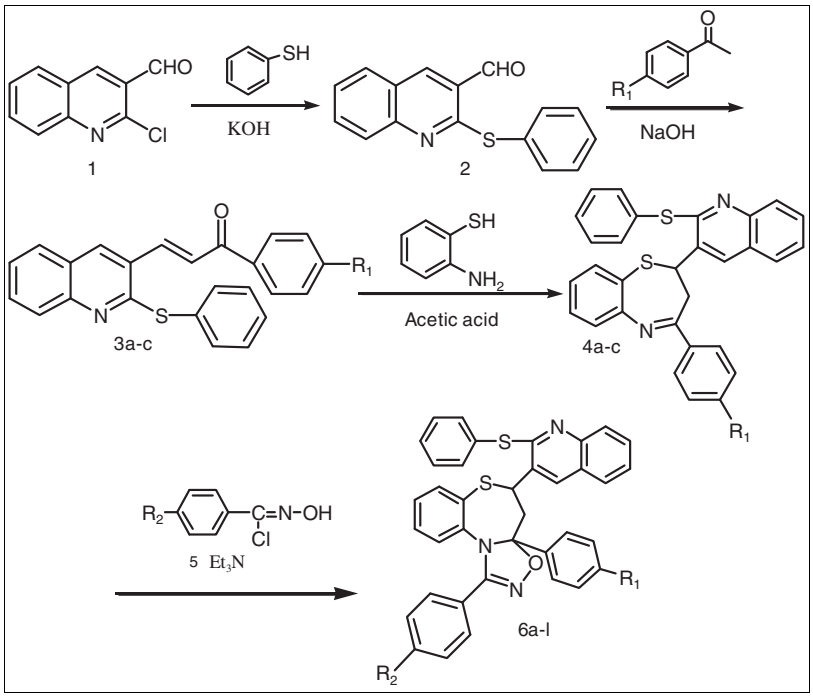
Synthesis and Structure Characterization of 1,5-Benzothiazepine Derivatives Bearing Quinoline Moiety

Y.-M. Zeng,[a]* H.-H. Zeng,[a] and F.-M. Liu[a,b]

[a]Department of Chemistry and Applied Chemistry, Changji University, Changji, 831100, People's Republic of China
[b]College of Materials and Chemical Engineering, Hangzhou Normal University, Hang Zhou 310036, People's Republic of China
*E-mail: zym903@126.com

Received June 30, 2011
DOI 10.1002/jhet.1519
Published online 15 July 2015 in Wiley Online Library (wileyonlinelibrary.com).



A series of 1,5-benzothiazepine derivatives bearing quinoline moiety were obtained by 1,5-benzothiazepine containing 2-phensulfanyl-quinoline (**4a–c**) with equimolar amounts of benzohydroximinoyl chlorides **5** in CH_2Cl_2 at room temperature. Structures of new compounds were confirmed by elemental analysis, IR, ^{1}H-NMR, MS, and X-ray diffraction analysis.

J. Heterocyclic Chem., **53**, 887 (2016).

INTRODUCTION

In recent years, quinoline is becoming increasingly important in the development of medicine and pesticide because of their excellent physiological activities such as antiproliferative [1], antimalarial [2], antitumor, DNA binding capacity [3], antiprion [4], and reversal of multidrug resistance in cancer [5] properties. Meanwhile, quinoline derivatives have been proven to show a broad spectrum of plant protection activities including bactericidal and herbicidal activities. Furthermore, quinoline derivatives are usually used as a vital intermediate for the design of numerous physiological important synthetic compounds [6–8]. Therefore, the design and synthesis of new quinoline derivatives represent a notable interest in the medicinal field.

In addition, 1,5-benzothiazepines are associated with diverse biological activities such as antibacterial [9], anticonvulsant [10], vasodilating [11], and antimicrobial [12], which is especially crucial nitrogen and sulfur-containing heterocyclic compounds. Besides, the 1,5-benzothiazepine skeleton is present in a number of drugs such as diltiazem hydrochloride [13] and thiazesim [14,15]. The different pharmacological properties associated with 1,5-benzothiazepine moiety have been commented by Bariwal *et al.* [16,17]. Recently, considerable interest has been shown in 1,5-benzothiazepines substituted with heterocyclic ring at position 2 or 4, or fixed with an additional heterocycle on the heptatomic nucleus of 1,5-benzothiazepine. Pharmaceutical properties of such compounds have received considerable attention [18,19].

Keeping the previous observations in mind and in continuation of our interest to prepare fused hetercyclic compounds [20,21], the purpose of the present work was to design and synthesize a series of novel tricyclic 1,5-benzothiazepine derivatives bearing quinoline moiety through 1,3-dipolar cycloaddition, which might exhibit enhanced biological

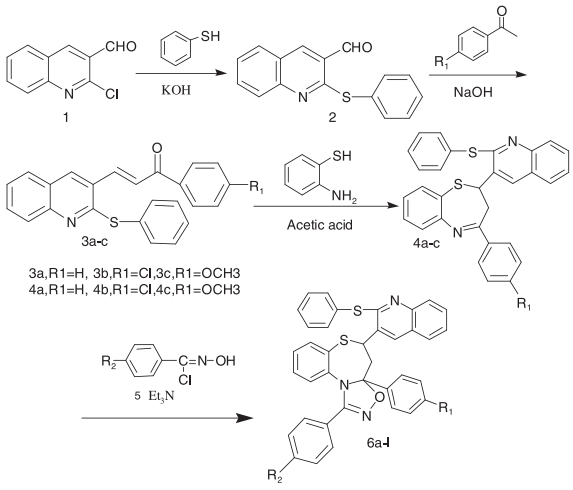
and curative activities owing to the combination of different pharmacophores into a single molecular scaffold.

RESULTS AND DISCUSSION

The syntheses of these compounds were carried out as shown in Scheme 1.

A key step in the synthesis was 1,3-dipolar cycloaddition of nitrile oxides to 1,5-benzothiazepines resulting in [1,2,4] oxadiazolo[5,4-*d*][1,5]benzothiazepines. Starting materials 2-chloro-3-quinilinecarboxaldehyde (**1**), which was easily prepared from treatment of acetanilide with a Vilsmeier reagent in excellent yield, reacted with an equimolar amount of the benzenethiol in DMSO in the presence of potassium hydroxide afforded 2-phenylthio-3-formylquinoline (**2**). Then, the α,β-unsaturated carbonyl compound (**3a–c**) were obtained by Claisen–Schmidt condensation of substituted acetophenones with **2**, which subsequently reacted with *o*-amino benzenthiol in EtOH/AcOH to give the xdesired 2,3-dihydro-2-(2-phensulfanyl-quinolin-3-yl)-4-(4-substituted-phenyl)-1,5-benzothiazepines (**4a–c**). Finally, through intermolecular 1,3-dipolar cycloaddition of **4a–c** with nitrile oxides, generated *in situ* from benzohydroximinoyl chlorides and triethylamine, leads to the target compounds 5-(2-phenylthio-quinolin-3-yl)-1,3a-diaryl-4,5-dihydro-3a*H*-[1,2,4] oxadiazolo[5,4-*d*][1,5]benzothiazepines (**6a–m**) in which an oxadiazole ring is fused at the "d" edge of the heptatomic nucleus.

Scheme 1. Synthetic process of the title compounds.



6a,R1=H,R2=H
6b,R1=H,R2=Cl
6c,R1=H,R2=OCH3
6d,R1=H,R2=CH3
6e,R1=OCH3,R2=H
6f,R1=OCH3,R2=CL
6g,R1=OCH3,R2=OCH3
6h,R1=OCH3,R2=CH3
6j,R1=Cl,R2=H
6k,R1=Cl,R2=Cl
6l,R1=Cl,R2=OCH3
6m,R1=Cl,R2=CH3

The structures of title compounds have been characterized by IR, ^{1}H-NMR, mass, and elemental analysis. The infrared spectra of these compounds show C-S-C absorption bands around 764 cm^{-1}. In ^{1}H-NMR spectra of **6a–m**, the CH_j (Ha, Hb) and CH (Hx) protons of the benzothiazepine ring resonated as a pair of doublets of doublets at δ 2.61–2.71 (Ha, dd, Jab = 14.4 Hz, Jax = 13.05–13.21 Hz), δ 3.11–3.14 (Hb, dd, Jab = 14.4 Hz, Jbx = 4.26–4.91 Hz), δ 4.11–4.15 (Hx, dd, Jax = 13.05–13.21 Hz, Jbx = 4.26–4.91 Hz). These splittings are due to vicinal coupling with the two magnetically non-equivalent protons of the methylene group at position 3 of the benzothiazepine ring. The protons belonging to the aromatic rings appeared at δ 8.04–6.70 ppm as multiplet signals. In the ^{1}H-NMR spectra of **6c**, a singlet that appeared at δ 3.82 was

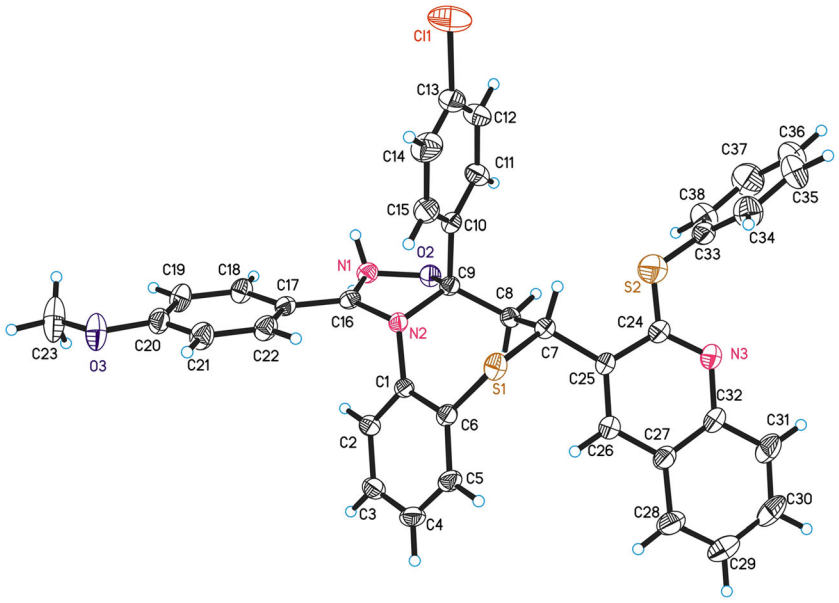


Figure 1. Molecular structure of **6l**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

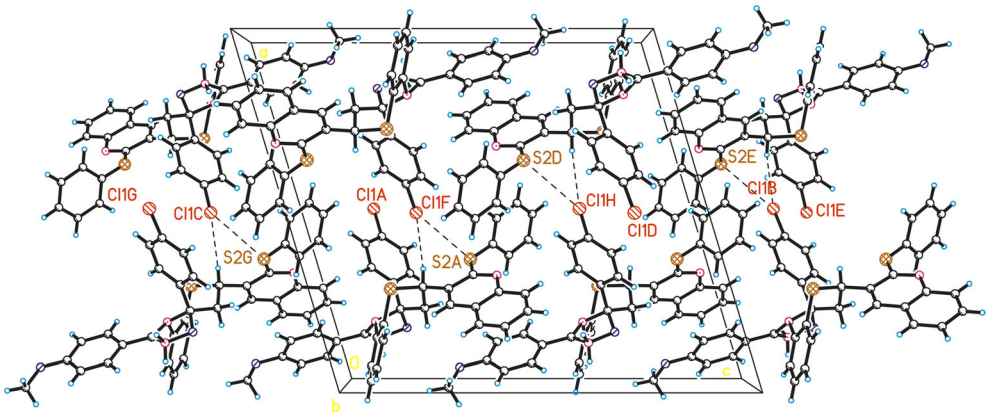


Figure 2. Packing of molecules in a unit cell of **6I**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1

Crystal data and structure refinement for compound **6I**.

Empirical formula	$C_{26}H_{18}Cl_2N_6S$	γ, deg	90
Formula weight	645.74	V, Å3	3172.5(6)
Temperature	296 K	Z	4
Wavelength	0.71073	Dc, Mg/m^3	1.352
Crystal system	Monoclinic	Crystal size, mm	0.36 × 0.26 × 0.19
Space group	P21/c	θ range, deg	1.2–27.53
a, Å	18.302(2)	μ,mm^{-1}	1.21
b, Å	8.8836(10)	reflections collected	27828
c, Å	20.370(2)	Data/restraints/parameters	7281/0/417
α, deg	90	Final R indices [I > 2σ(I)]	R1 = 0.0569, wR2 = 0.2081
β, deg	106.681(2)	Mu(MoKa) [/mm^{-1}]	0.262

Table 2

Selected bond lengths (Å), angles (°), and torsion angles (°) data of compound **6I**.

Cl(1)-C(13)	1.739(4)	N(1)-C(16)	1.282(3)
S(1)-C(6)	1.769(3)	N(2)-C(9)	1.474(3)
S(1)-C(7)	1.830(3)	N(2)-C(1)	1.426(3)
O(2)-N(1)	1.428(3)	N(2)-C(16)	1.411(3)
O(2)-C(9)	1.464(3)	N(3)-C(32)	1.374(4)
O(3)-C(20)	1.366(4)	N(3)-C(24)	1.301(4)
O(3)-C(23)	1.408(6)	C(25)-C(7)	1.525(4)
C(6)-S(1)-C(7)	101.76(13)	N(2)-C(9)-C(8)	116.2(2)
C(33)-S(2)-C(24)	118.7(3)	N(1)-C(16)-C(17)	123.4(2)
N(1)-O(2)-C(9)	104.54(18)	S(1)-C(6)-C(5)	119.9(2)
C(1)-N(2)-C(1)	119.5(2)	N(1)-C(16)-N(2)	114.0(2)

Table 3

Hydrogen-bonded geometry, distances, and angles are given in (Å) and (°).

D-H. . .A	d(D-H)	d(H. . .A)	d(D. . .A)	<(DHA)	Symmetry code
C(8)-H(8). . .S(2)	0.97	2.82	3.304(4)	111	Intra
C(7)-H(7). . .S(2)	0.98	2.36	2.756(4)	103	Intra
C(26)-H(26). . .S(1)	0.93	2.78	3.145(3)	105	Intra
C(2)-H(2). . .Cl(1)	0.98	2.77	3.670(3)	153	1 − x, 1/2 + y, 1/2 − z
C(5)-H(5). . .N(1)	0.93	2.61	3.257(3)	127	x, 1 + y, z
C(13)-Cl(1)-Cg(5)	3.856	3.955(2)	5.385(4)	138.76	1 − X, −1/2 + Y, 1/2 − Z

Table 4

Physical and analytical data of compounds **2**, **3**, and **4**.

% Analyses, Calcd/found			Formula	Color	Mp	Compound
N	H	C	mol wt	Yield%	°C	no.
5.28/5.26	4.18/4.22	72.43/72.43	$C_{16}H_{11}NOS$ 265.33	Yellow 88	123–124	**2**
3.81/3.95	4.66/4.54	78.45/78.71	$C_{24}H_{17}NOS$ 367.10	Yellow 94	135–136	**3a**
3.49/3.43	4.01/4.02	71.72/71.75	$C_{24}H_{16}NOSCl$ 401.10	White 91	121–122	**3b**
3.52/3.43	4.82/4.84	75.54/75.62	$C_{25}H_{19}NO_2S$ 397.11	Yellow 95	168–169	**3c**
5.90/5.90	4.67/4.80	75.91/75.89	$C_{30}H_{22}N_2S_2$ 474.12	White 71.3	196.8–197.6	**4a**
5.11/5.13	4.16/4.11	70.78/70.80	$C_{30}H_{21}ClN_2S_2$ 508.08	Yellow 69.5	169.1–170.5	**4b**
5.55/5.54	4.79/4.76	73.76/73.78	$C_{31}H_{24}N_2OS_2$ 504.67	Yellow 68.7	173.2–174.5	**4c**

Table 5

IR, ^{1}H-NMR, and mass of the compounds 2, 3, and 4.

Compound no.	IR (cm^{-1})	^{1}H-NMR ($CDCl_3$)	MS (EI):*m/z* (M^+)
2	1705 (C═O), 1626, (C═N), 762 (C-S-C)	9.58 (s, 1H, -CHO), 8.24 (s, 1H, quinolin-H_4), 8.10–7.19 (m, 9H, Ar-H)	265 (M^+), 236, 204, 165, 128, 101, 77, 56
3a	1659 (C═O), 1609, (C═N), 760 (C-S-C)	8.424 (s, 1H, quinolin-H_4), 8.15 (d, 1H, J = 15.6 Hz, H_β), 7.96(d, 1H, J = 15.6 Hz, H_α), 8.02–6.67 (m, 14H, Ar-H)	366 (M^+), 262, 229, 185, 105
3b	1661 (C═O), 1615 (C═N), 763 (C-S-C), 683 (C-Cl)	8.423 (s, 1H, quinolin-H_4), 8.10 (d, 1H, J = 15.6 Hz, H_β), 7.92 (d, 1H, J = 15.6 Hz, H_α), 8.03–6.69 (m, 14H, Ar-H)	402 (M^+), 292, 262, 185, 139, 111
3c	1662 (C═O), 1613 (C═N), 764 (C-S-C)	8.424 (s, 1H, quinolin-H_4), 8.18(d, 1H, J = 15.6 Hz, H_β), 7.97 (d, 1H, J = 15.6 Hz,H_α), 8.02–6.66(m, 13H, Ar-H), 3.89 (s, 3H, -OCH_3)	396 (M^+), 288, 262, 185, 135, 107
4a	3031 (Ar-H), 1613, 1513, 1473 (C═N,C═C), 761 (C-S-C)	8.20–7.12 (m, 18H, Ar-H), 5.62 (dd, 1H, H_{2x}, J_{ax} = 12.81 Hz, J_{bx} = 3.99 Hz), 3.63 (dd, 1H, H_{3b}, J_{bx} = 3.99 Hz, J_{ab} = 12.4Hz), 3.00 (dd, 1H, H_{3a}, J_{ax} = 12.81 Hz, J_{ab} = 12.4Hz)	474 (M^+), 365, 287, 211, 108
4b	3085 (Ar-H), 1599, 1515, 1474 (C═N,C═C), 762 (C-S-C)	8.19–7.10 (m, 17H, Ar-H), 5.61 (dd, 1H, H_{2x}, J_{ax} = 12.80 Hz, J_{bx} = 3.99 Hz), 3.63 (dd, 1H, H_{3b}, J_{bx} = 3.99 Hz, J_{ab} = 12.4Hz), 3.00 (dd, 1H, H_{3a}, J_{ax} = 12.80 Hz, J_{ab} = 12.4Hz)	508 (M^+), 399, 262, 245, 186, 139
4c	3049 (Ar-H), 1606, 1518, 1472 (C═N,C═C), 765 (C-S-C)	8.21–7.13(m, 17H, Ar-H), 5.60 (dd, 1H, H_{2x}, J_{ax} = 12.83 Hz, J_{bx} = 3.98 Hz), 3.83(s, 3H, -OCH_3), 3.64 (dd, 1H, H_{3b}, J_{bx} = 3.98 Hz, J_{ab} = 12.4Hz), 3.01 (dd, 1H, H_{3a}, J_{ax} = 12.83 Hz, J_{ab} = 12.4Hz)	504 (M^+), 395, 287, 241, 135

Table 6

Physical and analytical data of compound **6**.

% Analyses, Calcd/found						
N	H	C	Formula/mol wt	Color/yield%	Mp,°C	Compound no.
7.08/7.07	4.58/4.54	74.84./74.82	$C_{37}H_{27}N_2$ OS_2 593. 6	Yellow 36.7	221.1–221.8	**6a**
6.69/6.74	4.17/4.10	70.74/70.79	$C_{37}H_{26}ClN_3OS_2$ 627.12	Yellow 37.7	234.1–235.2	**6b**
6.74/6.72	4.69/4.74	73.17/73.37	$C_{38}H_{29}N_3O_2S_2$ 623.27	Yellow 35.6	205.1–206.4	**6c**
6.91/6.94	4.81/4.80	75.08/75.19	$C_{38}H_{29}N_3OS_2$ 607.18	Yellow 31.3	178.2–189.4	**6d**
6.72/6.72	4.66/4.64	73.24/73.27	$C_{38}H_{29}N_3S_2O_2$ 623.27	Yellow 39.5	215.1–215.8	**6e**
6.38/9.34	4.29/4.26	69.34/69.38	$C_{38}H_{28}N_3O_2S_2Cl$ 658.32	Yellow 38.7	245.7–246.4	**6f**
6.43/6.47	4.78/4.61	71.64/71.83	$C_{39}H_{31}N_3O_3S_2$ 653.81	Yellow 35.6	235.1–236.2	**6g**
6.59/6.64	4.90/4.83	73.44/73.44	$C_{39}H_{31}N_3O_2S_2$ 637.81	Yellow 32.8	195.7–196.3	**6h**
6.69/6.69	4.17/4.14	70.74/70.83	$C_{37}H_{26}ClN_3OS_2$ 628.20	Yellow 33.8	207.3–208.8	**6j**
6.36/6.25	3.80/3.76	67.05/67.22	$C_{37}H_{25}N_3OS_2Cl_2$ 662.65	Yellow 36.9	226.7–227.7	**6k**
6.38/6.37	4.29/4.24	69.34/69.38	$C_{38}H_{28}N_3S_2O_2Cl$ 658.23	Yellow 32.3	192.5–193.3	**6l**
6.54/6.56	4.39/4.32	71.07/71.12	$C_{38}H_{28}N_3OS_2Cl$ 642.23	Yellow 31.2	158.1–159.3	**6m**

Table 7

IR, ^{1}H-NMR, and mass of the compound (**6a–m**).

Compound no.	IR (cm^{-1})	^{1}H-NMR ($CDCl_3$)	MS (EI): *m/z* (M^+)
6a	3085 (Ar-H), 1631, 1512, 1474 (C=N,C=C), 764 (C-S-C)	8.03–6.71 (m, 24H, Ar-H), 4.01 (dd, 1H, H_{5x}, J_{ax} = 13.21 Hz, J_{bx} = 4.36 Hz), 3.11 (dd, 1H, H_{4b}, J_{bx} = 4.36 Hz, J_{ab} = 14.4 Hz), 2.71 (dd, 1H, H_{4a}, J_{ax} = 13.21 Hz, J_{ab} = 14.4 Hz)	593 (M^+), 484, 330, 263, 236, 211
6b	3043 (Ar-H), 1626, 1592, 1512 (C=N,C=C), 761 (C-S-C)	8.02–6.75 (m, 23H, Ar-H), 4.14 (dd, 1H, H_{5x}, J_{ax} = 13.14 Hz, J_{bx} = 4.38 Hz), 3.13 (dd, 1H, H_{4b}, J_{bx} = 4.38 Hz, J_{ab} = 14.4 Hz), 2.67 (dd, 1H, H_{4a}, J_{ax} = 13.14 Hz, J_{ab} = 14.4 Hz)	627 (M^+), 516, 364, 263, 236, 211
6c	3063 (Ar-H), 1632, 1538, 1462 (C=N,C=C), 764 (C-S-C)	8.02–6.79 (m, 23H, Ar-H), 4.12 (dd, 1H, H_{5x}, J_{ax} = 13.13 Hz, J_{bx} = 4.36 Hz), 3.13 (dd, 1H, H_{4b}, J_{bx} = 4.36 Hz, J_{ab} = 14.4 Hz), 2.68 (dd, 1H, H_{4a}, J_{ax} = 13.13 Hz, J_{ab} = 14.4 Hz), 3.82 (s, 3H, -OCH_3),	623 (M^+), 514, 360, 263, 236, 211
6d	3029 (Ar-H),1652,1583,1484 (C=N,C=C), 769(C-S-C)	8.01–6.74 (m, 23H, Ar-H), 4.15 (dd, 1H, H_{5x}, J_{ax} = 13.21 Hz, J_{bx} = 4.31 Hz), 3.13 (dd, 1H, H_{4b}, J_{bx} = 4.31 Hz, J_{ab} = 14.4 Hz), 2.64 (dd, 1H, H_{4a}, J_{ax} = 13.21 Hz, J_{ab} = 14.4 Hz); 2.35 (s, 3H, -CH_3).	607 (M^+), 598, 344, 246, 236, 211
6e	3056 (Ar-H), 1663, 1569, 1474 (C=N,C=C), 763 (C-S-C)	8.04–6.70 (m, 23H, Ar-H), 4.14 (dd, 1H, H_{5x}, J_{ax} = 13.21 Hz, J_{bx} = 4.35 Hz), 3.83 (s, 3H, -OCH_3), 3.11 (dd, 1H, H_{4b}, J_{bx} = 4.35 Hz, J_{ab} = 14.4 Hz), 2.65 (dd, 1H, H_{4a}, J_{ax} = 13.21 Hz, J_{ab} = 14.4 Hz)	623 (M^+), 514, 382, 360, 241, 236
6f	3049 (Ar-H), 1656, 1524, 1462 (C=N,C=C), 766 (C-S-C)	8.02–6.70 (m, 22H, Ar-H), 4.12 (dd, 1H, H_{5x}, J_{ax} = 13.12 Hz, J_{bx} = 4.31 Hz), 3.84 (s, 3H, -OCH_3), 3.13 (dd, 1H, H_{4b}, J_{bx} = 4.31 Hz, J_{ab} = 14.4 Hz), 2.67 (dd, 1H, H_{4a}, J_{ax} = 13.12 Hz, J_{ab} = 14.4 Hz)	658 (M^+), 549, 504, 394, 263, 241, 236
6g	3032 (Ar-H), 1646, 1575, 1468 (C=N,C=C), 1258 (C-O-C)	8.03–6.71 (m, 22H, Ar-H), 4.03 (dd, 1H, H_{5x}, J_{ax} = 13.05 Hz, J_{bx} = 4.26 Hz), 3.80, 3.82 (2s, 6H, -OCH_3), 3.12 (dd, 1H, H_{4b}, J_{bx} = 4.26 Hz, J_{ab} = 14.4 Hz), 2.71 (dd, 1H, H_{4a}, J_{ax} = 13.05 Hz, J_{ab} = 14.4 Hz).	653 (M^+), 544, 513, 391, 263, 241, 236
6h	3059 (Ar-H), 1689, 1574, 1457 (C=N,C=C), 762 (C-S-C)	8.03–6.69 (m, 22H, Ar-H), 4.15 (dd, 1H, H_{5x}, J_{ax} = 13.21 Hz, J_{bx} = 4.38 Hz), 3.78 (1s, 3H, -OCH_3), 3.13 (dd, 1H, H_{4b}, J_{bx} = 4.38 Hz, J_{ab} = 14.4 Hz), 2.64 (dd, 1H, H_{4a}, J_{ax} = 13.21 Hz, J_{ab} = 14.4 Hz) , 2.36 (s, 3H, -CH_3).	637 (M^+), 528, 495, 375, 264, 241, 236
6j	3018 (Ar-H), 1643, 1536, 1491 (C=N,C=C), 764 (C-S-C)	8.03–6.71 (m, 23H, Ar-H), 4.12 (dd, 1H, H_{5x}, J_{ax} = 13.21 Hz, J_{bx} = 4.89 Hz), 3.13 (dd, 1H, H_{4b}, J_{bx} = 4.89 Hz, J_{ab} = 14.4 Hz), 2.61 (dd, 1H, H_{4a}, J_{ax} = 13.21 Hz, J_{ab} = 14.4 Hz)	628 (M^+), 519, 399, 364, 263, 245, 236
6k	3035 (Ar-H), 1674, 1576, 1474 (C=N,C=C), 757 (C-S-C)	8.02–6.76 (m, 22H, Ar-H), 4.13 (dd, 1H, H_{5x}, J_{ax} = 13.14 Hz, J_{bx} = 4.79 Hz), 3.14 (dd, 1H, H_{4b}, J_{bx} = 4.79 Hz, J_{ab} = 14.4 Hz), 2.71 (dd, 1H, H_{4a}, J_{ax} = 13.14 Hz, J_{ab} = 14.4 Hz)	662 (M^+), 553, 399, 262, 245
6l	3024 (Ar-H), 1642, 1569, 1475 (C=N,C=C), 768 (C-S-C)	8.03–6.77 (m, 22H, Ar-H), 4.117 (dd, 1H, H_{5x}, J_{ax} = 13.12 Hz, J_{bx} = 4.87 Hz), 3.81 (s, 3H, -OCH_3), 3.13 (dd, 1H, H_{4b}, J_{bx} = 4.87 Hz, J_{ab} = 14.4 Hz), 2.66 (dd, 1H, H_{4a}, J_{ax} = 13.12 Hz, J_{ab} = 14.4 Hz)	658 (M^+), 549, 399, 394, 262, 245, 236
6m	3033 (Ar-H), 1674, 1576, 1474 (C=N,C=C), 767 (C-S-C)	8.04–6.69 (m, 22H, Ar-H), 4.12 (dd, 1H, H_{5x}, J_{ax} = 13.14 Hz, J_{bx} = 4.91 Hz), 3.14 (dd, 1H, H_{4b}, J_{bx} = 4.91 Hz, J_{ab} = 14.4 Hz), 2.70 (dd, 1H, H_{4a}, J_{ax} = 13.14 Hz, J_{ab} = 14.4 Hz) , 2.36 (s, 3H, -CH_3)	624 (M^+), 515, 399, 378, 262, 245, 236

attributed to the methoxy protons, a singlet at δ 4.12 due to 2-CH, two double singlets at δ2.68 and 3.13 assigned to 3-CH_2. The remaining 23 aromatic protons resonated as multiplets in the range δ 8.026–6.79. In MS spectra, molecular ion peaks of all target compounds were obtained from EI-MS, but the intensities of molecular ion peaks were very faint.

The crystal structure of **6I** is illustrated in Figure 1. An X-ray diffraction study of the compound **6I** has shown that the title compound $C_{38}H_{28}N_3S_2O_2Cl$ crystallizes in the monoclinic system with space grouping P21/c. The oxadiazoline ring displays an envelope conformation. The N1-C16 (1.282 Å) bond length is significantly shorter than N2-C16 (1.411 Å) bond distances, which clearly indicates the double bond nature of the N1-C16 bond and the single bond character of N2-C16. The phenyl ring (C17-C22) forms dihedral angles with the two phenyls (C10-C15 and C1-C6) is 88.26° and 72.73°, respectively. In addition, the quinoline ring is nearly perpendicular to the benzene ring C33-C38 with a dihedral angle of 87.30°.

Intramolecular hydrogen bonds of the type C-H. . .S are found in the three-dimensional packing arrangement of **6I** (Fig. 2). Atom C7, C8, and C26 acts as a hydrogen bond donor respectively, via H. . .S bond to generate the adjacent molecular structures. Furthermore, the structures of **6I** is linked layer by layer, in which up and down are connected by intermolecular hydrogen bonds(C-H. . .N, C-H. . .Cl) and a weak intermolecular C-C. . .Cg5 p-ring interaction at $1-X, -1/2+Y, 1/2-Z$. (Cg5 = center of gravity of a benzene ring C10-C15). Despite the fact that these interactions are not considered as formal hydrogen bonds, they contribute to crystal packing connecting the adjacent molecules in the crystal structure as illustrated in Figure 2.

EXPERIMENTAL

All melting points were recorded on an X-5 micro melting point apparatus, and temperatures were uncorrected (Maytag, Beijing, China). The IR spectra were recorded from KBr on a Bruker Tensor 27 spectrophotometer (Bruker Optics, Germany). MS results were recorded on an Agilent 5975 mass selective detector (Agilent, USA). X-ray diffraction data were obtained on a Hitachi F-4500 R-AXIS SPIDER diffractometer (Hitachi, Japan). Element analyses were performed on a Perkin-Elmer 240 CHN analyzer (Perkin-Elmer, Germany). Reactions were monitored by TLC. All starting materials and solvents were commercial materials, dried or purified by standard methods when necessary. Compounds **1** (22) and **5** (23) were prepared according to the literature methods (Tables 1–3).

General procedure for the synthesis of 2-phenylthio-3-quiniline carboxaldehyde (2). Equimolar amounts of benzenethiol (20 mmol) and potassium hydroxide (20 mmol) were dissolved in dimethyl sulfoxide (25 ml). After dissolution of the reactants, a solution of 2-chloro-3-quinilinecarboxaldehyde (**1**) was added to the mixture. The resulting solution was heated for 6 h (85–90°C). The reaction mixture was cooled to room temperature, then poured into water. A pale yellow precipitate appeared, which was filtered, washed with H_2O, and dried. The crude compound was then recrystallized from DMF/ethanol.

General procedure for the synthesis of (2*E*)-3-(2-phenylthio-quinolin-3-yl)-1-(4-substituted-phenyl)-2-propen-1-ones (3a–c). Aceto-phenone (20 mmol) was added to a solution of **2** (20 mmol) in aqueous KOH (10 mL, 35% KOH) at 0°C. The reaction mixture was stirred for 2 h at ice bath. After standing overnight, the solid was collected by filtration and washed with water. The solid was crystallized from ethanol to give crystals **3a–c**. The physical and analytical data of compound **3** are listed in Tables 4 and 5.

General procedure for the synthesis of 2,3-dihydro-2-(2-phenylthio-quinolin-3-yl)-4-(4-substituted-phenyl)-1,5-benzothia zepines (4a–c). Compound **3** (10 mmol) and *o*-aminothiophenol (10 mmol) were dissolved in anhydrous ethanol (25 mL) with 1 mL acetic acid as a catalyst. The reaction mixture was heated under reflex for 2 h, whereupon no starting materials were evident by TLC. After cooling, the separated precipitate was collected by filtration and crystallized from DMF/ethanol to yield compound **4a–c**. The physical and analytical data of compound **4** are presented in Tables 4 and 5.

General procedure for the synthesis of 5-(2-phenylthio-quinolin-3-yl)-1,3a-diaryl-4,5-dihydro-3a*H*-[1,2,4]oxadiazolo[5,4-*d*] [1,5]benzothiazepines (6a–m). To a solution of **4** (25 mmol) and benzohydroximinoyl chlorides (1.5 mmol) in 25 mL, CH_2Cl_2 was added dropwise a solution of Et_3N (0.5 mL) in the same solvent (10 mL) at room temperature over a period of 1 h. The reaction mixture was stirred for an additional 2 days at the same temperature. The solvent was evaporated under reduced pressure, and the residue was chromatographed on a silica gel column by using a mixture of EtOAc/petroleum ether(1:8 = v/v) as eulent to obtain **6a–m**. The physical and analytical data of compound **6a–m** are presented in Tables 6 and 7.

X-ray crystallography. A single crystal structure of the title compound was obtained from a solution of $CH_3COOCH_2CH_3$-CH_3CH_2OH after slow evaporation at room temperature. All non-hydrogen atoms were assigned anisotropic displacement parameters by full-matrix least-squares in the refinement. All hydrogen atoms were added at calculated positions and refined using a riding model. The crystal data and some details of the structure determination are summarized in Table 1. The selected bond lengths and bond angles are given in Table 2.

CCDC-820742 contains the supplementary crystallographic data for **6I**. These data can be obtained free of charge from the director of the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. http://www.ccdc.cam.ac.uk Fax:+44(0)1223-33 6033.

REFERENCES AND NOTES

[1] Tseng, C. H.; Tzeng, C. C.; Yang, C. L.; Lu, P. J.; Chen, H. L.; Li, H. Y.; Chuang, Y. C. J Med Chem 2002, 53, 61.

[2] Yadav, J. S.; Reddy Subba, B. V.; Premalatha, K.; Murty, M. S. R. J Mol Catalysis A: Chemical 2007, 271, 161.

[3] Sonar, S. S.; Sadaphal, S. A.; Pokalwa, R. U.; Shingate, B. B.; Shingare, M. S. J Het Chem 2010, 46, 435.

[4] Klingenstein, R.; Melnyk, P.; Leliveld, S. R.; Ryckebusch, A.; Korth, C. J Med Chem 2006, 49, 5300.

[5] Suzuki, T.; Fukazawa, N.; San-nohe, K. J Med Chem 1997, 40, 2047.

[6] Baruah, B.; Bhuyan, P. J. Tetrahedron 2009, 65, 7099.

[7] Comin, D. L.; Nolan, J. M. Org Lett 2001, 3, 1611.
[8] Carles, L.; Narkunan, K.; Penlou, S.; Rousset, L.; Bouchu, D.; Ciufolini, M. A. J Org Chem 2002, 67, 4304.
[9] Wu,X. L.; Liu, F. M.; Shen, S. W. J Het Chem 2010, 47, 1350.
[10] Garg, N.; Chandra, T.; Jain, A. B.; Kumar, A. Eur J Med Chem 2010, 45, 1529.
[11] Jiang, L.; Wan, X.; Xu, H.; Bian, J.; Han, W.; Zhu, K. J Med Coll PLA 2007, 22, 230.
[12] Wang, L.; Zhang, P.; Zhang, X.; Zhang, Y.; Li, Y.; Wang, Y. Eur J Med Chem 2009, 44, 2815.
[13] Zhang, B. X. China Pat. 2005, CN,1660117A
[14] Prakash, O.; Kumar A.; Sadana A.; Prakash R.; Singh, S. P.; Claramunt, R. M.; Sanz D. J Tetrahedron 2005, 61, 6642.
[15] Dandia, A.; Singh, R.; Khaturia, S. J Fluorine Chem 2007, 128, 524.
[16] Liu, K. C.; Shelton, B. R.; Howe, R. K. J Org Chem 1980, 45, 3916.
[17] Jitender, B.; Bariwal, K. D.; Upadhyay, A. T.; Manvar, J. C.; Trivedi, J. S.; Singh, K. S.; Jain, A. K. Eur J Med Chem 2008, 43, 2279.
[18] Greco, G.; Novellino, E.; Fiorini, I.; Nacci, V.; Campiani, G.; Ciani, S. M.; Garofalo, A.; Bernasconi, P.; Mennini, T. A. J Med Chem 1994, 37, 4100.
[19] Sarro, G. D.; Chimirri, A.; Sarro, A. D.; Gitto, R.; Grasso, S.; Zappala, M. Eur J Med Chem 1995, 30, 925.
[20] Yang, D. B.; Liu, F. M.; Xu, F.; Yang, C.; Ye, J. W.; Shen, S. W.; Zhou, Y. L.; Li, W. Mol Divers 2008, 12, 103.
[21] Zhou, Y. L.; Shen, S. W.; Liu, F. M. J Het Chem 2011, 48, 105.
[22] Devi I, Baruah B; Bhuyan P. J Syn lett 2006, 16, 2593.
[23] Shen, S.; Ye J.; Liu F. Phosphorus, Sulfur, and Silicon 2010, 185, 2366.