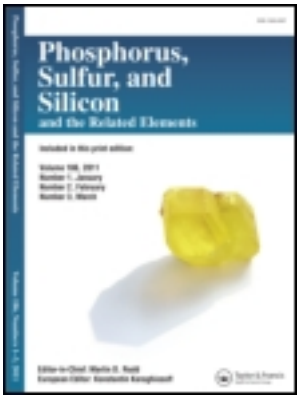

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Synthesis and Structure Characterization of Thiazolyl-Pyrazoline Derivatives Bearing Quinoline Moiety

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Version of record first published: 31 Jan 2012.

To cite this article: Yong-Ming Zen , Fei Chen & Fang-Ming Liu (2012): Synthesis and Structure Characterization of Thiazolyl-Pyrazoline Derivatives Bearing Quinoline Moiety, Phosphorus, Sulfur, and Silicon and the Related Elements, 187:3, 421-431

To link to this article: http://dx.doi.org/10.1080/10426507.2011.621002

Phosphorus, Sulfur, and Silicon, 187:421–431, 2012

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2011.621002

SYNTHESIS AND STRUCTURE CHARACTERIZATION OF THIAZOLYL-PYRAZOLINE DERIVATIVES BEARING QUINOLINE MOIETY

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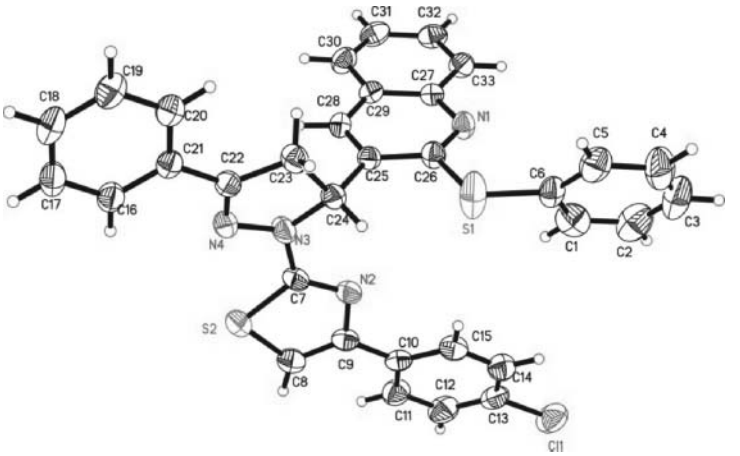
GRAPHICAL ABSTRACT



Abstract *A series of thiazolyl-pyrazoline derivatives containing the quinoline moiety were obtained by condensation of 2-bromo-1-phenyl-ethanone and 3-aryl-5-(2-substituted-quinolin-3-yl)-1-thiocarbamoyl-pyrazolines (**4a-f**). The structures of the newly synthesized compounds were characterized and their structures confirmed by IR, ^{1}H NMR, mass spectrometry and elemental analysis. The solid-state structure of 3-(4-chlorophenyl)-5-(2-phenylthio-quinolin-3-yl)-1-(4-phenyl-2-thiazoyl)-pyrazoline (**5n**) was further studied by a single-crystal X-ray diffraction analysis.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental resource: Figure S1 and Table S1.*

Keywords Thiazolyl-pyrazoline; quinoline; crystal structure; NMR spectroscopy

Received 30 June 2011; accepted 29 August 2011.

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INTRODUCTION

Quinoline ring systems represent a major class of heterocycles in which the benzene ring is fused with a pyridine ring and its derivatives have wide occurrence in natural products, as well as applications as drugs and pharmaceuticals.[1–4] Moreover, the quinoline skeleton is often used as a key intermediate for the design of pharmacologically important compounds.[5–7] Therefore, the design and synthesis of new quinoline derivatives have recently received great attention due to their broad biological and therapeutic properties such as antimalarial,[8–10] antimicrobial,[11] antibacterial,[12] and antiproliferative activities.[13] In addition, thiazole and pyrazoline derivatives are two major five-membered heterocycles, whose compounds, with these nuclei, are known to possess anticonvulsant, antidepressant, antibacterial, analgesic, antimicrobial, and anticancer activities.[14–20] The pyrazole derivative celebrex and thiazole derivative fentiazac are used as anti-inflammatory drugs.[21,22] Taking into consideration of the above properties as well as the combination principles for drug design, we herein report the synthesis of some new thiazolyl-pyrazoline derivatives with the quinoline moiety, which might exhibit enhanced activities.

REULTS AND DISCUSSION

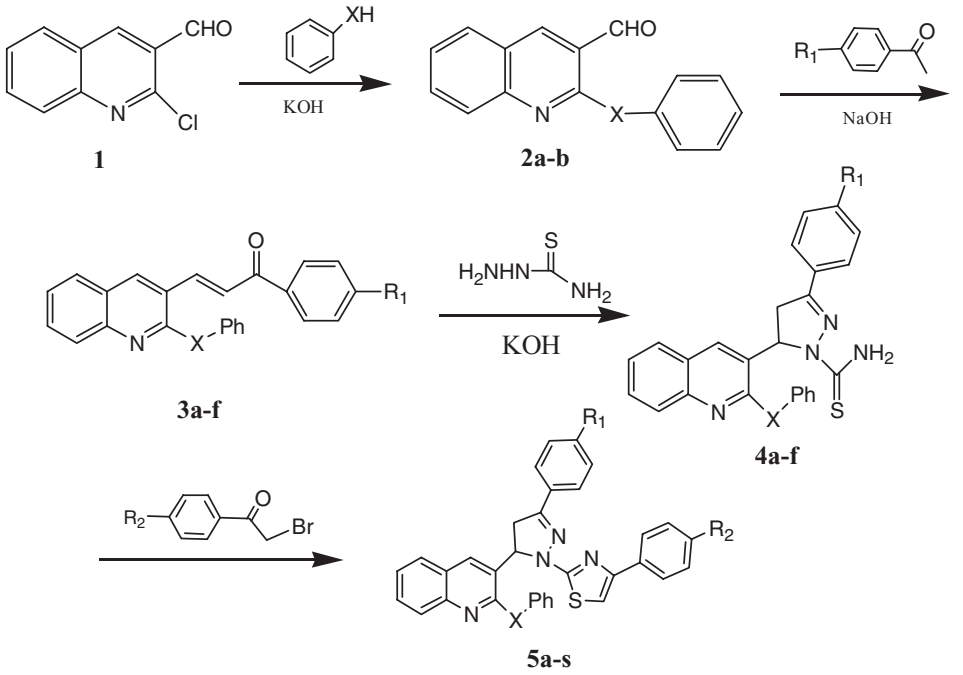
The structures of **2a–b**, **3a–f**, **4a–4f**, and **5a–s** were characterized by IR, ^{1}H NMR spectroscopy, and mass spectrometry. The structure of the compound **5n** was further elucidated by a single crystal X-ray diffraction analysis. Its crystal data, data collection, and refinement parameters are given in Table 1 and selected geometric parameters are given in Table 2. The target compounds **5a–s** were prepared as depicted in Scheme 1. In the initial step, using Claisen–Schmidt condensation, the α,β-unsaturated carbonyl compounds **3a–3f** were obtained by reacting substituted acetophenones and 2-substituted-3-formylquinoline **2a**,**b** (Tables 3 and 4). The IR spectra of **3a–f** exhibited C = O stretching modes at 1659–1663 cm^{-1}, C–O–C stretching 1241–1244 cm^{-1} and C–S–C stretching 760–763 cm^{-1} bands. In addition, in the ^{1}H NMR spectra of the compounds **3a–f**, the protons of α,β-unsaturated carbonyl compounds showed two doublets at 8.16 ppm for H_α and 7.96 ppm for H_β with 15.6 Hz as the coupling constant. So, it was inferred that they are in the trans conformations. The quinoline-H4 was observed as a doublet of doublets

Table 1 Crystal data and structure refinement for compound **5n**

Empirical formula	$C_{33}H_{23}N_4S_2Cl$	Compound	**5n**
Formula weight	575.15	γ/°	112.879 (2)
Temp (K)	296 (2) K	Z	16
Wavelength	0.71073 A	Dc (mg/m^3)	1.787
Crystal system/space group	Triclinic/P-1	Crystal size (mm)	0.45 × 0.22 × 0.16
Color/shape	White	Theta range for collection	1.76–27.53
a (Å)	10.8712 (13)	μ (mm$^{-1)}$	1.41
b (Å)	12.1353 (14)	Reflections collected	23504
c (Å)	12.2884 (3)	Data/restraints/parameters	6411/0/361
α/°	92.061 (3)	Largest difference peak/hole	0.704/−0.710
β/°	107.176 (3)	V, Å^3	1405.9(3)
Independent reflections	6411	Goodness of fit on F^2	1.042
R indices (all data)	$R1 = 0.0852$	Final R indices [I > 2σ(I)]	$R1 = 0.0521$
	$wR2 = 0.1626$		$wR2 = 0.1355$

Table 2 Selected bond lengths (Å) and angles (°) of compound **5n**

S(2)–C(8)	1.716 (3)	N(4)–N(3)	1.380 (3)
S(2)–C(7)	1.734 (2)	C(21)–C(20)	1.384 (4)
S(1)–C(6)	1.751 (3)	C(6)–C(16)	1.398 (3)
S(1)–C(5)	1.772 (2)	C(21)–C(22)	1.465 (3)
N(1)–C(26)	1.311 (3)	C(24)–N(3)	1.485 (3)
C(2)–C(7)	1.513 (3)	C(23)–C(24)	1.535 (3)
N(2)–C(7)	1.293 (3)	C(22)–C(23)	1.506 (3)
N(2)–C(9)	1.388 (3)	C(9)–C(8)	1.348 (4)
N(4)–C(22)	1.288 (3)	C(9)–C(10)	1.474 (3)
N(3)–C(7)	1.367 (3)	C(28)–C(25)–C(2)	120.9 (2)
C(26)–N(1)–C(27)	117.87 (19)	C(21)–S(1)–C(5)	106.26 (11)
C(7)–N(2)–C(9)	109.7 (2)	C(22)–N(4)–N(3)	107.96 (19)
C(20)–C(21)–C(2)	120.4 (2)	N(3)–C(24)–C(23)	100.53 (18)



(**2a**)X=O
(**3a,4a**)X=O, R_1=H
(**3b,4b**)X=O, R_1=Cl
(**5a**)X=O, R_1=H, R_2=H
(**5b**)X=O, R_1=H, R_2=Cl
(**5c**)X=O, R_1=H, R_2=OCH_3
(**5d**)X=O, R_1=Cl, R_2=H
(**5e**)X=O, R_1=Cl, R_2=Cl
(**5f**)X=O, R_1=Cl, R_2=OCH_3

(**2b**)X=S
(**3c,4c**)X=O, R_1=OCH_3
(**3d,4d**)X=S, R_1=H
(**5g**)X=O, R_1=OCH_3, R_2=H
(**5h**)X=O, R_1=OCH_3, R_2=Cl
(**5j**)X=O, R_1=OCH_3, R_2=OCH_3
(**5k**)X=S, R_1=H, R_2=H
(**5l**)X=S, R_1=H, R_2=Cl
(**5m**)X=S, R_1=H, R_2=OCH_3

(**3e,4e**)X=S, R_1=Cl
(**3f,4f**)X=S, R_1=OCH_3
(**5n**)X=S, R_1=Cl, R_2=H
(**5o**)X=S, R_1=Cl, R_2=Cl
(**5p**)X=S, R_1=Cl, R_2=OCH_3
(**5q**)X=S, R_1=OCH_3, R_2=H
(**5r**)X=S, R_1=OCH_3, R_2=Cl
(**5s**)X=S, R_1=OCH_3, R_2=OCH_3

Scheme 1

Table 3 Physical and analytical data of compounds **2–4**

Compd. no.	% Anal calcd./Found			Formula/mol. wt.	Color/yield%	Mp (°C)
	N	H	C			
2a	5.28/5.34	5.57/5.61	76.96/77.09	$C_{17}H_{15}NO_2$/265.11	Yellow/90	150–151
2b	4.98/4.86	5.37/5.42	72.57/72.73	$C_{17}H_{15}NOS$/281.09	Yellow/88	123–124
3a	3.99/3.96	4.88/4.90	82.03/82.22	$C_{24}H_{17}NO_2$/351.12	Yellow/89	183.6–184.7
3b	3.63/3.65	4.08/4.13	74.71/74.04	$C_{24}H_{161.12}ClNO_2$/410.12	Yellow/94	152.6–153.4
3c	3.67/3.74	5.02/5.21	78.72/78.63	$C_{25}H_{19}NO_3$/381.14	White/89	187–188
3d	3.81/3.95	4.66/4.54	78.45/78.71	$C_{24}H_{17}NOS$/367.10	Yellow/85	135–136
3e	3.35/3.73	4.82/4.62	71.84/71.75	$C_{25}H_{20}NOSCl$/417.10	White/91	121–122
3f	3.52/3.43	4.82/4.84	75.54/75.62	$C_{25}H_{19}NO_2S$/397.11	White/95	168–169
4a	13.20/13.16	4.75/4.74	70.73/70.67	$C_{25}H_{2o}N_4SO$/424.52	White/89	214.1–215.8
4b	12.21/12.14	4.17/4.13	65.42/65.38	$C_{25}H_{19}ClN_4SO$/458.16	Yellow/87.7	230.4–231.2
4c	12.72/12.35	4.58/4.74	68.15/68.01	$C_{25}H_{20}N_4S_2$/440.11	White/93	242.1–244.4
4d	10.02/9.94	4.15/4.10	70.68/70.79	$C_{33}H_{23}N_4SOCl$/559.08	White/94	198.8–199.6
4e	11.79/11.43	4.03/4.261	63.21/63.80	$C_{25}H_{19}ClN_4S_2$/474.07	Yellow/84	203.1–205.5
4f	11.91/11.54	4.71/4.86	66.36/67.08	$C_{26}H_{22}N_4OS_2$/470.12	Yellow/79	273.2–274.5

at 8.42–8.43 ppm, the protons belonging to the aromatic ring were seen at δ 8.13–6.66 as multiplet signals.

The chalcones were subsequently treated with thiosemicarbazide in the presence of potassium hydroxide in ethanol, to afford **4a–f**. The IR spectra of compounds **4a–f** showed the stretching band of N–H and C = S at 3410–3415 cm^{-1} and 1359–1365 cm^{-1}. Its ^{1}H NMR spectrum revealed three distinct doubles of doublets of the ABX system in the pyrazoline ring at δ 3.27–3.30 ppm, 4.01–4.04 ppm, and 6.17–6.20 ppm, respectively.

The condensation reaction between **4a–f** and 2-bromo-1-arylethanones in boiling ethanol led to the formation of **5a–s** in good yields (Tables 5 and 6). The progress of each reaction was monitored by thin layer chromatography. The IR spectra of **5a–s** showed strong stretching vibration at 1608–1589 cm^{-1}. Due to the presence of C = N and sharp absorption at 1257–1263 cm^{-1} for C–O–C single bond and strong absorption at 757–763 cm^{-1} for C–S–C bond. In addition, the ^{1}H NMR spectrum of compound **5I** shows a characteristic singlet of the quinoline-H4 at δ 7.98 ppm. Three distinct doublets of doublets at δ 3.29 ppm (Ha), δ 4.02 ppm (Hb), and δ 6.194 ppm (Hx) are attributed to the CH_2 (Ha, Hb) and CH (Hx) protons of the ABX system in the pyrazoline ring. The mass spectrum of the titled compounds revealed the existence of the molecular ion peaks and significant fragment ion peaks, which is strong evidence for the structures (Table 6).

The molecular structure of the title compound is shown in Figure 1. The higher occupancy in the three-dimensional packing arrangement is shown in Figure S 1 (Supplemental Materials).

The X-ray diffraction study of the compound **5n** has shown that 3-(4-Chlorophenyl)-5-(2-phenylthio-quinolin-3-yl)-1-(4-phenyl-2-thiazoyl)-pyrazoline($C_{33}H_{23}N_4S_2Cl$) crystallizes in the triclinic system with space grouping P-1. The compound **5n** contains four ring systems: the quinoline ring, the phenyl ring, the thiazole ring, and the pyrazoline ring. The thiazole ring as the center adopts an envelope conformation with N(2), C(7), C(8), and C(9) lying in a plane, and S(2) locates 0.23 Å out of the plane, which is nearly coplanar with the pyrazoline ring and phenyl ring C10–C15 (dihedral angle is 13.33° and 10.49°). The pyrazoline ring is almost planar with maximum deviations of 0.0339 Å for the C22 atoms,

Table 4 IR, ^{1}H NMR, and mass of compounds (**2a–b**, **3a–f**, **4a–f**)

Compd. no.	IR (cm^{-1})	^{1}H NMR ($CDCl_3$)	MS, m/z (M^+)
2a	1706 (C=O), 1617 (C=N), 1238 (C−O−C)	9.56 (s, 1H, –CHO), 8.26 (s, 1H, quinolin-H_4), 8.13–7.23 (m, 9H, Ar−H)	265 (M^+), 221, 192, 165, 143, 128, 101, 91, 78
2b	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)	281 (M^+), 236, 204, 165, 128, 101, 77, 56
3a	1661 (C=O), 1603 (C=N), 1242 (C−O−C)	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, 14H, Ar−H)	351 (M^+), 279, 258, 246,149, 135, 105, 77
3b	1663 (C=O), 1612 (C=N), 1244 (C−O−C), 689 (C−Cl)	8.42 (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, Ar−H)	410(M^+), 292, 246, 217, 139, 111, 77
3c	1660 (C=O), 1605 (C=N), 1241 (C−O−C)	8.44 (s, 1H, quinolin-H_4), 8.16 (d, 1H, J = 15.7 Hz, H_β), 7.96 (d, 1H, J = 15.7 Hz, H_α), 8.09–6.98 (m, 13H, Ar−H), 3.89 (s, 3H, $–OCH_3$)	381(M^+), 288, 246, 217, 135, 107, 92, 77
3d	1659 (C=O), 1609, (C=N), 760 (C−S−C)	8.42 (s, 1H, quinolin-H_4), 8.15 (d, 1H, J = 15.5 Hz, H_β), 7.96(d, 1H, J = 15.5 Hz, H_α), 8.02–6.67 (m, 14H, Ar−H)	366(M^+), 336, 262, 227,171, 151, 125
3e	1661 (C=O), 1615 (C=N), 763 (C−S−C) 683 (C−Cl)	8.43 (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^+), 383, 292, 262, 185, 139, 111
3f	1662 (C=O), 1613 (C=N), 762 (C−S−C)	8.44 (s, 1H, quinolin-H_4), 8.18 (d, 1H, J = 15.7 Hz, H_β), 7.97 (d, 1H, J = 15.7 Hz, H_α), 8.02–6.66 (m, 13H, Ar−H), 3.89 (s, 3H, $–OCH_3$)	396 (M^+), 288, 262, 230, 185, 135, 107
4a	3410, 3264 (N−H), 3094 (Ar−H), 1594, 1512, 1473 (C=N, C=C), 1361 (C=S)	6.15–7.85 (17H, m, Ar−H), 6.19 (dd, 1H, Hx, Jax = 12.0 Hz,Jbx = 6.4 Hz), 4.03 (dd, 1H, Ha, Jax = 12.0 Hz, Jab = 17.6 Hz), 3.29(dd, 1H, Hb, Jbx = 6.4 Hz, Jab = 17.6 Hz)	424 (M^+), 391, 364, 331, 246, 228, 201, 145, 128, 77
4b	3410, 3264 (N−H), 3043 (Ar−H), 1612, 1513, 1472 (C=N, C=C), 1364 (C=S), 763 (C−Cl)	6.83–7.69 (16H,m,Ar−H), 6.18 (dd, 1H, Hx, Jax = 12.1 Hz, Jbx = 6.3 Hz), 4.01 (dd, 1H, Ha, Jax = 12.1 Hz,Jab = 17.5 Hz), 3.27(dd, 1H, Hb, Jbx = 6.3Hz, Jab = 17.5Hz)	458 (M^+), 425, 398, 365, 320, 246, 228, 201, 128, 77
4c	3415, 3268(N−H), 3154 (Ar−H), 1592, 1516, 1472 (C=N,C=C), 1359 (C=S)	6.82–7.72 (16H, m, Ar−H), 6.17 (dd, 1H, Hx, Jax = 11.9 Hz, Jbx = 6.5 Hz), 4.04 (dd, 1H, Ha, Jax = 11.9 Hz, Jab = 17.6 Hz), 3.30 (dd, 1H, Hb, Jbx = 6.5 Hz, Jab = 17.6 Hz), 3.80 (3H, s, CH3O)	454 (M^+), 421, 394, 361, 320, 246, 228, 201, 175, 133, 77
4d	3412, 3264 (N−H), 3031(Ar−H), 1613, 1513, 1473 (C=N, C=C), 1361 (C=S)	6.70–7.59 (17H, m,Ar−H), 6.20 (dd, 1H, Hx, Jax = 12.0 Hz, Jbx = 6.4 Hz), 4.02 (dd, 1H, Ha, Jax = 12.0 Hz, Jab = 17.9 Hz), 3.28 (dd, 1H, Hb, Jbx = 6.4 Hz, Jab = 17.9 Hz)	336 (M^+), 262, 227, 200, 171, 108, 77
4e	3414, 3261 (N−H), 3085 (Ar−H), 1599, 1515, 1474 (C=N, C=C), 1365 (C=S),	6.82–7.79 (16H, m, Ar−H), 6.18 (dd, 1H, Hx, Jax = 12.0 Hz, Jbx = 6.3 Hz), 4.01 (dd, 1H, Ha, Jax = 12.0 Hz, Jab = 17.4 Hz), 3.30 (dd, 1H, Hb, Jbx = 6.3 Hz, Jab = 17.4 Hz)	365 (M^+), 330, 277, 262, 236, 228, 214, 201, 187, 153, 128

(Continued on next page)

Table 4 IR, ^{1}H NMR, and mass of compounds (**2a–b**, **3a–f**, **4a–f**) *(Continued)*

Compd. no.	IR (cm^{-1})	^{1}H NMR ($CDCl_3$)	MS, *m/z* (M^+)
4f	3415, 3265 (N−H), 3049 (Ar−H), 1606, 1518, 1472 (C=N, C=C), 1363 (C=S), 689 (C−Cl)	6.76–7.71 (16H, m, Ar−H), 6.22 (dd, 1H, Hx, Jax = 12.1 Hz, Jbx = 6.4 Hz), 4.03 (dd, 1H, Ha, Jax = 12.1 Hz, Jab = 17.6 Hz), 3.28 (dd, 1H, Hb, Jbx = 6.4 Hz, Jab = 17.6 Hz), 3.80 (3H, s, CH3O)	361 (M^+), 302, 262, 236, 187, 77, 60

whereas the quinoline ring is coplanar, which forms dihedral angles of 69.42° and 79.91° with the plane of phenyl ring C1–C6 and the pyrazoline ring, respectively. Noteworthy, the bond N(3)–N(4) (mean value 1.380(3) Å) is essentially a single bond, N(4)–C(22) (mean value 1.288(3) Å) approaches a double bond, and C(22)–C(21) (mean value 1.465(3) Å), the formal signal bond to the aryl residue, exhibits some conjugation effect (the normal C–C single bond (1.53 Å)). The C7–N3 bond distance of 1.367(3) Å is smaller than a typical C–N single bond (1.47–1.50 Å), which clearly indicates the double bond nature of the N(3)=C(7) bond due to the conjugation of N(3) with thiazole ring. The packing of the molecules in the unit cell results from the formation of C–H . . . . S intermolecular hydrogen bonding between two additional molecules. Sulfur atom (S1) forms hydrogen bonds with H–N(7) bond of the adjacent molecule but with no classical hydrogen bonds of the intramolecular type.

In conclusion, we have obtained a series of pyrazoline derivatives **5a–s** that contain both thiazole and quinoline moiety. Meanwhile, the X-ray crystallography further

Table 5 Physical and analytical data of compounds **5**

	% Anal calcd./Found					
Compd. no.	N	H	C	Formula/mol. wt.	Color/yield%	mp (°C)
5a	10.68/10.57	4.61/4.54	75.55/75.14	$C_{33}H_{24}N_4SO$/524.63	Yellow/36.7	221.1–221.8
5b	10.02/9.94	4.15/4.10	70.68/70.79	$C_{33}H_{23}ClN_4SO$/559.08	Yellow/37.7	241.1–242.4
5c	10.10/10.02	4.72/4.74	73.62/73.87	$C_{34}H_{26}N_4O2S$/554.66	Yellow/35.6	205.1–206.4
5d	10.02/9.94	4.15/4.10	70.68/70.79	$C_{33}H_{23}N_4SOCl$/559.08	Yellow/31.3	178.2–189.4
5e	9.44/9.43	3.74/3.61	66.78/66.80	$C_{33}H_{22}Cl_2N_4SO$/593.52	Yellow/39.5	215.1–215.8
5f	9.51/9.54	4.28/4.26	69.32/69.48	$C_{34}H_{25}N_4O2SCl$/589.11	Yellow/38.7	245.7–246.4
5g	10.10/10.17	4.72/4.61	73.62/73.83	C34H26N4O2S/554.66	Yellow/35.6	235.1–236.2
5h	9.51/9.44	4.28/4.23	69.32/69.64	$C_{34}H_{25}N_4O2SCl$/589.11	Yellow/32.8	195.7–196.3
5j	9.58/9.49	4.83/4.84	71.90/71.83	$C_{35}H_{28}N_4O_3S$/584.69	Yellow/33.8	207.3–208.8
5k	10.36/10.25	4.47/4.36	73.30/73.22	$C_{33}H_{24}N_4S_2$/540.70	Yellow/36.9	226.7–227.7
5l	9.74/9.69	4.03/4.14	68.91/68.88	$C_{33}H_{23}N_4S_2Cl$/575.15	Yellow/32.3	192.5–193.3
5m	9.82/9.87	4.59/4.47	71.55/71.78	$C_{34}H_{26}N_4OS_2$/570,73	Yellow/37.2	241.5–242.6
5n	9.74/9.67	4.03/4.15	68.91/68.97	$C_{33}H_{23}N_4S_2Cl$/575.15	Yellow/35.9	239.3–240.2
5o	9.19/9.14	3.64/3.25	65.02/65.18	$C_{33}H_{22}Cl_2N_4S_2$/609.59	Yellow/35.5	232.3–232.9
5p	9.26/9.28	4.16/4.33	67.48/67.43	$C_{34}H_{25}N_4OS_2Cl$/605.17	Yellow/32.4	221.3–222.4
5q	9.82/9.75	4.59/4.46	71.55/71.43	$C_{34}H_{26}N_4OS_2$/570.73	Yellow/39.7	185.2–186.5
5r	9.26/9.28	4.16/4.21	67.48/67.36	$C_{34}H_{25}ClN_4OS_2$/605.17	White/38.9	225.8–226.1
5s	9.33/9.38	4.70/4.59	69.97/70.11	$C_{35}H_{28}N_4O_2S_2$/600.75	Yellow/33.2	235.2–236.3

Table 6 IR, ^{1}H NMR, and mass of the compounds (**5a–s**)

Comp No.	IR (cm^{-1})	^{1}H NMR ($CDCl_3$)	MS.*m/z* (M^+)
5a	3085 (Ar−H), 1631, 1512, 1474 (C=N, C=C), 1257 (C−O−C)	6.15–7.85 (21H, m, Ar−H), 6.19 (dd, 1H, Hx, Jax = 11.0 Hz, Jbx = 5.1 Hz), 4.03 (dd, 1H, Ha, Jax = 11.0 Hz, Jab = 16.8 Hz), 3.29 (dd, 1H, Hb, Jbx = 5.1 Hz, Jab = 16.8 Hz)	524 (M^+), 491, 431, 328, 246, 174, 129, 77
5b	3043 (Ar−H), 1626, 1592, 1512 (C=N, C=C), 1261 (C−O−C)	6.46–7.77 (20H, m, phenyl–H), 6.21 (dd, 1H, H_x, J_{ax} = 10.9 Hz, J_{bx} = 4.9 Hz), 4.12 (dd, 1H, H_a, J_{ax} = 10.99 Hz, J_{ab} = 16.8 Hz), 3.31 (dd, 1H, H_b, J_{bx} = 4.97 Hz, J_{ab} = 16.8 Hz)	5 558 (M^+), 525, 465, 362, 246, 220, 127
5c	3063 (Ar−H), 1632, 1538, 1462 (C=N, C=C), 1261 (C−O−C)	6.15–7.85 (20H, m, Ar−H), 6.23 (dd, 1H, H_x, J_{ax} = 10.9 Hz,J_{bx} = 5.0 Hz), 3.99 (dd, 1H, H_a, J_{ax} = 10.9 Hz, J_{ab} = 16.8 Hz), 3.75 (3H, s, CH_3O), 3.30 (dd, 1H, H_b, J_{bx} = 5.0 Hz, J_{ab} = 16.8Hz)	554 (M^+), 482, 424, 364, 246, 145, 128
5d	3029 (Ar−H), 1652, 1583, 1484 (C=N, C=C), 1263 (C−O−C), 749 (C−Cl)	6.15–7.85 (20H, m, Ar−H), 6.20 (dd, 1H, H_x, J_{ax} = 11.0 Hz, J_{bx} = 4.9 Hz), 4.02 (dd, 1H, H_a, J_{ax} = 11.0 Hz, J_{ab} = 16.7 Hz), 3.31 (dd, 1H, H_b, J_{bx} = 4.9 Hz, J_{ab} = 16.7 Hz)	558 (M^+), 525, 465, 246, 220, 174, 129
5e	3056 (Ar−H), 1663, 1569, 1474 (C=N, C=C), 1264 (C−O−C), 783 (C−Cl)	6.15–7.85 (19H, m, Ar−H), 6.18 (dd, 1H, H_x, J_{ax} = 10.9 Hz, J_{bx} = 5.0 Hz), 4.01 (dd, 1H, H_a, J_{ax} = 10.9 Hz, J_{ab} = 16.8 Hz), 3.29 (dd, 1H, H_b, J_{bx} = 5.0 Hz, J_{ab} = 16.8 Hz)	592 (M^+), 499, 398, 362, 246, 220, 173, 139, 111, 77
5f	3049 (Ar−H), 1656, 1524, 1462 (C=N, C=C), 1263 (C−O−C), 689 (C−Cl)	6.15–7.85 (18H, m, Ar−H), 6.19 (dd, 1H, H_x, J_{ax} = 11.0 Hz, J_{bx} = 4.9 Hz), 4.02 (dd, 1H, H_a, J_{ax} = 11.0 Hz, J_{ab} = 16.7 Hz), 3.76 (3H, s, CH_3O), 3.30 (dd, 1H, H_b, J_{bx} = 4.9 Hz, J_{ab} = 16.7 Hz)	588 (M^+), 555, 495,374, 358, 294, 246, 189, 159, 127, 77, 60
5g	3032 (Ar−H), 1646, 1575, 1468 (C=N, C=C), 1258 (C−O−C)	6.15–7.85 (20H,m,Ar−H), 6.24 (dd, 1H, C_5–H_x, J_{ax} = 10.9 Hz, J_{bx} = 5.0 Hz), 4.10 (dd, 1H, C_4–H_a, J_{ax} = 10.9 Hz, J_{ab} = 16.8 Hz), 3.32 (dd, 1H, C_4–H_b, J_{bx} = 5.0 Hz, J_{ab} = 16.8 Hz)	554 (M^+), 506, 445, 292, 246, 189, 133
5h	3059 (Ar−H), 1689, 1574, 1457 (C=N, C=C), 1259 (C−O−C), 738 (C−Cl)	6.15–7.85 (19H, m, Ar−H), 6.16 (dd, 1H, H_x, J_{ax} = 11.0 Hz, J_{bx} = 5.0 Hz), 3.98 (dd, 1H, H_a, J_{ax} = 11.0 Hz, J_{ab} = 16.7 Hz), 3.32 (dd, 1H, H_b, J_{bx} = 5.0 Hz, J_{ab} = 16.7 Hz)	588 (M^+), 555, 495, 379, 264, 294, 246, 173, 133, 77
5j	3018 (Ar−H), 1643, 1536, 1491 (C=N, C=C), 1258 (C−O−C)	6.15–7.85 (19H, m, Ar−H), 6.21 (dd, 1H, H_x, J_{ax} = 11.0 Hz, J_{bx} = 5.0 Hz), 4.07 (dd, 1H, H_a, J_{ax} = 11.0 Hz, J_{ab} = 16.8 Hz), 3.81 (3H, s, CH_3O), 3.28 (dd, 1H, H_b, J_{bx} = 5.0 Hz, J_{ab} = 16.8 Hz)	584 (M^+), 536, 491, 246, 189, 133, 77
5k	3035 (Ar−H), 1674, 1576, 1474 (C=N, C=C), 757 (C−S−C)	6.15–7.85 (21H, m, Ar−H), 6.13 (dd, 1H, H_x, J_{ax} = 11.0 Hz, J_{bx} = 5.0 Hz), 4.02 (dd, 1H, H_a, J_{ax} = 11.0 Hz, J_{ab} = 16.8 Hz), 3.29 (dd, 1H, H_b, J_{bx} = 5.0 Hz, J_{ab} = 16.8 Hz)	539 (M^+), 508, 460,163, 127, 77, 57
5l	3024 (Ar−H), 1642, 1569, 1475 (C=N,	6.15–7.85 (20H, m, Ar−H), 6.19 (dd, 1H, H_x, J_{ax} = 11.0 Hz, J_{bx} = 5.0 Hz), 4.02	575 (M^+), 574, 541, 465, 438, 362, 287, 262, 236,

(Continued on next page)

Table 6 IR, ^{1}H NMR, and mass of the compounds (**5a–s**) *(Continued)*

Comp No.	IR (cm^{-1})	^{1}H NMR ($CDCl_3$)	MS.*m*/*z* (M^+)
	C=C), 768 (C−S−C), 723 (C−Cl)	(dd, 1H, H_a, J_{ax} = 11.0 Hz, J_{ab} = 16.8 Hz), 3.29 (dd, 1HH_b, J_{bx} = 5.0 Hz, J_{ab} = 16.8 Hz)	163, 127, 77
5m	3032 (Ar−H), 1646, 1576, 1474 (C=N, C=C), 763 (C−S−C)	6.15–7.85 (20H, m, Ar−H), 6.16 (dd, 1H, H_x, J_{ax} = 11.0 Hz, J_{bx} = 4.9 Hz), 4.03 (dd, 1H, H_a, J_{ax} = 11.0 Hz, J_{ab} = 16.7 Hz), 3.74 (3H, s, CH_3O), 3.30 (dd, 1H, H_b, J_{bx} = 4.9 Hz, J_{ab} = 16.7 Hz)	570 (M^+), 465, 304, 236, 163, 127, 77, 57
5n	3062 (Ar−H), 1647, 1579, 1476 (C=N, C=C), 761 (C−S−C), 692 (C−Cl)	6.15–7.85 (20H, m, Ar−H), 6.19 (dd, 1H, H_x, J_{ax} = 10.9 Hz, J_{bx} = 4.9 Hz), 3.99 (dd, 1H, H_a, J_{ax} = 10.9 Hz, J_{ab} = 16.8 Hz), 3.32 (dd, 1H, H_b, J_{bx} = 4.9 Hz, J_{ab} = 16.8 Hz)	575 (M^+), 512, 479, 378, 170, 133, 115, 77
5o	3051 (Ar−H), 1678, 1590, 1463(C=N, C=C), 762 (C−S−C), 749 (C−Cl)	6.15–7.85 (19H, m, Ar−H), 6.21 (dd, 1H, H_x, J_{ax} = 11.0Hz, J_{bx} = 4.9 Hz), 4.05 (dd, 1H, H_a, J_{ax} = 11.0 Hz, J_{ab} = 16.7 Hz), 3.29 (dd, 1H, H_b, J_{bx} = 4.9 Hz, J_{ab} = 16.7 Hz)	608 (M^+), 584, 479, 364, 337, 308, 274, 241, 186, 137, 121
5p	3022 (Ar−H), 1653, 1589, 1475 (C=N, C=C), 763 (C−S−C), 728 (C−Cl)	6.15–7.85 (19H, m, Ar−H), 6.15 (dd, 1H, H_x, J_{ax} = 11.0 Hz, J_{bx} = 5.0 Hz), 3.98 (dd, 1H, H_a, J_{ax} = 11.0 Hz, J_{ab} = 16.8 Hz), 3.76 (3H, s, CH_3O), 3.30 (dd, 1H, H_b, J_{bx} = 5.0 Hz, J_{ab} = 16.8 Hz)	605 (M^+), 540, 512, 479, 375, 321, 256, 191, 170, 159, 115
5q	3034 (Ar−H), 1665, 1574, 1488 (C=N, C=C), 758 (C−S−C)	6.15–7.85 (20H, m, Ar−H), 6.17 (dd, 1H, H_x, J_{ax} = 11.0 Hz, J_{bx} = 4.9 Hz), 3.99 (dd, 1H, H_a, J_{ax} = 11.0 Hz, J_{ab} = 16.8 Hz), 3.80 (3H, s, CH_3O), 3.29 (dd, 1H, H_b, J_{bx} = 4.9 Hz, J_{ab} = 16.8 Hz)	570 (M^+), 506, 478, 317, 239, 175, 77
5r	3040 (Ar−H), 1654, 1589, 1484 (C=N, C=C), 759 (C−S−C), 763 (C−Cl)	6.15–7.85 (19H, m, Ar−H), 6.24 (dd, 1H, H_x, J_{ax} = 11.0 Hz, J_{bx} = 4.9 Hz), 4.02 (dd, 1H, H_a, J_{ax} = 11.0 Hz, J_{ab} = 16.7 Hz), 3.80 (3H, s, CH_3O), 3.35 (dd, 1H, C_4–H_b, J_{bx} = 4.9 Hz, J_{ab} = 16.7 Hz)	605 (M^+), 541, 478, 344, 256, 239, 191, 115
5s	3052 (Ar−H), 1647, 1593, 1479 (C=N, C=C), 762 (C−S−C)	6.15–7.85 (19H, m, Ar−H), 6.18 (dd, 1H, H_x, J_{ax} = 10.9 Hz, J_{bx} = 5.0 Hz), 4.01 (dd, 1H, H_a, J_{ax} = 10.9 Hz, J_{ab} = 16.7 Hz), 3.82 (6H, s, CH_3O), 3.31 (3H, s, CH_3O), 3.34 (dd, 1H, H_b, J_{bx} = 5.0 Hz, J_{ab} = 16.7 Hz).	600 (M^+), 508, 475, 254, 205, 170

confirmed the molecular conformation of 3-(4-Chlorophenyl)-5-(2-phenylthio-quinolin-3-yl)-1-(4-phenyl-2-thiazoyl)-pyrazo-line.

EXPERIMENTAL

All purchased solvents and chemicals were of analytical grade and were used without further purification. All reagents were of commercial availability. The starting compound **1**[23] were prepared according to previously reported procedures. Melting points were measured on a mettler FP-5 capillary melting point apparatus and were uncorrected. Elemental

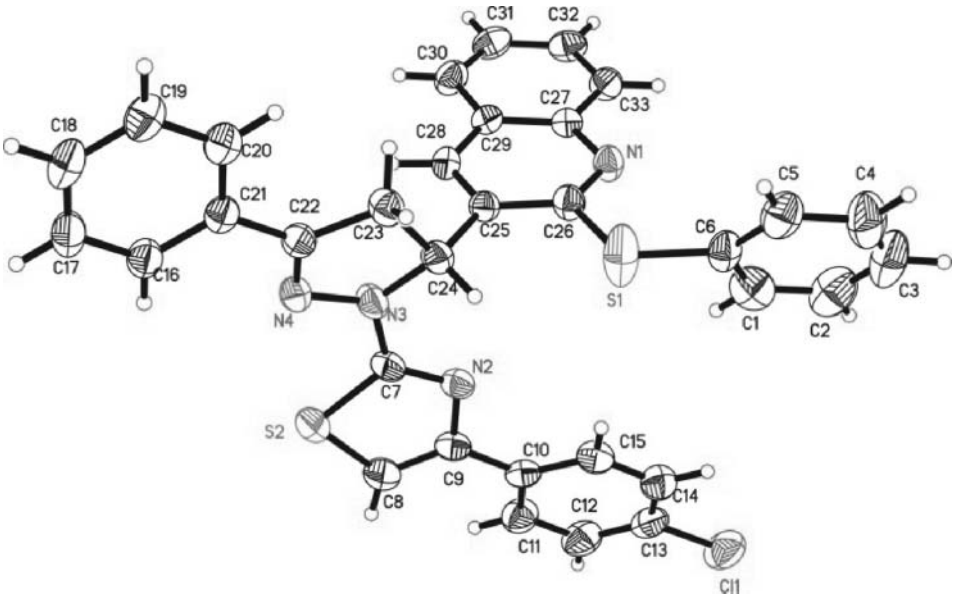


Figure 1 Molecular structure of **5n**.

analyses were performed on a PerkinElmer 2400 elemental analyzer. The solid-state IR spectra were recorded from potassium bromide pellet on a Bruker Tensor 27 Spectrophotometer. The ^{1}H NMR spectra were recorded on a Varian Inova-400 spectrophotometer using $CDCl_3$ as the deuterated solvent and TMS as the internal standard at room temperature. Electron-impact–mass spectrometry (EI-MS) spectra were obtained with an Agilent 5975 apparatus.

General Procedure (2a–b): 2-Substituted-3-formylquinoline

Equimolar amounts of the phenol or benzenethiol (20 mmol) and potassium hydroxide (20 mmol) were dissolved in dimethyl sulfoxide (10 mL). After dissolution of the reactants, a solution of **1** (20 mmol) was added dropwise to dimethyl sulfoxide. The mixture was refluxed for 6 h (85 °C–90 °C) and monitored by TLC until the reaction was completed. After cooling, the reaction mixture was poured into ice water and neutralized with dilute hydrochloric acid to pH 5–6.

General Procedure (3a–f): 3-(2-Substituted- quinolin-3-yl)-1-aryl-2-propen-1-ones

Acetophenone (20 mmol) was added to a solution of **2a–b** (20 mmol) in aqueous KOH (10 mL, 35% KOH) at 0 °C. The reaction mixture was stirred for 2 h at ice temperature. After standing overnight, the solid was collected by filtration and washed with water to give crystals **3a–f**.

General Procedure (4a–f): Reaction of α,β-unsaturated Ketone and Thiosemicarbazide

A mixture of the appropriate **3a–f** (5 mmol) and thiosemicarbazide (6 mmol) was refluxed in ethanol (50 mL). After dissolution of the reactants, a solution of KOH (12.5 mmol) in water (5 mL) was added dropwise. The solution was refluxed for a further 4 h. The reaction mixture was allowed to cool and poured into crushed ice, and the solid mass separated out was filtered, washed with cold ethanol, dried, and crystallized.

General Procedure (5a–s): Reaction with 2-bromo-1-phenyl-ethanone and Thiocarbamoyl-pyrazoline

A mixture of **4a–f** (0.5 mmol) and 2-bromo-1-phenyl-ethanone (0.5 mmol) in ethanol (30 mL) was heated under reflux for 30 min. The reaction mixture was cooled to room temperature. The crude product separated by filtered was recrystallized to give **5a–s**.

X-Ray Structure Determination of 5n. Single crystals were obtained by slow evaporation of an ethanol solution. The data on a crystal with dimensions 0.45 × 0.22 × 0.16 mm were collected on a Bruker SMART APEX-IICCD diffractometer up to (2θ) max of 55.03° at 296(2) K with graphite-monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å) using multiscan techniques. A total of 6411 (Rint = 0.0290) independent reflections were collected, among which 23504 reflections were considered as observed [$I > 2\sigma(I)$] and used for the structure refinement. The structures were solved by direct methods and refined by full matrix least squares with the Bruker's SHELXL-97 program. All nonhydrogen atoms were refined anisotropically, and the hydrogen atom involved in the hydrogen bond was found in the difference Fourier map; all other hydrogen atoms were located geometrically, and all hydrogens were refined as "riding model" with their Uiso's set at 1.2 (1.4 for methyl groups) times the Ueq values of the appropriate carrier atoms. Figure 1 was drawn using the XP program. Cell data for $C_{33}H_{23}N_4S_3Cl$, Triclinic, space group P-1, $a = 10.8712$ (13) Å, $b = 12.1353(14)$ Å, $c = 12.2884(915)$ Å, $Z = 16$, cell volume = 1405.9(3) Å^3, $\mu = 1.41$ mm^{-1}. The final R_1 and wR_2 values are 0.0521 and 0.1355, respectively, for 6411 independent reflections [$I > 2\sigma(I)$] and 361 parameters.

CCDC-819890 contains all bond lengths and angles, coordinates, and displacement parameters for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC) via e-mail: deposit @ccdc.cam.ac.uk.

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