

One-Pot Quinazolin-4-yl-thiourea Synthesis via *N*-(2-Cyano-phenyl)benzimidoyl isothiocyanate

Fathalla, W.¹, Čajan, M.^{1,2}, Marek, J.³ and Pazdera, P.^{1,*}

¹ Department of Organic Chemistry, Faculty of Science, Masaryk University, Brno, Czech Republic, Tel.: +420 5 41129305, Fax: +420 5 41211214,

² Laboratory of Biomolecular Structure and Dynamics, Faculty of Science, Masaryk University, Brno, Czech Republic.

³ Department of Inorganic Chemistry, Masaryk University, 611 37 Brno, Czech Republic.

*Author to whom correspondence should be addressed; E-mail: pazdera@chemi.muni.cz

Received: 10 November 2000; in revised form 22 May 2001 / Accepted: 23 May 2001 / Published: 30 June 2001

Abstract: 1-substituted-3-(2-phenylquinazolin-4-yl) thioureas (**7**) were produced by an intramolecular cycloaddition reaction of 1-substituted-3-[(2-cyanophenylimino)phenylmethyl] thioureas (**3**). These compounds in turn were prepared by the reaction of *N*-(2-cyanophenyl)benzimidoyl isothiocyanate (**2**) with primary amines. The structures of products **7** were confirmed by FTIR, ¹H-NMR, ¹³C-NMR, mass spectroscopy and X-ray crystallography.

Keywords: 1-(2-phenylquinazolin-4-yl)-3-substituted thioureas; 1-[(2-cyanophenylimino)phenylmethyl]-3-substituted thioureas; *N*-(2-cyanophenyl)-benzimidoyl isothiocyanate; *one-pot* synthesis; amidinoyl isothiocyanates.

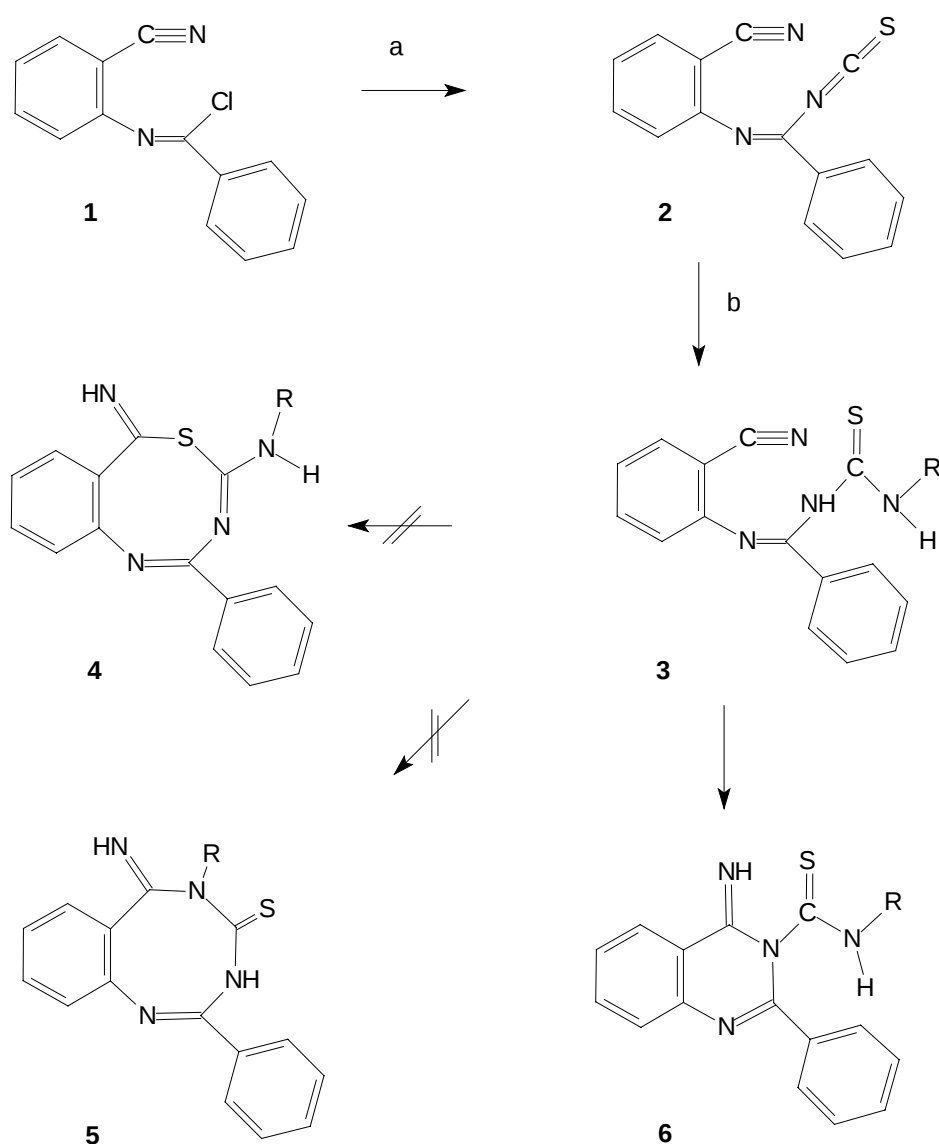
Introduction

This work is a continuation of our studies of the competition between the sulfur and nitrogen atoms in a thioamide moiety towards intermolecular and intramolecular reactions with electrophiles [1-3]. The intramolecular cycloaddition reaction of the product formed *in situ* by addition of

secondary amines to *N*-(2-cyanophenyl)benzimidoyl isothiocyanate affords 1,1-disubstituted-3-(2-phenyl-3*H*-quinazolin-4-ylidene)thioureas [3]. These cyclic products are formed via a *one-pot* reaction sequence including cyclization, Dimroth rearrangement and tautomerisation steps, as reported in [3].

Results and Discussion

The extension of such a reaction to include primary amines, anilines, heterocyclic amines, and adamantanamine derivatives is now reported in this paper. The reaction proceeds by the addition of primary amines to *N*-(2-cyanophenyl)benzimidoyl isothiocyanate (**2**) to predictably give the thiourea derivatives **3** [3] (Scheme 1).

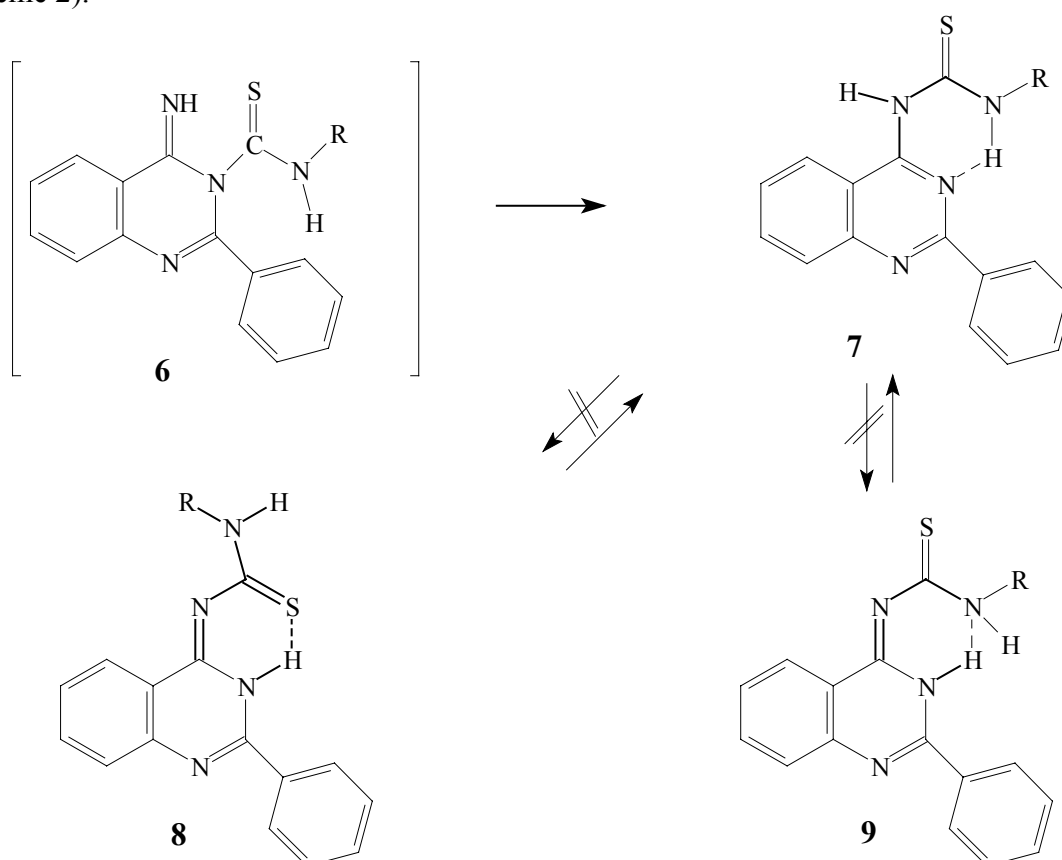


a: KSCN, acetone, -5°C , 2h; *b*: NH_2R , acetone, 25°C , 24 h.

Scheme 1. Reaction of the **2** with primary amines and possible reaction pathways

These thioureas **3** contain three active nucleophilic sites capable of attacking the available nitrile group *via* an intramolecular cycloaddition reaction. The expected products might conceivably be one or all of the following cyclic products: benzothiadiazocine derivatives (**4**) arising *via* sulfur attack [4-6], quinazoline derivatives (**6**) *via* nitrogen attack [3] or finally the benzotriazocines (**5**) *via* nitrogen attack. The reaction could be further extended to involve the Dimroth rearrangement product or could involve tautomerisation to the more stable tautomer [3].

The intramolecular addition reaction of thioureido derivatives containing functionalized carboxyl groups under neutral and basic conditions takes place on the nitrogen atom [7-8]. Consequently, the expected products formed were either the quinazoline **6** or the benzotriazocine **5** derivatives. Of these two options we might expect the quinazoline derivative **6** to be more favored due to the fact that their formation involves creation of a thermodynamically more stable six membered ring. The expected quinazoline derivative **6** might then undergo a Dimroth rearrangement to finally afford the 1-(2-phenylquinazolin-4-yl)-3-substituted thioureas **7**. The quinazolines **7** can be stabilized by hydrogen bond interactions to afford an extra six membered ring as shown in Scheme 2. These compounds **7** could undergo a tautomerisation reaction by the transition of the proton of the N(1) of the substituted thioureas to N(3) of the quinazoline ring to give either of the conformations **8** or **9** that might also be stabilized by hydrogen bond interactions (Scheme 2).



Scheme 2. Possible interconversions from **6** to **9** *via* Dimroth rearrangement and tautomerisation processes.

The spectral data confirmed that the structures of the isolated products were indeed **7**. The secondary amine examples behaved differently, undergoing tautomerisation to give the more stable tautomer to thus afford 1,1-disubstituted-3-(2-phenyl-3*H*-quinazolin-4-ylidene)thioureas [3]. Discrimination between the possible structures of compounds **4-9** was possible using their spectral data as follows: the infrared spectra show both the disappearance of the $\nu(\text{NCS})$ and $\nu(\text{CN})$ bands present in case of the isothiocyanate **2** and the presence of νNH and $\nu(\text{C}=\text{N})$ bands at 3220 cm^{-1} and 1613 cm^{-1} , respectively, for the cyclic forms **7**.

The most important peak shown by the ^{13}C -NMR, which plays an important role in the structure identification of the cyclic products, is the one corresponding to the $\text{C}=\text{S}$ group with a chemical shift of ca 183-184 ppm. Naturally, it is observed in the case of the quinazoline structures **6-9** and the benzotriazocines **5** but not the thiadiazocines **4**.

The ^1H -NMR spectra show great similarity to the simulated computer spectra; they display an important peak at ca 14 ppm (in the case of the substituted anilines) corresponding to the NH group, which together with X-ray analysis, confirms the hydrogen bond interactions between the quinazoline N(3) and the hydrogen atom of the arylamino group (Scheme 2). The spectra in the case of the aliphatic analogues displayed a peak at ca 12 ppm corresponding to the hydrogen of the alkylamino group. We might expect that the peaks corresponding to NH groups that have interactions with the thiocarbonyl group as in **8** will appear at ca 16 ppm as in the case of secondary amine analogues [3]. The ^1H -NMR spectrum of product **7f** ($\text{R} = \text{Ph}$) was measured in CDCl_3 at temperature ranging from -30°C to 30°C in order to check whether these three conformers **7-9** interconvert or not, but no changes were observed in the resultant spectra. The ^1H -NMR spectrum of **7b** gave a doublet peak at ca 4.98 ppm due to the interaction between the CH_2 group and the neighboring NH group. Measurement of the ^1H -NMR spectrum in $\text{CDCl}_3/\text{D}_2\text{O}$, to give a singlet peak at ca 4.97 ppm, proved this.

The mass spectra for all examined products **7** showed the molecular ion, followed by a molecular fragment at m/e 33 which represents the SH moiety and the tricyclic residue of the isolated product at m/e 337 of compound **7g** ($\text{R} = p\text{-tolyl}$). This last result confirms that the sulfur atom is exocyclic unlike the secondary amine examples where such a fragment is not formed indicating that the sulfur atom is endocyclic. Other fragmentations are represented in Figure 1

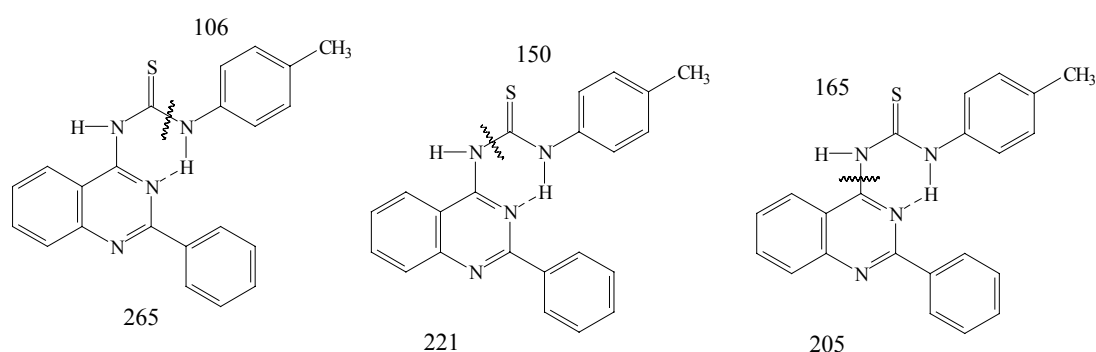


Figure 1. Mass spectral fragmentations of **7g**.

Single crystals of **7f**, **7a** and **7b** (R= Ph, n-butyl and benzyl, respectively) were used for X-ray analysis [9]. These substituents cover a range of different types to ensure that the structure of the final product is not dependent on the substituent, or the basicity of the amines compared to the anilines [3]. The structural data presented in Tables 1-3 correspond to a great extent with those calculated by the *ab initio* DFT quantum chemistry methods for **7f** (R= Ph) [9]. The ORTEP diagram and the calculated model of compound **7f** are shown in Figures 2 and 3, respectively.

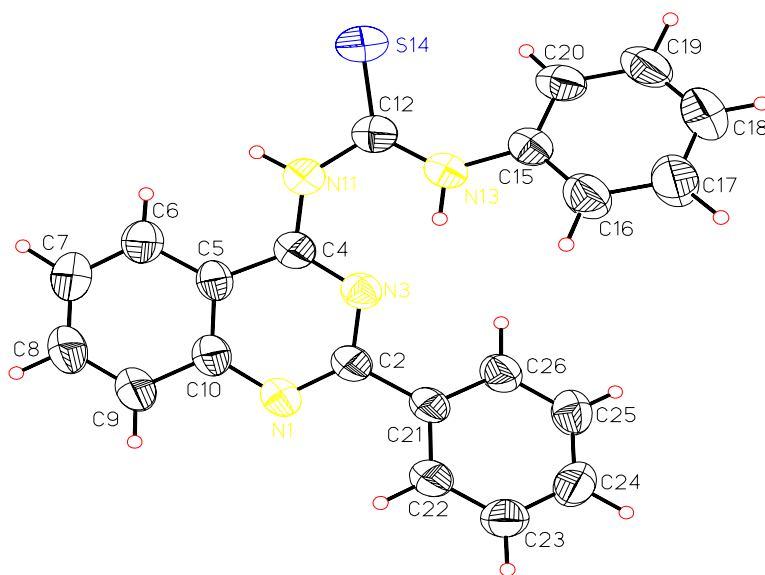


Figure 2: The ORTEP diagram of compound **7f**.

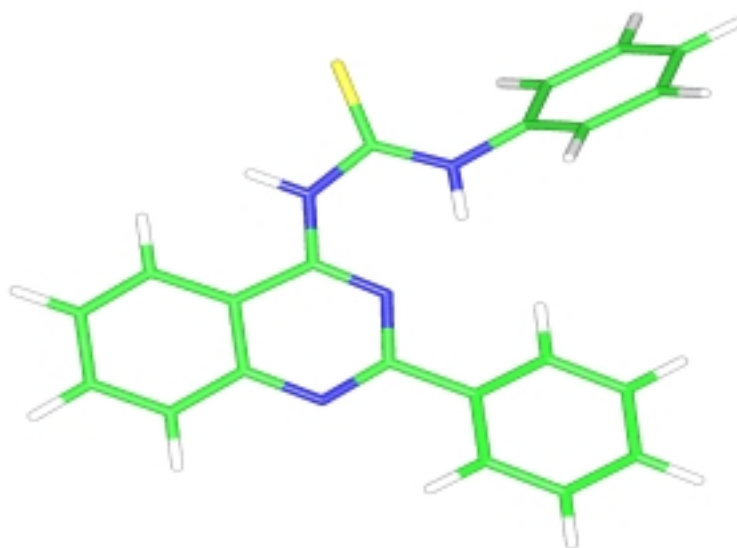


Figure 3: The calculated model of compound **7f**.

The X-ray structural analysis shows that the isolated products correspond to the Dimroth rearrangement products **7** and not to the two possible tautomeric conformations **8** and **9**. The *ab initio* computational studies together with the X-ray analysis show that the compound **7f** (R= Ph) is almost planar having the phenyl ring at position 2 slightly out of plane. The C(15) carbon of the phenylthiourea together with the thiourea moiety and the quinazoline cycle are almost in one plane. The π -electrons are in good conjugation as depicted in Figure 3. The hydrogen bond interactions between the NH group and the N(3) of the quinazoline ring add extra stability to the isolated product **7f** (Scheme 2). These hydrogen bond interactions were identified from the X-ray analysis and the computational studies, which show a bond distance of about 1.86 Å and 1.94 Å, respectively.

There were no great energy differences between the two structures **7f** (−891009.73 kcal.mol^{−1}) and **8f** (−891006.05 kcal.mol^{−1}). This led us to the conclusion that the sulfur atom could be involved in intermolecular hydrogen interactions. However, the probability of this conclusion was decreased after measuring the ¹H-NMR at a temperature ranging from −30 °C to 30 °C, which gave the same spectra. The other conclusion, based on the reaction sequence reported in Scheme 2, is that the major product is the one that is formed first, which identify the formation of the Dimroth rearrangement product as the first step and is the isolated product. On the contrary in the secondary amine application [3], the Dimroth rearrangement product is not stabilized by hydrogen interactions so it is less stable than the tautomeric form which have hydrogen bond interactions between the N3 hydrogen and the thiocarbonyl group.

Table 1. Selected interatomic distances in **7f**.

Bond	Bond Length [Å]		Bond	Bond Length [Å]	
	X-ray	HF/6-31G**		X-ray	HF/6-31G**
N1-C2	1.31	1.29	C4-C5	1.43	1.44
N1-C10	1.37	1.36	N11-C12	1.39	1.38
C2-N3	1.36	1.36	C12-N13	1.33	1.32
C2-C21	1.48	1.49	C12-S14	1.66	1.68
N3-C4	1.32	1.30	N13-C15	1.42	1.43
C4-N11	1.38	1.38	C5-C10	1.41	1.40

Table 2. The most important bond angles in **7f**.

Angle [°]	X-ray	HF/6-31G**	Angle [°]	X-ray	HF/6-31G**
N1-C2-C21	119.2	118.4	N13-C12-N11	114.9	116.8
C21-C2-N3	115.2	116.5	N13-C12-S14	127.6	126.4
C2-N1-C10	116.3	116.0	C12-N13-C15	131.5	126.8
N1-C2-N3	125.6	125.1	C16-C15-N13	115.8	118.4
C2-N3-C4	118.6	118.9	C4-N11-C12	130.7	132.7
N3-C4-N11	118.7	120.1	N1-C10-C5	122.8	122.3
N3-C4-C5	121.4	121.5	C2-C21-C22	120.8	119.7

Table 3. The most important torsion angles in **7f**.

Torsion angle [°]	X-ray	HF/6-31G**	Torsion angle [°]	X-ray	HF/6-31G**
S14-C12-N13-C15	1.16	0.2640	C10-N1-C2-C3	3.28	0.310
N3-C2-C21-C22	157.74	164.77	N1-C2- N3-C4	-1.38	-0.331
N3-C4-N11-C12	-4.41	-3.338	N1-C2-C21-C22	-23.62	-15.107
C4-N11-C12-N13	2.59	0.0585	C2-N3-C4-C5	-2.76	-0.026
N1-C2-C10-C5	-1.12	0.061	C2-N3-C4-N11	177.88	179.752
C2-N1-C10-C9	177.17	179.922	C4-N11-C12-S14	-177.39	-179.366

We confirmed the structures of the compounds 1-(2-phenylquinazolin-4-yl)-3-substituted thioureas **7a-7s** on the basis of the above spectral data, reference data from the computer simulated spectra and from knowledge about the chemistry of the isothiocyanate derivative **2** [3].

Conclusions

1-substituted-3-(2-phenylquinazolin-4-yl) thioureas **7a-s** were produced by a regioselective intramolecular cycloaddition reaction of the nitrogen attack at the available nitrile group of the thiourea derivatives **3**.

Acknowledgments

This work was supported by a grant from the Ministry of Education of the Czech Republic (Grant No. CEZ: J07/98:143100011) and from the Grant Agency of the Czech Republic (Grant No. 203/01/1333). We would like to thank the Analytical Department of Lachema Co., Brno, Czech Republic for elemental analysis. The authors wish to acknowledge the Academic Supercomputer Center in Brno for providing access to computer facilities.

Experimental

General

Melting points of all the compounds were measured on a Boetius Rapido PHMK 79/2106 (Wägetechnik) instrument. TLC was carried out on Silufol UV 254 plates (Kavalier, Votice). TLC detection was accomplished with a Fluotes universal (Quarzlampen, Hanau) instrument and iodine vapors. The eluent used was a (20: 80) mixture of acetone and benzene. Purity of compounds **7** was proven by their elemental analysis, measured on an Erba 1102 instrument. FTIR spectra (results reported as $\tilde{\nu}/\text{cm}^{-1}$) were taken on a Genesis (Unicam) spectrometer on potassium bromide pellets. NMR spectra were measured on a Bruker Avance DRX-500 spectrometer. Unless stated otherwise the ^1H - and ^{13}C -NMR spectra were measured in CDCl_3 solutions and tetramethylsilane was used as an internal standard. Results are reported in ppm on the δ scale. The measured ^{13}C - and ^1H -NMR spectra were correlated with those obtained by on-line simulation (Advanced Chemistry

Development, Inc., Toronto, Canada). The X-ray crystal data and structure refinement of compound **7f** (Table 4) were collected with a KUMA KM-4 kappa four-circle diffractometer. The structure was solved by direct methods using SHELXS86 [10] and refined on F^2 for all reflections using SHELXL93 [11]. Crystals suitable for X-ray determination were obtained in the form of white prisms by recrystallization from CHCl_3 /petroleum ether at room temperature. The crystallographic data for **7a**, **7b** and **7f** have been deposited with the Cambridge Crystallographic Data Center as supplementary publications number CCDC 149679 – 149681. Geometry optimization of structures **7a**, **7b**, and **7f** was performed at *ab initio* level of quantum chemical calculation, RHF/6-316** and DFT/VWN/6-316**, respectively. Mass spectra were determined (electron impact, 70 eV) with a Fisons TRIO 1000 and GC 8000 series instrument.

Table 4: Crystal data and structure refinement for **7f**.

Empirical formula	$\text{C}_{21}\text{H}_{16}\text{N}_4\text{S}$
Molecular weight	356.44
Temperature, K	293(2)
Wavelength, Å	0.71073
Crystal system, space group	monoclinic, $P2_1/c$
Unit cell dimensions	
a, Å; α , °	9.8405 (8) Å, $\alpha = 90^\circ$
b, Å; β , °	21.327 (2) Å, $\beta = 95.710 (8)^\circ$
c, Å; γ , °	16.722 (2) Å, $\gamma = 90^\circ$
Volume, Å ³	3492.0(5) Å ³
Z; density calculated, mg m ⁻³	8; 1.356 mg m ⁻³
Absorption coefficient, mm ⁻¹	0.197 mm ⁻¹
F(000)	1488
Crystal size, mm	0.65 X 0.25 X 0.10 mm
θ Range for data collection,	3.50–25.00°
Range of h, k, l	$-12 < h < 13$, $-27 < k < 26$, $-28 < l < 21$,
Reflections collected	18128
Independent reflections	6123 [R(INT) = 0.04231]
Refinement method	full-matrix least-squares on F^2
Data; restraints; parameters	5483 / 0 / 597
Goodness-of-fit on F^2	0.950
Final R indices [I > 2 σ (I)]	R1 = 0.0462, wR2 = 0.1192
R indices (all data)	R1 = 0.0818, wR2 = 0.1322
Largest diff. Peak and hole	0.230 and −0.260 e. Å ⁻³

N-(2-cyanophenyl)benzimidoyl isothiocyanate (2) - acetone solution.

A mixture of *N*-(2-cyanophenyl)benzamide [3] (0.5 g, 2.25 mmol), and phosphorous pentachloride (0.5 g, 2.4 mmol) in dry toluene were refluxed for 8 h. The solvent was removed under reduced pressure to give a brownish colored oil of *N*-(2-cyanophenyl)benzimidoyl chloride (1) [3] which was not further purified. A solution of potassium thiocyanate (0.22 g, 2.25 mmol) in dry acetone was added portionwise over 2 h to a stirred and cooled (-5°C) solution of crude 1 in dry acetone. The precipitated potassium chloride was filtered off to give the acetone solution of *N*-(2-cyanophenyl)benzimidoyl isothiocyanate (2). The IR spectrum of this solution displayed a strong peak at 2059 cm^{-1} corresponding to the νNCS band. The isothiocyanate was used without further isolation and purification (to avoid polymerization and destruction of this very reactive compound).

General procedure for the synthesis of 1-substituted-3-(2-phenylquinazolin-4-yl) thioureas (7).

The appropriate primary amine (2.25 mmol) was added portionwise while stirring at room temperature over a period of 1 h to the acetone solution of isothiocyanate 3. An additional amount of triethylamine (0.6 ml, 4.5 mmol) was added in case of the adamantylamine hydrochloride examples 7q-7s. The reaction mixture was then stirred for 24 h. The precipitated quinazoline thiourea 7 was filtered off and recrystallized from ethyl alcohol. Spectral data are given below.

1-Butyl-3-(2-phenylquinazolin-4-yl) thiourea (7a).

(NH_2R = butylamine); Yield: 0.21 g (29%); M.p. $165\text{--}166^{\circ}\text{C}$; Calc. for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{S}$ (336.45): 67.83% C, 5.99% H, 16.65% N, 9.53% S; Found: 67.64% C, 5.81% H, 16.48% N, 9.43% S; FTIR: 3427.6 (NH), 2952.8, 2928.0, 2869.2 (CH), 1618.2 (C=N); ^1H -NMR: 12.16 (1H, s, NH), 8.79 (1H, s, NH), 8.24-7.48 (9H, m, ArH), 3.79-3.75 (2H, m, NHCH_2), 1.83-1.76 (2H, m, NCH_2CH_2), 1.49-1.42 (2H, m, $\text{HNCH}_2\text{CH}_2\text{CH}_2$), 0.94 (3H, t, CH_2CH_3) ($J_{\text{A,B}} = 7.31\text{ Hz}$); ^{13}C -NMR: 180.11 (C=S), 158.90 (C_q), 156.16 (C_q), 151.57 (C_q), 137.70 (C_q), 134.57 (CH_{Ar}), 131.18 (CH_{Ar}), 129.89 (CH_{Ar}), 128.93 (CH_{Ar}), 128.38 (CH_{Ar}), 127.81 (CH_{Ar}), 120.67 (CH_{Ar}), 112.70 (C_q), 46.55 (NCH_2), 31.05 (NCH_2CH_2), 20.60 ($\text{HNCH}_2\text{CH}_2\text{CH}_2$), 13.99 (CH_3); MS, m/z ($I_r/\%$): 337 (24), 336 (71), 304 (15), 303 (82), 264 (58), 247 (28), 222 (59), 221 (100), 206 (37), 205 (89), 130 (15), 118 (38), 104 (25), 102 (36), 77 (50), 72 (18), 41 (17).

1-Benzyl-3-(2-phenylquinazolin-4-yl) thiourea (7b).

(NH_2R = benzylamine); Yield: 0.3 g (36%); M.p. $189\text{--}190^{\circ}\text{C}$; Calc. for $\text{C}_{22}\text{H}_{18}\text{N}_4\text{S}$ (370.47): 71.33% C, 4.90% H, 15.12% N, 8.65% S; Found: 71.24% C, 4.88% H, 15.03% N, 8.59% S; FTIR: 3292.1 (NH), 3024.58 (CH), 1619.81 (C=N); ^1H -NMR: 12.31 (1H, s, NHCH_2), 8.88 (1H, s, NH), 8.03-7.18 (14H, m, ArH), 4.98 (2H, d, NHCH_2) ($J_{\text{A,B}} = 4.66\text{ Hz}$); ^{13}C -NMR: 179.82 (C=S), 158.90 (C_q), 156.00 (C_q), 151.36 (C_q), 136.89 (C_q), 136.49 (C_q), 134.62 (CH_{Ar}), 130.94 (CH_{Ar}), 129.77 (CH_{Ar}), 129.37 (CH_{Ar}), 129.20 (CH_{Ar}), 128.85 (CH_{Ar}), 128.59 (CH_{Ar}), 128.15 (CH_{Ar}), 127.83 (CH_{Ar}),

120.59 (CH_{Ar}), 112.57 (C_q), 51.31 (NCH₂); MS, m/z (I_r/%) : 371 (12), 370 (28), 339 (9), 337 (48), 264 (22), 263 (41), 239 (11), 222 (64), 221 (100), 206 (27), 205 (94), 149 (32), 118 (38), 104 (25), 102 (34), 91 (100), 77 (53), 65 (45), 51 (25).

1-Allyl-3-(2-phenylquinazolin-4-yl) thiourea (7c).

(NH₂R= allylamine); Yield: 0.18 g (25%); M.p. 189-190°C; Calc. for C₁₈H₁₆N₄S (320.41): 67.48% C, 5.03% H, 17.49% N, 10.01% S; found: 67.32% C, 4.98% H, 17.37% N, 9.83% S; FTIR: 3441.6 (NH), 3021.8 (CH), 1620.6 (C=N); ¹H-NMR: 12.30 (1H, s, NH), 8.83 (1H, s, NH), 8.30-7.49 (9H, m, ArH), 6.19-6.06 (1H, m, CH=CH₂), 5.47 (1H, d, CH=CH₂) (J_{A,B}= 17.2 Hz), 5.38 (1H, d, CH=CH₂) (J_{A,B}= 9.9 Hz), 4.49 (2H, m, HNCH₂); ¹³C-NMR: 180.16 (C=S), 158.65 (C_q), 156.04 (C_q), 151.53 (C_q), 137.27 (C_q), 134.61 (CH_{Ar}), 132.73 (1H, m, CH=CH₂), 131.21 (CH_{Ar}), 129.85 (CH_{Ar}), 128.90 (CH_{Ar}), 128.42 (CH_{Ar}), 127.83 (CH_{Ar}), 120.63 (CH_{Ar}), 118.98 (1H, m, CH=CH₂), 112.59 (C_q), 49.16 (NCH₂).

1-Isobutyl-3-(2-phenylquinazolin-4-yl) thiourea (7d).

(NH₂R= isobutylamine); Yield: 0.14 g (19%); M.p. 150-151°C; Calc. for C₁₉H₂₀N₄S (336.45): 67.83% C, 5.99% H, 16.65% N, 9.53% S; found: 67.75% C, 5.92% H, 16.59% N, 9.52% S; FTIR: 3427.65 (NH), 2957.7, 2918.7 (CH), 1620.29 (C=N); ¹H-NMR: 12.26 (1H, s, NH), 8.95 (1H, s, NH), 8.41-7.61 (9H, m, ArH), 3.78 (2H, t, NHCH₂) (J_{A,B}= 6.57 Hz), 2.32-2.25 (1H, m, CH(CH₃)₂), 1.18 (6H, d, CH(CH₃)₂) (J_{A,B}= 6.57 Hz); ¹³C-NMR: 180.18 (C=S), 158.83 (C_q), 156.12 (C_q), 151.41 (C_q), 137.52 (C_q), 134.57 (CH_{Ar}), 131.18 (CH_{Ar}), 129.75 (CH_{Ar}), 128.83 (CH_{Ar}), 128.31 (CH_{Ar}), 127.80 (CH_{Ar}), 120.68 (CH_{Ar}), 112.60 (C_q), 54.38 (NHCH₂), 28.16 (NCH₂CH), 20.75 (CH₃).

1-Cyclohexyl-3-(2-phenylquinazolin-4-yl) thiourea (7e).

(NH₂R= cyclohexylamine); Yield: 0.25 g (30%); M.p. 154-155°C; Calc. for C₂₁H₂₂N₄S (362.49): 69.58% C, 6.12% H, 15.46% N, 8.84% S; Found: 69.41% C, 6.12% H, 15.38% N, 8.74% S; FTIR: 3441.7, 3425.8 (NH), 1619.3 (C=N); ¹H-NMR: 12.08 (1H, b, NHCH), 8.75 (1H, s, NH), 8.32-7.54 (9H, m, ArH), 4.28-4.38 (1H, m, NHCH), 2.34-2.27 (2H, m, CH₂), 1.91-1.71 (4H, m, 2CH₂), 1.55-1.38 (4H, m, 2CH₂); ¹³C-NMR: 178.54 (C=S), 158.90 (C_q), 156.07 (C_q), 151.45 (C_q), 137.69 (C_q), 134.55 (CH_{Ar}), 131.15 (CH_{Ar}), 129.77 (CH_{Ar}), 128.92 (CH_{Ar}), 128.40 (CH_{Ar}), 127.80 (CH_{Ar}), 120.65 (CH_{Ar}), 112.66 (C_q), 55.49 (CH), 32.78 (CH₂), 32.78 (CH₂), 25.87 (CH₂), 25.17 (CH₂).

1-Phenyl-3-(2-phenylquinazolin-4-yl)thiourea (7f).

(NH₂R= aniline); Yield: 0.35 g (43%); M.p. 165-166°C; Calc. for C₂₁H₁₆N₄S (356.44): 70.76% C, 4.52% H, 15.72% N, 8.99% S; Found: 70.58% C, 4.52% H, 15.64% N, 8.83% S; FTIR:

3436.3, 3418.7 (NH), 1617.3 (C=N); $^1\text{H-NMR}$: 14.26 (1H, s, NHPh), 8.93 (1H, s, NH), 8.35-7.29 (14H, m, ArH); $^{13}\text{C-NMR}$: 178.62 (C=S), 158.57 (C_q), 155.96 (C_q), 151.64 (C_q), 144.85(C_q), 138.49 (C_q), 137.36 (C_q), 134.85 (CH_Ar), 131.31 (CH_Ar), 129.93 (CH_Ar), 129.24 (CH_Ar), 128.39 (CH_Ar), 128.03 (CH_Ar), 126.88 (CH_Ar), 124.13 (CH_Ar), 120.65 (CH_Ar), 112.62 (C_q); MS, m/z ($I_\text{r}/\%$): 356 (6), 323 (7), 276 (9), 264 (12), 263 (51), 222 (13), 221 (100), 205 (95), 178 (8), 135 (49), 118 (17), 104 (7), 102 (20), 93 (21), 91 (6), 77 (57), 51 (25).

1-(4-Methylphenyl)-3-(2-phenylquinazolin-4-yl) thiourea (7g).

(NH_2R = p-toluidine); Yield: 0.31 g (38%); M.p. 179-180°C; Calc. for $\text{C}_{22}\text{H}_{18}\text{N}_4\text{S}$ (370.47): 71.33% C, 4.90% H, 15.12% N, 8.65% S; Found: 71.21% C, 4.89% H, 15.11% N, 8.62% S; FTIR: 3422.5 (NH), 1619.9(C=N); $^1\text{H-NMR}$: 14.16 (1H, s, NHPh), 8.92 (1H, s, NH), 8.36-7.29 (13H, m, ArH), 2.40 (3H, s, CH_3); $^{13}\text{C-NMR}$: 178.62 (C=S), 158.57 (C_q), 155.99 (C_q), 151.52 (C_q), 144.85 (C_q), 138.49 (C_q), 137.30 (C_q), 136.83 (C_q), 134.84 (CH_Ar), 131.32 (CH_Ar), 129.82 (CH_Ar), 129.09 (CH_Ar), 128.38 (CH_Ar), 128.03 (CH_Ar), 124.18 (CH_Ar), 120.67 (CH_Ar), 112.63 (C_q), 21.33 (CH_3); MS, m/z ($I_\text{r}/\%$): 337 (4), 264 (18), 263 (62), 222 (33), 221 (85), 206 (19), 205 (100), 149 (54), 148 (18), 118 (15), 107 (71), 106 (58), 91 (29), 77 (29).

1-(3-Methylphenyl)-3-(2-phenylquinazolin-4-yl) thiourea (7h).

(NH_2R = m-toluidine); Yield: 0.36 g (43%); M.p. 157-158°C; Calc. for $\text{C}_{22}\text{H}_{18}\text{N}_4\text{S}$ (370.47): 71.33% C, 4.90% H, 15.12% N, 8.65% S; Found: 71.32% C, 4.90% H, 15.10% N, 8.65% S; FTIR: 3405.2 (NH), 1618.7 (C=N); $^1\text{H-NMR}$: 14.22 (1H, s, NHPh), 8.91 (1H, s, NH), 8.38-7.11 (13H, m, ArH), 2.41 (3H, s, CH_3); $^{13}\text{C-NMR}$: 178.53 (C=S), 158.56 (C_q), 155.84 (C_q), 151.38 (C_q), 144.76(C_q), 138.49 (C_q), 137.30 (C_q), 136.83 (C_q), 134.86 (CH_Ar), 131.37 (CH_Ar), 129.87 (CH_Ar), 129.06 (CH_Ar), 128.46 (CH_Ar), 128.05 (CH_Ar), 127.66 (CH_Ar), 124.64 (CH_Ar), 121.07 (CH_Ar), 120.67 (CH_Ar), 112.63 (C_q), 21.69 (CH_3).

1-(2-Methylphenyl)-3-(2-phenylquinazolin-4-yl) thiourea (7I).

(NH_2R = o-toluidine); Yield: 0.42 g (51%); M.p. 157-158°C; Calc. for $\text{C}_{22}\text{H}_{18}\text{N}_4\text{S}$ (370.47): 71.33% C, 4.90% H, 15.12% N, 8.65% S; Found: 71.03% C, 4.64% H, 14.92% N, 8.41% S; FTIR: 3325.2 (NH), 1623.59 (C=N); $^1\text{H-NMR}$: 14.22 (1H, s, NHPh), 8.91 (1H, s, NH), 8.38-7.11 (13H, m, ArH), 2.41 (3H, s, CH_3); $^{13}\text{C-NMR}$: 178.53 (C=S), 158.56 (C_q), 155.84 (C_q), 151.38 (C_q), 144.76(C_q), 138.49 (C_q), 137.30 (C_q), 136.83 (C_q), 134.86 (CH_Ar), 131.37 (CH_Ar), 129.87 (CH_Ar), 129.06 (CH_Ar), 128.46 (CH_Ar), 128.05 (CH_Ar), 127.66 (CH_Ar), 124.64 (CH_Ar), 121.07 (CH_Ar), 120.67 (CH_Ar), 112.63 (C_q), 21.69 (CH_3).

1-(4-Methoxyphenyl)-3-(2-phenylquinazolin-4-yl) thiourea (7j).

(NH₂R= p-anisidine); Yield: 0.34 g (40%); M.p. 168-169°C; Calc. for C₂₂H₁₈N₄OS (386.47): 68.37% C, 4.69% H, 14.50% N, 8.30% S; Found: 68.24% C, 4.57% H, 14.49% N, 8.23% S; FTIR: 3428.2 (NH), 2934.9 (CH), 1616.8 (C=N); ¹H-NMR: 14.09 (1H, s, NHPh), 8.91 (1H, s, NH), 8.35-6.98 (13H, m, ArH), 3.86 (3H, s, OCH₃); ¹³C-NMR: 178.78 (C=S), 158.39 (C_q), 155.98 (C_q), 152.49 (C_q), 151.55 (C_q), 141.78 (C_q), 137.32 (C_q), 134.86 (CH_{Ar}), 131.4 (C_q), 131.32 (CH_{Ar}), 129.87 (CH_{Ar}), 129.09 (CH_{Ar}), 128.35 (CH_{Ar}), 128.03 (CH_{Ar}), 125.78 (CH_{Ar}), 120.67 (CH_{Ar}), 114.48 (CH_{Ar}), 113.45 (C_q), 112.63 (C_q), 55.75 (OCH₃).

1-(4-nitrophenyl)-3-(2-phenylquinazolin-4-yl) thiourea (7k).

(NH₂R= p-nitroaniline); Yield: 0.48 g (53%); M.p. 165-166°C; Calc. for C₂₁H₁₅N₅O₂S (401.44): 62.83% C, 3.77% H, 17.45% N, 7.99% S; Found: 62.66% C, 3.58% H, 17.24% N, 7.84% S; FTIR: 3333.0 (NH), 1615.7 (C=N); ¹H-NMR (CF₃COOD): 8.87-7.94 (13H, m, ArH); ¹³C-NMR: 179.93 (C=S), 161.56 (C_q), 160.34 (C_q), 147.97 (C_q), 145.71 (C_q), 142.34 (C_q), 142.01 (CH_{Ar}), 138.41 (CH_{Ar}), 133.84 (CH_{Ar}), 132.67 (CH_{Ar}), 131.27 (C_q), 130.90 (CH_{Ar}), 127.36 (CH_{Ar}), 126.21 (CH_{Ar}), 125.73 (CH_{Ar}), 122.65 (CH_{Ar}), 114.20 (C_q).

1-(3-nitrophenyl)-3-(2-phenylquinazolin-4-yl)thiourea (7l).

(NH₂R= m-nitroaniline); Yield: 0.39 g (41%); M.p. 174-175°C; Calc. for C₂₁H₁₅N₅O₂S (401.44): 62.83% C, 3.77% H, 17.45% N, 7.99% S; Found: 62.74% C, 3.64% H, 17.32% N, 7.87% S; FTIR: 3315.6 (NH), 1620.8 (C=N); ¹H-NMR (CF₃COOD): 8.87-7.75 (13H, m, ArH); ¹³C-NMR: 180.60 (C=S), 161.55 (C_q), 160.60 (C_q), 150.54 (C_q), 142.41 (C_q), 142.34 (C_q), 142.07 (CH_{Ar}), 140.60 (C_q), 138.47 (CH_{Ar}), 133.90 (CH_{Ar}), 132.91 (CH_{Ar}), 132.82 (CH_{Ar}), 132.76 (CH_{Ar}), 131.27 (C_q), 130.97 (CH_{Ar}), 125.91 (CH_{Ar}), 124.93 (CH_{Ar}), 122.71 (CH_{Ar}), 121.58 (CH_{Ar}), 114.30 (C_q).

1-(4-Chlorophenyl)-3-(2-phenylquinazolin-4-yl) thiourea (7m).

(NH₂R= p-chloroaniline); yield: 0.48 g (55%); M.p. 187-188°C; Calc. for C₂₁H₁₅ClN₄S (390.89): 64.53% C, 3.87% H, 9.07% Cl, 14.33% N, 8.20% S; found: 64.34% C, 3.69% H, 9.01% Cl, 14.21% N, 8.16% S; FTIR: 3430.3, 3339.3 (NH), 1620.40 (C=N); ¹H-NMR (CF₃COOD): 8.74-7.48 (13H, m, ArH); ¹³C-NMR: 180.40 (C=S), 161.44 (C_q), 160.73 (C_q), 142.28 (C_q), 141.98 (CH_{Ar}), 138.41 (CH_{Ar}), 137.24 (C_q), 136.92 (C_q), 133.80 (CH_{Ar}), 132.63 (CH_{Ar}), 131.07 (C_q), 130.88 (CH_{Ar}), 127.84 (CH_{Ar}), 125.86 (CH_{Ar}), 122.58 (CH_{Ar}), 114.27 (C_q).

1-(1-Naphthyl)-3-(2-phenylquinazolin-4-yl) thiourea (7n).

(NH₂R= 1-naphthylamine); Yield: 0.41 g (45%); M.p. 168-169°C; Calc. for C₂₅H₁₈N₄S (406.50): 73.87% C, 4.46% H, 13.78% N, 7.89% S; Found: 73.83% C, 4.46% H, 13.77% N, 7.84% S; FTIR: 3250.1 (NH), 3055.0, 2943.4 (CH), 1619.4 (C=N); ¹H-NMR: 14.27 (1H, s, NHPh), 9.16 (1H, s, NH), 8.28-7.29 (19H, m, ArH); ¹³C-NMR: 180.79 (C=S), 164.76 (C_q), 158.76 (C_q), 156.24 (C_q), 151.73 (C_q), 141.70 (C_q), 137.02 (C_q), 134.90 (CH_{Ar}), 134.61 (C_q), 131.19 (CH_{Ar}), 129.97 (CH_{Ar}), 129.02 (CH_{Ar}), 128.87 (CH_{Ar}), 128.55 (CH_{Ar}), 128.24 (CH_{Ar}), 128.05 (CH_{Ar}), 127.16 (CH_{Ar}), 126.64 (CH_{Ar}), 125.65 (CH_{Ar}), 124.71 (CH_{Ar}), 122.41 (CH_{Ar}), 120.19 (CH_{Ar}), 112.74 (C_q).

1-(2-Naphthyl)-3-(2-phenylquinazolin-4-yl) thiourea (7o).

(NH₂R= 2-naphthylamine); Yield: 0.55 g (66%); M.p. 179-180°C; Calc. for C₂₅H₁₈N₄S (406.50): 73.87% C, 4.46% H, 13.78% N, 7.89% S; Found: 73.74% C, 4.38% H, 13.61% N, 7.80% S; FTIR, $\tilde{\nu}$ /cm⁻¹: 3429.1, 3374.2 (NH), 3057.6 (CH), 1618.4 (C=N); ¹H-NMR (CF₃COOD): 8.72-7.63 (19H, m, ArH); ¹³C-NMR (CF₃COOD): 179.30 (C=S), 161.29 (C_q), 160.30 (C_q), 142.09 (C_q), 141.83 (CH_{Ar}), 138.41 (CH_{Ar}), 136.08 (C_q), 135.59 (C_q), 135.02 (C_q), 133.68 (CH_{Ar}), 132.59 (CH_{Ar}), 131.86 (CH_{Ar}), 131.05 (C_q), 130.99 (CH_{Ar}), 130.67 (CH_{Ar}), 129.89 (CH_{Ar}), 129.63 (CH_{Ar}), 126.46 (CH_{Ar}), 125.68 (CH_{Ar}), 124.82 (CH_{Ar}), 122.41 (CH_{Ar}), 114.07 (C_q).

1-(2-phenylquinazolin-4-yl)-3-(2-pyridyl) thiourea (7p).

(NH₂R= 2-aminopyridine); Yield 0.33 g (41%); M.p. 207-208°C; Calc. for C₂₀H₁₅N₅S (357.43): 67.21% C, 4.23% H, 19.59% N, 8.97% S; Found: 67.04% C, 3.97% H, 19.22% N, 8.83% S; FTIR, $\tilde{\nu}$ /cm⁻¹: 3348.7 (NH), 3059.4 (CH), 1621.7 (C=N); ¹H-NMR (DMSO-d₆): 8.71-7.27 (13H, m, ArH); ¹³C-NMR: 179.57 (C=S), 161.05 (C_q), 155.96 (C_q), 151.64 (C_q), 144.85 (C_q), 138.49 (C_q), 135.90 (C_q), 137.73 (CH_{Ar}), 134.08 (CH_{Ar}), 130.36 (CH_{Ar}), 127.98 (CH_{Ar}), 127.69 (CH_{Ar}), 126.76 (CH_{Ar}), 123.26 (CH_{Ar}), 119.93 (CH_{Ar}), 114.25 (C_q); MS, m/z (I_r/%) : 357 (14), 324 (7), 264 (30), 263 (49), 222 (21), 221 (100), 205 (82), 178 (8), 136 (55), 118 (28), 104 (13), 102 (29), 94 (27), 78 (56), 77 (38), 51 (27).

1-(1-Adamantyl)-3-(2-phenylquinazolin-4-yl) thiourea (7q).

(NH₂R= 1-adamantanamine hydrochloride); Yield: 0.29g (31%); M.p. 202-203°C; Calc. for C₂₅H₂₆N₄S (414.50): 72.43% C, 6.32% H, 13.52% N, 7.73% S; Found: 72.31% C, 6.27% H, 13.41% N, 7.54% S; FTIR, $\tilde{\nu}$ /cm⁻¹: 3445.3 (NH), 2909.9 (CH), 2854.9 (CH), 1622.5 (C=N); ¹H-NMR: 11.77 (1H, s, NH), 8.53 (1H, s, NH), 8.27-7.43 (9H, m, ArH), 2.53-2.41 (6H, m, 3CH₂), 2.26-2.09 (6H, m, 3CH₂), 1.84-1.68 (3H, m, 3CH); ¹³C-NMR: 177.48 (C=S), 156.07 (C_q), 149.83 (C_q), 137.91 (C_q), 134.63 (CH_{Ar}), 131.02 (CH_{Ar}), 129.81 (CH_{Ar}), 128.70 (CH_{Ar}), 127.68 (CH_{Ar}), 120.67 (CH_{Ar}), 112.75 (C_q), 55.91 (NHC_{Ad}), 41.10 (CH₂), 36.67 (CH₂), 29.97 (CH); MS, m/z

(I_r/%) : 414.2 (4), 380.3 (2), 264 (7), 263 (21), 222 (32), 221 (75), 205 (65), 193 (15), 151 (16), 135 (100), 118 (17), 94 (45), 77 (29).

1-(3-Homoadamantyl)-3-(2-phenylquinazolin-4-yl) thiourea (7r).

(NH₂R= 3-homoadamantanamine hydrochloride); Yield: 0.3 g (33%); M.p. 217-218 °C; Calc. for C₂₆H₂₈N₄S (428.59): 72.86% C, 6.58% H, 13.07% N, 7.48% S; Found: 72.43% C, 6.48% H, 13.01% N, 7.24% S; FTIR, $\tilde{\nu}$ /cm⁻¹: 3436.2 (NH), 2909.9 (CH), 2849.9 (CH), 1620.4 (C=N); ¹H-NMR: 11.98 (1H, s, NH), 8.64 (1H, s, NH), 8.36-7.54 (9H, m, ArH), 2.61-1.53 (15H, m, Ad); ¹³C-NMR: 176.92 (C=S), 159.19 (C_q), 156.03 (C_q), 151.30 (C_q), 137.86 (C_q), 134.45 (CH_{Ar}), 131.03 (CH_{Ar}), 129.71 (CH_{Ar}), 128.71 (CH_{Ar}), 127.72 (CH_{Ar}), 120.73 (CH_{Ar}), 112.65 (C_q), 60.98 (CH₂), 43.15 (CH₂), 37.84 (CH₂), 35.56 (CH₂), 31.22 (CH), 31.18 (CH₂), 27.82 (CH); MS, m/z (I_r/%) : 428.2 (3), 264 (12), 263 (34), 222 (48), 221 (86), 205 (83), 165 (12), 149 (100), 118 (13), 94 (23), 77 (29).

1-(1-Adamantylmethyl)-3-(2-phenylquinazolin-4-yl) thiourea (7s).

[NH₂R= 1-(1-adamantylmethylamine hydrochloride)]; Yield: 0.33 g (34%); M.p. 197-198 °C; Calc. for C₂₆H₂₈N₄S (428.53): 72.86% C, 6.59% H, 13.07% N, 7.48% S; Found: 72.86% C, 6.57% H, 13.04% N, 7.39% S; FTIR, $\tilde{\nu}$ /cm⁻¹: 3450.3 (NH), 2909.9 (CH), 2849.5 (CH), 1620.0 (C=N); ¹H-NMR: 12.04 (1H, s, NH), 8.90 (1H, s, NH), 8.31-7.51 (9H, m, ArH), 3.69 (2H, d, NHCH₂) (J_{A,B}= 6.14 Hz), 1.96-1.56 (15H, m, Ad); ¹³C-NMR: 180.75 (C=S), 156.08 (C_q), 151.43 (C_q), 138.70 (C_q), 137.76 (C_q), 134.63 (CH_{Ar}), 131.04 (CH_{Ar}), 129.78 (CH_{Ar}), 128.78 (CH_{Ar}), 127.85 (CH_{Ar}), 120.77 (CH_{Ar}), 112.67 (C_q), 58.74 (NHCH₂), 40.85 (CH₂ Ad), 36.95 (CH₂ Ad), 34.82 (C_qAd), 28.38 (CH); MS, m/z (I_r/%) : 428 (9), 395 (5), 264 (15), 263 (24), 222 (41), 221 (49), 205 (64), 165 (11), 149 (12), 135 (100), 118 (9), 93 (19), 77 (23).

References and Notes

1. Fathalla, W.; Čajan, M. and Pazdera, P., *Molecules*, **2001**, 6, 557-573.
2. Fathalla, W.; Čajan, M. and Pazdera, P., *Molecules*, **2000**, 5, 1210-1223.
3. Fathalla, W., Marek, J. and Pazdera, P., *Molecules*, **2001**, 6, 574-587.
4. Bodajla, M.; Stankovský, Š.; Špirková, K.: *Collect. Czech. Chem. Commun.*, **1995**, 60, 1415.
5. Bodajla, M.; Stankovský, Š.; Špirková, K.; Jantová, S.: *Collect. Czech. Chem. Commun.*, **1996**, 61, 1681.
6. Bodajla, M.; Stankovský, Š.; Jantová, S.; Hudecová, D.; Špirková, K.: *Chem. Papers*, **1996**, 50, 28.
7. Pazdera, P.; Nováček, E.; Kalviňš, I.; Trapencieris, P.; Pugovics, O.: *Chem. Papers*, **1991**, 45, 527.
8. Pazdera, P.; Ondráček, D.; Nováček, E.: *Chem. Papers*, **1989**, 43(6), 771.

9. The complete computational analysis of all the predicted structures and the X-ray analysis data for compounds **7a** and **7b** are available from the authors.
10. Sheldrick, G. M.: *Acta Crystallogr., Sect. A.: Fundam. Crystallogr.*, **1990**, *46*, 467.
11. Sheldrick, G. M.: *SHELXL93: Program for Structure Refinement. University of Göttingen, Göttingen*, **1993**.

Sample Availability: Available from the authors.

© 2001 by MDPI (<http://www.mdpi.org>). Reproduction is permitted for noncommercial purposes.