Reactivity Study on Morpholine-1-carbothioic Acid (2-Phenyl-3*H*-quinazolin-4-ylidene) Amide

Walid Fathalla [1], MichalČajan [1,2], Jaromír Marek [3] and Pavel Pazdera [1]*

[1] Department of Organic Chemistry, Faculty of Science, Masaryk University, Brno, Czech Republic
[2] National Center for Biomolecular Research, Faculty of Science, Masaryk University, Brno, Czech Republic
[3]Laboratory of Functional GENOMICS and PROTEOMICS, Masaryk University, 611 37 Brno, Czech Republic

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Regioselective reactions of morpholine-1-carbothioic acid (2-phenyl-3*H*-quinazolin-4-ylidene) amide (**1**) with electrophiles and nucleophiles were studied. The compound (**1**) reacts with alkyl halides in basic medium to afford *S*-substituted isothiourea derivatives, with amines to give 1,1-disubstituted-3-(2-phenyl-3*H*-quinazolin-4-ylidene) thioureas and 1-substituted-3-(2-phenyl-quinazolin-4-yl) thioureas *via* transamination reaction. The reaction of (**1**) with amines in the presence of H_2O_2 provided N^4-disubstituted-N'^4-(2-phenylquinazolin-4-yl)morpholin-4-carboximidamide *via* oxidative desulfurization. Estimation of reactivity sites on (**1**) was supported using the *ab initio* (HF/6-31G**) quantum chemistry calculations. The ir, ^{1}H nmr, ^{13}C nmr, mass spectroscopy and x-ray identified the isolated products.

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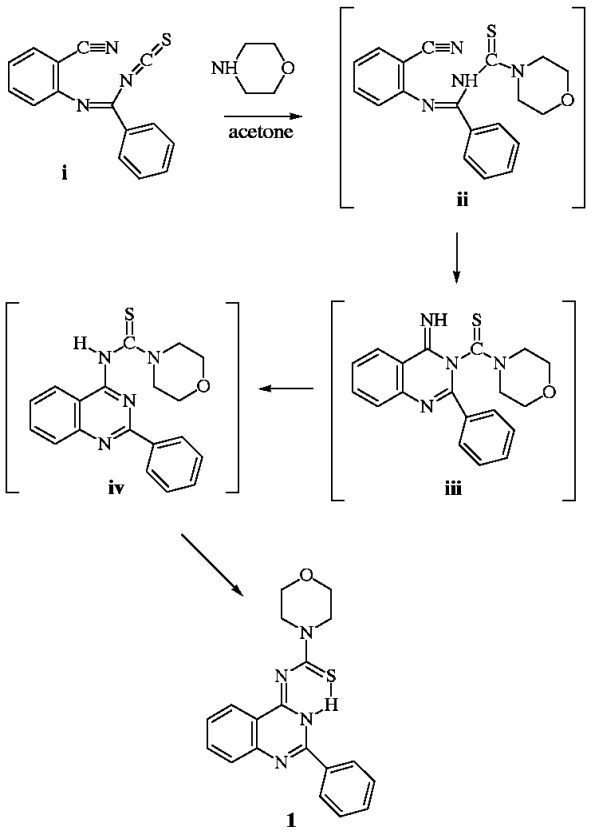
Introduction.

Reactions of electrophiles with the nitrogen or sulfur atom in thioamides including thioureas are an important element of preparation of various heterocyclic compounds. Despite the well-known regioselectivity of these reactions under different reaction conditions, the reason for *S*-versus *N*-regioselectivity remains incompletely understood. As reported in this paper, thiourea derivative (**1**) is an excellent model compound that has allowed us to extend our previous research on *S- versus N*-regioselectivity in the reaction of thioamides with electrophiles [1-4].

Scheme 1



Preparation of morpholine-1-carbothioic acid (2-phenyl-3*H*-quinazolin-4-ylidene) amide 1.

Results and Discussion.

The thiourea (**1**) was prepared by the domino reaction of *N*-(2-cyanophenyl)benzimidoyl isothicyanate with morpholine [1]. The intermediate open chain thiourea derivative (**ii**) reacts by a regioselective *N*-attack at the cyano group to give the quinazoline derivative (**iii**). This second intermediate subsequently undergoes Dimroth rearrangement to give the quinazolin-4-yl-thiourea (**iv**). Tautomerisation of **iv** provides morpholine-1-carbothioic acid (2-phenyl-3*H*-quinazolin-4-ylidene) amide (**1**) (Scheme 1).

X-ray structural analysis of pyrrolidine-1-carbothioic acid (2-phenyl-3*H*-quinazolin-4-ylidene) amide (**2b**) as an analogue for the model compound (**1**) (Figure 1) together with the *ab initio* (HF/6-31G**) computational analysis

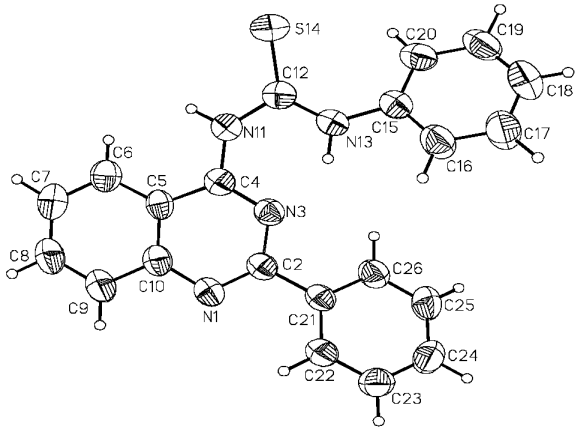


Figure 1. ORTEP diagram of thiourea (**2b**).

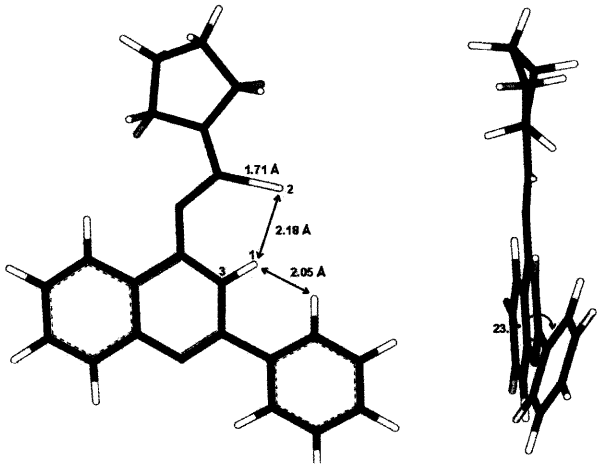
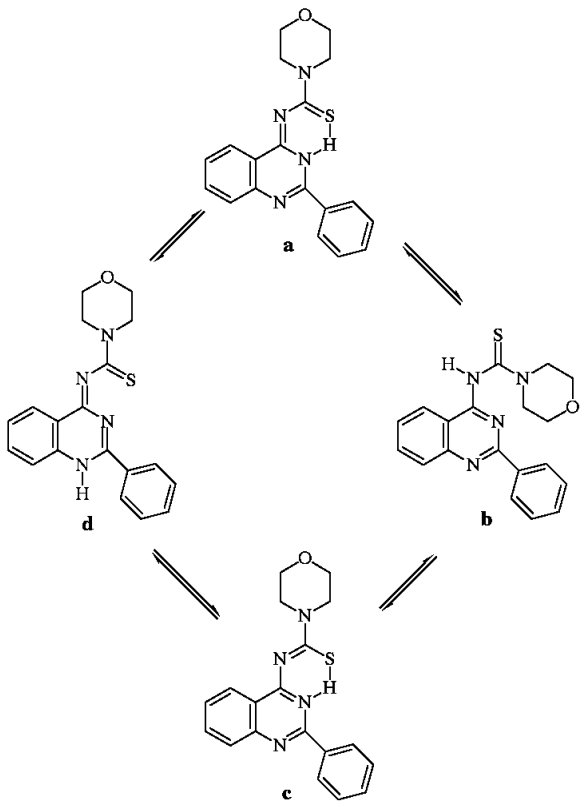


Figure 2. Molecular design of (**2b**) according to quantum computations.

(Figure 2), show that compound (**1**) is almost planar having both the phenyl ring at position 2 and the pyrrolidine ring slightly out of plane of the molecule. The *p*-electron system is conjugated throughout the basic skeleton. The hydrogen bond interactions between the thiocarbonyl

Scheme 2



The possible tautomeric forms of (**1**).

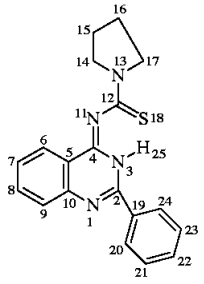


Figure 3. Atom numbering of (**2b**).

group and the NH of the quinazoline ring make the isolated product (**1**) extra stable. These intramolecular interactions were obtained from both the x-ray analysis and *ab initio* computational studies [1].

The possible tautomer forms of (**1**) demonstrate a nucleophilic character on N1, N3, N11 and S18 atoms (Scheme 2). On the other hand, the possible electrophilic sites into (**1**) are likely centralized on C2, C4 or C12.

An elucidation of real nucleophilic and electrophilic sites was provided by using the Hartree-Fock theory with 6-31G** basis set.

The presented above computational characteristics of compound **1** analogue (**2b**) together with the x-ray structure analysis, expected tautomeric forms and the know reactivity of thioamides demonstrate that: 1) The partial charge distributed on the nitrogen atom N3 is larger than that on the other competing nucleophilic active sites N1,

Table 1

The Partial Charge of Values of the Most Important Atoms in the Anion of Thiourea (**2b**)

Atom	Partial charge		Atom	Partial charge	
	Mulliken	ESP		Mulliken	ESP
N1	-0.6613	-0.8690	C14	-0.0701	0.1142
C2	0.6747	0.8407	C15	-0.3560	-0.1923
N3	-0.9575	-0.9199	C16	-0.3566	0.0368
C4	0.8185	1.1639	C17	-0.0826	0.0266
C5	-0.1384	-0.7515	S18	-0.4071	-0.5267
C6	-0.1563	0.1454	C19	-0.0607	-0.1202
C8	-0.1795	0.0184	C20	-0.1748	-0.0916
C9	-0.2162	-0.4577	C21	-0.2097	-0.1617
C10	0.2883	0.8778	C22	-0.1847	-0.0934
N11	-0.7575	-0.6808	C23	-0.2115	-0.1705
C12	0.4841	0.2182	C24	-0.2150	-0.0863
N13	-0.6422	0.0260	H25	0.4658	0.3805

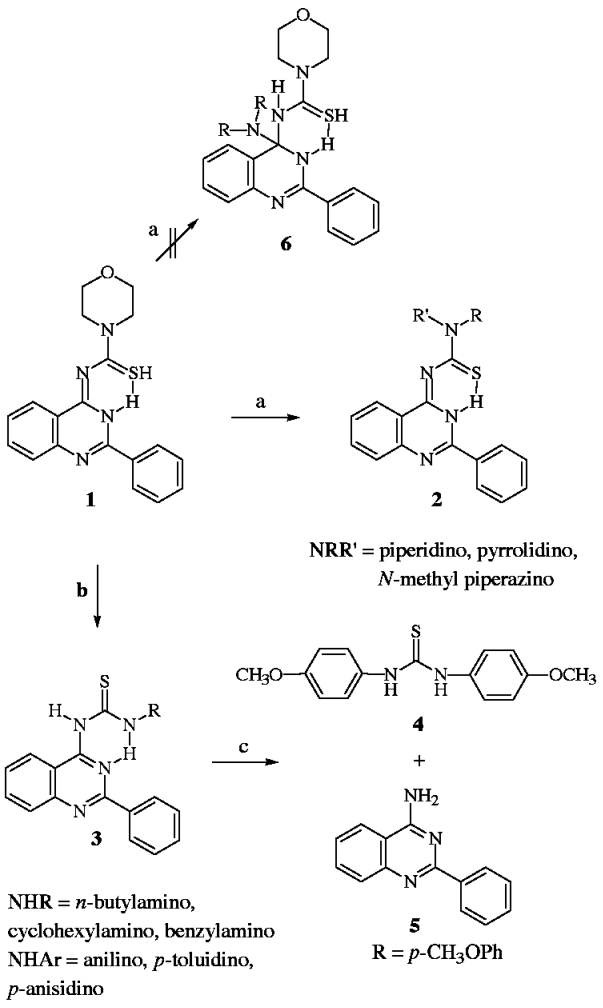
S18 and N11 (Table 1); 2) The sulfur atom S18 has a larger HOMO coefficient *c* value than that on the nitrogen atoms N1, N3 and N11 (Table 2, Figure 4); 3) Reactions of compound **1** with electrophiles were expected to give

Table 2

The Molecular Obital Coefficient Values of the Most Important Atoms of the Anion form of Thiourea

Atom	Orbital	Coefficient c		Atom	Orbital	Coefficient c	
		HOMO	LUMO			HOMO	LUMO
N1	2pz	0.22112	0.17442	N11	2pz	0.18225	-0.10565
C2	2pz	0.14672	-0.13205	C12	2pz	0.00426	-0.18878
N3	2pz	-0.07179	-0.09735	N13	2pz	0.00612	0.13384
C4	2pz	-0.02033	0.29923	S18	2pz	-0.10544	-0.05194
C10	2pz	-0.17359	-0.07876		3pz	-0.20149	0.11356

Scheme 3



Competitions in reactivity of thiourea (**1**). a: HNRR, DMF, 80 °C, 5-6 hours; b: H_2NR, DMF, 80 °C, 5-6 hours; c: *p*-anisidine, DMF, 80 °C, 5-6 hours.

either the *N3*-substituted products [3,4] *via* strong Coulombic attraction with electrophiles having large charge content, whereas the *S*-substituted product is created *via* orbital-orbital interactions; 4) A residual bond order determined between the H-25 and S-18 atoms show the hydrogen bond interaction between them. This interaction plays an important role in the stability and reaction of the model compound **1** (Figure 2); 5) Compound **1** is almost planar having the phenyl ring at position 2 slightly out of plane (Figure 2); 6) Compound **1** contains three active electrophilic sites, which are represented by C2, C4, and C12. It is apparent from the molecular orbital coefficient values and the partial charge distributed on these atoms that C4 represent the hard electrophilic fragment of the ambident electrophile (Tables 1 and 2)

The reaction of thiourea (**1**) with amines as nucleophiles gave the 1,1-disubstituted-3-(2-phenyl-3*H*-quinazolin-4-ylidene) thioureas (**2**) and 1-substituted-3-(2-phenyl-quinazolin-4-yl) thioureas (**3**) *via* transamination reactions (Scheme 3). These compounds were previously prepared by the reaction of *N*-(2-cyanophenyl)-benzimidoyl isothiocyanate (**i**) with amines [1,2]. The above-mentioned reactions confirmed the role of the

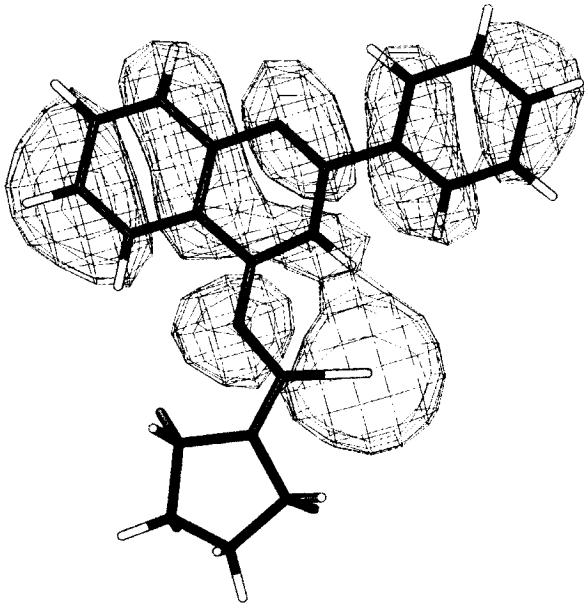


Figure 4. HOMO graphical representation of the anion form of thiourea (**2b**).

hydrogen bond in the stabilization of isolated products and gave evidence for the tautomer interconversions of compound (**1**) (Scheme 2). The reaction proceeds by the addition of amines at the soft thiocarbonyl carbon C12 with the subsequent elimination of the morpholino moiety. The reaction gave the more stable quinazolines (**2**) (secondary amine applications) [1] or (**3**) (primary amine applications) [2].

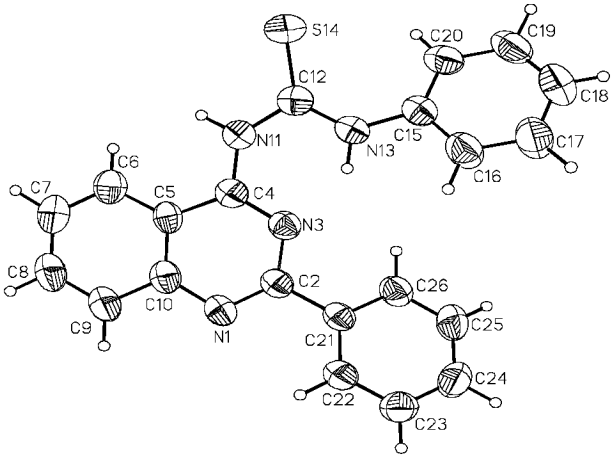


Figure 5. The x-ray analysis of thiourea (**3d**).

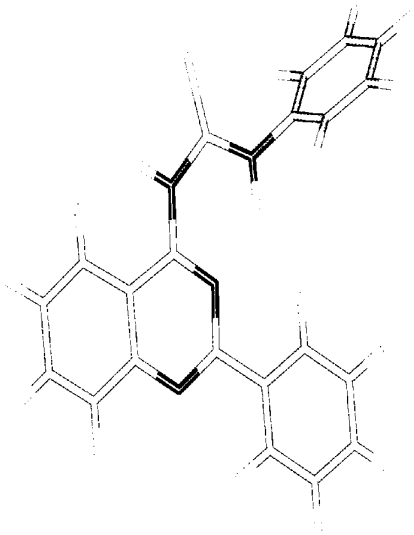


Figure 6. Calculated model of thiourea (**3d**).

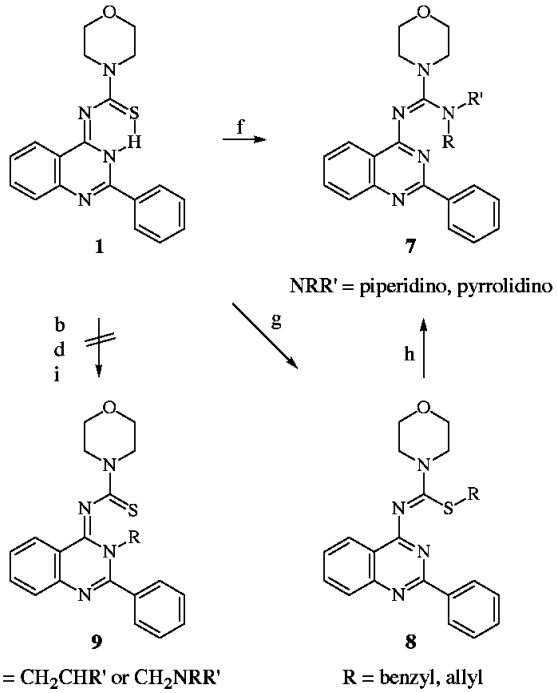
Amines as soft nucleophiles were not expected to react with the model compound **1** at the hard imino carbon C4 to provide compound (**6**). The computational analysis - (HF/6-31G**) supported this expectation as presented above.

The compound (**1**) reacts also with equimolar amount of anilines to afford 1-aryl-3-(2-phenylquinazolin-4-yl) thiourea (**3**). The addition of an extra mole of *p*-anisidine to the reaction mixture leads to 1,3-di(4-methoxyphenyl) thiourea (**4**) and 4-amino-2-phenylquinazoline (**5**) (Scheme 3). This reaction proceeds in the first step by a similar manner to the former reaction and the quinazoline derivative (**3**) is formed *in situ*. Further, the second equivalent of *p*-anisidine attacks the thiocarbonyl group allowing for elimination of the symmetrical diaryl thiourea (**4**) to generate 4-amino-2-phenylquinazoline (**5**) (Scheme 3). This process is likely under thermodynamic control due to the high thermodynamic stability of symmetrical diarylthioureas.

Guanidine derivatives (**7**) were prepared by the oxidative desulfurization reaction of (**1**) with hydrogen peroxide in the presence of excess amine. Pfeiffer [5] used this synthetic method for transformation of thioureido compounds into guanidines.

Reaction of (**1**) with benzyl chloride provide 4-benzyl-N^4-(2-phenylquinazolin-4-yl)morpholin-4-carboximidothioate (**8a**) (R= CH_2Ph). The isothiourea (**8a**) reacted with amines to afford guanidine (**7a**) (NRR`= piperidino, Scheme 4).

Scheme 4



b: HNRR, DMF, CH_2O, 80 °C, 5-6 hours; d: H_2NR, DMF, CH_2O, 80 °C, 5-6 hours; f: HNRR', H_2O_2, 25 °C, 2-24 hours; g: XR, DMF, NEt_3, 25 °C, 3 hours; h: HNRR, DMF, 80 °C, 5-6 hours. i: CH_2 = CHR, DMF, NEt_3, 80 °C, 5-6 hours.

The preparation of compound (**8**) due to regioselective *S*-substitution reaction is enabled by orbital-orbital interactions between the LUMO of the electrophile and the HOMO of the ambident nucleophile (**1**) [3,4] as discussed above.

The reactivity of N3 in compound (**1**) with hard electrophiles *via* large Coulombic attractions has been tested, as well. Unfortunately, cyanoethylation and similar reactions of compound (**1**) at this N3 nitrogen to give N^3-alkyl products (**9**) were not successful (R=CH_2CH_2CN, $CH_2CH_2COOCH_3$, Scheme 4). The reaction of (**1**) with amines and formaldehyde under Mannich reaction conditions [4] was also expected to give N^3-alkyl products (**9**) (R=CH_2NRR', Scheme 4). However, the system underwent the transamination reaction to give either quinazolines (**2**) (secondary amine applications) [1] or **3** (primary amine applications) [2] (Scheme 3).

Concurrent reactivity of thiourea (**1**).

The identities of all synthesized compounds were confirmed by the spectral data as follows: The structure of compounds (**1-3**) was confirmed by comparison of the ^1H, ^{13}C nmr, ms and ir spectra with standard samples of completely identified structures. Standards were prepared from different precursors [1,2]. The ^1H nmr spectra of compounds (**1**) and (**2**) show an important peak at *ca.* 16 ppm corresponding to the NH group of the quinazoline ring. These results together with x-ray analysis and quantum chemistry computations confirm the hydrogen bond interactions between the thiocarbonyl group and the hydrogen of the NH group. On the other hand, the peak corresponding to the same hydrogen in compound (**3**) is positioned on 12 or *ca*. 14 ppm. These results corresponding to the NH group, together with x-ray analysis, confirms the presence of the hydrogen bond interactions between the N3 and the hydrogen atom of the NHR or NHAr group, respectively. A molecular ion is observed in the mass spectra for all the examined products (**1-3**).

Structure of (**7**) was confirmed by the absence of (C=S) peak in ^{13}C nmr spectrum. Also additional peaks corresponding to pyrrolidine carbons at *ca.* 49.31 and 25.61 ppm were observed. The ^1H nmr spectrum shows additional peaks corresponding to the pyrrolidine ring protons at *ca.* 3.2 ppm and 1.9 ppm, and the resonance corresponding to the NH *ca.* 16.5 ppm is not observed. The molecular ion with m/z 387 (NRR= pyrrolidine) is observed.

The ^1H nmr and ^{13}C nmr of compound (**8**) are influenced by the contribution of the sulfur atom. In the ^1H nmr spectrum an SCH_2 signal is observed at *ca.* 3.23 ppm (R= allyl), while signal for the same group is observed at 36.51 ppm in the ^{13}C nmr spectrum. A resonance corresponding to the (C=S) is not observed in the ^{13}C nmr spectrum of (**1**). According to simulating computer spectra and to references [3,4], the *N*-substituted products (**9**, Scheme 4) would be expected to give higher chemical shifts.

Conclusions.

The model thiourea, *i.e.*, morpholine-1-carbothioic acid (2-phenyl-3*H*-quinazolin-4-ylidene) amide (**1**) contains both multi-functional nucleophilic and electrophilic character in a conjugated system. This compound reacts with amines, amines in the presence of H_2O_2 and alkyl halides regioselectively to give the transamination reaction products (**2-5**), the oxidative desulfurization guanidine products (**7**) and the *S*-alkyl products (**8**), respectively.

The reactivity sites for (**1**) were estimated by using *ab initio* quantum chemistry calculations.

EXPERIMENTAL

General Details.

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). The eluent used was a 20:80 mixture of acetone:-benzene, detection by Fluotes Universal (Quarzlampen, Hanau) and in iodine vapors, respectively. Purity of compounds (**1-5,7, 8** and **13**) was proved by elemental analysis on an Erba 1102 instrument. Ir spectra (ν/cm^{-1}) were taken on a Genesis (Unicam) spectrometer in potassium bromide pellets. Nmr spectra (d/ppm) were measured on a Bruker Avance DRX-500 spectrometer in deuteriochloroform and tetramethylsilane was used as an internal standard. The measured ^{13}C and ^1H nmr spectra were correlated with those obtained by simulation (Advanced Chemistry Development, Inc., Toronto, Canada). Mass spectrometry were acquired (electron impact, 70 eV) using a FISONS Instruments TRIO 1000 and GC 8000 series.

The theoretical results were obtained using the Hartree-Fock method on the 6-31G** basis set [6,7]. Mulliken [8], ESP [9] and NBO [10-12] methods were used to calculate the partial charges and properties of molecular orbitals.

The starting material (**1**) was prepared according to literature [1] from *N*-(2-cyanophenyl) benzamide [13].

1,1-Disubstituted-3-(2-phenyl-3*H*-quinazolin-4-ylidene)-thioureas (**2**) and 1-Substituted-3-(2-phenylquinazolin-4-yl)-thioureas (**3**).

The appropriate amine (2.9 mmol) was added to a stirred solution of morpholine-1-carbothioic acid (2-phenyl-3*H*-quinazolin-4-ylidene) amide (**1**) (1.0 g, 2.8 mmol) in DMF (30 mL). The reaction mixture was heated at 80 °C for 2-4 hours. The solvent was then evaporated under reduced pressure and the residue was crystallized from ethanol.

Piperidine-1-carbothioic Acid (2-Phenyl-3H-quinazolin-4-ylidene) Amide (**2a**).

Compound **2a** (NHRR=piperidine) was obtained in 72% yield (0.72 g); mp 135-136 °C; ir: 3180 (NH), 2926, 2852 (CH), 1610 (C=N) cm^{-1}; ^1H nmr: δ 8.42 – 7.39 (9H, m, ArH), 4.25-4.29 (4H, m, NCH_2); 1.70 – 1.74 (6H, m, CH_2); ^{13}C nmr: δ 183.35 (C=S), 154.28 (C_2), 149.70 (C_4), 148.76 (C_q), 134.29 (CH_{Ar}), 132.65 (C_q), 131.62 (CH_{Ar}), 129.34 (CH_{Ar}), 128.14 (CH_{Ar}), 127.61 (CH_{Ar}), 127.15 (CH_{Ar}), 125.56 (CH_{Ar}), 121.17 (C_q), 49.06

(NCH_2), 48.55 (NCH_2), 26.53 (CH_2), 25.92 (CH_2), 24.82 (CH_2); Ms: m/z 348 (M^+), 264, 263, 206, 205, 132, 103, 102, 85, 84, 77, 76, 75, 56.

Anal. Calcd. for $C_{20}H_{20}N_4S$ (348.47): C 68.94; H 5.78; N 16.08; S 9.20. Found: C 68.79; H 5.70; N 16.10; S 9.09.

Pyrrolidine-1-carbothioic Acid (2-Phenyl-3*H*-quinazolin-4-ylidene) Amide (**2b**).

Compound **2b** (NHRR=pyrrolidine) was obtained in 66% yield (0.69 g); mp 205-206 °C; ir: 3200 (NH), 2968, 2867 (CH), 1611 (C=N) cm^{-1}; ^1H nmr: δ 8.45–7.44 (9H, m, ArH), 4.01 (2H, t, NCH_2) ($J_{A,B}$= 6.90 Hz), 3.87 (2H, t, NCH_2) ($J_{A,B}$= 6.90 Hz), 1.99-2.07 (4H, m, CH_2); ^{13}C nmr: δ 183.19 (C=S), 155.66 (C_2), 151.04 (C_4), 149.18 (C_q), 134.72 (CH_{Ar}), 133.17 (CH_{Ar}), 132.11 (CH_{Ar}), 129.68 (CH_{Ar}), 128.59 (CH_{Ar}), 128.02 (CH_{Ar}), 127.34 (CH_{Ar}), 125.96 (CH_{Ar}), 121.84 (C_q), 52.21 (NCH_2), 51.69 (NCH_2), 27.05 (CH_2), 26.31 (CH_2); Ms: m/z 334 (M^+), 301, 265, 264, 263, 232, 206, 205, 103, 102, 77, 70.

Anal. Calcd. for $C_{19}H_{18}N_4S$ (334.44): C 68.24; H 5.42; N 16.75; S 9.59. Found: C 68.07; H 5.33; N 16.60; S 9.43.

4-Methylpiperazine-1-carbothioic Acid (2-Phenyl-3*H*-quinazolin-4-ylidene) Amide (**2c**).

Compound **2c** (NHRR=*N*-methylpiperazine) was obtained in 53% yield (0.54 g); mp 244-245 °C; ir: 3240 (NH), 2934 (CH), 1610 (C=N) cm^{-1}; ^1H nmr: δ 8.43–7.48 (9H, m, ArH), 4.42-4.37 (4H, m, NCH_2), 2.60-2.56 (4H, m, NCH_2), 2.39 (3H, s, CH_3); ^{13}C nmr: δ 184.38 (C=S), 154.85 (C_2), 149.51 (C_4), 149.13 (C_q), 134.73 (CH_{Ar}), 132.86 (CH_{Ar}), 132.00 (CH_{Ar}), 129.37 (CH_{Ar}), 128.43 (CH_{Ar}), 127.60 (CH_{Ar}), 127.34 (CH_{Ar}), 125.65 (CH_{Ar}), 121.51 (C_q), 55.06 (NCH_2), 54.71(NCH_2), 47.21 (CH_3NCH_2), 46.78 (CH_3NCH_2), 45.53 (NCH_3); ms: m/z 363 (M^+), 264, 263, 206, 205, 131, 103, 102, 100, 99, 83, 77, 75, 74, 70, 58, 56.

Anal. Calcd. for $C_{20}H_{21}N_5S$ (363.48): C 66.09; H 5.82; N 19.27; S 8.82. Found: C 65.90; H 5.70; N 19.07; S 8.69.

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

Compound **3a** (NH_2R=butylamine) was obtained in 60% yield (0.58 g); mp 165-166 °C; ir: 3427 (NH), 2952, 2928, 2869 (CH), 1618 (C=N) cm^{-1}; ^1H nmr: δ 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, $HNCH_2CH_2CH_2$), 0.94 (3H, t, CH_2CH_3) ($J_{A,B}$= 7.31 Hz); ^{13}C nmr: δ 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 ($HNCH_2CH_2CH_2$), 13.99 (CH_3); ms: m/z 336 (M^+), 304, 303, 264, 247, 222, 221, 206, 205, 130, 118, 104, 102, 77, 72, 41.

Anal. Calcd. for $C_{19}H_{20}N_4S$ (336.45): C 67.83% ; H 5.99; N 16.65; S 9.53. Found: C 67.64; H 5.81; N 16.48; S 9.43.

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

Compound **3b** (NH_2R=benzylamine) was obtained in 68% yield (0.72 g); mp 189-190 °C; ir: 3292 (NH), 3024 (CH), 1619 (C=N) cm^{-1}; ^1H nmr: δ 12.31 (1H, s, $NHCH_2$), 8.88 (1H, s, NH), 8.03-7.18 (14H, m, ArH), 4.98 (2H, d, $NHCH_2$) ($J_{A,B}$= 4.66 Hz); ^{13}C nmr: δ 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 (NCH_2); ms: m/z 370 (M^+), 339, 337, 264, 263, 239, 222, 221, 206, 205, 149, 118, 104, 102, 91, 77, 65, 51.

Anal. Calcd. for $C_{22}H_{18}N_4S$ (370.47): C 71.33; H 4.90; N 15.12; S 8.65. Found: C 71.24; H 4.88; N 15.03; S 8.59.

1-Cyclohexyl-3-(2-phenylquinazolin-4-yl)thiourea (**3c**).

Compound **3c** (NH_2R=cyclohexylamine) was obtained in 77% yield (0.81 g); mp 154-155 °C; ir: 3441, 3425 (NH), 1619 (C=N) cm^{-1}; ^1H nmr: δ 12.08 (1H, b, *NH*CH), 8.75 (1H, s, NH), 8.32-7.54 (9H, m, ArH), 4.28-4.38 (1H, m, NH*CH*), 2.34-2.27 (2H, m, CH_2), 1.91-1.71 (4H, m, $2CH_2$), 1.55-1.38 (4H, m, $2CH_2$); ^{13}C nmr: δ 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 (CH_2), 32.78 (CH_2), 25.87(CH_2), 25.17(CH_2).

Anal. Calcd. for $C_{21}H_{22}N_4S$ (362.49): C 69.58; H 6.12; N 15.46; S 8.84. Found: C 69.41; H 6.12; N 15.38; S 8.74.

1-Phenyl-3-(2-phenylquinazolin-4-yl)thiourea (**3d**).

Compound **3d** (NH_2R=aniline) was obtained in 43% yield (0.35 g); mp 165-166 °C; ir: 3436, 3418 (NH), 1617 (C=N) cm^{-1}; ^1H nmr: δ 14.26 (1H, s, *NH*Ph), 8.93 (1H, s, NH), 8.35-7.29 (14H, m, ArH); ^{13}C nmr: δ 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 356 (M^+), 323, 276, 264, 263, 222, 221, 205, 178, 135, 118, 104, 102, 93, 91, 77, 51.

Anal. Calcd. for $C_{21}H_{16}N_4S$ (356.44): C 70.76; H 4.52; N 15.72; S 8.99. Found: C 70.58; H 4.52; N 15.64; S 8.83.

1-(4-Methylphenyl)-3-(2-phenylquinazolin-4-yl)thiourea (**3e**).

Compound **3e** (NH_2R=*p*-toluidine) was obtained in 38% yield (0.31 g); mp 179-180 °C; ir: 3422 (NH), 1619 (C=N) cm^{-1}; ^1H nmr: δ 14.16 (1H, s, *NH*Ph), 8.92 (1H, s, NH), 8.36-7.29 (13H, m, ArH), 2.40 (3H, s, CH_3); ^{13}C nmr: δ 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 337, 264, 263, 222, 221, 206, 205, 149, 148, 118, 107, 106, 91, 77.

Anal. Calcd. for $C_{22}H_{18}N_4S$ (370.47): C 71.33; H 4.90; N 15.12; S 8.65. Found: C 71.21; H 4.89; N 15.11; S 8.62.

1-(4-Methoxyphenyl)-3-(2-phenylquinazolin-4-yl)thiourea (**3f**).

Compound **3f** (NH_2R=*p*-anisidine) was obtained in 40% yield (0.34 g); mp 168-169 °C; ir: 3428 (NH), 2934 (CH), 1616 (C=N) cm^{-1}; ^1H nmr: δ 14.09 (1H, s, *NH*Ph), 8.91 (1H, s, NH), 8.35-6.98 (13H, m, ArH), 3.86 (3H, s, OCH_3); ^{13}C nmr: δ 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}), 131.45(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 (OCH_3).

Anal. Calcd. for $C_{22}H_{18}N_4OS$ (386.47): C 68.37; H 4.69; N 14.50; S 8.30. Found: C 68.24; H 4.57; N 14.49; S 8.23.

1,3-Di(4-methoxyphenyl)thiourea (**4**).

Compound **4** (6 mmol NH_2R=p-anisidine) was obtained in 52% yield (0.35 g); mp 149-150 °C; ^{1}H nmr: δ 7.76 (2H, s, *NH*), 7.38-7.31 (4H, m, CHAr), 6.97-6.83 (4H, m, CHAr), 3.81 (6H, s, OCH_3); ^{13}C nmr: δ 181.34 (C=S), 158.79 (C_q), 129.95 (C_q), 127.50 (CH_{Ar}), 114.82 (CH_{Ar}), 54.54 (OCH_3).

Anal. Calcd. for $C_{15}H_{16}N_2O_2S$ (288.37): C 62.48; H 5.95; N 9.71; S 11.12. Found: C 62.32; H 5.45; N 9.51; S 11.02.

2-Phenylquinazolin-4-amine (**5**).

Compound **5** (6 mmol NH_2R=aniline) was obtained in 73% yield (0.48 g); mp 145-146 °C; the compound was identified by comparison of mp [14] and the TLC with authentic standard prepared by the reaction of N^1-(2-cyanophenyl)-1-benzenecarboximidoyl chloride with ammonia.

N^4-[1-Substituted-1-morpholinomethylidene]-2-phenylquinazolin-4-amine(guanidine derivative) **7**.

Method A.

The stirred solution of morpholine-1-carbothioic acid (2-phenyl-3*H*-quinazolin-4-ylidene) amide (**1**) (1.0 g, 2.8 mmol) was dissolved in the appropriate amine (15 mL). Hydrogen peroxide (five drops) was added drop wise to this reaction mixture. The reaction mixture was stirred at room temperature for 2 hours to afford white crystals. The reaction mixture was filtered and the solid residue thus collected was crystallized from ethyl alcohol. The mother liquor was poured on crushed ice to give an additional portion of the product.

Method B.

Morpholine-1-carbothioic acid (2-phenyl-3*H*-quinazolin-4-ylidene) amide (**1**) (1.0 g, 2.8 mmol) was dissolved in DMF (30 mL). Benzyl bromide (0.34 mL, 2.9 mmol) and sodium hydride (0.14 g, 5.6 mmol) was added to this solution. The jhetreaction mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure. The oily residue was evaporated under reduced pressure and was dissolved in DMF without further purification. The appropriate amine was then added amine (5 mmol). The reaction mixture was refluxed at 80°C for 3 hours, evaporated under reduced pressure and the oily residue was crystallized from ethyl alcohol

N^4-[1-Morpholino-1-piperidinomethylidene]-2-phenylquinazolin-4-amine (**7a**).

Comound **7a** (Method A; NHRR=piperidine) was obtained in 61% yield (0.69 g); (method B); overall-yield: 0.46 g (40%); mp 165-166 °C; ir: 3055, 2993, 2858 (CH), 1613 (C=N) cm^{-1}; ^{1}H nmr: δ 8.44-7.46 (9H, m, ArH), 3.92-3.83 (4H, m, CH_2), 3.69-3.53 (4H, m, NCH_2), 3.51-3.37 (4H, m, NCH_2), 1.78-1.53 (4H, m, $2CH_2$); ^{13}C nmr: δ 164.45 (C_q), 157.24 (C_q), 156.81 (C_q), 148.73 (C_q), 148.63 (C_q), 134.66 (CH_{Ar}), 132.98 (C_q), 131.93 (CH_{Ar}), 129.41 (CH_{Ar}), 129.33 (CH_{Ar}), 128.24 (CH_{Ar}), 127.13 (CH_{Ar}), 126.97 (CH_{Ar}), 120.56 (C_q), 67.29 (OCH_2), 47.55 (NCH_2), 43.51 (NCH_2), 42.89 (NCH_2), 26.57 ($NCH_2CH_2CH_2$), 26.20 ($NCH_2CH_2CH_2$), 25.00 ($NCH_2CH_2CH_2$).

Anal. Calcd. for $C_{24}H_{27}N_5O$ (401.51): C 71.80; H 6.78; N 17.44. Found: C 71.69; H 6.78; N 17.35.

N^4-[1-Morpholino-1-pyrrolidinomethylidene]-2-phenylquinazolin-4-amine (**7b**).

Compound **7b** (Method A; NHRR=pyrrolidine) was obtained in 53% yield (0.58 g); mp 181-182 °C; ir: 3058, 2971, 2850 (CH), 1610 (C=N) cm^{-1}; ^{1}H nmr: δ 8.46-7.18 (9H, m, ArH), 3.65-3.58 (4H, m, OCH_2), 3.61-3.42 (4H, m, NCH_2), 3.23-3.11 (4H, m, NCH_2), 1.91-1.84 (4H, m, $2CH_2$); ^{13}C nmr δ: 166.24 (C_q), 162.39 (C_q), 161.17 (C_q), 151.80 (C_q), 139.87 (C_q), 132.54 (CH_{Ar}), 129.81 (CH_{Ar}), 128.50 (CH_{Ar}), 128.35 (CH_{Ar}), 127.78 (CH_{Ar}), 125.94 (CH_{Ar}), 125.09 (CH_{Ar}), 119.66 (C_q), 66.81 (OCH_2), 49.93 (NCH_2), 49.31 (NCH_2), 25.61 ($NCH_2CH_2CH_2$).

Anal. Calcd. for $C_{23}H_{25}N_5O$ (387.48): C 71.29; H 6.50; N 18.07. Found: C 71.13; H 6.48; N 17.98.

4-Substituted- N^4-(2-phenylquinazolin-4-yl)morpholine-4-carboximidothioate (**8**).

General Procedure.

Morpholine-1-carbothioic acid (2-phenyl-3*H*-quinazolin-4-ylidene) amide **1** (1.0 g, 2.8 mmol) was dissolved in DMF (30 mL). The appropriate alkyl halide (2.9 mmol) and sodium hydride (0.14 g, 5.6 mmol) was added to this solution. The reaction mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure. The oily residue was dissolved in chloroform, washed with water, dried with sodium sulfate and finally evaporated. The solid residue was crystallized from ethanol.

4-Benzyl-N^4-(2-phenylquinazolin-4-yl)morpholine-4-carboximidothioate (**8a**).

Compound **8a** (RX=benzyl bromide) was obtained in 56% yield (0.71 g); mp 139-140 °C; ^{1}H nmr: δ 8.53-7.00 (14H, m, ArH), 3.71 (2H, s, SCH_2), 3.65 (4H, t, OCH_2) ($J_{A,B}$= 4.79Hz), 3.55 (4H, t, NCH_2) ($J_{A,B}$=4.79Hz); ^{13}C nmr: δ 164.85 (C_q), 160.93 (C_q), 151.91 (C_q), 139.23 (C_q), 136.32 (C_q), 133.07 (CH_{Ar}), 130.12 (CH_{Ar}), 129.23 (CH_{Ar}), 128.95 (CH_{Ar}), 128.59 (CH_{Ar}), 128.07 (CH_{Ar}), 125.78 (CH_{Ar}), 125.56 (CH_{Ar}), 119.19 (C_q), 66.47 (OCH_2), 48.51 (NCH_2), 38.18 (SCH_2).

Anal. Calcd. for $C_{26}H_{24}N_4OS$ (440.56): C 70.88; H 5.49; N 12.72; S 7.28. Found: C 70.67; H 5.46; N12.63; S 7.17.

4-Allyl-N^4-(2-phenylquinazolin-4-yl)morpholine-4-carboximidothioate (**8b**).

Compound **8b** (RX=allyl bromide) was obtained in 58% yield (0.64 g); mp 127-128 °C; ^{1}H nmr: δ 8.60-7.42 (9H, m, ArH), 5.71-5.58 (1H, m, C*H*=CH_2), 4.95 (1H, d, CH=CH_2, $J_{A,B}$ = 8.79 Hz), 4.86 (1H, d, CH=CH_2, $J_{A,B}$ =8.37 Hz), 3.87 (4H, t, OCH_2) ($J_{A,B}$= 4.78 Hz), 3.77 (4H, t, NCH_2) ($J_{A,B}$= 4.79 Hz), 3.23 (2H, d, SCH_2, J= 6.93 Hz); ^{13}C nmr: δ 164.56 (C_q), 161.66 (C_q), 160.90 (C_q), 151.77 (C_q), 139.14 (C_q), 133.07 (CH_{Ar}), 132.36 (CH_{Ar}), 130.11 (CH_{Ar}), 128.54 (CH_{Ar}), 128.45 (CH_{Ar}), 127.97 (CH_{Ar}), 125.76 (CH_{Ar}), 125.55 (CH_{Ar}), 119.14 (C_q), 118.92 (CH=*C*H_2), 66.57 (OCH_2), 48.57 (NCH_2), 36.51 (SCH_2).

Anal. Calcd. for $C_{22}H_{22}N_4OS$ (390.50): C 67.67; H 5.68; N 14.35; S 8.21. Found: C 67.65; H 5.63; N 14.29; S 8.19.

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REFERENCES AND NOTES

[*] Corresponding author; E-mail: pazdera@chemi.muni.cz; Phone: +420 5 41129305; Fax: +420 5 41211214.

[1] W. Fathalla, M. Čajan, J. Marek and P. Pazdera, *Molecules*, **6**, 574 (2001).

[2] W. Fathalla, M.Čajan, J. Marek and P. Pazdera, *Molecules*, **6**, 588 (2001).

[3] W. Fathalla, M.Čajan, and P. Pazdera, *Molecules*, **5**, 1210 (2000).

[4] W. Fathalla, M. Čajan, and P. Pazdera, *Molecules*, **6**, 557 (2001).

[5] W.-D. Pfeiffer, A. Hetzheim, P. Pazdera, A.Bodtke and J. Mücke, *J. Heterocyclic Chem.*, **36**, 1327 (1999).

[6] C. Lee, W. Yang and R. G. Parr, *Phys. Rev*. B **37**, 785 (1988).

[7] N. Godbout, D. R. Salahub, J. Andulm and E. Wimmer, *Can. J. Chem*. **70**, 560 (1992).

[8] R. S. Mulliken, *J. Chem. Phys*., **23**, 1833 (1955).

[9] E. R. Davidson, *J. Chem. Phys*., **46**, 3320 (1967).

[10] J. P. Foster and F. Weinhold, *J. Am. Chem. Soc*., **102**, 7211 (1980).

[11] A. E. Reed and F. Weinhold, *J. Chem. Phys*., **78**, 4066 (1983).

[12] A. E. Reed, R. B. Weistock and F. Weinhold, *J. Chem. Phys*., **83**, 735 (1985).

[13] K. Osamu, Y. Shigeo and K. Toshiro, *Agric. Biol. Chem*., **44**, 2143 (1980).

[14] N. Latif, I. F. Zeid, N. Mishriky and F. M. Assad, *Tetrahedron Lett*., 1355 (1974).