Synthesis of Novel Tricyclic 1,5-Benzothiazepine Derivatives Bearing Quinoline Moiety via [2 + 2] Cycloaddition Reaction

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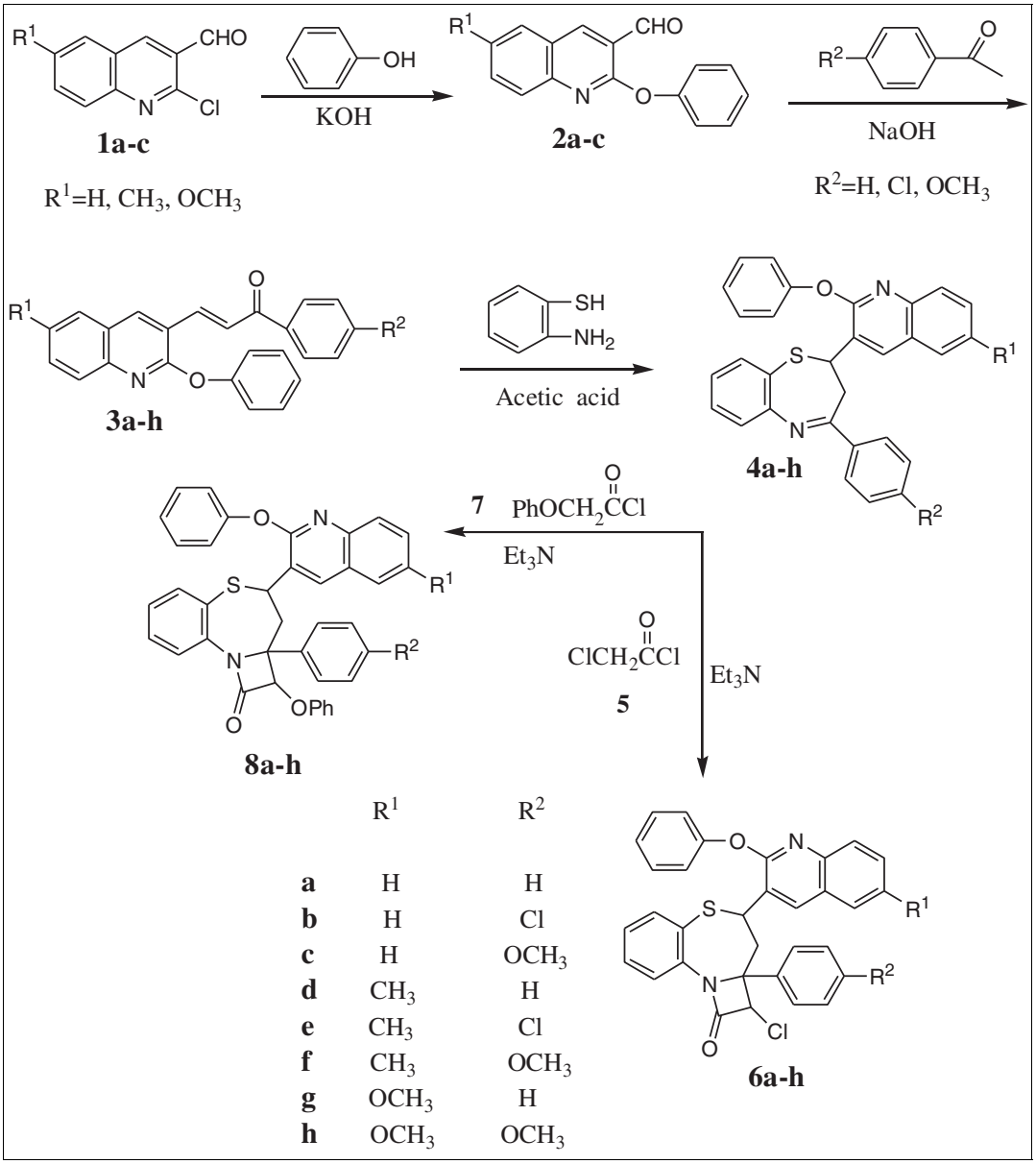


	R^1	R^2
a	H	H
b	H	Cl
c	H	OCH_3
d	CH_3	H
e	CH_3	Cl
f	CH_3	OCH_3
g	OCH_3	H
h	OCH_3	OCH_3

A series of new tricyclic 1,5-benzothiazepine derivatives were synthesized by the reaction of 1,5-benzothiazepine containing 2-phenoxy-quinoline with chloracetyl chloride and phenoxyacetyl chloride. The structures of the target compounds were confirmed by IR, ^{1}H NMR MS, and elemental analysis.

INTRODUCTION

1,5-Benzothiazepine is an important seven-membered heterocyclic ring system. It has attracted considerable attention to synthetic and medicinal chemists because of their broad spectrum of biological activities. It has been used as a calcium antagonist [1], antibacterial [2], anticancer drug [3,4], anticonvulsant, tranquilizer [5], and antidepressant [6]. For example, the drug diltiazem, intensively used in clinical practice, contains this system. It is well documented that pharmaceutical properties of such compounds are magnified when an additional heterocyclic is bound to the heptatomic nucleus [7–9]. To search for new potential useful 1,5-benzothiazepine derivatives, a great deal of work has been carried out on the synthesis of tricyclic 1,5-benzothiazepine derivatives in recent years [10].

Quinoline ring systems represent a major class of heterocycles as they occur in various natural products especially in alkaloids [11]; it possesses diverse biological and physiological activities such as antimalarial [12], anti-inflammatory [13], antitumor [14], and antibacterial properties [15]. By all means, quinoline acts as "privileged substructure" for drug design.

The role of β-lactams, which are endowed with unique structure, showed biological activities that include inhibition of prostate-specific antigen [16], thrombin [17], human cytomegalovirus protein [18], human leukocyte elastase [19], and cholesterol absorption [20]. Most importantly, antibiotics possess a representative structure of a β-lactam-fused five- or six-membered heterocyclic ring containing nitrogen and sulfur atoms [21–24], for example, tazobactams, which have been widely used as chemotherapeutic agents to treat bacterial infections and microbial diseases.

Considering the important biological activities of these heterocyclic ring system as well as the combination principles for drug design, we herein report the synthesis of new β-lactam-fused 1,5-benzothiazepine derivatives containing quinoline moiety via [2 + 2] cycloadditions reaction. The synthetic route is shown in Scheme 1.

RESULTS AND DISCUSSION

A series of novel benzothiazepine derivatives bearing a 2-phenoxy-quinoline moiety were synthesized by using 2-chloro-3-quinolinecarbaldehyde (**1**) as starting material. The synthesis of intermediate 2-phenoxy-3-quinolinecarbaldehyde (**2a–c)** was used by compound **1** with phenol at 85–90°C for 6 h. Via the Claisen–Schmidt condensation, we can synthesize compounds α,β-unsaturated ketones (**3a–h**) between **2a–c** and 1-arylethanones. Using acetic acid as catalyst, we synthesized benzothiazepine derivatives (**4a–h**) by α,β-unsaturated ketones **3a–h** with *o*-aminothiophenol in ethanol. Compounds **4a–h** underwent the reaction of [2 + 2] cycloadditions with chloracetyl chlorides or phenoxyacetyl chlorides in the presence of Et_3N that lead to the formation of cycloadducts **6a–h** and **8a–h**, respectively. Various analytical techniques, such as IR, ^{1}H-NMR, mass spectrum, and elemental analysis, were utilized to confirm the structural identities of the final products.

In IR spectra of the final compounds, there is a strong absorption at 1609–1588 cm^{-1} due to the presence of C═N and a weak absorption at 1251–1234 cm^{-1} for C–O–C single bond of the 2-phenoxy-quinoline moiety. Meanwhile, the absorption recorded at 1787–1767 cm^{-1} is attributed to the C═O group. In the ^{1}H-NMR spectra of compounds **2a–h**, the presence of a singlet at δ 8.66 ppm is ascribed to the quinoline-H_4 and a singlet at δ 10.64 ppm is ascribed to the formyl group. For compounds **3a–h**, the protons of α,β-unsaturated carbonyl compounds have shown two doublets at δ 8.17 ppm for H_β and 7.94 ppm for H_α with 15.6 Hz as coupling constant. So, it was inferred that they are in a trans conformation. For compounds **4a–h**, the presence of a singlet at δ 8.35–8.30 ppm is ascribed to the quinoline-H_4, and the ^{1}H-NMR spectrum revealed three distinct doubled doublets at δ 5.67–5.60, 3.67–3.60, and 3.02–2.96 ppm, which could be attributed to the characteristic signal of the dihydrobenzothiazepine moiety as ABX pattern. For the titled compounds **6a–h** and **8a–h**, the presence of a singlet at δ 5.09–5.06 ppm and 5.42–5.36 ppm is ascribed to the β-lactam, respectively. Also, the ^{1}H-NMR spectrum revealed three distinct doubled doublets, which could be attributed to the characteristic signal of the dihydrobenzothiazepine moiety as ABX pattern. In the MS spectra, molecular ion signals of all target compounds were attained from EIMS, but the abundance of molecular ion signals was very low.

The formation of **4** may proceed via a two-step mechanism [25–27]. Nucleophilic attack by the sulfohydryl electrons of *o*-aminothiophenol takes place on the activated β-carbon atom of the α,β-unsaturated ketone to obtain Michael-adduct type intermediates, which simultaneously undergo dehydrative cyclization to give desired products.

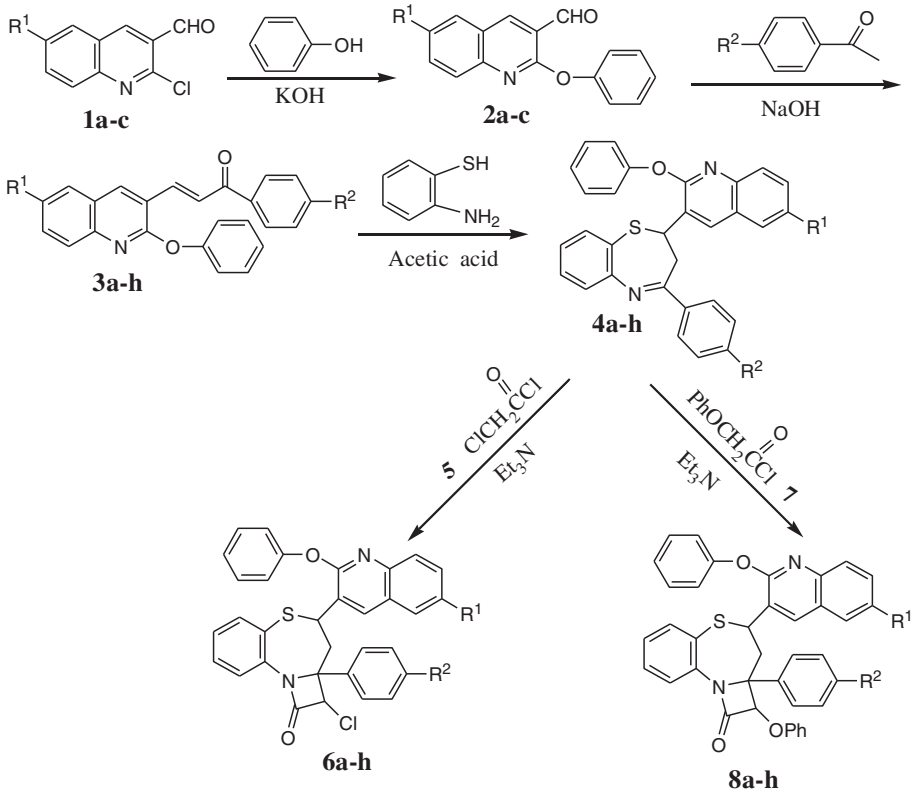
CONCLUSION

In summary, we have synthesized a series of new tricyclic 1,5-benzothiazepine derivatives **6a–h** and **8a–h** containing 2-phenoxy-quinoline moiety by [2 + 2] cycloaddition reaction. These compounds might have useful biological and therapeutic activities. The structures of the target compounds were confirmed by IR, ^{1}H-NMR, MS, and elemental analysis.

EXPERIMENTAL

General procedures. Reactions were monitored by TLC. Melting points were determined by a mettler FP-5 melting point

Scheme 1. Synthesis route for titled compounds.



1、2

	a	b	c
R¹ =	H	CH_3	CH_3O

3、4、5、6

	a	b	c	d	e	f	g	h
R¹ =	H	H	H	CH_3	CH_3	CH_3	CH_3O	CH_3O
R² =	H	Cl	CH_3O	H	Cl	CH_3O	H	CH_3O

apparatus and were uncorrected. Elemental analyses were conducted on a Perkin-Elmer 2400 elemental analyzer. The IR spectra were recorded on potassium bromide pellets using a Bruker Equinox 55 FTIR spectrophotometer. The ^{1}H-NMR spectra were recorded on a Bruker NMR spectrophotometer (400 MHz) using TMS as an internal reference and $CDCl_3$ as solvent. Multiplicities are indicated as the following: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doubled doublet. Coupling constants (*J* values) were noted and are quoted in Hertz. Mass spectra were recorded on an Agilent 5975 apparatus (EI, 70 eV). Compounds **1** [28], **2** [29], and **7** [30] were synthesized according to the reported literature.

Compounds **3** were prepared according to the literature [31].

3-(2-Phenoxy-quinolin-3-yl)-1-phenyl-2-propen-1-one (3a). Pale yellow solid (86%); mp 133–134°C; FTIR ν 1661 (C═O), 1603 (C═N), 1242 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.43 (s, 1H, quinolin-H_4), 8.17 (d, 1H, J = 15.6 Hz, H_β), 7.98 (d, 1H, J = 15.6 Hz, H_α), 8.11–6.71 (m, 14 H, ArH); MS (EI): *m/z* 351 (M^+); *Anal*. Calcd for $C_{24}H_{17}NO_2$: C, 82.30; H, 4.88; N, 3.99; Found: C, 82.24; H, 4.85; N, 4.03.

3-(2-Phenoxy-quinolin-3-yl)-1-(4-chlorophenyl)-2-propen-1-one (3b). Yellow solid (81%); mp 124–125°C; FTIR ν 1663 (C═O), 1612 (C═N), 1247 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.43 (s, 1H, quinolin-H_4), 8.19 (d, 1H, J = 15.6 Hz, H_β), 7.99 (d, 1H, J = 15.6 Hz, H_α), 8.13–6.72 (m, 13H, ArH); MS (EI): *m/z* 385 (M^+); *Anal*. Calcd for $C_{24}H_{16}ClNO_2$: C, 74.71; H, 4.18; N, 3.63; Found: C, 74.68; H, 4.16; N, 3.67.

3-(2-Phenoxy-quinolin-3-yl)-1-(4-methoxyphenyl)-2-propen-1-one (3c). Yellow solid (84%); mp 187–188°C; FTIR ν 1660 (C═O), 1605 (C═N), 1241 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.42 (s, 1H, quinolin-H_4), 8.16 (d, 1H, J = 15.6 Hz, H_β), 7.96 (d, 1H, J = 15.6 Hz, H_α), 8.09–6.98 (m, 13H, ArH), 3.89 (s, 3H, –OCH_3); MS (EI): *m/z* 381 (M^+); *Anal*. Calcd for $C_{25}H_{19}NO_3$: C, 78.72; H, 5.02; N, 3.67; Found: C, 78.67; H, 4.98; N, 3.71.

3-(2-Phenoxy-7-methyl-quinolin-3-yl)-1-phenyl-2-propen-1-one (3d). Pale yellow solid (78%); mp 187–188°C; FTIR ν

1659 (C=O), 1604 (C=N), 1252 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.34 (s, 1H, quinolin-H_4), 8.17 (d, 1H, J = 15.6 Hz, H_β), 7.94 (d, 1H, J = 15.6 Hz, H_α), 8.07–7.26 (m, 13H, ArH), 2.50 (s, 3H, –CH_3); MS (EI): *m/z* 365 (M^+); *Anal*. Calcd for $C_{25}H_{19}NO_2$: C, 82.17; H, 5.24; N, 3.83; Found: C, 82.09; H, 5.18; N, 3.91.

3-(2-Phenoxy-7-methyl-quinolin-3-yl)-1-(4-chlorophenyl)-2-propen-1-one (3e). Pale yellow solid (80%); mp 161–162°C; FTIR ν 1662 (C=O), 1611 (C=N), 1249 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.34 (s, 1H, quinolin-H_4), 8.18 (d, 1H, J = 15.6 Hz, H_β), 7.94 (d, 1H, J = 15.6 Hz, H_α), 8.09–7.18 (m, 12H, ArH), 2.51 (s, 3H, –CH_3); MS (EI): *m/z* 399 (M^+); *Anal*. Calcd for $C_{25}H_{18}ClNO_2$: C, 75.09; H, 4.54; N, 3.50; Found: C, 74.98; H, 4.59; N, 3.43.

3-(2-Phenoxy-7-methyl-quinolin-3-yl)-1-(4-methoxyphenyl)-2-propen-1-one (3f). Pale yellow solid (75%); mp 172–173°C; FTIR ν 1661 (C=O), 1608 (C=N), 1253 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.33 (s, 1H, quinolin-H_4), 8.17 (d, 1H, J = 15.6 Hz, H_β), 7.94 (d, 1H, J = 15.6 Hz, H_α), 8.06–7.25 (m, 12H, ArH), 3.89 (s, 3H, –OCH_3), 2.51 (s, 3H, –CH_3); MS (EI): *m/z* 395 (M^+); *Anal*. Calcd for $C_{26}H_{21}NO_3$: C, 78.97; H, 5.35; N, 3.54; Found: C, 78.88; H, 5.27; N, 3.61.

3-(2-Phenoxy-7-methoxy-quinolin-3-yl)-1-phenyl-2-propen-1-one (3g). Pale yellow solid (79%); mp 163–164°C; FTIR ν 1660 (C=O), 1607 (C=N), 1254 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.33 (s, 1H, quinolin-H_4), 8.18 (d, 1H, J = 15.6 Hz, H_β), 7.96 (d, 1H, J = 15.6 Hz, H_α), 8.09–7.29 (m, 13H, ArH), 3.91 (s, 3H, –OCH_3); MS (EI): *m/z* 381 (M^+); *Anal*. Calcd for $C_{25}H_{19}NO_3$: C, 78.72; H, 5.02; N, 3.67; Found: C, 78.64; H, 4.93; N, 3.74.

3-(2-Phenoxy-7-methoxy-quinolin-3-yl)-1-(4-methoxyphenyl)-2-propen-1-one (3h). Pale yellow solid (77%); mp 162–163°C; FTIR ν 1661 (C=O), 1604 (C=N), 1251 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.33 (s, 1H, quinolin-H_4), 8.14 (d, 1H, J = 15.6 Hz, H_β), 7.95 (d, 1H, J = 15.6 Hz, H_α), 8.08–6.97 (m, 12H, ArH), 3.92 (s, 3H, –OCH_3), 3.89 (s, 3H, –OCH_3); MS (EI): *m/z* 411 (M^+); *Anal*. Calcd for $C_{26}H_{21}NO_4$: C, 75.90; H, 5.14; N, 3.40; Found: C, 75.81; H, 5.06; N, 3.49.

General procedure for the synthesis of compounds 4. Chalcone **3** (10 mmol) and *o*-aminothiophenol (1.25 g, 10 mmol) were dissolved in anhydrous ethanol (60 mL). The reaction mixture was heated to reflux for 2 h in the presence of acetic acid (1.0 mL) under stirring. The solid product was separated by filtration and recrystallized from anhydrous ethanol and benzene to give compounds **4a–h** after allowing the reaction mixture to cool down to room temperature.

2,3-Dihydro-2-(2-phenoxy-quinolin-3-yl)-4-phenyl-1,5-benzothiazepine (4a). Yellow solid (71%); mp 223–224°C; FTIR ν 1592 (C=N), 1244 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.35 (s, 1H, quinolin-H_4), 8.23–7.15 (m, 18H, ArH), 5.65 (dd, 1H, H_{2x}, J_{ax} = 12.8 Hz, J_{bx} = 4.0 Hz), 3.66 (dd, 1H, H_{3b}, J_{bx} = 4.0 Hz, J_{ab} = 12.4 Hz), 3.02 (dd, 1H, H_{3a}, J_{ax} = 12.8 Hz, J_{ab} = 12.4 Hz); MS (EI): *m/z* 458 (M^+); *Anal*. Calcd for $C_{30}H_{22}N_2OS$: C, 78.57; H, 4.84; N, 6.11; Found: C, 78.53; H, 4.81; N, 6.16.

2,3-Dihydro-2-(2-phenoxy-quinolin-3-yl)-4-(4-chlorophenyl)-1,5-benzothiazepine (4b). Pale yellow solid (69%); mp 240–241°C; FTIR ν 1596 (C=N), 1249 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.34 (s, 1H, quinolin-H_4), 8.26–7.17 (m, 17H, ArH), 5.64 (dd, 1H, H_{2x}, J_{ax} = 12.8 Hz, J_{bx} = 4.0 Hz), 3.65 (dd, 1H, H_{3b}, J_{bx} = 4.0 Hz, J_{ab} = 12.4 Hz), 3.02 (dd, 1H, H_{3a}, J_{ax} = 12.8 Hz, J_{ab} = 12.4 Hz); MS (EI): *m/z* 492 (M^+); *Anal*. Calcd for $C_{30}H_{21}ClN_2OS$: C, 73.08; H, 4.29; N, 5.68; Found: C, 73.04; H, 4.26; N, 5.71.

2,3-Dihydro-2-(2-phenoxy-quinolin-3-yl)-4-(4-methoxyphenyl)-1,5-benzothiazepine (4c). Pale yellow solid (76%); mp 217–218°C; FTIR ν 1587 (C=N), 1242 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.35 (s, 1H, quinolin-H_4), 8.24–7.13 (m, 17H, ArH), 5.67 (dd, 1H, H_{2x}, J_{ax} = 12.8 Hz, J_{bx} = 4.0 Hz), 3.83 (s, 3H, –OCH_3), 3.66 (dd, 1H, H_{3b}, J_{bx} = 4.0 Hz, J_{ab} = 12.4 Hz), 3.02 (dd, 1H, H_{3a}, J_{ax} = 12.8 Hz, J_{ab} = 12.4 Hz); MS (EI): *m/z* 488 (M^+); *Anal*. Calcd for $C_{31}H_{24}N_2O_2S$: C, 76.20; H, 4.95; N, 5.73; Found: C, 76.16; H, 4.92; N, 5.78.

2,3-Dihydro-2-(2-phenoxy-7-methyl-quinolin-3-yl)-4-phenyl-1,5-benzothiazepine (4d). Yellow solid (67%); mp 214–215°C; FTIR ν 1593 (C=N), 1251 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.32 (s, 1H, quinolin-H_4), 8.20–7.16 (m, 17H, ArH), 5.62 (dd, 1H, H_{2x}, J_{ax} = 12.8 Hz, J_{bx} = 4.0 Hz), 3.60 (dd, 1H, H_{3b}, J_{bx} = 4.0 Hz, J_{ab} = 12.4 Hz), 2.96 (dd, 1H, H_{3a}, J_{ax} = 12.8 Hz, J_{ab} = 12.4 Hz); MS (EI): *m/z* 472 (M^+); *Anal*. Calcd for $C_{31}H_{24}N_2OS$: C, 78.78; H, 5.12; N, 5.93; Found: C, 78.71; H, 5.06; N, 5.97.

2,3-Dihydro-2-(2-phenoxy-7-methyl-quinolin-3-yl)-4-(4-chlorophenyl)-1,5-benzothiazepine (4e). Yellow solid (65%); mp 261–262°C; FTIR ν 1594 (C=N), 1246 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.30 (s, 1H, quinolin-H_4), 8.18–7.18 (m, 17H, ArH), 5.60 (dd, 1H, H_{2x}, J_{ax} = 12.8 Hz, J_{bx} = 4.0 Hz), 3.61 (dd, 1H, H_{3b}, J_{bx} = 4.0 Hz, J_{ab} = 12.4 Hz), 2.97 (dd, 1H, H_{3a}, J_{ax} = 12.8 Hz, J_{ab} = 12.4 Hz), 2.49 (s, 3H, -CH_3); MS (EI): *m/z* 506 (M^+); *Anal*. Calcd for $C_{31}H_{23}ClN_2OS$: C, 73.43; H, 4.57; N, 5.52; Found: C, 73.36; H, 4.48; N, 5.58.

2,3-Dihydro-2-(2-phenoxy-7-methyl-quinolin-3-yl)-4-(4-methoxyphenyl)-1,5-benzothiazepine (4f). Yellow solid (73%); mp 255–256°C; FTIR ν 1595 (C=N), 1243 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.35 (s, 1H, quinolin-H_4), 8.24–7.12 (m, 16H, ArH), 5.66 (dd, 1H, H_{2x}, J_{ax} = 12.8 Hz, J_{bx} = 4.0 Hz), 3.87 (s, 3H, –OCH_3), 3.65 (dd, 1H, H_{3b}, J_{bx} = 4.0 Hz, J_{ab} = 12.4 Hz), 3.01 (dd, 1H, H_{3a}, J_{ax} = 12.8 Hz, J_{ab} = 12.4 Hz), 2.51 (s, 3H, –CH_3); MS (EI): *m/z* 458 (M^+); *Anal*. Calcd for $C_{32}H_{26}N_2O_2S$: C, 76.47; H, 5.21; N, 5.57; Found: C, 76.38; H, 5.16; N, 5.61.

2,3-Dihydro-2-(2-phenoxy-7-methoxy-quinolin-3-yl)-4-phenyl-1,5-benzothiazepine (4g). Yellow solid (67%); mp 218–219°C; FTIR ν 1592 (C=N), 1259 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.33 (s, 1H, quinolin-H_4), 8.23–7.08 (m, 17H, ArH), 5.65 (dd, 1H, H_{2x}, J_{ax} = 12.8 Hz, J_{bx} = 4.0 Hz), 3.91 (s, 3H, –OCH_3), 3.67 (dd, 1H, H_{3b}, J_{bx} = 4.0 Hz, J_{ab} = 12.4 Hz), 3.01 (dd, 1H, H_{3a}, J_{ax} = 12.8 Hz, J_{ab} = 12.4 Hz); MS (EI): *m/z* 488 (M^+); *Anal*. Calcd for $C_{31}H_{24}N_2O_2S$: C, 76.20; H, 4.95; N, 5.73; Found: C, 76.11; H, 4.86; N, 5.79.

2,3-Dihydro-2-(2-phenoxy-7-methoxy-quinolin-3-yl)-4-(4-methoxyphenyl)-1,5-benzothiazepine (4h). Yellow solid (70%); mp 247–248°C; FTIR ν 1596 (C=N), 1248 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.34 (s, 1H, quinolin-H_4), 8.19–7.01 (m, 16H, ArH), 5.66 (dd, 1H, H_{2x}, J_{ax} = 12.8 Hz, J_{bx} = 3.9 Hz), 3.90 (s, 3H, –OCH_3), 3.86 (s, 3H, –OCH_3), 3.66 (dd, 1H, H_{3b}, J_{bx} = 3.9 Hz, J_{ab} = 12.4 Hz), 3.02 (dd, 1H, H_{3a}, J_{ax} = 12.8 Hz, J_{ab} = 12.4 Hz); MS (EI): *m/z* 518 (M^+); *Anal*. Calcd for $C_{32}H_{26}N_2O_3S$: C, 74.11; H, 5.05; N, 5.40; Found: C, 74.02; H, 4.96; N, 5.47.

General procedure for the synthesis of compounds 6 and **8**. The reaction mixture of compounds **4** (1.0 mmol) was dissolved in toluol (20 mL) in the presence of Et_3N. The reaction mixture was heated in an oil bath to reflux. Then, chloracetyl chlorides **5** (2.0 mmol) or phenoxyacetyl chlorides **7** (2.0 mmol) dissolved in the same solvent (10 mL) were added dropwise into the reaction mixture, and the reaction mixture was heated to reflux for 5 h. After allowing the reaction mixture to cool down to room

temperature, the by-product of triethylamine hydrochloride was removed by filtration, and we removed the solution *in vacuo*. Finally, the residue was purified by silica gel column chromatography (ethylacetate/petroleum ether = 1:8, v/v) to afford the desired products **6a–h** and **8a–h**, respectively.

2-Chloro-2a-phenyl-4-(2-phenoxy-quinolin-3-yl)-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepine-1-one (6a). Yellow solid (36%); mp 181–182°C; FTIR ν 1785 (C=O), 1607 (C=N), 1251 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.19 (s, 1H, quinolin-H_4), 7.94–6.73 (m, 18H, ArH), 5.08 (s, 1H, ClCH), 4.58 (dd, 1H, H_{4x}, J_{ax} = 10.9 Hz, J_{bx} = 4.7 Hz), 3.72 (dd, 1H, H_{3b}, J_{bx} = 4.7 Hz, J_{ab} = 14.4 Hz), 3.24 (dd, 1H, H_{3a}, J_{ax} = 10.9 Hz, J_{ab} = 14.4 Hz); MS (EI): *m/z* 535 (M^+); *Anal*. Calcd for $C_{32}H_{23}ClN_2O_2S$: C, 71.83; H, 4.33; N, 5.24; Found: C, 71.74; H, 4.26; N, 5.29.

2-Chloro-2a-(4-chlorophenyl)-4-(2-phenoxy-quinolin-3-yl)-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepine-1-one (6b). Yellow solid (32%); mp 187–188°C; FTIR ν 1783 (C=O), 1597 (C=N), 1247 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.16 (s, 1H, quinolin-H_4), 7.95–6.74 (m, 17H, ArH), 5.06 (s, 1H, ClCH), 4.56 (dd, 1H, H_{4x}, J_{ax} = 10.9 Hz, J_{bx} = 4.7 Hz), 3.72 (dd, 1H, H_{3b}, J_{bx} = 4.7 Hz, J_{ab} = 14.4 Hz), 3.22 (dd, 1H, H_{3a}, J_{ax} = 10.9 Hz, J_{ab} = 14.4 Hz); MS (EI): *m/z* 568 (M^+); *Anal*. Calcd for $C_{32}H_{22}Cl_2N_2O_2S$: C, 67.49; H, 3.89; N, 4.92; Found: C, 67.41; H, 3.79; N, 5.07.

***2-Chloro-2a-(4-methoxyphenyl)-4-(2-phenoxy-quinolin-3-yl)-2,2a,3,4-tetrahydro-1H-*azeto[2,1-*d*][1,5]benzothiazepine-1-one** (**6c**). Yellow solid (37%); mp 212–213°C; FTIR ν 1784 (C=O), 1609 (C=N), 1252 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.20 (s, 1H, quinolin-H_4), 7.96–6.77 (m, 17H, ArH), 5.08 (s, 1H, ClCH), 4.59 (dd, 1H, H_{4x}, J_{ax} = 10.9 Hz, J_{bx} = 4.7 Hz), 3.72 (s, 3H, –OCH_3), 3.71 (dd, 1H, H_{3b}, J_{bx} = 4.7 Hz, J_{ab} = 14.4 Hz), 3.23 (dd, 1H, H_{3a}, J_{ax} = 10.9 Hz, J_{ab} = 14.4 Hz); MS (EI): *m/z* 564 (M^+); *Anal*. Calcd for $C_{33}H_{25}ClN_2O_3S$: C, 70.14; H, 4.46; N, 4.96; Found: C, 70.02; H, 4.37; N, 4.91.

2-Chloro-2a-phenyl-4-(2-phenoxy-7-methyl-quinolin-3-yl)-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepine-1-one (6d). Yellow solid (39%); mp 203–204°C; FTIR ν 1786 (C=O), 1589 (C=N), 1241 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.14 (s, 1H, quinolin-H_4), 8.01–7.17 (m, 17H, ArH), 5.09 (s, 1H, ClCH), 4.58 (dd, 1H, H_{4x}, J_{ax} = 10.9 Hz, J_{bx} = 4.7 Hz), 3.72 (dd, 1H, H_{3b}, J_{bx} = 4.7 Hz, J_{ab} = 14.4 Hz), 3.24 (dd, 1H, H_{3a}, J_{ax} = 10.9 Hz, J_{ab} = 14.4 Hz), 2.52 (s, 1H, –CH_3); MS (EI): *m/z* 548 (M^+); *Anal*. Calcd for $C_{33}H_{25}ClN_2O_2S$: C, 72.18; H, 4.59; N, 5.10; Found: C, 72.09; H, 4.67; N, 5.14.

2-Chloro-2a-(4-chlorophenyl)-4-(2-phenoxy-7-methyl-quinolin-3-yl)-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepine-1-one (6e). Yellow solid (31%); mp 219–220°C; FTIR ν 1786 (C=O), 1601 (C=N), 1239 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.13 (s, 1H, quinolin-H_4), 8.02–7.19 (m, 16H, ArH), 5.07 (s, 1H, ClCH), 4.57 (dd, 1H, H_{4x}, J_{ax} = 10.9 Hz, J_{bx} = 4.7 Hz), 3.72 (dd, 1H, H_{3b}, J_{bx} = 4.7 Hz, J_{ab} = 14.4 Hz), 3.23 (dd, 1H, H_{3a}, J_{ax} = 10.9 Hz, J_{ab} = 14.4 Hz), 2.52 (s, 1H, –CH_3); MS (EI): *m/z* 582 (M^+); *Anal*. Calcd for $C_{33}H_{24}Cl_2N_2O_2S$: C, 67.92; H, 4.15; N, 4.80; Found: C, 67.86; H, 4.07; N, 4.85.

2-Chloro-2a-(4-methoxyphenyl)-4-(2-phenoxy-7-methyl-quinolin-3-yl)-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepine-1-one (6f). Yellow solid (35%); mp 235–236°C; FTIR ν 1785 (C=O), 1592 (C=N), 1241 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.14 (s, 1H, quinolin-H_4), 7.96–7.03 (m, 16H, ArH), 5.06 (s, 1H, ClCH), 4.59 (dd, 1H, H_{4x}, J_{ax} = 10.9 Hz, J_{bx} = 4.8 Hz), 3.72 (s, 3H, –OCH_3), 3.71 (dd, 1H, H_{3b}, J_{bx} = 4.8 Hz, J_{ab} = 14.4 Hz), 3.22 (dd, 1H, H_{3a}, J_{ax} = 10.9 Hz, J_{ab} = 14.4 Hz), 2.51 (s, 1H, –CH_3); MS (EI): *m/z* 578 (M^+); *Anal.* Calcd for $C_{34}H_{27}ClN_2O_3S$: C, 70.52; H, 4.70; N, 4.84; Found: C, 70.43; H, 4.62; N, 4.92.

2-Chloro-2a-phenyl-4-(2-phenoxy-7-methoxy-quinolin-3-yl)-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepine-1-one (6g). Yellow solid (30%); mp 195–196°C; FTIR ν 1787 (C=O), 1588 (C=N), 1234 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.12 (s, 1H, quinolin-H_4), 7.98–7.09 (m, 17H, ArH), 5.09 (s, 1H, ClCH), 4.55 (dd, 1H, H_{4x}, J_{ax} = 10.9 Hz, J_{bx} = 4.7 Hz), 3.92 (s, 1H, –OCH_3), 3.72 (dd, 1H, H_{3b}, J_{bx} = 4.7 Hz, J_{ab} = 14.4 Hz), 3.23 (dd, 1H, H_{3a}, J_{ax} = 10.9 Hz, J_{ab} = 14.4 Hz); MS (EI): *m/z* 564 (M^+); *Anal*. Calcd for $C_{33}H_{25}ClN_2O_3S$: C, 70.14; H, 4.46; N, 4.96; Found: C, 70.06; H, 4.39; N, 5.05.

2-Chloro-2a-(4-methoxyphenyl)-4-(2-phenoxy-7-methoxy-quinolin-3-yl)-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepine-1-one (6h). Yellow solid (38%); mp 276–277°C; FTIR ν 1783 (C=O), 1589 (C=N), 1244 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.12 (s, 1H, quinolin-H_4), 7.95–6.76 (m, 16H, ArH), 5.06 (s, 1H, ClCH), 4.57 (dd, 1H, H_{4x}, J_{ax} = 11.0 Hz, J_{bx} = 4.7 Hz), 3.92 (s, 1H, –OCH_3), 3.71 (s, 1H, –OCH_3), 3.72 (dd, 1H, H_{3b}, J_{bx} = 4.7 Hz, J_{ab} = 14.4 Hz), 3.20 (dd, 1H, H_{3a}, J_{ax} = 11.0 Hz, J_{ab} = 14.4 Hz); MS (EI): *m/z* 594 (M^+); *Anal*. Calcd for $C_{34}H_{27}ClN_2O_4S$: C, 68.62; H, 4.57; N, 4.71; Found: C, 68.54; H, 4.49; N, 4.81.

2-Phenoxy-2a-phenyl-4-(2-phenoxy-quinolin-3-yl)-2,2a,3,4-tetrahydro-1-1H-azeto[2,1-d][1,5]benzothiazepine-1-one (8a). Yellow solid (32%); mp 247–248°C; FTIR ν 1772 (C=O), 1588 (C=N), 1241 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.14 (s, 1H, quinolin-H_4), 7.95–6.71 (m, 23H, ArH), 5.41 (s, 1H, PhOCH), 4.63 (dd, 1H, H_{4x}, J_{ax} = 10.9 Hz, J_{bx} = 4.7 Hz), 3.70 (dd, 1H, H_{3b}, J_{bx} = 4.7 Hz, J_{ab} = 14.4 Hz), 3.30 (dd, 1H, H_{3a}, J_{ax} = 10.9 Hz, J_{ab} = 14.4 Hz); MS (EI): *m/z* 592 (M^+); *Anal*. Calcd for $C_{38}H_{28}N_2O_3S$: C, 77.00; H, 4.76; N, 4.73; Found: C, 76.92; H, 4.87; N, 4.81.

2-Phenoxy-2a-(4-chlorophenyl)-4-(2-phenoxy-quinolin-3-yl)-2,2a,3,4-tetrahydro-1-1H-azeto[2,1-d][1,5]benzothiazepine-1-one (8b). Yellow solid (36%); mp 202–203°C; FTIR ν 1771 (C=O), 1597 (C=N), 1247 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.16 (s, 1H, quinolin-H_4), 8.03–6.62 (m, 22H, ArH), 5.39 (s, 1H, PhOCH), 4.61 (dd, 1H, H_{4x}, J_{ax} = 10.9 Hz, J_{bx} = 4.8 Hz), 3.70 (dd, 1H, H_{3b}, J_{bx} = 4.8 Hz, J_{ab} = 14.4 Hz), 3.30 (dd, 1H, H_{3a}, J_{ax} = 10.9 Hz, J_{ab} = 14.4 Hz); MS (EI): *m/z* 626 (M^+); *Anal*. Calcd for $C_{38}H_{27}ClN_2O_3S$: C, 72.77; H, 4.34; N, 4.47; Found: C, 72.69; H, 4.26; N, 4.56.

2-Phenoxy-2a-(4-methoxyphenyl)-4-(2-phenoxy-quinolin-3-yl)-2,2a,3,4-tetrahydro-1-1H-azeto[2,1-d][1,5]benzothiazepine-1-one (8c). Yellow solid (30%); mp 217–218°C; FTIR ν 1767 (C=O), 1590 (C=N), 1239 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.15 (s, 1H, quinolin-H_4), 7.97–6.71 (m, 22H, ArH), 5.41 (s, 1H, PhOCH), 4.58 (dd, 1H, H_{4x}, J_{ax} = 11.0 Hz, J_{bx} = 4.7 Hz), 3.71 (dd, 1H, H_{3b}, J_{bx} = 4.7 Hz, J_{ab} = 14.4 Hz), 3.67 (s, 1H, –OCH_3), 3.31 (dd, 1H, H_{3a}, J_{ax} = 11.0 Hz, J_{ab} = 14.4 Hz); MS (EI): *m/z* 622 (M^+); *Anal.* Calcd for $C_{39}H_{30}N_2O_4S$: C, 75.22; H, 4.86; N, 4.50; Found: C, 75.13; H, 4.79; N, 4.56.

2-Phenoxy-2a-phenyl-4-(2-phenoxy-7-methyl-quinolin-3-yl)-2,2a,3,4-tetrahydro-1-1H-azeto[2,1-d][1,5]benzothiazepine-1-one (8d). Yellow solid (36%); mp 251–252°C; FTIR ν 1751 (C=O), 1596 (C=N), 1241 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.01 (s, 1H, quinolin-H_4), 7.71–6.65 (m, 22H, ArH), 5.36 (s, 1H, PhOCH), 5.26 (dd, 1H, H_{4x}, J_{ax} = 11.0 Hz, J_{bx} = 4.7 Hz), 3.94 (dd, 1H, H_{3b}, J_{bx} = 4.7 Hz, J_{ab} = 14.4 Hz), 3.30 (dd, 1H, H_{3a}, J_{ax} = 11.0 Hz, J_{ab} = 14.4 Hz), 2.49 (s, 3H, –CH_3); MS (EI): *m/z* 606 (M^+); *Anal.* Calcd for $C_{39}H_{30}N_2O_3S$: C, 77.20; H, 4.98; N, 4.62; Found: C, 77.11; H, 4.89; N, 4.71.

2-Phenoxy-2a-(4-chlorophenyl)-4-(2-phenoxy-7-methyl-quinolin-3-yl)-2,2a,3,4-te-trahydro-1-1H-azeto[2,1-d][1,5]benzothiazepine-1-one (8e). Yellow solid (39%); mp 242–243°C; FTIR ν 1772 (C═O), 1594 (C═N), 1232 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.15 (s, 1H, quinolin-H_4), 7.99–6.74 (m, 21H, ArH), 5.42 (s, 1H, PhOCH), 4.56 (dd, 1H, H_{4x}, J_{ax} = 11.2 Hz, J_{bx} = 4.8 Hz), 3.70 (dd, 1H, H_{3b}, J_{bx} = 4.8 Hz, J_{ab} = 14.4 Hz), 3.31 (dd, 1H, H_{3a}, J_{ax} = 11.2 Hz, J_{ab} = 14.4 Hz), 2.51 (s, 3H, $–CH_3$); MS (EI): *m/z* 640 (M^+); *Anal*. Calcd for $C_{39}H_{29}ClN_2O_3S$: C, 73.06; H, 4.56; N, 4.37; Found: C, 72.95; H, 4.47; N, 4.48.

2-Phenoxy-2a-(4-methoxyphenyl)-4-(2-phenoxy-7-methyl-quinolin-3-yl)-2,2a,3,4-tetrahydro-1-1H-azeto[2,1-d][1,5] benzothiazepine-1-one (8f). Yellow solid (32%); mp 233–234°C; FTIR ν 1772 (C═O), 1589 (C═N), 1246 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.17 (s, 1H, quinolin-H_4), 8.01–6.67 (m, 21H, ArH), 5.39 (s, 1H, PhOCH), 4.65 (dd, 1H, H_{4x}, J_{ax} = 10.9 Hz, J_{bx} = 4.7 Hz), 3.71 (dd, 1H, H_{3b}, J_{bx} = 4.7 Hz, J_{ab} = 14.4 Hz), 3.67 (s, 3H, $–OCH_3$), 3.30 (dd, 1H, H_{3a}, J_{ax} = 10.9 Hz, J_{ab} = 14.4 Hz), 2.52 (s, 3H, $–CH_3$); MS (EI): *m/z* 636 (M^+); *Anal*. Calcd for $C_{40}H_{32}N_2O_4S$: C, 75.45; H, 5.07; N, 4.40; Found: C, 75.36; H, 4.99; N, 4.48.

2-Phenoxy-2a-phenyl-4-(2-phenoxy-7-methoxy-quinolin-3-yl)-2,2a,3,4-tetrahydro-1-1H-azeto[2,1-d][1,5]benzothiazepine-1-one (8g). Yellow solid (30%); mp 257–258°C; FTIR ν 1768 (C═O), 1592 (C═N), 1236 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.16 (s, 1H, quinolin-H_4), 8.03–6.65 (m, 22H, ArH), 5.41 (s, 1H, PhOCH), 4.62 (dd, 1H, H_{4x}, J_{ax} = 11.1 Hz, J_{bx} = 4.7 Hz), 3.92 (s, 3H, $–OCH_3$), 3.69 (dd, 1H, H_{3b}, J_{bx} = 4.7 Hz, J_{ab} = 14.4 Hz), 3.31 (dd, 1H, H_{3a}, J_{ax} = 11.1 Hz, J_{ab} = 14.4 Hz); MS (EI): *m/z* 622 (M^+); *Anal*. Calcd for $C_{39}H_{30}N_2O_4S$: C, 75.22; H, 4.86; N, 4.50; Found: C, 75.14; H, 4.77; N, 4.59.

2-Phenoxy-2a-(4-methoxyphenyl)-4-(2-phenoxy-7-methoxy-quinolin-3-yl)-2,2a,3,4-tetrahydro-1-1H-azeto[2,1-d][1,5] benzothiazepine-1-one (8h). Yellow solid (37%); mp 211–222°C; FTIR ν 1773 (C═O), 1589 (C═N), 1235 (C–O–C) cm^{-1}; ^{1}H-NMR δ 8.17 (s, 1H, quinolin-H_4), 7.99–6.66 (m, 21H, ArH), 5.38 (s, 1H, PhOCH), 4.64 (dd, 1H, H_{4x}, J_{ax} = 10.9 Hz, J_{bx} = 4.7 Hz), 3.92 (s, 3H, $–OCH_3$), 3.71 (dd, 1H, H_{3b}, J_{bx} = 4.7 Hz, J_{ab} = 14.4 Hz), 3.66 (s, 3H, $–OCH_3$) 3.28 (dd, 1H, H_{3a}, J_{ax} = 10.9 Hz, J_{ab} = 14.4 Hz); MS (EI): *m/z* 652 (M^+); *Anal.* Calcd for $C_{40}H_{32}N_2O_5S$: C, 73.60; H, 4.94; N, 4.29; Found: C, 73.51; H, 4.87; N, 4.18.

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