for $C_{24}H_{26}N_8O_4$: C, 58.77; H, 5.34; N, 22.84%. Found: C, 58.24; H, 5.10; N, 23.04%.

4.6.3 (E)-4,6-dimorpholino-N-(4-((3-nitrobenzylidene) amino) phenyl)-1,3,5-triazin-2-amine (**7c**)

Yellow solid; Mp. 280-282 °C; IR (KBr, cm^{-1}) 3417, 2854, 1612 (CH=N),1504; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.61-3.69 (16H, m, 8×CH_2), 7.32 (2H, d, *J* = 7.5 Hz, ArH), 7.72-7.81 (3H, m, ArH), 8.29-8.33 (2H, m, ArH), 8.69 (1H, s, ArH), 8.83 (1H, s, CH=N), 9.28 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 40.9, 63.7, 117.5, 119.3, 119.9, 122.6, 128.1, 131.8, 135.5, 137.0, 141.1, 145.8, 153.6, 161.3, 162.1; GC-MS m/z 490.21 [M^+]; Analysis calculated for $C_{24}H_{26}N_8O_4$: C, 58.77; H, 5.34; N, 22.84%. Found: C, 58.12; H, 5.48; N, 23.15%.

4.7: General procedure for preparation of Schiff bases **9a-c**

A stirred mixture of aldehyde **5** (1.00 mmol) and one of the aniline derivatives (1.00 mmol) was refluxed in ethanol containing 2-3 small drops of glacial AcOH for an appropriate time. The mixture was then cooled to room temperature, and the precipitate was filtered and recrystallized from ethanol to give Schiff bases **9a-c**.

4.7.1 (E)-1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) oxy) phenyl)-N-(4-methoxyphenyl) methanimine (**9a**)

Cream-colored solid; Mp. 180-182 °C; IR (KBr, cm^{-1}) 2962, 2854, 1581 (CH=N),1504; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.53-3.79 (16H, m, 8×CH_2), 3.86 (2H, s, OCH_3), 6.96 (2H, d, *J* = 5.0 Hz, ArH), 7.25-7.30 (4H, m, ArH), 7.91 (2H, d, *J* = 5.0 Hz ArH), 8.50 (1H, s, CH=N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.7, 55.5, 66.7, 114.4, 122.1, 122.3, 129.3, 133.2, 144.7, 154.7, 157.4, 158.3, 166.0, 170.7; GC-MS m/z 476.22 [M^+]; Analysis calculated for $C_{25}H_{28}N_6O_4$: C, 63.01; H, 5.92; N, 17.64%. Found: C, 63.34; H, 5.71; N, 17.31%.

4.7.2 (E)-1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) oxy) phenyl)-N-(4-ethoxyphenyl) methanimine (**9b**)

Cream-colored solid; Mp. 166-168 °C; IR (KBr, cm^{-1}) 2962, 2854, 1573 (CH=N), 1504; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.43 (3H, t, *J* = 7.0 Hz, CH_3), 3.60-3.83 (16H, m, 8×CH_2), 4.06 (2H, td, *J* = 6.5, 6.25 Hz, CH_2), 6.92 (2H, d, *J* = 7.5 Hz, ArH), 7.18-7.28 (3H, m, ArH), 7.28 (1H, br, ArH), 7.89 (2H, d, *J* = 8.5 Hz, ArH), 8.48 (1H, s, CH=N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 43.7, 63.9, 66.7, 114.9, 122.1, 122.3, 129.3, 133.3, 144.6, 154.6, 157.3, 157.7, 166.0, 170.7; GC-MS m/z 490.23 [M^+]; Analysis calculated for $C_{26}H_{30}N_6O_4$: C, 63.66; H, 6.16; N, 17.13%. Found: C, 63.20; H, 6.42; N, 16.93%.

4.7.3(E)-4-((4-((4,6-dimorpholino-1,3,5-triazin-2-yl) oxy) benzylidene) amino)-N, N-dimethylaniline (**9c**)

Green solid; Mp. 172-174 °C; IR (KBr, cm^{-1}) 2954, 2854, 1573 (CH=N), 1496; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.99 (6H, s, CH_3), 3.63-3.70 (16H, m, 8×CH_2), 6.74 (1H, d, *J* = 2.5 Hz, ArH), 6.78 (1H, d, *J* = 2.5 Hz, ArH), 7.24 (2H, d, *J* = 5.0 Hz, ArH), 7.27 (2H, d, *J* = 2.5 Hz, ArH), 7.86 (1H, d, *J* = 2.5 Hz, ArH), 7.90 (1H, d, *J* = 2.5 Hz, ArH), 8.52 (1H, s, CH=N); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 40.7, 43.5, 66.7, 112.7, 122.1, 128.9, 133.6, 140.6,149.5, 154.3, 155.3, 166.0,

170.8; GC-MS m/z 489.25 [M^+]; Analysis calculated for $C_{26}H_{31}N_7O_3$: C, 63.79; H, 6.38; N, 20.03%. Found: C, 63.98; H, 6.22; N, 19.83%.

4.8: General procedure for preparation of Schiff base **11**

A stirred mixture of 4-((4,6-dimorpholino-1,3,5-triazin-2-yl)oxy)benzaldehyde (**4**) (1.00 mmol) and *N*1-(4,6-dimorpholino-1,3,5-triazin-2-yl)benzene-1,4-diamine (**6**) (1.00 mmol) was refluxed in ethanol containing 2-3 small drops of glacial AcOH for an appropriate time. The mixture was then cooled to room temperature, and the precipitate was filtered and recrystallized from ethanol to give Schiff base **11**.

4.8.1 (E)-N-(4-((4-((4,6-dimorpholino-1,3,5-triazin-2-yl)oxy)benzylidene)amino)phenyl)-4,6-dimorpholino-1,3,5-triazin-2-amine (**11**)

Lemon yellow solid; Mp. 252-254 °C; IR (KBr, cm^{-1})2923, 2854, 1542 (CH=N), 1496; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (16H, d, *J* = 4.0 Hz, 8×CH_2), 3.66 (16H, d, *J* = 4.0 Hz, 8×CH_2), 6.71 (1H, s, NH), 7.16 (1H, s, ArH), 7.18 (2H, d, *J* = 4.0 Hz, ArH), 7.21 (1H, s, ArH), 7.51 (2H, d, *J* = 8.0 Hz, ArH), 7.83 (2H, d, *J* = 8.0 Hz, ArH), 8.44 (1H, s, CH=N); ^{13}C NMR (100 MHz, DMSO) δ 43.1, 66.0, 101.6, 120.0, 121.3, 122.1, 129.3,133.1, 138.8, 154.2, 157.3, 163.9, 164.6, 165.4, 170.0; GC-MS m/z 710.34 [M^+]; Analysis calculated for $C_{35}H_{42}N_{12}O_5$: C, 59.14; H, 5.96; N, 23.65%. Found: C, 58.98; H, 6.12; N, 23.93%.

4.9: General procedure for the synthesis of novel di morpholino-1,3,5-triazin β-lactam hybrids **8a-l**, **10a-f** and **12a-c.**

A mixture of Schiff bases **7a-c** or **9a-b** or **11** (1.00 mmol), triethylamine (5.00 mmol), a substituted acetic acid (1.50 mmol) and tosyl chloride (1.50 mmol) in dry CH_2Cl_2 (15 ml) was stirred overnight at room temperature. Then the mixture was washed with 1N aqueous HCl (20 ml), saturated aqueous $NaHCO_3$ (20 ml) and brine (20 ml). The organic layer was dried (anhydrous Na_2SO_4), filtered and evaporated to give crude products **8a-l** or **10a-f** and **12a-c** that were purified by recrystallization from CH_2Cl_2.

4.9.1 1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) amino) phenyl)-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one **(8a**)

White solid; Mp.228-230°C; IR (KBr, cm^{-1}) 3417,2854, 1751, (CO β-lactam),1566, 1512; ^1H NMR (250 MHz, $CDCl_3$) δ 3.60-3.68 (16H,m, 8×CH_2), 5.47 (1H, d, *J* = 5.0 Hz, H-4), 5.63 (1H, d, *J* = 5.0 Hz, H-3), 6.71 (1H, s, NH), 6.74 (1H, s, ArH), 6.80 (1H, d, *J* = 7.5 Hz, ArH), 6.91 (1H, t, *J* = 7.5 Hz, ArH), 7.05 (1H, t, *J* = 10.0 Hz, ArH), 7.14 (2H, t, *J* = 7.5 Hz, ArH), 7.24-7.30 (2H, m, ArH), 7.43-7.53 (3H, m, ArH), 8.11 (2H, d, *J* = 7.5 Hz, ArH); ^{13}C NMR (100 MHz, DMSO) δ 43.3, 60.0, 65.7, 80.8,114.3, 117.21, 120.1, 120.7, 122.1, 123.2, 129.4, 136.0, 140.9, 147.4, 157.7, 162.3, 164.1, 165.6; GC-MS m/z 624.24 [M^+]; Analysis calculated for $C_{32}H_{32}N_8O_6$: C, 61.53; H, 5.16; N, 17.94%. Found: C, 61.01; H, 5.82; N, 17.94%.

4.9.2 4-(4-chlorophenyl)-1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) amino) phenyl)-3-phenoxyazetidin-2-one (**8b**)

White solid; Mp. 271-273°C; IR (KBr, cm^{-1}): 3402, 2854, 1759 (CO β-lactam), 1366, 1504; ^1H-NMR (250 MHz, $CDCl_3$) δ 3.70-3.77 (16H,m, 8×CH_2), 5.36 (1H, d, *J* = 5.0 Hz, H-4), 5.57 (1H, d, *J* = 5.0 Hz, H-3), 6.67 (1H, s, NH), 6.78 (2H, d, *J* = 7.5 Hz, ArH), 6.94 (1H, t, *J* = 7.5 Hz, ArH), 7.21 (2H, t, *J* = 7.5 Hz, ArH), 7.25-7.34 (6H, m, ArH), 7.47 (2H, d, *J* = 7.5 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.6, 61.4, 66.6, 81.1, 115.5, 117.9, 120.2, 122.3, 128.7, 129.3, 129.4, 131.3, 131.4, 134.6, 136.3, 156.7, 162.3, 164.1, 165.1; GC-MS m/z 613.22 [M^+]; Analysis calculated for $C_{32}H_{32}ClN_7O_4$: C, 62.59; H, 5.25; N, 15.97%. Found: C, 62.09; H, 5.62; N, 16.13%.

4.9.3 3-(4-chlorophenoxy)-1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) amino) phenyl)-4-(3-nitrophenyl) azetidin-2-one (**8c**)

White solid; Mp. 268-270°C; IR (KBr, cm^{-1}) 3417, 2854, 1759 (CO β-lactam), 1612, 1573, 1504; ^1H NMR (250 MHz, DMSO-d_6) δ 3.60-3.64 (16H, m, 8×CH_2), 5.91 (1H, d, *J* = 5.0, H-4), 5.96 (1H, d, *J* = 5.0, H-3) 6.75-6.85 (2H, m, ArH), 7.23 (4H, t, *J* = 10.0 Hz, ArH), 7.57 (1H, t, *J* = 7.5 Hz, ArH), 7.63 (2H, d, *J* = 9.0 Hz, ArH), 7.77 (1H, d, *J*= 7.5 Hz ArH), 8.09 (1H, d, *J*= 7.5 Hz, ArH), 8.19 (1H, s, ArH), 9.15 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.2, 59.5, 65.9,80.4, 116.7,114.9, 117.4, 120.1, 122.8, 123.3, 125.7, 128.6, 129.1, 130.2, 134.4, 135.6, 137.2, 147.3, 154.7, 161.4, 163.8, 164.6; GC-MS m/z 658.21 [M^+]; Analysis calculated for $C_{32}H_{31}ClN_8O_6$: C, 58.31; H, 4.74; N, 17.00%. Found: C, 57.91; H, 4.13; N, 17.31%.

4.9.4 3-(2,4-dichlorophenoxy)-1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) amino) phenyl)-4-(4-nitrophenyl) azetidin-2-one (**8d**)

White solid; Mp. 190-192 °C; IR (KBr, cm^{-1}) 3440, 2854, 1759 (CO β-lactam), 1620, 1573, 1504; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.58-3.63 (16H, m, 8×CH_2), 5.90 (1H, d, *J* = 5.0 Hz, H-4), 6.06 (1H, d, *J* = 5.0 Hz, H-3), 6.79 (1H, d, *J* = 7.5 Hz, ArH), 7.21 (3H, d, *J* = 7.5 Hz, ArH), 7.36-7.43 (1H, m, ArH), 7.50-7.75 (4H, m, ArH), 8.13 (1H, d, *J* = 10.0 Hz, ArH), 9.15 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.2, 59.5, 66.0, 81.0, 115.0, 116.3, 117.4, 120.1, 123.2, 126.0, 127.3, 127.9, 128.6, 129.3, 130.1, 137.3, 140.8, 147.4, 161.0, 163.8, 164.6; GC-MS m/z = 692.17 [M^+]; Analysis calculated for $C_{32}H_{30}Cl_2N_8O_6$: C, 55.42; H, 4.36; N, 16.16%. Found: C, 55.01; H, 4.64; N, 15.91%.

4.9.5 4-(4-chlorophenyl)-3-(2,4-dichlorophenoxy)-1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) amino) phenyl) azetidin-2-one (**8e**)

White solid; Mp. 275-277 °C; IR (KBr, cm^{-1}) 3417, 2854, 1751 (CO β-lactam), 1612, 1573, 1504; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.59-3.63 (16H, m, 8×CH_2), 5.71 (1H, d, *J* = 4 Hz, H-4), 5.97 (1H, d, *J* = 4 Hz, H-3), 7.20 (3H, d, *J* = 7.5 Hz, ArH), 7.30-7.44 (6H, m, ArH) 7.62 (2H, d, *J* = 7.5 Hz, ArH), 9.14 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 44.5, 60.8, 67.2, 81.9, 117.3, 118.7, 121.3, 123.4, 127.1, 120.0, 129.4, 130.6, 131.1, 131.6, 133.1, 134.2, 138.4, 151.8, 162.3, 165.0, 165.8; GC-MS m/z 681.14 [M^+]; Analysis calculated for $C_{32}H_{30}Cl_3N_7O_4$: C, 56.28; H, 4.43; N, 14.36%. Found: C, 56.71; H, 4.23; N, 13.96%.

4.9.6 1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl)amino)phenyl)-4-(3-nitrophenyl)-3-phenoxyazetidin-2-one **(8f)**

White solid; Mp. 233-235 °C; IR (KBr, cm^{-1}) 3417, 2854, 1751 (CO β-lactam) 1612, 1566, 1527; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.34-3.75 (16H, m, 8×CH_2), 5.33 (2H, br, H-3, H-4), 6.78 (2H, d, *J* = 7.5 Hz, ArH), 6.86 (1H, t, *J* = 7.5 Hz, ArH), 6.91 (1H, d, *J* = 7.5 Hz, ArH), 7.11-7.16 (2H, m, ArH), 7.20 (1H, d, *J* = 4.5 Hz, ArH), 7.25 (1H, d, *J*= 7.5 Hz, ArH), 7.33 (1H, d, *J* = 7.5 Hz, ArH), 7.55 (1H, t, *J* = 7.5 Hz, ArH), 7.79 (1H, d, *J*= 7.5 Hz, ArH), 8.06-8.10 (1H, m, ArH), 8.21 (1H, s, ArH), 9.14 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.2 ,59.7 ,65.7 , 80.5, 114.3, 114.9, 117.2, 120.7, 122.0, 123.4, 129.4, 134.4, 134.9, 136.1, 147.3, 155.8, 157.7, 162.4, 164.1, 165.6; GC-MS m/z 624.24 [M^+]; Analysis calculated for $C_{32}H_{32}N_8O_6$: C, 61.53; H, 5.16; N,

17.94%. Found: C, 61.09; H, 5.62; N, 17.33%.

4.9.7 3-(4-chlorophenoxy)-1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) amino) phenyl)-4-(4-nitrophenyl) azetidin-2-one **(8g)**

Cream solid; Mp. 218-220 °C; IR (KBr, cm^{-1}) 3417, 2854, 1759 (CO β-lactam), 1612, 1573, 1504; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.59-3.63 (16H, m, 8×CH_2), 5.72 (1H, d, J = 4.2 Hz, H-4), 5.97 (1H, d, J = 4.2 Hz, H-3), 7.20 (4H, d, J = 7.5 Hz ArH), 7.30-7.49 (6H, m , ArH), 7.62 (2H, d J = 7.5 Hz, ArH), 9.14 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.2, 59.7, 65.7, 80.5, 114.3, 114.9, 117.2, 120.7, 122.0, 123.4, 129.4, 134.4, 134.9, 136.1, 147.3, 155.8, 157.7, 162.4, 164.1, 165.6; GC-MS m/z 658.21 [M^+]; Analysis calculated for $C_{32}H_{31}ClN_8O_6$: C, 58.31; H, 4.74; N, 17.00%. Found: C, 57.96; H, 4.01; N, 17.43%.

4.9.8 3-(4-chlorophenoxy)-4-(4-chlorophenyl)-1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) amino) phenyl) azetidin-2-one (**8h**)

White solid; Mp. 208-210 °C; IR (KBr, cm^{-1}) 3417, 2854, 1759 (CO β-lactam), 1612, 1573, 1504; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 3.64-3.73 (16H, m, 8×CH_2), 5.48 (1H, d, J = 5.0 Hz, H-4), 5.58 (1H, d, J = 5.0 Hz, H-3), 6.69 (1H, s, N-H), 6.74 (2H, d, J = 10 Hz, ArH), 7.14 (2H, d, J = 7.5 Hz, ArH), 7.24-7.27 (3H, m, ArH), 7.49 (2H, d, J = 10.0 Hz, ArH), 7.55 (2H, d, J = 10.0 Hz, ArH) 8.18 (1H, d, J = 4.5 Hz, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.3 ,60.2 , 63.1, 65.7 , 80.6, 114.9,116.7,118.5, 121.6, 125.5, 128.9, 129.0, 129.5, 129.7, 152.0, 155.2, 155.3, 161.5, 165.3, 170.3; GC-MS m/z 647.18 [M^+]; Analysis calculated for $C_{32}H_{31}Cl_2N_7O_4$: C, 59.26; H, 4.82; N, 15.12%. Found: C, 59.41; H, 4.32; N, 15.59%.

4.9.9 3-(2,4-dichlorophenoxy)-1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) amino) phenyl)-4-(3-nitrophenyl) azetidin-2-one (**8i**)

White solid; Mp. 273-275 °C; IR (KBr, cm^{-1}) 3417, 2854, 1759 (CO β-lactam), 1612, 1573, 1504; ^{1}H-NMR (250 MHz, DMSO-d_6) δ 3.59-3.63 (16H, m, 8×CH_2), 5.91 (1H, d, J = 5.0 Hz, H-4), 6.08 (1H, d, J = 5.0 Hz, H-3) 7.24-7.33 (4H, m, ArH), 7.35-7.39 (1H, m, ArH), 7.54 (1H, t, J = 8 Hz, H-3), 7.64 (2H, d, J = 10 Hz, ArH), 7.76 (1H, d, J = 7.5 Hz, ArH), 8.09-8.12 (1H, m, ArH), 8.18 (1H, s, ArH), 9.15 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.2, 59.1, 65.9, 80.0, 116.1, 117.4, 120.1, 122.0, 122.7, 129.3, 129.8, 130.1, 134.5, 135.2, 137.3, 147.3,150.2, 161.0, 163.8,

164.6; GC-MS m/z = 692.17 [M^+]; Analysis calculated for $C_{32}H_{30}Cl_2N_8O_6$: C, 55.42; H, 4.36; N, 16.16%. Found: C, 55.01; H, 4.64; N, 15.91%.

4.9.10 1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) amino) phenyl)-2-(4-nitrophenyl) spiro[azetidine-3,9'-xanthen]-4-one **(8j**)

White solid; Mp. 283-285 °C; IR (KBr, cm^{-1}) 3417, 2854, 1751 (CO β-lactam),1604, 1573, 1512; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.43-3.66 (16H, m, 8×CH_2), 5.55 (1H, s, H-4), 6.83 (1H, t, J = 7.0 Hz, ArH), 7.02 (1H, d, J = 7.5 Hz, ArH), 7.08-7.16 (2H, m, ArH), 7.23 (2H, d, J = 7.5 Hz, ArH), 7.30 (2H, d, J = 10.0 Hz, ArH), 7.36-7.50 (4H, m, ArH), 7.72 (2H, d, J = 10.0 Hz, ArH), 7.95 (2H, d, J = 7.5 Hz, ArH), 9.21 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 43.2, 63.2, 65.9, 72.4, 115.9, 116.1,116.79, 118.0, 120.1, 120.4, 122.6, 122.8, 123.1, 124.7, 125.7, 127.1, 128.1, 128.5, 129.6,129.7, 130.3, 137.4, 141.6, 146.6, 150.9, 151.4, 163.8, 164.4, 164.6; GC-MS m/z 698.26 [M^+]; Analysis calculated for $C_{38}H_{34}N_8O_6$: C, 65.32; H, 4.90; N, 16.04%. Found: C, 65.71; H, 4.21; N, 16.52%.

4.9.11 1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) amino) phenyl)-2-(3-nitrophenyl) spiro[azetidine-3,9'-xanthen]-4-one (**8k**)

White solid; Mp. 269-271 °C; IR (KBr, cm^{-1}) 3417, 2854, 1751 (CO β-lactam), 1573, 1514; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.59-3.65 (16H, m, 8×CH_2), 5.59 (1H, s, H-4), 6.87-7.09 (6H, m, ArH), 7.30-7.42 (7H, m, ArH), 7.73 (2H, s, ArH), 7.92 (1H, s, ArH), 9.21 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO) δ 43.2, 63.1, 65.9, 71.9, 116.5, 117.9, 120.1, 121.2, 122.6, 122.8, 123.5, 124.7, 125.4, 125.7, 127.1, 128.0, 128.3, 129.7, 130.1, 130.3, 133.3, 136.3, 137.4, 147.1, 151.0, 151.5, 163.8, 164.3, 164.6; GC-MS m/z 698.26 [M^+]; Analysis calculated for $C_{38}H_{34}N_8O_6$: C, 65.32; H, 4.90; N, 16.04%. Found: C, 65.61; H, 4.38; N, 15.74%.

4.9.12 2-(4-chlorophenyl)-1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) amino) phenyl) spiro[azetidine-3,9'-xanthen]-4-one (**8l**)

White solid; Mp. 273-275 °C; IR (KBr, cm^{-1}) 3417, 2854, 1751 (CO β-lactam), 1504; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.42-3.67 (16H, m, 8×CH_2), 5.33 (1H, s, H-4), 6.87 (1H, d, J = 5 Hz, ArH), 6.95 (4H, t, J = 7.5 Hz, ArH), 7.02 (1H, d, J = 7.5 Hz, ArH), 7.08 (1H, d, J = 7.5 Hz, ArH), 7.12-7.17 (2H, m, ArH), 7.25 (2H, t, J = 8.5 Hz, ArH), 7.33-7.39 (3H, m, ArH), 7.45 (1H, d, J =

7.5 Hz, ArH), 7.70 (1H, d, *J* = 7.5 Hz, ArH), 9.20 (1H, s, N-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.3, 62.8, 65.9, 72.6, 116.5,116.8, 118.0, 120.1, 120.8, 122.6, 122.7, 123.5, 124.6, 125.4,125.7, 127.1, 128.0, 128.5, 129.4,129.6, 130.1,132.2,132.7, 137.2, 151.2, 163.8, 164.5, 164.6; GC-MS m/z = 687.24 [M$^+$]; Analysis calculated for $C_{38}H_{34}ClN_7O_4$: C, 66.32; H, 4.98; N, 14.25%. Found: C, 66.07; H, 5.04; N, 14.61%.

4.9.13 4-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) oxy) phenyl)-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (**10a**)

White solid; Mp. 193-195 °C; IR (KBr, cm^{-1}) 2962, 2916, 2854, 1759 (CO β-lactam), 1573, 1504; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.32-3.66 (16H, m, 8×CH_2), 3.68 (3H, s, OCH_3), 5.71 (1H, d ,*J* =.5 Hz, H-4), 5.81 (1H, d ,*J* =.5 Hz, H-3) 6.81 (2H, d ,*J* = 7.5 Hz, ArH), 6.88-6.93 (3H, m, ArH), 7.03 (2H, d, *J* = 7.5 Hz, ArH), 7.16 (2H, d, *J*= 7.5 Hz ArH), 7.20 (1H, d, *J*= 4.5 Hz, ArH), 7.25 (1H, d, *J*= 7.5 Hz, ArH), 7.33 (1H, d, *J*= 7.5 Hz, ArH), 7.23 (2H, d, *J*= 10.0 Hz, ArH), 7.37 (2H, d, *J*= 10.0 Hz, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.3, 55.2, 60.4, 65.7, 80.6, 114.4, 115.1, 118.4, 121.6, 128.9, 129.3, 129.7, 129.9, 152.0, 155.9, 156.5, 162.0, 165.4, 170.3; GC-MS m/z 610.25 [M$^+$]; Analysis calculated for $C_{33}H_{34}N_6O_6$: C, 64.91; H, 5.61; N, 13.76%. Found: C, 65.12; H, 5.83; N, 13.36%.

4.9.14 3-(4-chlorophenoxy)-4-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) oxy) phenyl)-1-(4-methoxyphenyl) azetidin-2-one (**10b**)

White solid; Mp. 203-205 °C; IR (KBr, cm^{-1}) 2962, 2854, 1743 (CO β-lactam), 1581; ^{1}H-NMR (250 MHz, DMSO-d_6) δ 3.33-3.62 (16H, m, 8×CH_2), 3.76 (3H, s, OCH_3), 5.70 (1H, d, *J* = 4.5 Hz, H-4), 5.81 (1H, d, *J* = 4.5 Hz, H-3), 6.86 (4H, t , *J* = 10.0 Hz, ArH), 7.20-7.24 (4H, m, ArH), 7.35 (2H, d, *J* = 7.5 Hz, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.2, 55.2, 60.2, 65.7, 80.6, 114.5, 116.7, 118.5, 122.6, 125.5, 128.9, 129.0, 129.5, 129.9, 129.9, 152.0, 155.2, 155.9, 161.5, 165.3, 170.3; GC-MS m/z 644.22 [M$^+$]; Analysis calculated for $C_{33}H_{33}ClN_6O_6$: C, 61.44; H, 5.16; N, 13.03%. Found: C, 61.12; H, 5.42; N, 13.35%.

4.9.15 3-(2,4-dichlorophenoxy)-4-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) oxy) phenyl)-1-(4-methoxyphenyl) azetidin-2-one (**10c**)

White solid; Mp. 269-267 °C; IR (KBr, cm^{-1}) 2962, 2923, 2854, 1735 (CO β-lactam), 1620, 1573,

1504; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 3.47-3.64 (16H, m, 8×CH_2), 3.76 (3H, s, OCH_3), 5.40 (1H, d, *J* = 5.0 Hz, H-4), 5.49 (1H, d , *J* = 5.0 Hz, H-3) 6.81 (2H, d , *J* = 10.0 Hz, ArH), 7.12-7.23 (5H, m, ArH), 7.31 (2H, d, *J* = 10.0 Hz, ArH), 7.40 (2H, d, *J*= 10.0 Hz ArH; ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.7, 55.4, 61.1, 66.6, 81.8, 114.4, 116.8, 118.9, 122.1, 125.4, 127.5, 127.6, 128.8, 128.9, 129.9, 130.1, 151.6, 152.9, 156.7, 161.7, 166.0, 170.7; GC-MS m/z 678.18 [M^+]; Analysis calculated for $C_{33}H_{32}Cl_2N_6O_6$: C, 58.33; H, 4.75; N, 12.37%. Found: C, 58.69; H, 4.32; N, 12.73%.

4.9.16 4-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) oxy) phenyl)-1-(4-ethoxyphenyl)-3-phenoxyazetidin-2-one (**10d**)

White solid; Mp. 218-220 °C; IR (KBr, cm^{-1}) 2970, 2908, 2854, 1759 (CO β-lactam), 1573, 1504; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.26 (3H, t, *J* =.7.5 Hz, OCH_3) 3.34-3.62 (16H, m, 8×CH_2), 3.93 (2H, q, *J* = 7.0 Hz, CH_2), 5.70 (1H, d ,*J* = 4.8 Hz, H-4), 5.80 (1H, d , *J* = 4.8 Hz, H-3) 6.80 (2H, d ,*J* = 7.5 Hz, ArH), 6.81-6.93 (3H, m, ArH), 7.03 (2H, d, *J* = 10.0 Hz, ArH), 7.15-7.23 (4H, m, ArH), 7.36 (2H, d, *J*= 7.5 Hz ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.55, 43.1, 60.4, 63.1, 65.7, 80.6, 114.9, 115.0, 118.4, 121.6, 121.8, 128.9, 129.2, 129.7, 129.8, 152.0, 155.2, 156.5, 162.0, 165.3, 170.3; GC-MS m/z 624.27 [M^+]; Analysis calculated for $C_{34}H_{36}N_6O_6$: C, 65.37; H, 5.81; N, 13.45%. Found: C, 65.11; H, 5.32; N, 13.78%.

4.9.17 3-(4-chlorophenoxy)-4-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) oxy) phenyl)-1-(4-ethoxyphenyl) azetidin-2-one (**10e**)

White solid; Mp. 204-206 °C; IR (KBr, cm^{-1}) 2923, 1743 (CO β-lactam), 1589, 1496; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.26 (3H, t ,*J* = 7.5 Hz, OCH_3), 3.34-3.82 (16H, m, 8×CH_2), 3.93 (2H, q *J* = 7.5 Hz, CH_2), 5.71 (1H, d, *J* = 5.0 Hz, H-4), 5.82 (1H, d, *J* = 5.0 Hz, H-3), 6.83-6.90 (4H, m, ArH), 7.04 (2H, d, *J* = 7.5 Hz, ArH), 7.19-7.25 (4H, m, ArH),7.36 (2H, d, *J* = 10.0 Hz ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.55, 43.2, 60.2, 63.1, 65.7, 80.6, 114.9, 116.7, 118.5, 121.6, 125.5, 128.9, 129.5, 129.7, 152.0, 155.2, 155.3, 161.5, 165.3, 170.3; GC-MS m/z 658.23 [M^+]; Analysis calculated for $C_{34}H_{35}ClN_6O_6$: C, 61.96; H, 5.35; N, 12.75%. Found: C, 62.1; H, 5.63; N, 12.23%.

4.9.18 2-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl) oxy) phenyl)-1-(4-methoxyphenyl) spiro[azetidine-3,9'-xanthen]-4-one (**10f**)

White solid; Mp. 232-234 °C; IR (KBr, cm^{-1}) 2970, 2900, 2854, 1751 (CO β-lactam), 1573, 1504; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.43-3.71 (16H, m, 8×CH_2), 3.76 (3H, s, OCH_3), 5.35 (1H, s , H-4), 6.91 (3H, d, *J* = 5.0 Hz), 6.99 (4H, t, *J* = 5.0 Hz, ArH), 7.05 (1H, d, *J* = 5.0 Hz, ArH), 7.15 (1H, d, *J* =7.5 Hz, ArH), 7.20 (1H, d, *J* = 7.5 Hz, ArH), 7.30 (2H, d, *J*= 7.5 Hz, ArH), 7.35 (1H, d, *J* = 4.5 Hz, ArH), 7.43 (2H, d, *J* = 5.0 Hz, ArH), 7.47 (1H, d, *J* = 4.8 Hz, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.3, 55.3, 62.8, 65.7, 73.0, 114.5, 115.9, 116.6, 119.2, 121.1, 121.3, 122.7, 124.5, 125.7, 127.5, 128.8, 129.1, 129.5, 129.9, 151.0, 151.4, 151.5, 156.2, 164.7, 165.4, 170.0; GC-MS m/z 684.27 [M^+]; Analysis calculated for $C_{39}H_{36}N_6O_6$: C, 68.41; H, 5.30; N, 12.27%. Found: C, 68.74; H, 5.12; N, 12.67%.

4.9.19 1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl)amino)phenyl)-4-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl)oxy)phenyl)-3-phenoxyazetidin-2-one (**12a**)

White solid; Mp. 263-265 °C; IR (KBr, cm^{-1}) 2854, 1759 (CO β-lactam), 1612, 1573, 1504; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.55-3.62 (16H, m, 8×CH_2), 3.66-3.67 (16H, m, 8×CH_2), 5.72 (1H, d, *J* = 4.8 Hz, H-4), 5.83 (1H, d, *J* = 4.8 Hz, H-3) 6.83 (2H, d, *J* = 8.0 Hz, ArH), 6.92 (1H, t, *J* = 7.6 Hz, ArH), 7.05 (2H, d, *J* = 12.0 Hz, ArH), 7.21 (4H, t, *J* =8.8 Hz, ArH) 7.37 (2H, d, *J* = 8.8 Hz, ArH), 7.64 (2H, d, *J*= 8.8 Hz, ArH), 9.18 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.2, 60.2, 65.9, 80.4, 115.0, 117.3, 119.9, 121.6, 121.8, 126.7, 128.9, 129.3, 136.8, 151.9, 152.9, 156.5, 162.0, 163.8, 165.3, 170.3; GC-MS m/z 844.38 [M^+]; Analysis calculated for $C_{43}H_{48}N_{12}O_7$: C, 61.13; H, 5.73; N, 19.89%. Found: C, 60.84; H, 5.13; N, 19.27%.

4.9.20 3-(4-chlorophenoxy)-1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl)amino)phenyl)-4-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl)oxy)phenyl)azetidin-2-one (**12b**)

White solid; Mp. 275-277 °C; IR (KBr, cm^{-1}) 2854, 1751 (CO β-lactam), 1573, 1504; ^{1}H NMR (400 MHz, $CDCl_3$): 3.73 (16H, d, *J* = 4.4 Hz, 8×CH_2), 3.75 (16H, d, *J* = 4.8 Hz, 8×CH_2), 5.45 (1H, d, *J* = 4.8 Hz H-4), 5.51 (1H, d, *J* = 4.8 Hz, H-3) 6.72 (1H, s, N-H) 7.15 (1H, s, ArH), 7.17 (1H, d, *J* = 2.0 Hz, ArH), 7.21 (2H, d, *J* = 8.4 Hz, ArH), 7.26 (1H, d, *J* = 2.0 Hz, ArH), 7.35 (3H, d, *J*= 8.8 Hz, ArH), 7.43 (2H, d , *J* = 8.4 Hz, ArH), 7.50 (2H, d , *J* = 8.8 Hz, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.6, 60.7, 66.9, 81.2, 115.7, 118.0, 120.1, 122.2, 123.5, 128.6, 129.6, 129.8, 135.3, 150.7, 155.9, 160.7, 163.1, 164.7, 165.2, 170.7; GC-MS m/z 878.34 [M^+]; Analysis calculated for $C_{43}H_{47}ClN_{12}O_7$: C, 58.73; H, 5.39; N, 19.11%. Found: C, 59.04; H, 5.01; N, 19.77%.

4.9.21 3-(2,4-dichlorophenoxy)-1-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl)amino)phenyl)-4-(4-((4,6-dimorpholino-1,3,5-triazin-2-yl)oxy)phenyl)azetidin-2-one (**12c**)

White solid; Mp. 285-287 °C; IR (KBr, cm^{-1}) 2854, 1751 (CO β-lactam), 1612, 1573, 1504; ^1H NMR (400 MHz, $CDCl_3$) δ 3.75-3.78 (32H, m, 16×CH_2), 5.42 (1H, d , *J* = 4.4 Hz, H-4), 5.57 (1H, d , *J* = 4.4 Hz, H-3), 6.88 (1H, s ,NH), 6.95 (1H, t, *J* = 7.2 Hz, ArH), 7.13 (2H, d, *J* = 8.4 Hz, ArH), 7.19 (2H, t, *J* =7.6 Hz, ArH), 7.35 (2H, d, *J* = 8.8 Hz, ArH), 7.40 (2H, d, *J* = 8.0 Hz, ArH), 7.49 (2H, d , *J* = 8.4 Hz, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 43.7, 61.7, 66.8, 81.4, 115.7, 117.9, 120.1, 121.9, 122.50,122.3 128.6, 129.3, 131.6, 136.3, 152.8, 155.9, 157.0 162.5, 164.1, 165.1, 165.9, 170.8; GC-MS m/z 912.30 [M^+]; Analysis calculated for $C_{43}H_{46}Cl_2N_{12}O_7$: C, 56.52; H, 5.07; N, 18.39%. Found: C, 56.84; H, 5.41; N, 18.97%.

4.10: DPPH radical-scavenging activity assay

For evaluating radical-scavenging activity, the diphenylpicrylhydrazyl (DPPH) scavenging assay was performed as described previously. [58-60] Briefly, a suitably dilution of test compound (0.05 ml) (dissolved in DMSO) was mixed with a solution of DPPH in methanol (A_{517} = 1.0; 2.95 ml) and the UV absorbance at 517 nm was measured for 5 min. Percent radical scavenging was calculated as 100 × (A_{start} - A_{end})/(A_{start}), where A_{start} is the absorbance before addition of test compound and A_{end} is the absorbance value after 5 min of reaction time.

4.11: Antiproliferative activity assay

The antiproliferative activity assay was carried out as described by Rowan et al. [68] with slight modifications. The HepG2 and SW 1116 cell lines were used in which the cell monolayers were seeded at 5×10^4 cells per well (in RPMI 1640 medium plus 10% fetal calf serum) in a 96-well plate. Various concentration of tested compounds (5,10, 50, 100 and 200 μM) were prepared and inoculated into the cell monolayer and repeated in triplicate for each compound. Monolayers containing the tested compounds were incubated overnight at 37 °C in a 5% CO_2 atmosphere. After overnight incubation, the suspension from each well was discarded and 25 μl of fresh complete medium (RPMI+10% fetal calf serum) containing 0.004 g/ml of MTT reagent (Sigma, Ronkonkoma, NY, USA) was added. Samples were incubated for 3 hours at 37 °C in 5% CO_2 and the formazan product was solubilized by the addition of 100 ml of DMSO. Optical densities of the

suspensions were measured at 540 nm using an ELISA reader (Biotek, Power Wave, Winooski, VT, USA). The absorbance (optical density) was measured and percentage inhibition or percentage cell death was calculated. Doxorubicin was used as a reference positive control compound. The results of the MTT assay are expressed as mean IC_{50} values.

4.12: UV-Visible spectroscopy

Calf thymus DNA (CT-DNA) and all reagents and materials were purchased from Sigma-Aldrich. Experiments were done in 50 mM Tris–HCl buffer containing 100 mM NaCl, pH 7.4. CT-DNA stock solution was prepared by dissolving the solid DNA into doubly-distilled water overnight, and stored at 4 ^{o}C in the dark for no more than one week. The concentration of CT-DNA was determined by absorption spectrometry, using its known extinction coefficient at 260 nm (6600 M^{-1} cm^{-1}) [70]. Solutions of CT-DNA in Tris–HCl buffer gave a ratio of UV absorbance at 260 and 280 nm (A_{260}/A_{280}) of 1.8-1.9, showing that DNA is sufficiently protein-free. [55] The stock solutions of compound **7b** (68 μM), **8g, 8l,** and **8f** (40 μM) were prepared by dissolving their powder into suitable amounts of DMSO solutions. All spectroscopic measurements were done at 25 ºC and 2 min after addition of the test compounds.

Conflict of interest

The authors declare that they have no conflict of interest.

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Notes

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Abbreviations
MTT, Methyl Thiazol Tetrazolium bromide; IC50, Half Maximal Inhibitory Concentration; ORTEP, Oak Ridge Thermal Ellipsoid Plot; CK2, Casein kinase 2; PDB, Protein Data Bank; RMSD, Root-Mean-Square Deviation; CLogP, Calculation LogP; OD, Optical Density.

Appendix A. Supplementary data
Electronic Supplementary Information (ESI) available: Spectra for new compounds (IR, ^{1}H NMR, ^{13}C NMR spectral data), crystallographic data and structure determination and General experimental methods**.**

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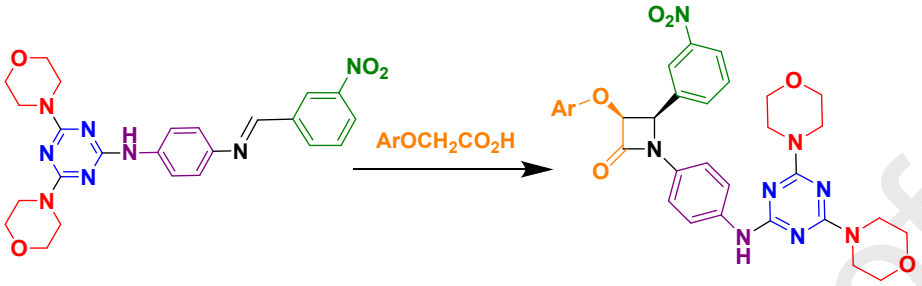

IC_{50} = 1.98 μM against SW 1116 (colon) cell line.

Conflict of interest

The authors declare that they have no conflict of interest.