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Synthesis and anticancer activity evaluation of benzo[6,7]oxepino[3,2-*b*] pyridine derivatives

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ABSTRACT

A cascade reaction of 3-hydroxy-2-methylpyridine 1-oxide and substituted 2-fluorobenzal-dehydes involving nucleophilic aromatic substitution (S_NAr) and Knoevenagel condensation has been developed. This reaction provided easy access to benzo[6,7]oxepino[3,2-*b*]pyridine 1-oxide derivatives in moderate to good yields. Subsequent reduction of these compounds provided their deoxygenated forms in good to excellent yields. Moreover, some of the synthesized compounds were found to be active against human colorectal cancer cells (HCT-116 cell lines) with IC_{50} values in the range of 24.95–45.80 μM.

1. Introduction

Dibenzo[*b,f*]oxepine (**1**) (Fig. 1) is an important framework in medicinal chemistry. It can be found in the core structure of several bioactive natural products. For example, bauhinoxepin A (**3**) and bauhinoxepin B (**4**) isolated from the roots of *Bauhinia saccocalyx* displayed significant antimycobacterial activity [1]. Pacharin (**5**) and bauhiniastatins 2–3 (**6**–**7**) isolated from the roots of *Bauhinea purpurea* were found to exhibit significant growth inhibition against several human cancer cell lines [2].

There are several methods to prepare substituted dibenzo[*b,f*] oxepines. For example, the Ullmann-type coupling reaction has been used to form biaryl ethers [3], which can subsequently undergo ring-closing metathesis [3a,4] or the Friedel-Crafts acylation to form the seven-membered ring [3b,3c,5]. The combination of nucleophilic aromatic substitution reaction (S_NAr) and palladium-catalyzed coupling reaction [6] or the Friedel-Crafts acylation [7] can also be used to synthesize dibenzo[*b,f*]oxepine scaffolds. Other methods include the Wagner-Meerwein rearrangement [8], intramolecular McMurry reaction [9], manganese(III)based oxidative 1,2-radical rearrangement [10], and sequential Heck reaction and palladium-catalyzed cyclization [11].

Benzo[6,7]oxepino[3,2-*b*]pyridine (**2**) is an analog of compound **1**, in which a carbon atom at the 1 position is replaced by a nitrogen. There are only two methods available to synthesize benzo[6,7] oxepino[3,2-*b*]pyridine derivatives [12]. For example, pyridines **10a**–**10c** were prepared in three steps from 3-bromo-6-methoxypicolinaldehyde (**8**) and phosphate esters **9a**–**9c** (Scheme 1) [12a,12b].

These syntheses began with a Horner-Wadsworth-Emmons (HWE) reaction (47–51% yields) followed by removal of the MOM protecting group (75–88% yields) and finally an Ullmann coupling reaction (31–64% yields). The other method used the intramolecular Friedel-Crafts alkylation-dehydration reaction to form the seven-membered ring of a tetracyclic product, whose structure is quite different from our target [12c].

We became interested in the synthesis of benzo[6,7]oxepino [3,2-*b*]pyridine derivatives because we envisioned that they could be synthesized in one pot from 3-hydroxy-2-methylpyridine (**11**)

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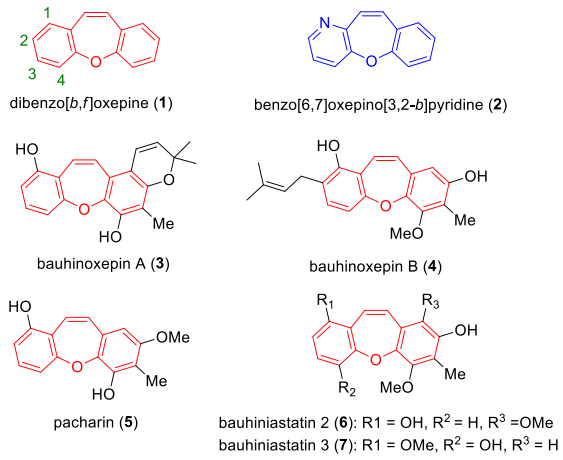
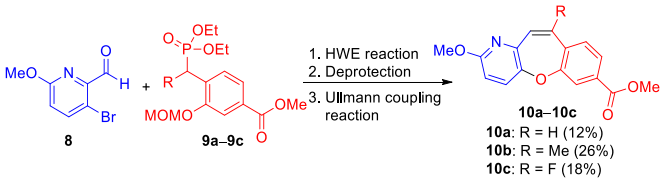


Fig. 1. Structures of dibenzo[*b*,*f*]oxepine (**1**), benzo[6,7]oxepino[3,2-*b*] pyridine (**2**) and natural products containing the dibenzo[*b*,*f*]oxepine core structure.

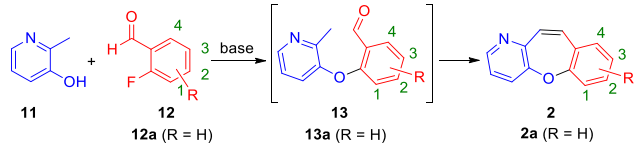


Scheme 1. A known method to synthesize benzo [6,7]oxepino[3,2-*b*] pyridine derivatives.

and substituted 2-fluorobenzaldehydes **12** (Scheme 2). It has been known that the methyl (–CH_3) group of 2-methylpyridine (pK_a = 34) [13] is more acidic than that of toluene (pK_a = 41) [14] because the C=N double bond adjacent to the methyl group can act as an electron-withdrawing group, thus increasing the acidity of this methyl group. Therefore, with a suitable base, we expected that an intermolecular nucleophilic aromatic substitution reaction would occur first to give biaryl ethers **13**, which would then undergo an intramolecular Knoevenagel condensation reaction to give desired compounds **2**.

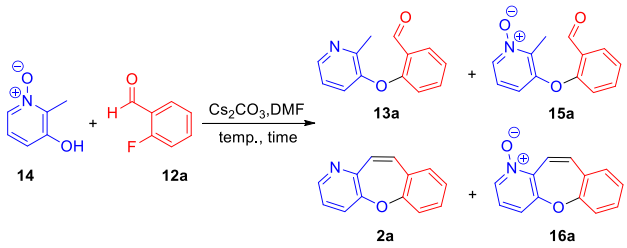
2. Results and discussion

We previously employed Cs_2CO_3 as a base in DMF at elevated temperatures for this type of transformation when we synthesized substituted indolo[1,2-*a*]quinolines [15]. Therefore, we began our studies by heating a mixture of 3-hydroxy-2-methylpyridine (**11**), 2-fluorobenzaldehyde (**12a**), and Cs_2CO_3 in DMF at 120 °C. After 1 h, the corresponding biaryl ether **13a** was obtained in 94% yield. Unfortunately, the seven-membered ring of benzo[6,7]oxepino[3,2-*b*] pyridine (**2a**) could not be formed even when the reaction mixture was heated at reflux (153 °C) for 24 h. We also attempted to use a two-step protocol by treating intermediate **13a** with stronger bases such as KOH or LiOH in DMF at elevated temperatures, but no



Scheme 2. Proposed one-pot synthesis of benzo[6,7]oxepino[3,2-*b*]pyridine and its derivatives.

Table 1
Optimization of reaction conditions by varying temperature and time.[a]



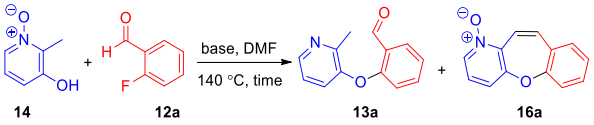
Entry	Temp. (°C)	Time (h)	Yield (%)[b]			
			13a[c]	**15a**	**2a**	**16a**
1	rt.	24[d]	6	3	0	2
2	60	24[d]	10	5	0	18
3	90	12[e]	–	0	0	56
4	120	4[e]	8	0	0	60
5	140	4[e]	–	0	0	66
6	153	4[e]	–	0	0	51
7	120	24	–	0	0	56
8	140	24	–	0	0	46
9	153	24	–	0	36	trace

[a] Reaction conditions: **14** (0.80 mmol), **12a** (1.30 mmol), Cs_2CO_3 (2.90 mmol), DMF (3 mL).
[b] Isolated yields.
[c] For entries 3 and 5–9, a small amount of compound **13a** was still observed by TLC analysis but it was not isolated.
[d] Compound **14** was not completely consumed.
[e] The reaction was terminated after compound **14** was completely consumed.

reaction took place. Treatment of intermediate **13a** with LHMDS in THF also resulted no reaction after 24 h (−78 °C to rt). Treating intermediate **13a** with LDA or *n*-BuLi for 24 h (−78 °C to rt) or heating it with ^{t}BuOK in DMSO at 100 °C for 1 h resulted in complex mixtures of unidentified products. Surprisingly, when the reaction was carried out with NaH in THF at 60 °C for 18 h, the formyl group (–CHO) of compound **13a** was reduced to the corresponding alcohol (35% yield). The identity of this alcohol was unambiguously confirmed by reducing compound **13a** with $NaBH_4$.

To overcome the difficulty of cyclization, 3-hydroxy-2-methylpyridine (**11**) was then oxidized with *m*CPBA to form the more reactive 3-hydroxy-2-methylpyridine 1-oxide (**14**) (87% yield) [16]. The *N*-oxide functionality of this compound can act as an electron-withdrawing group, thus increasing the acidity of the adjacent methyl group, which in turn would facilitate the desired cyclization. The reaction of *N*-oxide **14** with 2-fluorobenzaldehyde (**12a**) was initially performed with Cs_2CO_3 as a base and DMF as a solvent (Table 1). At room temperature, most of starting material **14** still remained after 24 h (entry 1). Fortunately, benzo[6,7]oxepino[3,2-*b*]pyridine 1-oxide (**16a**) was obtained, albeit in a very low yield (2%). In addition, uncyclized intermediate **15a** and its deoxygenated form (**13a**) were also obtained in 3% and 6% yields, respectively. When the temperature was raised to 60 °C (entry 2), the yield of **16a** increased to 18%, but compounds **13a**, **14** and **15a** were still present after 24 h. When the reaction was performed at 90 °C for 12 h (entry 3), **14** was completely consumed, and the desired product was obtained in 56% yield. When the temperature was raised to 120 °C and 140 °C (entries 5–6), the reaction rate was greatly accelerated. Both of the reactions went to completion within 4 h, and the yields of **16a** were improved to 62% and 66%, respectively. However, when the temperature was raised above 140 °C, the yield dropped to 51% as shown in entry 6. The deoxygenation of *N*-heteroarene *N*-oxides under basic conditions at an elevated temperature (160 °C) has been reported by Bjørsvik and

Table 2
Optimization of reaction conditions by varying base and time.[a]

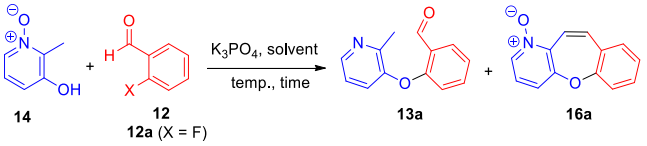


14 12a 13a 16a

Entry	Base	Time (h)[b]	Yield (%)[c]	
			13a[d]	16a
1[e]	Li_2CO_3	4	0	0
2	Na_2CO_3	4	20	0
3	K_2CO_3	4	–	20
4	Cs_2CO_3	4	–	66
5	KOH	2	–	30
6	^tBuOK	8	–	6
7	K_3PO_4	2	11	73
8[e]	Et_3N	4	0	0
9[e]	DBU	2	0	0

[a] Reaction conditions: **14** (0.80 mmol), **12a** (1.30 mmol), base (2.90 mmol), DMF (3 mL).
[b] The reaction was terminated after compound **14** was completely consumed.
[c] Isolated yields.
[d] For entries 3–6, a small amount of compound **13a** was still observed by TLC analysis but it was not isolated.
[e] A complex mixture of unidentified products was obtained.

Table 3
Optimization of reaction conditions by varying leaving group, solvent, temperature and time.[a]



14 12 12a (X = F) 13a 16a

Entry	X	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	
					13a	16a
1	F	DMF	140	2[c]	11	73
2	Cl	DMF	140	18[d]	8	6
3	Br	DMF	140	18[d]	15	13
4	I	DMF	140	18[d]	1	7
5	F	DMF	120	6[c]	12	52
6	F	DMSO	140	4[c]	7	49
7	F	dioxane	101[f]	24[d]	8	0
8	F	toluene	111[f]	24[d]	5	0
9[e]	F	acetonitrile	82[f]	24[d]	0	0

[a] Reaction conditions: **14** (0.80 mmol), **12** (1.30 mmol), K_3PO_4 (2.90 mmol), solvent (3 mL).
[b] Isolated yields.
[c] The reaction was terminated after compound **14** was completely consumed.
[d] Compound **14** was not completely consumed.
[e] A complex mixture of unidentified products was obtained.
[f] Reflux temperature.

coworkers [17]. Therefore, we also attempted to repeat the reactions in entries 4–6 with longer reaction times to deoxygenate compound **16a** to product **2a**. The reactions performed at 120 °C and 140 °C for 24 h still provided compounds **16a** in slightly lower yields (entries 7–8) compared to those performed for 4 h. Fortunately, compound **2a** was obtained when the reaction was performed at reflux for 24 h (entry 9). However, the reaction yield was low (36%) because decomposition also occurred. Therefore, we turned our goal to first synthesize **16a** since it was formed much faster and in a much higher yield than **2a**. Compound **16a** would then be reduced to **2a** in a subsequent step.

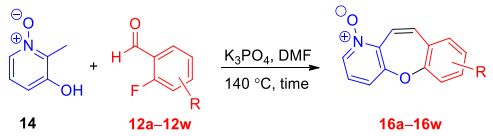
In addition to product **16a** or **2a**, a small amount of by-product **13a** also formed in entries 3–9 as indicated by TLC analysis but we only attempted to isolate this by-product from the reaction performed at 120 °C for 4 h (8%, entry 4). We assumed that this compound was formed from the deoxygenation of intermediate **15a** or the reaction between compound **11**, generated from the deoxygenation of **14**, and **12a**.

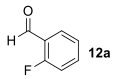
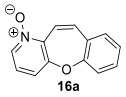
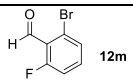
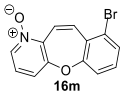
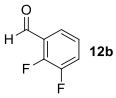
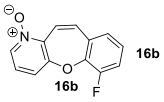
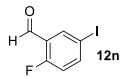
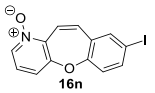
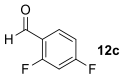
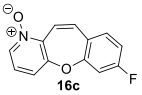
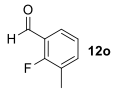
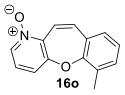
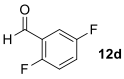
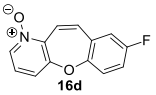
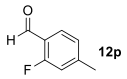
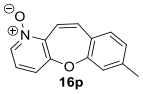
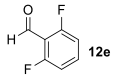
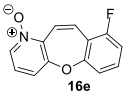
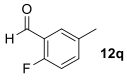
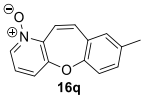
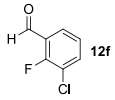
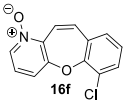
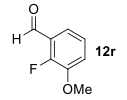
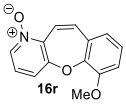
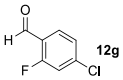
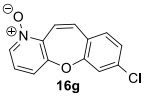
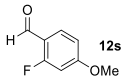
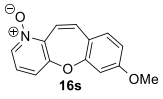
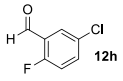
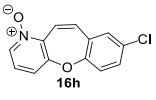
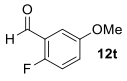
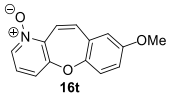
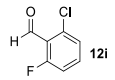
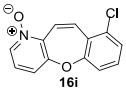
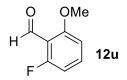
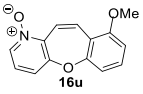
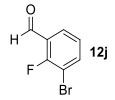
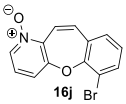
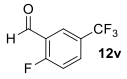
Then, various bases were investigated in order to search for the optimal conditions (Table 2). For this study, the solvent employed was DMF, and the temperature was selected as 140 °C since it provided the desired product with the highest yield in Table 1. We first attempted to replace Cs_2CO_3 with Li_2CO_3, Na_2CO_3 and K_2CO_3 (entries 1–3) but Cs_2CO_3 still gave the best result (entry 4). Other stronger bases such as KOH and ^tBuOK gave disappointing results (entries 5 and 6, respectively) possibly because HO^- could act as a nucleophile in a competing S_NAr reaction and $^tBuO^-$ was too bulky for this transformation. Surprisingly, the use of K_3PO_4 (entry 7) gave a better yield (73%) in a shorter reaction time compared to the use of Cs_2CO_3. This could be due to the fact that K_3PO_4 (pK_a of HPO_4^{2-} = 12.32) is a stronger base than Cs_2CO_3 (pK_a of HCO_3^- = 10.33) [18]. Although the improvement was not significant, K_3PO_4 is much cheaper than Cs_2CO_3. Therefore, K_3PO_4 was selected as the best base for further optimization. It should be noted that by-product **13a** still formed (11% yield) with the use of K_3PO_4. Organic bases such as Et_3N and DBU were also employed. Unfortunately, they only gave complex mixtures of unidentified products.

Next, we investigated the effect of leaving groups by performing the reaction with K_3PO_4 as a base and DMF as solvent (entries 1–4 in Table 3). Since the reactivity of the benzaldehyde in the S_NAr reaction depends on the polar effect, replacing the fluorine atom of 2-fluorobenzaldehyde (**12a**) with a chlorine, bromine or iodine atom gave lower yields as expected. We also tried to lower the temperature to 120 °C (entry 5), but the product yield decreased quite dramatically. Then, we tried to replace DMF with DMSO, dioxane, toluene and acetonitrile (entries 6–9). Among these solvents, we found that only DMSO gave the desired product in a moderate yield (49%). Therefore, DMF was still the best solvent for this transformation. We also attempted to expand the scope of this reaction by replacing the aldehyde with less electrophilic substrates: a ketone and an ester. For this purpose, a mixture of **14** and 2′-fluoroacetophenone in the presence of K_3PO_4 in DMF was heated at 140 °C for 24 h (see supporting information). This reaction proceeded very slowly and only the S_NAr reaction took place to give the corresponding biaryl ether *N*-oxide and its deoxygenated form in very low yields (15% and 11%, respectively). When 2′-fluoroacetophenone was replaced with methyl 2-fluorobenzoate, the corresponding biaryl ether *N*-oxide and its deoxygenated form were obtained in only trace amounts (1% and 4% yields, respectively). Because of these disappointing results, we only focused on using benzaldehydes as a starting material.

With the optimized reaction conditions in hand, benzo[6,7]oxepino[3,2-*b*]pyridine 1-oxide analogs were then synthesized from various substituted 2-fluorobenzaldehydes (Table 4). The reactions were performed in DMF at 140 °C in the presence of K_3PO_4 as a base. As shown in entries 1–2 and 4–23, most of the reactions gave substituted benzo[6,7]oxepino[3,2-*b*]pyridine 1-oxides (**16a–16b** and **16d–16w**) in moderate to good yields. In entry 3, where 2,4-difluorobenzaldehyde was employed, the desired pyridine 1-oxide (**2c**) was obtained in a very low yield (2%). Our attempt to improve the reaction yield by replacing K_3PO_4 with Cs_2CO_3 was unsuccessful. The presence of an additional fluorine atom at the para position relative to the carbonyl group lowered the reaction yield. This was presumably because this fluorine atom could act as a leaving group in a competing S_NAr reaction, thus producing a biaryl ether intermediate that could not be cyclized to a seven-membered

Table 4
Synthesis of substituted benzo [6,7]oxepino[3,2-*b*]pyridine 1-oxides.[a]



Entry	Benzaldehyde	Time (h)	Product	Yield (%)[b]	Entry	Benzaldehyde	Time (h)	Product	Yield (%)[b]
1	 12a	2	 16a	73	13	 12m	2	 16m	55
2	 12b	4	 16b	54	14	 12n	4	 16n	58
3	 12c	4	 16c	2	15	 12o	6	 16o	49
4	 12d	3	 16d	46	16	 12p	2	 16p	40
5	 12e	2	 16e	34	17	 12q	6	 16q	57
6	 12f	4	 16f	54	18	 12r	4	 16r	65
7	 12g	2	 16g	55	19	 12s	4	 16s	71
8	 12h	2	 16h	66	20	 12t	4	 16t	29
9	 12i	2	 16i	62	21	 12u	6	 16u	58
10	 12j	2	 16j	63	22	 12v	1	16v	23
11	12k	4	16k	60	23	12w	1	16w	32
12	12l	2	16l	45					

[a] Reaction conditions: **14** (1.60 mmol), **12** (2.56 mmol), K_3PO_4 (5.76 mmol), DMF (4 mL). [b] Isolated yields.

ring. However, we were unable to isolate this intermediate to confirm our hypothesis. When benzo[6,7]oxepino[3,2-*b*]pyridine 1-oxide analogs were treated with Zn in aqueous NH_4Cl and THF, the desired deoxygenated forms (**2a**–**2b** and **2d**–**2w**) were obtained in good to excellent yields (Table 5). Due to the limited amount, the deoxygenation of **2c** was not performed. It should be noted that the nitro group (–NO_2) of **16w** was also reduced to an amino group (–NH_2) under these reaction conditions.

Moreover, we attempted to prepare benzo [6,7]oxepino[3,2-*b*] pyridine 1-oxide analogs from nitrogen-containing aromatic aldehydes (Scheme 3). In this synthesis, 2-fluorobenzaldehyde (**12a**) was replaced with 2-fluoronicotinaldehyde (**12x**), 3-fluoroisonicotinaldehyde (**12y**) or 3-fluoropicolinaldehyde (**12z**), and the corresponding oxepinodipyridine 1-oxides (**16x**–**16z**) were obtained in relatively low yields (23%, 21% and 33%, respectively). Reduction of **16x** with Zn in aqueous NH_4Cl and THF provided oxepino-dipyridine **2x** in 32% yield. Surprisingly, the C=C double bond at the 10 and 11 positions of compounds **16y** and **16z** were also reduced with this reagent to give compounds **17y** and **17z** in 69% and 39% yields, respectively (reduction of **16z** also gave **2z** in 25% yield). We proposed that compounds **16y** and **16z** were generated via intermediates **18y** and **18z**, respectively, since the nitrogen atom at the Y and Z position can stabilize a negative charge.

All of the synthesized benzo [6,7]oxepino[3,2-*b*]pyridines, their analogs and intermediates **13a** were tested against breast cancer cell lines (MCF-7 and MDA-MB-231) and colorectal cancer cell lines (HCT-116) at the Excellent Center for Drug Discovery (ECDD) (see supporting information). We found that **13a**, **16x** and **16y** could inhibit the growth of the HCT-116 cell line with IC_{50} values of 24.95, 45.80 and 45.58 μM, respectively (Table 6).

3. Conclusion

We were able to synthesize substituted benzoxepino[3,2-*b*] pyridines in 2 steps from 3-hydroxy-2-methylpyridine 1-oxide. Our successful strategy included a cascade reaction involving nucleophilic aromatic substitution (S_NAr) and Knoevenagel condensation to provide benzo [6,7]oxepino[3,2-*b*]pyridine 1-oxides and a reduction reaction of these *N*-oxide derivatives to provide benzo [6,7]oxepino[3,2-*b*]pyridines. Most of the desired products were obtained in moderate to good overall yields. Moreover, compounds **13a**, **16x** and **16y** were active against colorectal cancer cell lines (HCT-116) with IC_{50} values in the range of 24.95–45.80 μM.

4. Experimental section

4.1. General

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a 400 MHz spectrometer and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 100 MHz spectrometer using VARIANUNITY INOVA 400 spectrometer. Chemical shifts (δ) for ^{1}H NMR spectra are reported in parts per million relative to the solvent residual signal of $CDCl_3$ (δ 7.26 ppm), DMSO-d_6 (δ 2.50 ppm) or CD_3OD (δ 3.31 ppm). Chemical shifts (δ) for ^{13}C NMR spectra are reported in parts per million relative to the center line of $CDCl_3$ (δ 77.16 ppm), DMSO-d_6 (δ 39.52 ppm) or CD_3OD (δ 49.0 ppm). Multiplicities are given as the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), and br (broad). Coupling constants (*J*) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a Bruker, micro-TOPQIII spectrometer using an electrospray ionization mode (ESI) or an atomic pressure chemical ionization (APCI). HRMS data were given in *m*/*z* within a tolerance of 5 ppm of the theoretically calculated value, and measurements are given in Da. Infrared (IR) spectra were recorded on a Bruker, EQUINOX 55 Fourier transform infrared (FT-IR) spectrometer using KBr disc or NaCl. Melting points (m.p.) were determined using a melting point apparatus by hot-stage microscope from Bibby Stuart Scientific Company. All reactions were monitored by thin-layer chromatography (TLC) performed on a silica gel 60Å F_{254} aluminum sheet. Visualization of the developed chromatogram was performed by UV absorbance at 254 nm and 368 nm. Flash column chromatography was performed on silica gel F_{60} (mesh size 40–63 μm) purchased from SiliCycle Inc.

All commercially available reagents were used without further purification unless otherwise noted. All reactions were set up under a nitrogen or an argon atmosphere and anhydrous reactions were performed using flame-dried glassware and standard syringe/septum techniques. Anhydrous solvents were obtained either by filtration through molecular sieves (CH_3CN, $CHCl_3$) or by distillation over CaH_2 (CH_2Cl_2, CH_3CN, 1,4-dioxane, toluene). *N*,*N*-Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were dried over 3Å molecular sieve, for 3 days followed by distillation under high vacuum and stored over in 3Å molecular sieve. Methanol (MeOH) was distilled from magnesium under a nitrogen atmosphere. Other solvents were used from commercial bottles.

4.2. Synthesis of 2-[(2-methylpyridin-3-yl)oxy]benzaldehyde (**13a**)

To a suspension of 3-hydroxy-2-methylpyridine (**11**) (500 mg, 4.58 mmol) and Cs_2CO_3 (3.00 g, 9.17 mmol) in DMF (6 mL) was added 2-fluorobenzaldehyde (**12a**) (770 μL, 7.31 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at 120 °C for 1 h, then allowed to cool down to room temperature and diluted with water (100 mL). The resulting mixture was extracted with EtOAc (3 × 100 mL). The combined organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:3) to afford 2-[(2-methylpyridin-3-yl)oxy] benzaldehyde (**13a**) as a yellow solid (918 mg, 94% yield). R_f = 0.19 (EtOAc/hexane = 1:3); m.p. 68–70 °C; IR (KBr) 1693, 1600, 1477 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (d, J = 0.8 Hz, 1H), 8.36 (dd, J = 4.7, 1.5 Hz, 1H), 7.94 (dd, J = 7.8, 1.8 Hz, 1H), 7.50 (dd, J = 8.3, 7.3, 1.8 Hz, 1H), 7.24 (dd, J = 8.1, 1.6 Hz, 1H), 7.22–7.14 (m, 2H), 6.70 (dd, J = 8.4, 1.0 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0, 159.3, 151.6, 150.5, 145.4, 136.0, 129.1, 127.0, 126.4, 123.6, 122.5, 117.0, 19.5; HRMS (ESI) calcd for $C_{13}H_{12}NO_2^+$ $(M + H)^+$ requires 214.0863, found 214.0885.

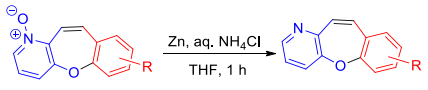
4.3. Synthesis of 3-hydroxy-2-methylpyridine 1-oxide (**14**)

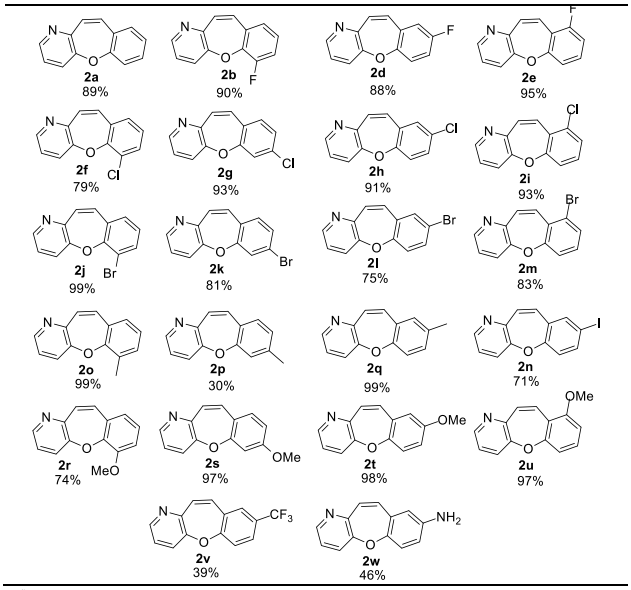
To a solution of 3-hydroxy-2-methylpyridine (**11**) (1.00 g, 9.17 mmol) in $CHCl_3$ (20 mL) was added 70–75% *m*CPBA (2.06 g, 11.92 mmol) at 0 °C. The resulting mixture was stirred vigorously at room temperature for 1 h. The desired product **14** precipitated as a white solid, which was collected by filtration and washed several times with EtOAc (998 mg, 87% yield). m.p. 182–184 °C; IR (KBr) 3391, 1570 cm^{-1}; ^{1}H NMR (400 MHz, MeOD) δ 7.92 (dd, J = 6.4, 0.5 Hz, 1H), 7.19 (dd, J = 8.3, 6.6 Hz, 1H), 7.04 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 156.0, 132.3, 124.0, 116.7, 10.6; HRMS (ESI) calcd for $C_6H_7NO_2Na^+$ $(M + Na)^+$ requires 148.0369, found 148.0388.

4.4. General procedure for the synthesis of substituted benzo [6,7] oxepino[3,2-b]pyridine 1-oxides (**16a**–**16w**)

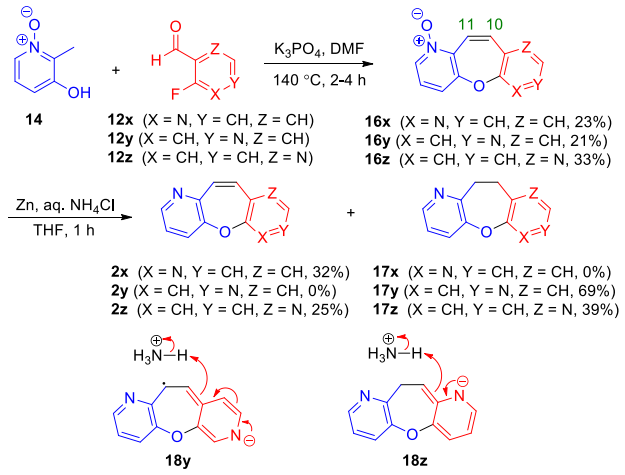
To a suspension of 3-hydroxy-2-methylpyridine 1-oxide (**14**) (200 mg, 1.60 mmol) and K_3PO_4 (1.22 g, 5.76 mmol) in DMF (4 mL)

Table 5
Reduction of substituted benzo[6,7]oxepino[3,2-*b*]pyridine 1-oxides.[a]





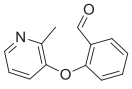
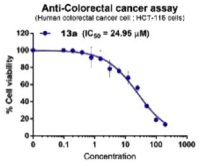
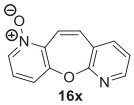
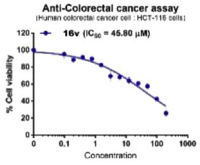
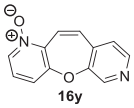
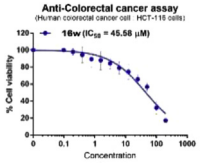
[a] Reaction condition: **16** (0.24 mmol), zinc powder (0.71 mmol), 0.2M aq. NH_4Cl (2 mL), THF (2 mL), temp. = rt, and time = 1 h.



Scheme 3. Synthesis of benzo [6,7]oxepino[3,2-*b*]pyridine 1-oxide analogs and their deoxygenated forms using nitrogen-containing aromatic aldehydes.

was added substituted 2-fluorobenzaldehyde (**12a–12w**) (2.56 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at 140 °C until **14** was completely consumed (monitored by TLC). The reaction mixture was then allowed to cool down to room temperature and diluted with water (100 mL). The resulting mixture was extracted with EtOAc (3 × 100 mL). The combined organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 3:1) to afford the desired substituted benzo [6,7]oxepino [3,2-*b*]pyridine 1-oxide

Table 6
Evaluation of anticancer activity in human colorectal cancer cells (HCT-116).[a,b]

Entry	Compound	IC_{50} (μM)
1	 13a	
2	 16x	
3	 16y	

[a] DMSO was used as vehicle in the test of all compounds.
[b] Doxorubicin was used as a positive control (IC_{50} = 6.65 μM).

(**16a–16w**): R_f (**16a–16w**) ≈ 0.15 (EtOAc/hexane = 3:1).

Benzo [6,7]*oxepino[3,2-b]pyridine 1-oxide* (***16a***): The reaction was completed in 2 h, and the desired product was obtained as a light yellow solid (247 mg, 73% yield). m.p. 182–184 °C; IR (KBr)

3073, 1597, 1481, 1425, 1249, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, J = 5.0, 2.7 Hz, 1H), 7.41–7.31 (m, 2H), 7.23 (dd, J = 7.6, 2.2 Hz, 1H), 7.20 (dd, J = 7.0, 1.2 Hz, 1H), 7.18–7.13 (m, 3H), 7.05 (d, J = 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 156.4, 136.6, 135.2, 131.2, 130.0, 129.7, 126.2, 124.3, 121.2, 121.0, 119.9; HRMS (ESI) calcd for $C_{13}H_9NO_2Na^+$ $(M + Na)^+$ requires 234.0525, found 234.0537.

*3-(2-formylphenoxy)-2-methylpyridine 1-oxide (**15a**)*: When 2-fluorobenzaldehyde (**12a**) was employed, a by-product **15a** was also isolated as a light yellow solid. R_f = 0.08 (EtOAc: hexane = 3:1); m.p. 129–131 °C; IR (KBr) 2852, 1694, 1601, 1478, 1276, 1211, 1075, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.52 (d, J = 6.3 Hz, 1H), 8.02 (dd, J = 7.7, 1.8 Hz, 1H), 7.68 (td, J = 8.4, 8.0, 1.8 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.33–7.29 (m, 1H), 7.04 (d, J = 8.5 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 156.1, 154.1, 136.3, 135.4, 131.1, 127.2, 125.9, 122.9, 119.5, 119.4, 11.6; HRMS (ESI) calcd for $C_{13}H_{11}N\ NaO_3^+$ $(M + Na)^+$ requires 252.0631, found 252.0646.

6-Fluorobenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16b**)*: The reaction was completed in 4 h, and the desired product was obtained as a light brown solid (198 mg, 54% yield). m.p. 213–215 °C; IR (KBr) 3079, 1580, 1468, 1430, 1287, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, J = 6.4, 1.2 Hz, 1H), 7.40 (d, J = 11.9 Hz, 1H), 7.33–7.28 (m, 1H), 7.24 (dd, J = 8.5, 6.4 Hz, 1H), 7.20–7.11 (m, 2H), 7.08 (dd, J = 11.9, 1.2 Hz, 1H), 7.00 (dt, J = 7.4, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9 (d, J = 82.1 Hz), 153.0, 143.6 (d, J = 12.8 Hz), 142.6, 137.0, 133.9 (d, J = 3.3 Hz), 132.3, 126.3 (d, J = 7.7 Hz), 124.7 (d, J = 3.6 Hz), 124.6, 122.1 (d, J = 0.6 Hz), 119.4, 117.9 (d, J = 19.0 Hz); HRMS (ESI) calcd for $C_{13}H_8FNO_2Na^+$ $(M + Na)^+$ requires 252.0431, found 252.0461.

*7-Fluorobenzo[6,7oxepino[3,2-b]pyridine 1-oxide (**16c**)*: The reaction was completed in 4 h, and the desired product was obtained as a white solid (5 mg, 2% yield). Since the desired product was obtained in a very small amount, ^{13}C NMR data could not be obtained. IR (KBr) 3068, 1611, 1501, 1428, 1261, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, J = 6.4, 0.9 Hz, 1H), 7.32 (d, J = 11.9 Hz, 1H), 7.24–7.13 (m, 1H), 7.18–7.15 (m, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.99 (d, J = 11.8 Hz, 1H), 6.96–6.88 (m, 2H); HRMS (ESI) calcd for $C_{13}H_8FNO_2Na^+$ $(M + Na)^+$ requires 252.0431, found 252.0436.

8-Fluorobenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16d**)*: The reaction was completed in 3 h, and the desired product was obtained as a slightly brown solid (155 mg, 46% yield). m.p. 226–228 °C; IR (KBr) 3069, 1580, 1480, 1432, 1255, 1189 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, J = 6.0, 1.7 Hz, 1H), 7.39 (d, J = 11.8 Hz, 1H), 7.25–7.18 (m, 2H), 7.14 (dd, J = 8.9, 4.7 Hz, 1H), 7.05 (dd, J = 8.9, 7.6, 3.0 Hz, 1H), 7.00 (d, J = 11.8 Hz, 1H), 6.93 (dd, J = 8.5, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (d, J = 245.1 Hz), 156.6, 152.6, 142.5, 136.8, 133.6 (d, J = 2.0 Hz), 131.3 (d, J = 8.4 Hz), 124.7, 122.7, 122.6, 118.9, 117.5 (d, J = 23.5 Hz), 116.0 (d, J = 23.9 Hz); HRMS (ESI) calcd for $C_{13}H_8FNO_2Na^+$ $(M + Na)^+$ requires 252.0431, found 252.0450.

9-Fluorobenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16e**)*: The reaction was completed in 2 h, and the desired product was obtained as a white solid (125 mg, 34% yield). m.p. 254–256 °C; IR (KBr) 3074, 1614, 1458, 1427, 1255, 1189 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 6.3 Hz, 1H), 7.39 (d, J = 12.0 Hz, 1H), 7.31 (td, J = 8.3, 6.3 Hz, 1H), 7.20 (d, J = 11.6 Hz, 1H), 7.16 (d, J = 6.4 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 8.6 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (d, J = 253.7 Hz), 158.0, 156.4, 142.8, 136.9, 131.4 (d, J = 10.3 Hz), 127.2 (d, J = 6.1 Hz), 124.7, 122.4 (d, J = 1.4 Hz), 119.1, 119.0, 117.0 (d, J = 3.5 Hz), 113.2 (d, J = 21.7 Hz); HRMS (ESI) calcd for $C_{13}H_8FNO_2Na^+$ $(M + Na)^+$ requires 252.0431, found 252.0446.

6-Chlorobenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16f**)*: The reaction was completed in 4 h, and the desired product was obtained as a brown solid (212 mg, 54% yield). m.p. 243–245 °C; IR (KBr) 3077, 1596, 1473, 1429, 1282, 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, J = 6.5, 1.0 Hz, 1H), 7.45–7.32 (m, 3H), 7.19 (dd, J = 8.4, 6.6 Hz, 1H), 7.17–7.08 (m, 2H), 7.04 (d, J = 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 151.3, 142.5, 137.0, 134.0, 131.7, 131.3, 128.2, 127.0, 126.5, 124.6, 122.1, 119.9; HRMS (ESI) calcd for $C_{13}H_8ClNO_2Na^+$ $(M + Na)^+$ requires 268.0136, found 268.0145.

7-Chlorobenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16g**)*: The reaction was completed in 2 h, and the desired product was obtained as a brown solid (216 mg, 55% yield). m.p. 218–220 °C; IR (KBr) 3079, 1595, 1480, 1432, 1288, 1195 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 6.3 Hz, 1H), 7.35 (d, J = 11.8 Hz, 1H), 7.21–7.14 (m, 4H), 7.11 (t, J = 9.0 Hz, 1H), 6.97 (d, J = 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 142.6, 136.9, 136.5, 133.6, 130.6, 128.5, 126.5, 124.5, 122.0, 121.7, 118.9; HRMS (ESI) calcd for $C_{13}H_8Cl\ NO_2Na^+$ $(M + Na)^+$ requires 268.0136, found 268.0148.

8-Chlorobenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16h**)*: The reaction was completed in 2 h, and the desired product was obtained as a brown solid (260 mg, 66% yield). m.p. 180–182 °C; IR (KBr) 3084, 1598, 1477, 1432, 1254, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, J = 6.4, 1.0 Hz, 1H), 7.38 (d, J = 11.9 Hz, 1H), 7.29 (dd, J = 8.6, 2.6 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.18–7.14 (m, 1H), 7.10 (d, J = 8.2 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H), 6.93 (d, J = 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 155.1, 142.5, 136.8, 133.3, 131.5, 131.3, 130.8, 129.5, 124.7, 122.6, 118.8; HRMS (ESI) calcd for $C_{13}H_8ClNO_2Na^+$ $(M + Na)^+$ requires 268.0136, found 268.0131.

9-Chlorobenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16i**)*: The reaction was completed in 2 h, and the desired product was obtained as a white solid (244 mg, 62% yield). m.p. 199–201 °C; IR (KBr) 3056, 1593, 1480, 1424, 1260, 1184 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 6.2 Hz, 1H), 7.43 (d, J = 12.0 Hz, 1H), 7.36 (d, J = 12.0 Hz, 1H), 7.30–7.24 (m, 2H), 7.19 (dd, J = 8.3, 6.5 Hz, 1H), 7.15–7.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 156.6, 142.5, 136.9, 134.3, 131.4, 131.1, 128.3, 127.4, 124.7, 122.5, 120.0, 118.8; HRMS (ESI) calcd for $C_{13}H_8Cl\ NO_2Na^+$ $(M + Na)^+$ requires 268.0136, found 268.0128.

6-Bromobenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16j**)*: The reaction was completed in 2 h, and the desired product was obtained as a white solid (292 mg, 63% yield). m.p. 239–241 °C; IR (KBr) 3076, 1595, 1473, 1433, 1280, 1186 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 6.3 Hz, 1H), 7.58 (dd, J = 7.9, 1.3 Hz, 1H), 7.44–7.38 (m, 2H), 7.22–7.14 (m, 2H), 7.07 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 12.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 152.4, 142.4, 136.9, 134.3, 133.9, 131.6, 129.0, 127.0, 124.5, 122.1, 119.9, 116.1; HRMS (ESI) calcd for $C_{13}H_8BrNO_2Na^+$ $(M + Na)^+$ requires 311.9631, found 311.9619.

7-Bromobenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16k**)*: The reaction was completed in 4 h, and the desired product was obtained as a brown solid (279 mg, 60% yield). m.p. 222–224 °C; IR (KBr) 3082, 1590, 1478, 1431, 1287, 1194 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J = 6.4, 0.8 Hz, 1H), 7.39–7.30 (m, 3H), 7.15 (dd, J = 8.4, 6.5 Hz, 1H), 7.11–7.04 (m, 2H), 6.94 (d, J = 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 156.2, 142.6, 136.9, 133.7, 130.8, 129.4, 128.9, 124.9, 124.6, 124.3, 121.8, 118.9; HRMS (ESI) calcd for $C_{13}H_8BrNO_2Na^+$ $(M + Na)^+$ requires 311.9631, found 311.9615.

8-Bromobenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16l**)*: The reaction was completed in 2 h, and the desired product was obtained as a brown solid (209 mg, 45% yield). m.p. 183–185 °C; IR (KBr) 3086, 1597, 1476, 1431, 1255, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09–8.03 (m, 1H), 7.41 (dd, J = 8.6, 2.4 Hz, 1H), 7.36 (d, J = 11.8 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.14 (dd, J = 8.3, 6.5 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.90 (d, J = 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 155.6, 142.4, 136.8, 133.7, 133.1, 132.4, 131.7, 124.7, 123.0, 122.7, 119.0, 118.7; HRMS (ESI) calcd for $C_{13}H_8BrNO_2Na^+$ $(M + Na)^+$ requires 311.9631, found 311.9609.

9-Bromobenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16 m**)*: The reaction was completed in 2 h, and the desired product was

obtained as a brown solid (255 mg, 55% yield). m.p. 181–183 °C; IR (KBr) 3049, 1590, 1478, 1428, 1261, 1183 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 6.2 Hz, 1H), 7.46 (dd, J = 7.8, 1.3 Hz, 1H), 7.41 (d, J = 12.0 Hz, 1H), 7.36–7.27 (m, 1H), 7.24–7.10 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 156.6, 142.3, 136.9, 133.9, 131.4, 130.8, 129.9, 124.7, 124.2, 122.5, 120.7, 118.6; HRMS (ESI) calcd for $C_{13}H_8BrNO_2Na^+$ $(M + Na)^+$ requires 311.9631, found 311.9636.

8-Iodobenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16n**)*: The reaction was completed in 4 h, and the desired product was obtained as a slightly brown solid (313 mg, 58% yield). m.p. 182–184 °C; IR (KBr) 3075, 1595, 1474, 1428, 1254, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (dt, J = 6.4, 1.6 Hz, 1H), 7.65 (dd, J = 8.5, 2.2 Hz, 1H), 7.55 (d, J = 2.2 Hz, 1H), 7.38 (d, J = 11.8 Hz, 1H), 7.20 (dd, J = 8.2, 6.4, 1.3 Hz, 1H), 7.16–7.08 (m, 1H), 6.98–6.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 156.3, 142.4, 139.8, 138.4, 136.8, 133.3, 131.9, 124.6, 123.2, 122.3, 119.4, 89.7; HRMS (ESI) calcd for $C_{13}H_8INO_2Na^+$ $(M + Na)^+$ requires 359.9492, found 359.9505.

6-Methylbenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16o**)*: The reaction was completed in 6 h, and the desired product was obtained as a slightly brown solid (177 mg, 49% yield). m.p. 164–166 °C; IR (KBr) 3077, 1594, 1477, 1430, 1281, 1185 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 5.5, 2.1 Hz, 1H), 7.33 (d, J = 11.8 Hz, 1H), 7.23 (dd, J = 6.1, 2.9 Hz, 1H), 7.19–7.11 (m, 2H), 7.10–7.00 (m, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 154.7, 143.2, 136.5, 135.2, 132.7, 130.6, 129.9, 127.7, 125.6, 124.0, 121.0, 118.9, 16.7; HRMS (ESI) calcd for $C_{14}H_{11}NO_2Na^+$ $(M + Na)^+$ requires 248.0682, found 248.0710.

7-Methylbenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16p**)*: The reaction was completed in 2 h, and the desired product was obtained as a sticky brown amorphous (144 mg, 40% yield). m.p. 167–169 °C; IR (KBr) 3047, 1597, 1476, 1428, 1256, 1191 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, J = 6.3, 1.4 Hz, 1H), 7.35–7.28 (m, 2H), 7.27 (s, 1H), 7.13 (d, J = 7.7 Hz, 1H), 7.08 (d, J = 11.8 Hz, 1H), 7.03 (dd, J = 7.7, 1.6, 0.8 Hz, 1H), 6.99 (d, J = 1.6 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 156.2, 142.7, 136.7, 136.6, 130.0, 127.1, 126.5, 124.3, 121.8, 119.3, 21.2; HRMS (ESI) calcd for $C_{14}H_{11}NO_2Na^+$ $(M + Na)^+$ requires 248.0682, found 248.0685.

8-Methylbenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16q**)*: The reaction was completed in 6 h, and the desired product was obtained as a slightly brown solid (205 mg, 57% yield). m.p. 189–191 °C; IR (KBr) 3069, 1598, 1475, 1434, 1288, 1197 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, J = 6.2, 1.4 Hz, 1H), 7.33 (d, J = 11.8 Hz, 1H), 7.15–7.09 (m, 2H), 7.09–7.02 (m, 2H), 7.01 (d, J = 1.8 Hz, 1H), 6.98 (d, J = 11.8 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 154.7, 142.9, 136.5, 135.8, 134.8, 131.7, 130.3, 129.5, 124.2, 121.3, 121.0, 118.7, 20.8; HRMS (ESI) calcd for $C_{14}H_{11}NO_2Na^+$ $(M + Na)^+$ requires 248.0682, found 248.0708.

6-Methoxybenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16r**)*: The reaction was completed in 4 h, and the desired product was obtained as a light brown solid (251 mg, 65% yield). m.p. 160–162 °C; IR (KBr) 3008, 1574, 1473, 1434, 1278, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 6.3 Hz, 1H), 7.38 (d, J = 11.8 Hz, 1H), 7.27 (d, J = 9.7 Hz, 1H), 7.17 (d, J = 6.5 Hz, 1H), 7.15–7.10 (m, 1H), 7.07 (d, J = 11.7 Hz, 1H), 6.98 (dd, J = 8.2, 1.2 Hz, 1H), 6.82 (d, J = 6.6 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 151.7, 144.5, 143.0, 136.5, 134.6, 131.2, 126.1, 124.2, 121.5, 121.1, 119.4, 113.6, 56.3; HRMS (ESI) calcd for $C_{14}H_{11}NO_3Na^+$ $(M + Na)^+$ requires 264.0631, found 264.0644.

7-Methoxybenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16s**)*: The reaction was completed in 4 h, and the desired product was obtained as a brown solid (239 mg, 62% yield). m.p. 181–183 °C; IR (KBr) 3081, 1612, 1478, 1424, 1260, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 6.2, 1.0 Hz, 1H), 7.23 (d, J = 11.8 Hz, 1H), 7.16–7.06 (m, 3H), 6.96 (d, J = 11.8 Hz, 1H), 6.76–6.68 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 157.7, 155.8, 136.7, 134.9, 130.9, 123.9, 122.6, 119.3, 118.9, 111.8, 107.3, 55.8; HRMS (ESI) calcd for $C_{14}H_{11}NO_3Na^+$ $(M + Na)^+$ requires 264.0631, found 264.0649.

8-Methoxybenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16t**)*: The reaction was completed in 4 h, and the desired product was obtained as a yellow solid (112 mg, 29% yield). m.p. 166–168 °C; IR (KBr) 3058, 1590, 1497, 1428, 1258, 1191 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, J = 6.1, 1.3 Hz, 1H), 7.35 (d, J = 11.8 Hz, 1H), 7.20–7.04 (m, 2H), 7.08 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 11.8 Hz, 1H), 6.86 (dd, J = 8.8, 3.0 Hz, 1H), 6.71 (d, J = 3.0 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 156.8, 150.4, 142.8, 136.5, 134.9, 130.5, 124.4, 122.0, 121.6, 119.4, 116.5, 114.2, 55.9; HRMS (ESI) calcd for $C_{14}H_{11}NO_3Na^+$ $(M + Na)^+$ requires 264.0631, found 264.0649.

9-Methoxybenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16u**)*: The reaction was completed in 6 h, and the desired product was obtained as a light yellow solid (224 mg, 58% yield). m.p. 236–238 °C; IR (KBr) 3050, 1599, 1468, 1432, 1280, 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, J = 6.3, 1.3 Hz, 1H), 7.35 (d, J = 12.0 Hz, 1H), 7.32–7.27 (m, 2H), 7.11 (dd, J = 8.4, 6.3 Hz, 1H), 7.06 (dd, J = 8.4, 1.0 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 157.8, 156.4, 136.6, 131.4, 130.0, 124.1, 120.4, 119.3, 118.7, 113.4, 108.2, 56.2; HRMS (ESI) calcd for $C_{14}H_{11}NO_3Na^+$ $(M + Na)^+$ requires 264.0631, found 264.0646.

8-(Trifluoromethyl)benzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16v**)*: The reaction was completed in 1 h, and the desired product was obtained as a light yellow solid (103 mg, 23% yield). m.p. 84–86 °C; IR (NaCl) 3067, 2920, 1446, 1340, 1168, 1112, 906 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, J = 6.3, 1.2 Hz, 1H), 7.60 (dd, J = 8.5, 2.2 Hz, 1H), 7.49 (d, J = 2.2 Hz, 1H), 7.43 (d, J = 11.9 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.19 (dd, J = 8.5, 6.4 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 156.0, 142.4, 137.0, 133.8, 130.2, 128.9, 128.6, 128.1 (q, J = 3.6 Hz), 127.2 (q, J = 3.7 Hz), 124.9, 122.6, 122.0, 120.0; HRMS (ESI) calcd for $C_{14}H_9F_3NO_2^+$ $(M + H)^+$ requires 280.0580, found 280.0574.

8-Nitrobenzo [6,7]*oxepino[3,2-b]pyridine 1-oxide (**16w**)*: The reaction was completed in 1 h, and the desired product was obtained as a light brown solid (131 mg, 32% yield). m.p. 240–242 °C; IR (NaCl) 3061, 1519, 1474, 1344, 1287, 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, J = 8.8, 2.8 Hz, 1H), 8.14–8.07 (m, 2H), 7.47 (d, J = 11.9 Hz, 1H), 7.29 (d, J = 8.9 Hz, 1H), 7.21 (dd, J = 8.5, 6.5 Hz, 1H), 7.12 (dt, J = 8.5, 0.9 Hz, 1H), 7.01 (d, J = 11.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 155.7, 145.6, 142.0, 137.2, 132.4, 130.8, 126.0, 125.2, 125.0, 123.7, 122.5, 118.7; HRMS (ESI) calcd for $C_{13}H_9N_2O_4^+$ $(M + H)^+$ requires 257.0557, found 257.0559.

4.5. General procedure for the synthesis of substituted benzo [6,7] oxepino[3,2-b]pyridines (**2a–2b**, **2d–2w**)

To a solution of substituted benzo [6,7]oxepino[3,2-*b*]pyridine 1-oxide (50 mg, 0.24 mmol) in THF (2 mL) was added a 0.2 M solution of NH_4Cl in water (2 mL) followed by zinc powder (46 mg, 0.71 mmol). The reaction mixture was stirred at room temperature for 1 h. The resulting mixture was filtered through a Celite® pad, and the filtrate was diluted with EtOAc (20 mL). The filtrate was washed with water (3 × 25 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:3) to afford the desired substituted benzo [6,7]-oxepino[3,2-*b*]pyridine (**2a–2b**, **2d–2w**): R_f (**2a–2b**, **2d–2v**) ≈ 0.22 (EtOAc/hexane = 1:3) and R_f (**2w**) = 0.22 (EtOAc/hexane = 1:1).

Benzo [6,7]*oxepino[3,2-b]pyridine (**2a**)*: The desired product was obtained as a white solid (42 mg, 89% yield). m.p. 67–69 °C; IR (KBr) 3055, 1579, 1484, 1438, 1182 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (dd, J = 4.6, 1.4 Hz, 1H), 7.46 (dd, J = 8.1, 1.4 Hz, 1H), 7.32 (dd, J = 8.0,

7.2, 1.8 Hz, 1H), 7.24–7.12 (m, 4H), 6.90 (2 × s, 2 × 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 153.7, 150.1, 145.9, 132.9, 131.4, 130.6, 130.0, 130.0, 128.9, 125.5, 124.3, 121.3; HRMS (ESI) calcd for $C_{13}H_{10}NO^+$ $(M + H)^+$ requires 196.0757, found 196.0752.

6-Fluorobenzo [6,7]*oxepino[3,2-b]pyridine* (***2b***): The desired product was obtained as a white solid (45 mg, 90% yield). m.p. 97–99 °C; IR (KBr) 3062, 1578, 1472, 1443, 1268, 1192 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.58 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.28 (dd, *J* = 5.4, 2.7 Hz, 1H), 7.18–7.05 (m, 2H), 7.01–6.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6 (d, *J* = 204.4 Hz), 153.2, 149.8, 146.3, 144.1 (d, *J* = 12.5 Hz), 132.5, 132.2 (d, *J* = 0.8 Hz), 131.9 (d, *J* = 3.4 Hz), 129.2, 125.5 (d, *J* = 7.7 Hz), 124.7 (d, *J* = 3.5 Hz), 124.5, 117.2 (d, *J* = 19.2 Hz); HRMS (ESI) calcd for $C_{13}H_9FNO^+$ $(M + H)^+$ requires 214.0663, found 214.0683.

8-Fluorobenzo [6,7]*oxepino[3,2-b]pyridine* (***2d***): The desired product was obtained as a white solid (49 mg, 88% yield). m.p. 113–115 °C; IR (KBr) 3057, 1581, 1491, 1417, 1249, 1191 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 4.6, 1.3 Hz, 1H), 7.47 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.29–7.23 (m, 1H), 7.15 (dd, *J* = 8.8, 4.8 Hz, 1H), 7.01 (dd, *J* = 7.8, 3.0 Hz, 1H), 6.97 (d, *J* = 11.4 Hz, 1H), 6.91 (dd, *J* = 8.7, 3.0 Hz, 1H), 6.84 (d, *J* = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9 (d, *J* = 243.7 Hz), 153.7, 153.1 (d, *J* = 2.6 Hz), 149.6, 146.1, 132.5, 131.7 (d, *J* = 2.0 Hz), 131.4 (d, *J* = 8.4 Hz), 128.7, 124.6, 122.4 (d, *J* = 8.7 Hz), 116.8 (d, *J* = 23.4 Hz), 115.9 (d, *J* = 23.6 Hz); HRMS (ESI) calcd for $C_{13}H_9FNO^+$ $(M + H)^+$ requires 214.0663, found 214.0681.

9-Fluorobenzo [6,7]*oxepino[3,2-b]pyridine* (***2e***): The desired product was obtained as a white solid (49 mg, 95% yield). m.p. 128–130 °C; IR (KBr) 3064, 1561, 1437, 1232, 1176 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.38 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.23–7.13 (m, 2H), 7.03 (d, *J* = 11.7 Hz, 1H), 6.93–6.87 (m, 2H), 6.82 (dd, *J* = 9.4, 8.4, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (d, *J* = 252.2 Hz), 158.7 (d, *J* = 4.7 Hz), 153.6, 149.9, 146.3, 132.2, 130.6 (d, *J* = 10.5 Hz), 128.9, 124.9 (d, *J* = 6.6 Hz), 124.5, 119.1 (d, *J* = 14.4 Hz), 116.8 (d, *J* = 3.3 Hz), 112.5 (d, *J* = 22.0 Hz); HRMS (ESI) calcd for $C_{13}H_9FNO^+$ $(M + H)^+$ requires 214.0663, found 214.0683.

6-Chlorobenzo [6,7]*oxepino[3,2-b]pyridine* (***2f***): The desired product was obtained as a white solid (44 mg, 79% yield). m.p. 127–129 °C; IR (KBr) 3053, 1613, 1441, 1257, 1181 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.62 (dd, *J* = 8.2, 1.4, 0.4 Hz, 1H), 7.32 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.22–7.16 (m, 1H), 7.04 (dd, *J* = 7.7, 1.8 Hz, 1H), 6.99 (t, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 11.7 Hz, 1H), 6.84 (d, *J* = 11.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 151.9, 149.7, 146.4, 132.1, 132.0, 131.9, 130.7, 129.6, 128.2, 126.9, 125.8, 124.5; HRMS (ESI) calcd for $C_{13}H_9ClNO^+$ $(M + H)^+$ requires 230.0367, found 230.0386.

7-Chlorobenzo [6,7]*oxepino[3,2-b]pyridine* (***2g***): The desired product was obtained as a white solid (51 mg, 93% yield). m.p. 139–141 °C; IR (KBr) 3057, 1564, 1481, 1444, 1183 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.44 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.23 (dd, *J* = 8.1, 4.7 Hz, 1H), 7.19 (s, 1H), 7.12 (d, *J* = 1.5 Hz, 2H), 6.89 (d, *J* = 11.6 Hz, 1H), 6.83 (d, *J* = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 153.4, 149.7, 146.3, 135.8, 131.8, 131.7, 130.6, 128.9, 128.7, 125.8, 124.5, 121.9; HRMS (ESI) calcd for $C_{13}H_9ClNO^+$ $(M + H)^+$ requires 230.0367, found 230.0385.

8-Chlorobenzo [6,7]*oxepino[3,2-b]pyridine* (***2h***): The desired product was obtained as a white solid (50 mg, 91% yield). m.p. 127–129 °C; IR (KBr) 3039, 1593, 1484, 1443, 1185 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 3.7 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.31–7.22 (m, 2H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 6.95 (d, *J* = 11.6 Hz, 1H), 6.82 (d, *J* = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 153.6, 149.6, 146.2, 132.6, 131.5, 131.4, 130.7, 130.1, 129.4, 128.8, 124.6, 122.5; HRMS (ESI) calcd for $C_{13}H_9ClNO^+$ $(M + H)^+$ requires 230.0367, found 230.0378.

9-Chlorobenzo [6,7]*oxepino[3,2-b]pyridine* (***2i***): The desired product was obtained as a white solid (51 mg, 93% yield). m.p. 126–128 °C; IR (KBr) 3062, 1588, 1556, 1439, 1244, 1183 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.49 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.30–7.22 (m, 4H), 7.17–7.12 (m, 1H), 7.06 (d, *J* = 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 153.8, 149.8, 146.4, 134.1, 132.3, 130.4, 129.3, 128.7, 128.4, 126.9, 124.5, 119.9; HRMS (ESI) calcd for $C_{13}H_9ClNO^+$ $(M + H)^+$ requires 230.0367, found 230.0383.

6-Bromobenzo [6,7]*oxepino[3,2-b]pyridine* (***2j***): The desired product was obtained as a white solid (65 mg, 99% yield). m.p. 136–138 °C; IR (KBr) 3061, 1558, 1434, 1233, 1175 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.81 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.58 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.31–7.25 (m, 1H), 7.18 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.06–6.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 152.9, 149.6, 146.4, 133.7, 132.1, 132.1, 131.8, 129.7, 129.0, 126.3, 124.5, 116.1; HRMS (ESI) calcd for $C_{13}H_9BrNO^+$ $(M + H)^+$ requires 273.9862, found 273.9879.

7-Bromobenzo [6,7]*oxepino[3,2-b]pyridine* (***2k***): The desired product was obtained as a white solid (53 mg, 81% yield). m.p. 127–129 °C; IR (KBr) 3034, 1587, 1480, 1442, 1229, 1181 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.46 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.37 (d, *J* = 1.9 Hz, 1H), 7.32–7.28 (m, 1H), 7.25 (dd, *J* = 8.1, 4.7 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.93 (d, *J* = 11.6 Hz, 1H), 6.84 (d, *J* = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 153.4, 149.7, 146.3, 131.8, 131.8, 130.8, 129.1, 128.9, 128.7, 124.7, 124.5, 123.6; HRMS (ESI) calcd for $C_{13}H_9BrNO^+$ $(M + H)^+$ requires 273.9862, found 273.9875.

8-Bromobenzo [6,7]*oxepino[3,2-b]pyridine* (***2l***): The desired product was obtained as a white solid (49 mg, 75% yield). m.p. 147–149 °C; IR (KBr) 3036, 1478, 1442, 1229, 1181 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 4.6, 1.3 Hz, 1H), 7.46 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.42 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.29–7.23 (m, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 6.95 (d, *J* = 11.6 Hz, 1H), 6.82 (d, *J* = 11.6 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 153.6, 149.6, 146.2, 133.1, 132.7, 132.4, 131.9, 131.4, 128.8, 124.6, 123.0, 118.9; HRMS (ESI) calcd for $C_{13}H_9BrNO^+$ $(M + H)^+$ requires 273.9862, found 273.9873.

9-Bromobenzo [6,7]*oxepino[3,2-b]pyridine* (***2 m***): The desired product was obtained as a white solid (55 mg, 83% yield). m.p. 129–131 °C; IR (KBr) 3063, 1586, 1551, 1438, 1242, 1181 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 4.7, 1.3 Hz, 1H), 7.48 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.44 (dd, *J* = 6.1, 3.1 Hz, 1H), 7.28 (t, *J* = 3.1 Hz, 1H), 7.25 (s, 1H), 7.19 (s, 1H), 7.18 (d, *J* = 3.1 Hz, 1H), 7.05 (d, *J* = 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 153.9, 149.6, 146.4, 132.2, 131.9, 130.8, 130.2, 129.9, 128.7, 124.5, 124.2, 120.6; HRMS (ESI) calcd for $C_{13}H_9BrNO^+$ $(M + H)^+$ requires 273.9862, found 273.9881.

8-Iodobenzo [6,7]*oxepino[3,2-b]pyridine* (***2n***): The desired product was obtained as a white solid (55 mg, 71% yield). m.p. 163–165 °C; IR (KBr) 3054, 1440, 1226, 1177 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.61 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.54 (d, *J* = 2.2 Hz, 1H), 7.47 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.29–7.23 (m, 1H), 6.99–6.92 (m, 2H), 6.81 (d, *J* = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 153.5, 145.7, 139.2, 138.4, 132.1, 131.9, 131.5, 129.1, 124.5, 123.2, 88.9; HRMS (ESI) calcd for $C_{13}H_9INO^+$ $(M + H)^+$ requires 321.9723, found 321.9719.

6-Methylbenzo [6,7]*oxepino[3,2-b]pyridine* (***2o***): The desired product was obtained as a white solid (50 mg, 99% yield). m.p. 93–95 °C; IR (KBr) 3055, 1440, 1226, 1182 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.49 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.22–7.16 (m, 2H), 7.06–6.99 (m, 2H), 6.94–6.86 (m, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 153.6, 150.5, 145.8, 133.3, 132.1, 130.9, 130.4, 130.0, 128.9, 127.7, 124.9, 123.9, 16.8; HRMS (ESI) calcd for $C_{14}H_{12}NO^+$ $(M + H)^+$ requires 210.0913, found 210.0926.

7-Methylbenzo [6,7]*oxepino[3,2-b]pyridine* (***2p***): The desired

product was obtained as a white solid (15 mg, 30% yield). m.p. 60–62 °C; IR (KBr) 3057, 1610, 1501, 1443, 1184 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, J = 4.7, 1.4 Hz, 1H), 7.44 (dd, J = 8.1, 1.2 Hz, 1H), 7.20 (dd, J = 8.1, 4.7 Hz, 1H), 7.09 (d, J = 7.7 Hz, 1H), 7.00 (s, 1H), 6.96 (d, J = 7.7 Hz, 1H), 6.91–6.80 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 157.0, 145.7, 141.2, 132.8, 130.3, 129.7, 128.8, 127.0, 126.1, 124.0, 121.7, 21.1; HRMS (ESI) calcd for $C_{14}H_{12}NO^+$ $(M + H)^+$ requires 210.0913, found 210.0915.

8-Methylbenzo [6,7]*oxepino[3,2-b]pyridine (**2q**)*: The desired product was obtained as a white solid (50 mg, 99% yield). m.p. 93–95 °C; IR (KBr) 3061, 1583, 1493, 1444, 1203 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, J = 4.7, 1.4 Hz, 1H), 7.43 (dd, J = 8.1, 1.2 Hz, 1H), 7.19 (dd, J = 8.1, 4.7 Hz, 1H), 7.10 (dd, J = 8.2, 1.6 Hz, 1H), 7.06 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 1.6 Hz, 1H), 6.91–6.82 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 153.8, 150.1, 145.8, 135.0, 132.9, 131.3, 131.1, 130.3, 129.6, 128.7, 124.2, 120.9, 20.7; HRMS (ESI) calcd for $C_{14}H_{12}NO^+$ $(M + H)^+$ requires 210.0913, found 210.0919.

6-Methoxybenzo [6,7]*oxepino[3,2-b]pyridine (**2r**)*: The desired product was obtained as a white solid (40 mg, 74% yield). m.p. 91–93 °C; IR (KBr) 3006, 1569, 1469, 1438, 1271, 1182 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, J = 4.7, 1.4 Hz, 1H), 7.63 (dd, J = 8.1, 1.4 Hz, 1H), 7.29–7.23 (m, 1H), 7.10 (t, J = 7.9 Hz, 1H), 7.01–6.93 (m, 3H), 6.84 (dd, J = 7.7, 1.5 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 151.8, 150.3, 145.9, 145.2, 132.7, 131.4, 129.4, 125.3, 124.2, 121.2, 113.1, 56.3, 29.8; HRMS (ESI) calcd for $C_{14}H_{12}NO_2^+$ $(M + H)^+$ requires 226.0863, found 226.0884.

7-Methoxybenzo [6,7]*oxepino[3,2-b]pyridine (**2s**)*: The desired product was obtained as a white solid (52 mg, 97% yield). m.p. 61–63 °C; IR (KBr) 3051, 1577, 1494, 1443, 1197 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, J = 4.7, 1.4 Hz, 1H), 7.41 (dd, J = 8.1, 1.3 Hz, 1H), 7.18 (dd, J = 8.1, 4.7 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.85–6.74 (m, 2H), 6.73 (d, J = 2.5 Hz, 1H), 6.69 (dd, J = 8.4, 2.5 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 158.3, 153.1, 150.3, 145.9, 132.6, 130.8, 129.0, 128.8, 123.9, 122.8, 111.2, 107.1, 55.7; HRMS (ESI) calcd for $C_{14}H_{12}NO_2^+$ $(M + H)^+$ requires 226.0863, found 226.0881.

8-Methoxybenzo [6,7]*oxepino[3,2-b]pyridine (**2t**)*: The desired product was obtained as a white solid (53 mg, 98% yield). m.p. 89–91 °C; IR (KBr) 3065, 1599, 1577, 1495, 1442, 1202 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, J = 4.7, 1.4 Hz, 1H), 7.44 (dd, J = 8.1, 1.1 Hz, 1H), 7.21 (dd, J = 8.1, 4.7 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 11.6 Hz, 1H), 6.86 (d, J = 9.6 Hz, 1H), 6.84–6.81 (m, 1H), 6.71 (d, J = 3.0 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 154.0, 151.0, 150.0, 145.8, 132.7, 131.8, 130.6, 128.7, 124.3, 121.9, 115.7, 114.3, 55.8; HRMS (ESI) calcd for $C_{14}H_{12}NO_2^+$ $(M + H)^+$ requires 226.0863, found 226.0881.

9-Methoxybenzo [6,7]*oxepino[3,2-b]pyridine (**2u**)*: The desired product was obtained as a white solid (52 mg, 97% yield). m.p. 127–129 °C; IR (KBr) 3053, 1603, 1469, 1444, 1271 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (dd, J = 4.7, 1.3 Hz, 1H), 7.46 (dd, J = 8.1, 1.3 Hz, 1H), 7.32–7.23 (m, 2H), 7.22 (dd, J = 8.1, 4.7 Hz, 1H), 6.94 (d, J = 11.8 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 157.7, 153.6, 150.7, 145.9, 130.7, 130.2, 128.8, 127.6, 124.0, 119.3, 113.5, 107.6, 56.1; HRMS (ESI) calcd for $C_{14}H_{12}NO_2^+$ $(M + H)^+$ requires 226.0863, found 226.0882.

8-(Trifluoromethyl)benzo [6,7]*oxepino[3,2-b]pyridine (**2v**)*: The reaction was completed in 24 h, and the desired product was obtained as a brown solid (25 mg, 39% yield). m.p. 140–142 °C; IR (NaCl) 3078, 2926, 1478, 1421, 1333, 1189, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, J = 4.7, 1.4 Hz, 1H), 7.58 (dd, J = 8.4, 2.3 Hz, 1H), 7.53–7.48 (m, 2H), 7.32–7.27 (m, 2H), 7.02 (d, J = 11.6 Hz, 1H), 6.91 (d, J = 11.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 153.3, 149.1, 145.8, 132.3, 131.8, 130.3, 129.2, 128.2, 127.4 (q, J = 3.6 Hz), 127.1 (q, J = 3.7 Hz), 124.7, 121.8, 100.0; HRMS (ESI) calcd for $C_{14}H_9F_3NO^+$ $(M + H)^+$ requires 264.0631, found 264.0637.

Benzo [6,7]*oxepino[3,2-b]pyridin-8-amine (2**w**)*: The reaction was completed in 24 h, and the desired product was obtained as a yellow solid (23 mg, 46% yield). m.p. 91–93 °C; IR (NaCl) 3401, 2922, 1579, 1495, 1444, 1262, 1203, 1025 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.34 (dd, J = 4.6, 1.5 Hz, 1H), 7.58 (dd, J = 8.1, 1.4 Hz, 1H), 7.36 (dd, J = 8.1, 4.6 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 11.6 Hz, 1H), 6.77 (d, J = 11.6 Hz, 1H), 6.56 (dd, J = 8.5, 2.8 Hz, 1H), 6.48 (d, J = 2.7 Hz, 1H), 5.05 (s, 2H).; ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.8, 149.8, 147.5, 146.7, 145.9, 133.6, 130.9, 130.0, 128.9, 125.0, 121.7, 116.0, 114.2; HRMS (ESI) calcd for $C_{13}H_{11}N_2O^+$ $(M + H)^+$ requires 211.0866, found 211.0875.

4.6. Synthesis of benzo [6,7]oxepino[3,2-b]pyridine analogs using nitrogen-containing aromatic aldehydes

4.6.1. Typical procedure for the synthesis of benzo [6,7]oxepino[3,2-b]pyridines 1-oxide analogs (**16x–16z**)

To a suspension of 3-hydroxy-2-methylpyridine 1-oxide (**14**) (200 mg, 1.60 mmol) and K_3PO_4 (1.22 g, 5.76 mmol) in DMF (4 mL), nitrogen-containing aromatic aldehyde (**12x–12z**) (2.56 mmol) was added under a nitrogen atmosphere. The reaction mixture was stirred at 140 °C until **14** was completely consumed (monitored by TLC). The reaction mixture was then allowed to cool down to room temperature and diluted with water (100 mL). The resulting mixture was extracted with EtOAc (3 × 100 mL). The combined organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (5% MeOH in CH_2Cl_2) to afford the desired benzo [6,7]oxepino[3,2-*b*]pyridine 1-oxide analog (**16x–16z**): $R_f \approx 0.22$ (5% MeOH in CH_2Cl_2).

*Oxepino[2,3-b:6,7-b']dipyridine 1-oxide (**16x**)*: The reaction was completed in 4 h, and the desired product was obtained as a brown solid (78 mg, 23% yield). m.p. 150–152 °C; IR (KBr) 2984, 1480, 1427, 1269, 1074, 801 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, J = 4.9, 1.9 Hz, 1H), 8.14 (dd, J = 6.5, 1.2 Hz, 1H), 7.66 (dd, J = 7.5, 1.9 Hz, 1H), 7.45 (d, J = 11.8 Hz, 1H), 7.31 (dt, J = 8.5, 0.9 Hz, 1H), 7.26–7.19 (m, 2H), 6.96 (d, J = 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 154.9, 149.2, 141.8, 139.4, 136.8, 131.9, 124.9, 124.6, 122.7, 122.6, 120.0; HRMS (ESI) calcd for $C_{12}H_8N_2NaO_2^+$ $(M + Na)^+$ requires 235.0478, found 235.0472.

*Oxepino[3,2-b:7,6-c']dipyridine 1-oxide (**16y**)*: The reaction was completed in 4 h, and the desired product was obtained as a brown solid (71 mg, 21% yield). m.p. 217–219 °C; IR (KBr) 2878, 1488, 1433,1277, 1066, 787 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.45 (d, J = 4.9 Hz, 1H), 8.11 (dd, J = 6.4, 1.2 Hz, 1H), 7.57 (d, J = 11.8 Hz, 1H), 7.22 (dd, J = 8.5, 6.4 Hz, 1H), 7.20–7.12 (m, 2H), 6.96 (d, J = 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 152.7, 146.8, 142.6, 137.3, 136.9, 131.5, 126.3, 125.6, 123.1, 118.4; HRMS (ESI) calcd for $C_{12}H_8N_2$ NaO_2^+ $(M + Na)^+$ requires 235.0478, found 235.0477.

*Oxepino[3,2-b:6,7-b']dipyridine 1-oxide (**16z**)*: The reaction was completed in 4 h, and the desired product was obtained as a brown solid (112 mg, 33% yield). m.p. 227–229 °C; IR (KBr) 2981, 1477, 1424, 1288, 1027, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, J = 4.7, 1.4 Hz, 1H), 8.09 (dd, J = 6.4, 1.2 Hz, 1H), 7.58 (d, J = 12.1 Hz, 1H), 7.48 (dd, J = 8.2, 1.4 Hz, 1H), 7.30 (dd, J = 8.2, 4.7 Hz, 1H), 7.23–7.13 (m, 2H), 7.10 (dt, J = 8.4, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 153.1, 148.9, 146.8, 142.1, 136.9, 135.1, 128.9, 125.1, 124.7, 123.8, 118.1; HRMS (ESI) calcd for $C_{12}H_8N_2NaO_2^+$ $(M + Na)^+$ requires 235.0478, found 235.0486.

4.6.2. Typical procedure for the synthesis of benzo [6,7]oxepino [3,2-b]pyridine analogs

To a solution of benzo [6,7]oxepino[3,2-*b*]pyridine 1-oxide analog (**16x–16z**) in THF (2 mL) was added a 0.2 M solution of

NH_4Cl in water (2 mL) followed by zinc powder (46 mg, 0.71 mmol). The reaction mixture was stirred at room temperature for 1 h. The resulting mixture was filtered through a Celite® pad, and the filtrate was diluted with EtOAc (20 mL). The filtrate was washed with water (3 × 25 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (100% EtOAc) to afford the deoxygenated product.

*Oxepino[2,3-b:6,7-b']dipyridine (**2x**)*: The desired product was obtained as a white solid (11 mg, 32% yield). $R_f = 0.56$ (100% EtOAc); m.p. 135–138 °C; IR (KBr) 2976,1424, 1248, 1181, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, J = 4.8, 1.4 Hz, 1H), 8.30 (dd, J = 4.8, 1.9 Hz, 1H), 7.75 (dd, J = 8.2, 1.4 Hz, 1H), 7.64 (dd, J = 7.5, 2.0 Hz, 1H), 7.38 (dd, J = 8.2, 4.8 Hz, 1H), 7.21 (dd, J = 7.5, 4.8 Hz, 1H), 7.08 (d, J = 11.6 Hz, 1H), 6.88 (d, J = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 152.1, 148.7, 148.5, 146.3, 139.2, 132.6, 130.2, 129.8, 124.9, 124.6, 122.0; HRMS (ESI) calcd for $C_{12}H_9N_2O^+$ $(M + H)^+$ requires 197.0709, found 197.0696.

*10,11-Dihydrooxepino[3,2-b:7,6-c']dipyridine (**17y**)*: The product was obtained as a light brown oil (33 mg, 69% yield). $R_f = 0.31$ (100% EtOAc); IR (NaCl) 3054,1602, 1549, 1447, 1275, 1101, 807, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.33 (dd, J = 4.7, 1.5 Hz, 1H), 8.29 (d, J = 4.9 Hz, 1H), 7.56 (dd, J = 8.2, 1.5 Hz, 1H), 7.22 (dd, J = 8.2, 4.7 Hz, 1H), 7.15 (d, J = 4.9 Hz, 1H), 3.45–3.39 (m, 2H), 3.26–3.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 153.0, 151.4, 145.0, 144.8, 142.8, 139.7, 128.6, 124.8, 122.8, 33.7, 29.2; HRMS (ESI) calcd for $C_{12}H_{11}N_2O^+$ $(M + H)^+$ requires 199.0866, found 199.0850.

*Oxepino[3,2-b:6,7-b']dipyridine (**2z**)*: The desired product was obtained as a white solid (18 mg, 39% yield). $R_f = 0.42$ (100% EtOAc); m.p. 146–148 °C; IR (KBr) 3063, 1595, 1446, 1272, 1172, 1109, 812 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, J = 4.6, 1.5 Hz, 2H), 7.50 (dd, J = 8.1, 1.5 Hz, 2H), 7.43–7.23 (m, 2H), 7.13 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 149.0, 146.2, 133.8, 128.7, 124.7; HRMS (ESI) calcd for $C_{12}H_9N_2O^+$ $(M + H)^+$ requires 197.0709, found 197.0714.

*10,11-Dihydrooxepino[3,2-b:6,7-b']dipyridine (**17z**)*: The by-product was obtained as a white solid (12 mg, 25% yield). $R_f = 0.42$ (100% EtOAc); m.p. 56–58 °C; IR (KBr) 2978, 1443, 1243, 1180, 1094, 806 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, J = 4.7, 1.5 Hz, 2H), 7.49 (dd, J = 8.1, 1.5 Hz, 2H), 7.17 (dd, J = 8.2, 4.7 Hz, 2H), 3.41 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 151.8, 144.7, 128.6, 122.7, 32.8; HRMS (ESI) calcd for $C_{12}H_{11}N_2O^+$ $(M + H)^+$ requires 199.0866, found 199.0876.

4.7. Evaluation of anticancer activity at the Excellent Center for Drug Discovery (ECDD)

Cancer cells (MCF-7, MDA-MB-231 or HCT-116 cells) were seeded at 1×10^4 cells per well on 96-well plate and cultured it by DMEM (Dulbecco's Modified Eagle Medium) high glucose that supplemented with 10% FBS and 1% penicillin/streptomycin. It was incubated at 37 °C and 5% CO_2 for 24 h. After 24 h incubation, the compounds were screened by using high throughput liquid handling system in order to seek the active compound that can affect to cancer cell proliferation. The compounds were added into cell plates at 50 μM (For Primary screening) and additional incubation for 24 h at 37 °C, 5% CO_2. After 24 h incubation, the culture media containing compound was removed out and added serum-free media containing MTT into the same well and then additional incubation for 3 h at 37 °C, 5% CO_2. After 3 h incubation, the serum-free media containing MTT was removed out and added DMSO into the same well and then measurement of MTT absorbance at 570 nm by Multi-Mode Microplate Reader (ENVISION).

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

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