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Walid Fathalla[a]; Jaromír Marek[b]; Pavel Pazdera[c]
[a] Department of Mathematical and Physical sciences, Faculty of Engineering, Suez Canal University, Port-Said, Egypt [b] Laboratory of Functional Genomics and Proteomics, Institute of Experimental Biology, [c] Centre for Syntheses at Sustainable Conditions and Their Management, Faculty of Science, Masaryk University, Brno, Czech Republic

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RESEARCH ARTICLE

One-pot domino synthesis of 4-heteroaryl-2-phenyl-quinazolines bearing 5-aryl-1,3-oxathiol-2-ylidene amine and substituted 1,3-thiazole groups

Walid Fathalla[a]*, Jaromír Marek[b] and Pavel Pazdera[c]

[a]*Department of Mathematical and Physical sciences, Faculty of Engineering, Suez Canal University, Port–Said, Egypt;* [b]*Laboratory of Functional Genomics and Proteomics, Institute of Experimental Biology;* [c]*Centre for Syntheses at Sustainable Conditions and Their Management, Faculty of Science, Masaryk University, Brno, Czech Republic*

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The reaction of thioamides **1–5** with phenacyl halides offers the advantage of an efficient domino synthesis of the title 4-heteroaryl-2-phenylquinazolines bearing 1,3-oxathiol-2-ylidene amine **6a–d** and 1,3-thiazoles **7–11**. The reaction shows unexpected thermodynamic and kinetic control products. In the same manner, thioamides **1**, **2** and **4** react with methyl chloroacetate to afford 4-[2-dialkylamino-4(5*H*)-oxo-1, 3-thiazol-5-yl]-2-phenyl-quinazolin-4(3*H*)-ylidene **12**, **13** and 14, respectively. Similarly, 2-morpholino-5-(2-phenylquinazolin-4-yl)thiazol-4-amine **15** is formed by the reaction of **1** with chloroacetonitrile. Synthesized compounds were characterized on the basis of the well known reaction mechanisms elemental analysis, NMR, mass spectroscopy and X-ray data.

Keywords: 1,3-thiazoles; 1,3-oxathioles; thermodynamically controlled and kinetically controlled reactions; domino reactions; NK-3R antagonists; 4-heteroaryl-2-phenyl-quinazolines

1. Introduction

The neurokinin receptors (NKR) appear to mediate the functions of the peptidic neurotransmitters on diverse biological processes including smooth muscle contraction, blood pressure regulation, modulation of stress, anxiety, depression, nausea, bowel disorders, and regulation of certain immune and inflammatory states (*1*). The development of potent nonpeptide antagonists at the NKR has the potential to provide therapeutic benefits. NK-3 antagonists have been proposed for the treatment of asthma and chronic obstructive pulmonary disease (*2*), anxiety and depression (*3*), psychotic symptoms of schizophrenia (*4*), and panic disorders (*5*).

At present, only a few chemical classes of selective nonpeptidic NK-3 receptor antagonists have been developed: 2-arylquinoline-4-carboxamides including the potent and selective antagonist SB 218795 **I** (*6*) and taletant **II** (*7*) (Figure 1).

*Corresponding author. Email: walid399@yahoo.com

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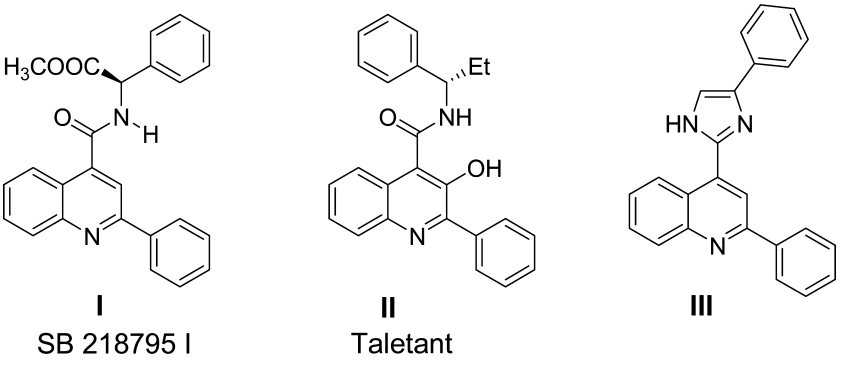


Figure 1. Selective nonpeptidic NK-3 receptor antagonists.

Substituted 4-heteroaryl-2-phenylquinolines can be regarded as bioisosters of the NK-3 antagonist SB 218795 **I**. 2-Phenyl-4-(4-phenylimidazol-2-yl) quinoline **III** displayed a preferential interaction with NK-3 receptor (*8*).

We have recently reported a new and efficient synthesis of novel 1,3-oxathioles **6a–d** and 4-aryl-4-[2-(morpholino4-yl)-1,3-thiazol-5-yl]-2-phenylquinazolines **7a–d** (*9*, *10*) based on domino reaction of *N*-(2-phenylquinazolin-4(3*H*)-ylidene)-morpholine-4-carbothioamide **(1)** with phenacylhalides.

This paper describes our development of a novel series of 4-heteroaryl-2-phenyl-quinazolines bearing 1,3-thiazoles **7–15** as active non-peptide NK3R antagonists relative to template **III** whose chemical modifications include quinazoline and thiazole ring moieties.

2. Result and discussion

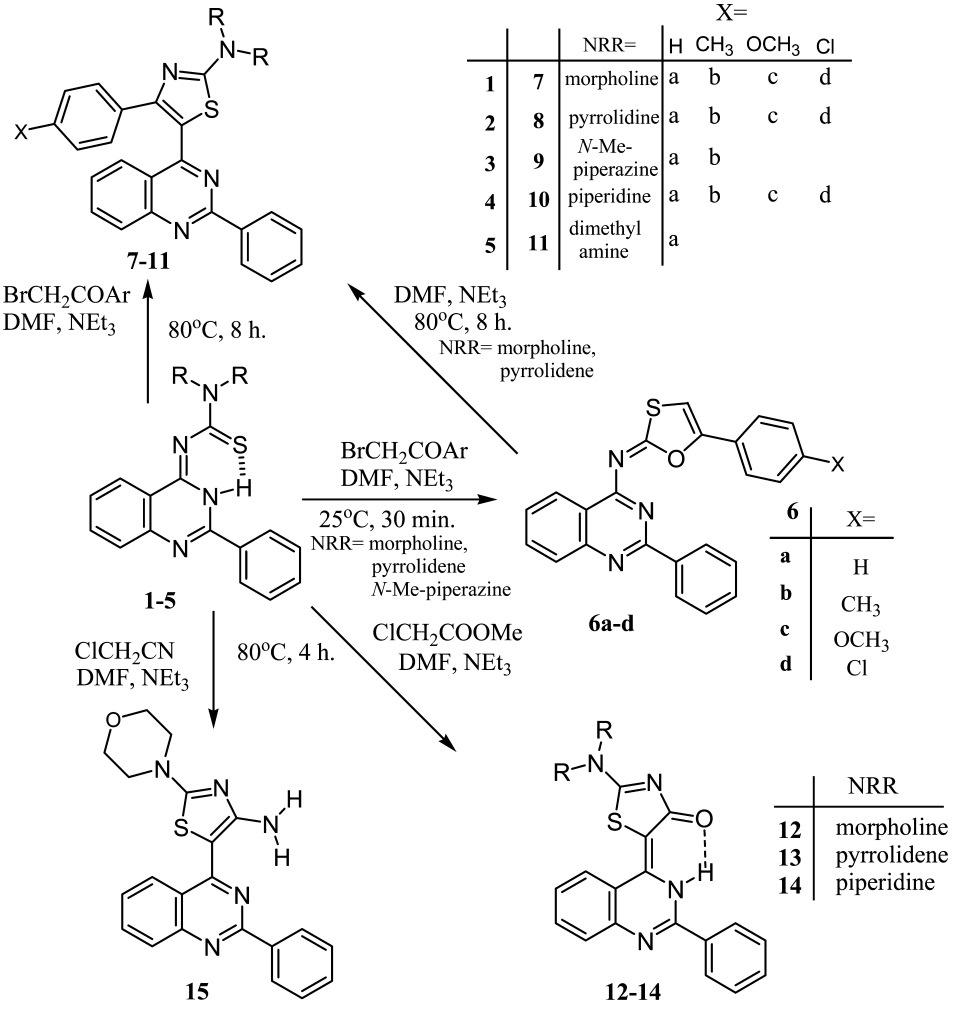
2.1. *Chemistry*

We have extended the preparative scope of our methodology to produce a series of new 4-[4-aryl-2-dialkylamino-1,3-thiazol-5-yl]-2-phenylquinazolines **7–11** using different thioamides **1–5** (*11*). In addition, we report what are, to the best of our knowledge, the first kinetic and thermodynamic-controlled domino reactions (*12*, *13*). The reaction of thioamides **1–5** (NRR = morpholine, piperidine, *N*-methyl piperazine, pyrrolidine, dimethylamine) with phenacyl bromides in the presence of triethyl amine furnished 1,3-oxathioles **6a–d** and/or 1,3-thiazoles **7–11,** Scheme 1.

The reaction is assumed to proceed through the following reaction sequence, Scheme 2 (*9*, *10*). The thioamide **1–5** undergoes *S*-alkylation with phenacyl halides to give the isothiourea intermediate **i**. Intermediate **i** cyclizes by intramolecular oxygen attack at the isothioureido moiety to afford 1,3-oxathiole **6a–d,** and the consequent secondary amine elimination as depicted in path A. The alternative pathway shows active methylene attack at C4 of the quinazoline ring to give the intermediate **ii**, path B (*14*, *15*). The five-membered ring rearranges *via N*-attack at the carbonyl group followed by subsequent hydroxyl group elimination to finally afford the 1,3-thiazoles **7–11**.

This Domino reaction represents an interesting complete change in the location of the starting functional thioamide reflected in the thiazole subunit scheme 2. This method has the advantage of a *one-pot* domino reaction with an overall moderate to good yield, beside many different substituents could be introduced in the quinazoline-thiazole and quinazoline-oxathiole basic skeleton.

On the basis of TLC and HPLC monitoring for reaction progress the following results were obtained: First, The kinetically controlled products 1,3-oxathioles **6a–d** are formed at 25 °C while

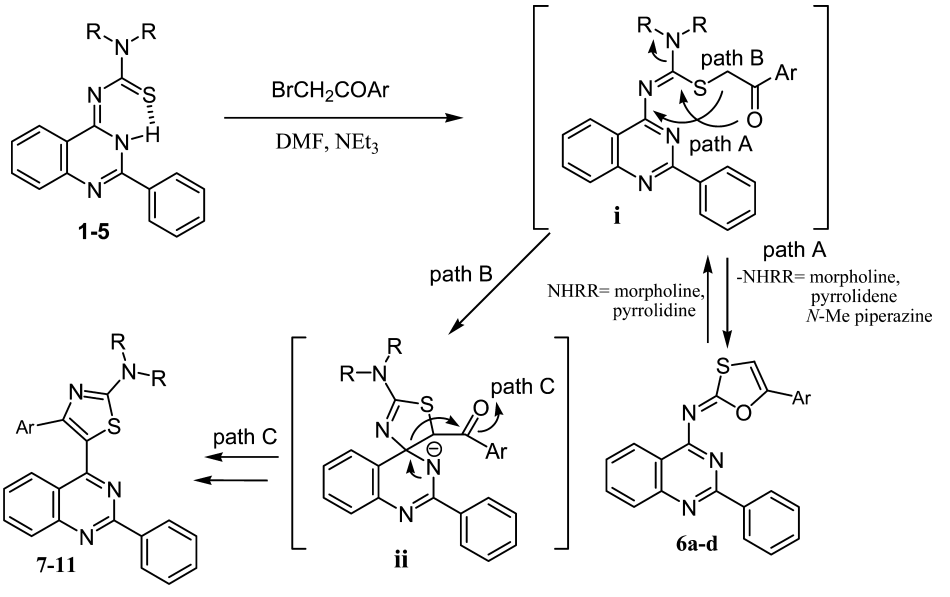


Scheme 1. Domino reactions of thioamides **1–5**.

at 80 °C and extended reaction time only the thermodynamically controlled 1,3-thiazoles **7a–d** and **8a–d** are formed.

This could be explained as follows: The kinetically controlled oxathioles **6a-d** is in equilibrium with their corresponding isothiourea intermediates **i** and the thermodynamic controlled 1,3-thiazoles **7a–d** and **8a–d** at elevated temperature and extended reaction time. The equilibrium once achieved, favors the more stable thiazole. Second, the reaction afforded almost an equal share from the 1,3-oxathioles **6a, b** and 1,3-thiazoles **9a, b** (NRR = *N*-methyl piperazine). The domino reaction involving the oxathioles **6a, b**, isothioureas **i** and the thiazoles **9a, b** are irreversible. Third, 1,3-thiazoles **10a–d** and **11a** (NRR = piperidine dimethyl amine) are the only isolated products obtained from the same reaction condition. The reversibility of the reaction was dramatically achieved dependent on the nucleophilicity, the leaving group ability of secondary amines and the activation energy barrier for the oxathiole formation.

The structures of all compounds: 1,3-oxathioles **6a–d** and 1,3-thiazoles **7–11** were assigned on the basis of the well-known reaction mechanisms (*9*, *10*), spectroscopic and X-ray structure analysis, (Figures 2, 3. The ^{1}H NMR spectrum of **6b** exhibits a signal at δ 6.79 ppm corresponding



Scheme 2. Postulated mechanistic steps of the domino reaction.

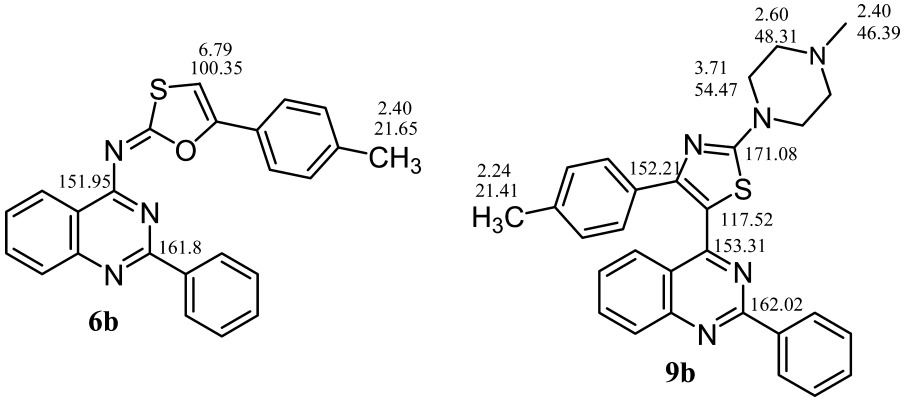


Figure 2. Selected ^{1}H and ^{13}C NMR data of oxathiole **6b** and thiazole **9b**.

to CH of the 1,3-oxathiole ring, while the ^{13}C NMR spectrum of **6a** reveals a signal at δ 101.39 ppm assigned to CH of the oxathiole. The ^{13}C NMR spectrum of **6b** also showed quaternary carbon signals at δ 161.8 and 151.95 ppm assigned to C2 and C4 of the quinazoline ring, respectively (*9*, *10*). The ^{1}H NMR spectrum of **9b** exhibits signals at δ 3.71, 2.60, 2.40 and 2.24 ppm corresponding to NCH_2, NCH_2, NCH_3 and CH_3, respectively. On the other hand, the ^{13}C NMR spectrum of **9b** reveals signals at δ 171.08, 152.21 and 117.52 attributed to C2, C4 and C5 of the thiazole ring, respectively, in addition to signals at δ 162.02 and 153.31 ppm due to quinazoline ring, (Figure 2).

Further development of this reaction was obtained by the reaction of thioamides **1, 2, 4** with chloromethyl acetate to afford 4-[2-dialkylamino-4(5*H*)-oxo-1,3-thiazol-5-yl]-2-phenylquinazolin-4(3*H*)-ylidene **12–14** Scheme 1. The reaction proceeded following the same mechanistic steps mentioned above with two exception: first, is the elimination of methyl alcohol instead

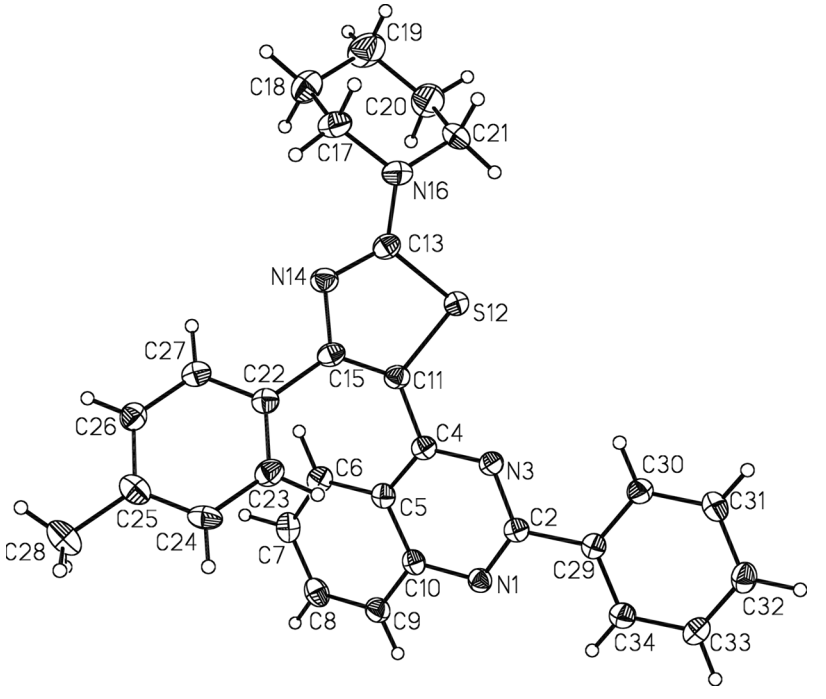


Figure 3. ORTEP plot of the molecular structure of **10b** with atomic numbering, drawn at 50% probability level.

of H_2O in the previous example (Scheme 2), second is the formation of the 1,3-thiazol-4-one **12–14** as the final product stabilized by a hydrogen bond interaction Scheme 1.

The structures of **12–14** were established by analytical and spectroscopic data.

The ^{1}H NMR spectrum of **12** was in good agreement with the proposed structure showing an interesting exchangeable signal at δ 15.66 ppm corresponding to one NH group. This implies that the NH group participate in an intramolecular hydrogen bond interaction of the type N–H$\cdots$O=C (*16*). The ^{13}C NMR spectrum of **12** reveals signals at δ 183.32, 173.17 and 92.78 attributed to C=O, C2 and C5 of the thiazole ring, respectively in addition to signals at δ 150.63 and 148.29 ppm due to C4 and C2 of the quinazoline ring, respectively Figure 4.

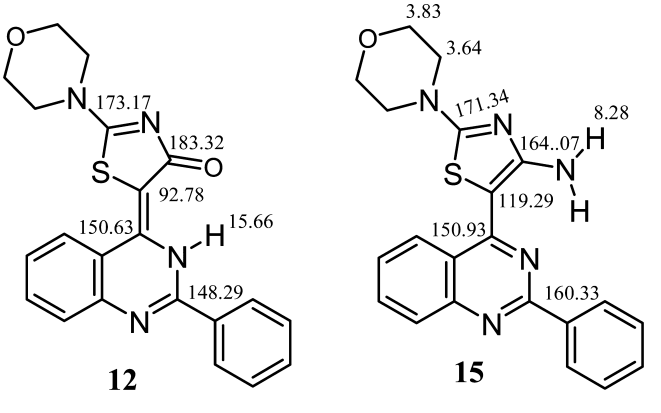


Figure 4. Selected ^{1}H and ^{13}C NMR data of thiazolidene **12** and thiazole **15**.

In the same manner, starting from thioamide **1**; 2-morpholino-5-(2-phenylquinazolin-4-yl) thiazol-4-amine (**15**) was prepared by the reaction with chloroacetonitrile in the presence of triethyl amine (Scheme 1).

The ^{1}H NMR spectrum of **15** gave signals at δ 8.28, 383 and 3.64 ppm attributed to NH, OCH_2 and NCH_2, respectively. It is apparent that no hydrogen bond is detected for this compound. The ^{13}C NMR spectrum of **15** reveals signals at δ 171.34, 164.07 and 119.29 attributed to C2, C4 and C5 of the thiazole ring, respectively in addition to signals at δ 160.33 and 150.93 ppm due to C4 and C2 of the quinazoline ring (Figure 4).

3. Experimental

3.1. *Chemistry*

Solvents were purified and dried in the usual way. The boiling range of the petroleum ether used was 35–65 °C.Thin layer chromatography (TLC): silica gel 60 F_{254} plastic plates (E. Merck, layer thickness 0.2 mm), eluent used was a 20:80 mixture of ethyl acetate-pet. ether detected by UV absorption Fluotes universal instrument (Quarzlampen, Hanau). Melting points were determined Boetius Rapido PHMK 79/2106 (Wägetechnik) instrument and the values are uncorrected. The purity of compounds **6–15** were proven by their elemental analysis, measured on an Erba 1102 instrument. NMR spectra were measured on a Bruker Avance DRX–500 spectrometer. TMS (0.00 ppm) or the signal of the deuterated solvent was used as internal standard. The X-ray structural data of compounds **8d** and **10b** were collected with a KUMA KM-4 kappa four-circle diffractometer. The structures have been solved by direct methods using SHELXS86 (*17*) and refined on F^2 for all reflections using SHELXl93 (*18*) (data and parameters for **10b** are in Tables 1 and 2). Crystals suitable for X-ray determination were obtained as white prisms by crystallization from $CHCl_3$-petroleum ether at room temperature. The crystallographic data for **8d** and **10b** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 652477 & 652476, respectively. Mass spectrometry was determined (electron impact, 70 eV) with a Fisons TRIO 1000 and GC 8000 series instrument. Compounds **1–4** and **7a–d** are prepared according to literature (*9–11*).

3.2. *1,1-Dimethyl-3-(2-phenyl-3H-quinazolin-4-ylidene) thiourea (5)*

To a solution of Me_2N.HCl. (0.4 g, 5 mmol) in acetonitrile (10 mL) was added triethyl amine (0.7 mL, 5 mmol). This solution was stirred at 5 °C for 30 min, filtered and subsequently added in portions to a freshly prepared solution of *N*-(2-cyanophenyl)benzimidoyl isothiocyanate (1.32 g,

Table 1. Bond length of the thiazole structure **10b**.

Bond	l, Å	Bond	l, Å
N(1)–C(2)	1.321(2)	C(13)–N(14)	1.315(3)
C(2)–N(3)	1.362(2)	N(14)–C(15)	1.380(2)
N(3)–C(4)	1.327(2)	C(15)–C(11)	1.369(3)
C(4)–C(5)	1.435(3)	C(13)–N(16)	1.355(3)
C(5)–C(10)	1.413(3)	N(16)–C(17)	1.465(3)
C(2)–C(29)	1.487(3)	C(17)–C(18)	1.510(3)
C(29)–C(30)	1.397(3)	C(18)–C(19)	1.515(4)
C(4)–C(11)	1.471(3)	C(15)–C(22)	1.480(3)
C(11)–S(12)	1.7537(19)	C(22)–C(27)	1.396(3)
S(12)–C(13)	1.7547(19)	C(25)–C(28)	1.503(3)

Table 2. Crystal data and structure refinement for thiazole **10b**.

Empirical formula	C_{29} H_{26} N_4S
Molecular weight	462.60
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, Pbca
Unit cell dimensions	a = 11.5568(4) Å α = 90°
	b = 19.9508(6) Å β= 90°
	c = 20.6951(8) Å γ= 90°
Volume	4771.6(3) Å ^3
Z; density calculated	8, 1.288 Mg/m^3
Absorption coefficient	0.161 mm^-1
F(000)	1952
Crystal size	0.40 × 0.30 × 0.30 mm
θ Range for data collection	3.34 to 25.00°
Index ranges	−13 <= h <= 13, −23 <= k <= 23, −24 <= l <= 20
Reflections collected/unique	23194/4192 [R(int) = 0.0448
Completeness to 2θ = 25.00	99.8%
Maximum and minimum transmission	0.9533 and 0.9384
Refinement method	full-matrix least-squares on F^2
Data/restraints/parameters	4192/0/412
Goodness-of-fit on F^2	1.113
Final R indices [I > 2sigma(I)]	R1 = 0.0475, wR2 = 0.1060
R indices (all data)	R1 = 0.0522, wR2 = 0.1092
Extinction coefficient	0.0005(3)
Largest different peak and hole	0.308 and −0.293 e.A^−30

5 mmol) in acetonitrile (30 mL). The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure, and the residue was crystallized from ethanol. White crystals (0.76 g, 48%); m.p. 189–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 16.43 (1H, s, N−H$\cdots$S=C), 8.44–8.32 (3H, m, ArH),7.81–7.31 (6H, m, ArH), 3.58 (3H, s, CH_3), 3.52 (3H, s, CH_3), ^{13}C NMR (75.5 MHz, CDCl3): δ 185.19 (C=S), 154.36 (C4), 149.72 (C2), 148.97 (C_{qAr}), 134.53 (CH_{Ar}), 132.89 (C_{qAr}), 131.89 (CH_{Ar}), 129.31 (CH_{Ar}), 128.33 (CH_{Ar}), 127.58 (CH_{Ar}), 127.23 (CH_{Ar}), 125.61 (CH_{Ar}), 121.62 (C_{qAr}), 41.56 (CH_3), 40.52 (CH_3).Anal. Calcd. for $C_{17}H_{16}N_4S$ (308.4): 66.21% C, 5.23% H, 18.17% N. found: 66.11% C, 5.02% H, 17.96% N.

3.3. *N^4-(5-Aryl-1,3-oxathiol-2-yliden)-2-phenylquinazolin-4-amine (6a–d)*

General procedure. To a solution of thioamide **1–5** (2.8 mmol) in DMF (30 mL) was added triethylamine (0.5 mL, 3.5 mmol) and the appropriate 4-substituted phenacyl bromide (2.8 mmol). The reaction mixture was stirred at room temperature for 30 min. The solvent was then evaporated under reduced pressure and the oily residue was chromatographed on silica gel column with petroleum ether/ethylacetate as eluent to give the products.

3.3.1. *N^4-(5-Phenyl-1,3-oxathiol-2-yliden)-2-phenylquinazolin-4-amine (6a)*

From **1**: NRR= morpholine, RX: phenacyl bromide (0.56 g): yellow crystals, yield: (0.63 g, 58%); m.p. 191–192 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.69 (2H, d, J = 6.6 Hz, ArH), 8.65 (1H, d, J = 8.25 Hz, ArH), 8.05 (1H, d, J = 8.25 Hz, ArH), 7.87 (1H, t, J = 8.25 Hz, ArH), 7.81 (2H, d, J = 6.6 Hz, ArH), 7.65–7.47 (7H, m, ArH), 6.90 (1H, s, C<u>H</u>–oxathiole).
From **2**: NRR= pyrrolidine (0.59 g, 55%).
From **3**: NRR= *N*-methyl piperazine (0.2 g, 19%).

3.3.2. *N^4-[5-(4-Methylphenyl)-1,3-oxathiol-2-yliden]-2-phenylquinazolin-4-amine (6b)*

From **1**: morpholine, (0.98 g), RX: 4-methylphenacyl bromide (0.60 g): yellow crystals (0.71 g, 63%); m.p. 177–178 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.67 (2H, d, $J = 6.6$ Hz, ArH), 8.63 (1H, d, $J = 8.25$ Hz, ArH), 8.03 (1H, d, $J = 8.25$ Hz, ArH), 7.85 (1H, t, $J = 8.25$ Hz, ArH), 7.67 (2H, d, $J = 8.25$ Hz, ArH), 7.64–7.45 (4H, m, ArH), 7.24 (2H, d, $J = 6.6$ Hz, ArH), 6.79 (1H, s, C<u>H</u>–oxathiole), 2.40 (3H, s, CH_3).
2: NRR = pyrrolidine (0.75 g, 68%).
3: NRR = *N*-methyl piperazine (0.23 g, 21%).

3.3.3. *N^4-[5-(4-Methoxyphenyl)-1,3-oxathiol-2-yliden]-2-phenylquinazolin-4-amine (6c)*

From **1**: morpholine, (0.98 g), RX: 4-methoxyphenacyl bromide (0.64 g): yellow crystals (0.78 g, 66%); m.p. 209–210 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (2H, d, $J = 6.6$ Hz, ArH), 8.64 (1H, d, $J = 8.25$ Hz, ArH), 7.99 (1H, d, $J = 8.25$ Hz, ArH), 7.87 (1H, t, $J = 8.25$ Hz, ArH), 7.81 (2H, d, $J = 6.6$ Hz, ArH), 7.65–7.47 (4H, m, ArH), 6.91 (2H, d, $J = 6.6$ Hz, ArH), 6.73 (1H, s, C<u>H</u>–oxathiole), 3.72 (3H, s, OCH_3).
2: NRR = pyrrolidine (0.55 g, 48%).

3.3.4. *N^4-[5-(4-Chlorophenyl)-1,3-oxathiol-2-yliden]-2-phenylquinazolin-4-amine (6d)*

From **1**: NRR = morpholine, RX: 4-chlorophenacyl bromide (0.66 g): yellow crystals (0.45 g, 38%); m.p. 174–175 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.70 (2H, d, $J = 7.32$ Hz, ArH), 8.67 (1H, d, $J = 8.25$ Hz, ArH), 8.05 (1H, d, $J = 8.43$ Hz, ArH), 7.88 (1H, t, $J = 8.25$ Hz, ArH), 7.82 (2H, d, $J = 7.32$ Hz, ArH), 7.63–7.45 (6H, m, ArH), 6.91 (1H, s, C<u>H</u>–oxathiole).
2: NRR = pyrrolidine (0.41g, 35%).

3.4. *Synthesis of 4-[4-aryl-2-dialkylamino-1,3-thiazol-5-yl] 2-phenylquinazoline 7–11*

General procedure. To a solution of thioamide**1–5** (2.8 mmol) in DMF (30 mL) was added triethylamine (0.5 mL, 3.5 mmol) and the appropriate 4-substituted phenacyl bromide (2.8 mmol). The reaction mixture was heated at 80 °C for 8 h. The solvent was then evaporated under reduced pressure. The oily residue was cooled till solidification and crystallized from ethyl alcohol.

3.4.1. *2-Phenyl-4-(4-phenyl-2-pyrrolidin-1-yl-1,3-thiazol-5-yl)quinazoline (8a)*

From **2:** NRR = pyrrolidine (0.94 g), RX: phenacyl bromide (0.56): yellow crystals (0.58 g, 48%); M.p.184–185 °C; ^{1}H–NMR ($CDCl_3$)δ: 8.56 (2H, d, $J = 8.04$ Hz, ArH), 7.97 (1H, d, $J = 8.04$ Hz, ArH), 7.69–7.62 (2H, m, ArH), 7.51–7.49 (3H, m, ArH), 7.42–7.40 (2H, m, ArH), 7.16–7.06 (4H, m, ArH), 3.63 (4H, t, $J = 5.10$ Hz, $2NCH_2$), 2.15 (4H, t, $J = 5.13$ Hz, $2CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.97 (C2-thiazole), 162.07 (C2-quinazoline), 160.29 (C_{qAr}), 153.31 (C4-quinazoline), 152.20 (C4-thiazole), 138.32 (C_{qAr}), 136.05 (C_{qAr}), 133.51 (CH_{Ar}), 130.60 (CH_{Ar}), 129.25 (CH_{Ar}), 128.84 (CH_{Ar}), 128.69 (CH_{Ar}), 128.52 (CH_{Ar}), 128.34 (CH_{Ar}), 127.76 (CH_{Ar}), 126.28 (CH_{Ar}), 120.99 (C_q), 118.17 (C5-thiazole), 49.83 (NCH_2), 26.03 (CH_2). Anal. Calcd. for $C_{27}H_{22}N_4S$(434.6): 74.63% C, 5.10% H, 12.89% N; found: 74.58% C, 5.03% H, 12.76% N.

3.4.2. *4-[4-(4-Methylphenyl)-2-pyrrolidin-1-yl-1,3-thiazol-5-yl]-2-phenyl-quinazoline (8b)*

From **2**: NRR = pyrrolidine (0.94 g), RX: 4-methylphenacyl bromide (0.6 g): yellow crystals (0.76 g, 61%); m.p. 176–177 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (2H, d, $J = 8.04$ Hz,

ArH), 7.97 (1H, d, $J = 8.04$ Hz, ArH), 7.71–7.62 (2H, m, ArH), 7.54–7.46 (3H, m, ArH), 7.30 (2H, d, $J = 7.59$ Hz, ArH), 7.09 (1H, t, $J = 7.59$ Hz, ArH), 6.92 (2H, d, $J = 7.59$ Hz, ArH), 3.60 (4H, t, $J = 5.15$ Hz, $2NCH_2$), 2.22 (3H, s, CH_3), 2.08 (4H, t, $J = 5.15$ Hz, $2CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.84 (C2-thiazole), 162.20 (C2-quinazoline), 160.23 (C_{qAr}), 154.10 (C4-quinazoline), 152.16 (C4-thiazole), 138.22 (C_{qAr}), 138.14 (C_{qAr}), 133.44 (CH_{Ar}), 133.17 (C_{qAr}), 130.55 (CH_{Ar}), 129.11 (CH_{Ar}), 128.74 (CH_{Ar}), 127.86 (CH_{Ar}), 126.26 (CH_{Ar}), 121.02 (C_{qAr}), 117.78 (C5-thiazole), 49.75 (NCH_2), 25.97 (CH_2), 21.42 (CH_3). Anal. Calcd. for $C_{28}H_{24}N_4S$(448.6): 74.97% C, 5.39% H, 12.49% N; found: 74.85% C, 5.36% H, 12.34% N.

3.4.3. *4-[4-(4-Methoxyphenyl)-2-pyrrolidin-1-yl-1,3-thiazol-5-yl]-2-phenyl-quinazoline (8c)*

From **2**: NRR = pyrrolidine (0.94 g), RX: 4-methoxyphenacyl bromide (0.64 g): yellow crystals (0.74 g, 57%); m.p. 150–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (2H, d, $J = 7.92$ Hz, ArH), 7.97 (1H, d, $J = 8.25$ Hz, ArH), 7.71–7.62 (2H, m, ArH), 7.57–7.43 (3H, m, ArH), 7.35 (2H, d, $J = 8.58$ Hz, ArH), 7.11 (1H, t, $J = 8.25$ Hz, ArH), 6.65 (2H, d, $J = 8.91$ Hz, ArH), 3.70 (3H, s, OCH_3), 3.62 (4H, t, $J = 5.1$ Hz, $2NCH_2$), 2.10 (4H, t, $J = 5.1$ Hz, $2CH_2$);^{13}C NMR (75.5 MHz, $CDCl_3$): δ 174.21 (C_{qAr}), 167.88 (C2-thiazole), 162.31 (C2-quinazoline), 160.39 (C_{qAr}), 159.77 (C_{qAr}), 152.85 (C4-quinazoline), 152.24 (C4-thiazole), 138.41 (C_{qAr}), 133.48 (CH_{Ar}), 130.58 (CH_{Ar}), 128.88 (CH_{Ar}), 128.73 (CH_{Ar}), 127.90 (CH_{Ar}), 126.33 (CH_{Ar}), 121.03 (C_{qAr}), 119.04 (C5-thiazole), 113.96 (CH_{Ar}), 55.43 (OCH_3), 49.79 (NCH_2), 26.01 (CH_2). Anal. Calcd. for $C_{28}H_{24}N_4OS$(464.6): 72.39% C, 5.21% H, 12.06% N; found: 72.39% C, 5.20% H, 12.05% N.

3.4.4. *4-[4-(4-Chlorophenyl)-2-(pyrrolidin-1-yl)-1,3-thiazol-5-yl]-2-phenyl-quinazoline (8d)*

From **2**: NRR = pyrrolidine (0.94 g), RX: 4-chlorophenacyl bromide (0.66 g): yellow crystals (0.51 g, 39%); m.p. 184–185 °C.^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (2H, d, $J = 8.04$ Hz, ArH), 7.94 (1H, d, $J = 8.04$ Hz, ArH), 7.73–7.62 (2H, m, ArH), 7.51–7.49 (3H, m, ArH), 7.38–7.08 (5H, m, ArH), 3.63 (4H, t, $J = 5.1$ Hz, $2NCH_2$), 2.17 (4H, t, $J = 5.1$ Hz, $2CH_2$). Anal. Calcd. for $C_{27}H_{21}ClN_4S$ (468.12): 69.14% C, 4.51% H, 11.95% N; found: 68.87% C, 4.43% H, 11.71% N.

3.4.5. *4-[2-(4-Methylpiperazin-1-yl)-4-phenyl-1,3-thiazol-5-yl]-2-phenylquin-azoline (9a)*

From **3**: NRR = *N*-Me piperazine (1.02 g), RX: phenacyl bromide (0.56 g): yellow crystals (0.41 g, 32%); m.p. 182–183 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (2H, d, $J = 8.07$ Hz, ArH), 8.00 (1H, d, $J = 8.04$ Hz, ArH), 7.69 (2H, d, $J = 8.04$ Hz, ArH), 7.55–7.45 (3H, m, ArH), 7.40 (1H, d, $J = 8.04$ Hz, ArH), 7.19–7.10 (4H, m, ArH), 3.72 (4H, t, $J = 5.10$ Hz, $2NCH_2$), 2.60 (4H, t, $J = 5.13$ Hz, $2NCH_2$), 2.40 (3H, s, NCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.20 (C2-thiazole), 161.86 (C2-quinazoline), 160.37 (C_{qAr}), 153.27 (C4-quinazoline), 152.24 (C4-thiazole), 138.26 (C_{qAr}), 135.76 (CH_{Ar}), 133.63 (CH_{Ar}), 130.70 (CH_{Ar}), 129.14 (CH_{Ar}), 128.94(CH_{Ar}), 128.73 (CH_{Ar}), 128.43 (CH_{Ar}), 127.64 (CH_{Ar}), 126.47 (CH_{Ar}), 121.08 (C_{qAr}), 118.08 (C5-thiazole), 54.47 (NCH_2), 48.33 (NCH_2), 46.43 (NCH_3). Anal. Calcd. for $C_{28}H_{25}N_5S$(463.6): 72.54% C, 5.44% H, 15.11% N; found: 72.49% C, 5.44% H, 15.03% N.

3.4.6. *4-[4-(4-Methylphenyl)-2-(4-methylpiperazin-1-yl)-1,3-thiazol-5-yl]-2-phenylquin-azoline (9b)*

From **3**: NRR = *N*-Me piperazine (1.02 g), RX: 4-methylphenacyl bromide (0.60 g): yellow crystals (0.48 g, 36%); m.p. 229–230 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 ((2H, d, $J = 8.07$ Hz,

ArH), 8.01 (1H, d, $J = 8.04$ Hz, ArH), 7.70 (2H, t, $J = 8.04$ Hz, ArH), 7.53–7.47 (3H, m, ArH), 7.32–7.26 (2H, m, ArH), 7.14 (1H, t, $J = 8.04$ Hz, ArH), 6.94 (2H, d, $J = 7.7$ Hz, ArH), 3.71 (4H, t, $J = 5.12$ Hz, $2NCH_2$), 2.60 (4H, t, $J = 5.13$ Hz, $2NCH_2$), 2.40 (3H, s, NCH_3), 2.24 (3H, s, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.08 (C2-thiazole), 162.02 (C2-quinazoline), 160.33 (C_{qAr}), 153.31 (C4-quinazoline), 152.21 (C4-thiazole), 138.29 (C_{qAr}), 133.59 (CH_{Ar}), 132.91 (C_{qAr}), 130.63 (CH_{Ar}), 129.13 (CH_{Ar}), 129.04 (CH_{Ar}), 128.93 (CH_{Ar}), 128.73 (CH_{Ar}), 128.67 (CH_{Ar}), 127.74 (CH_{Ar}), 126.47 (CH_{Ar}), 121.15 (C_{qAr}), 117.52 (C5-thiazole), 54.47 (NCH_2), 48.31 (NCH_2), 46.39 (NCH_3), 21.41 (CH_3). Anal. Calcd. for $C_{29}H_{27}N_5S$(477.6): 72.93% C, 5.70% H, 14.66% N; found: 72.91% C, 5.67% H, 14.63% N.

3.4.7. *2-Phenyl-4-(4-phenyl-2-(piperidin-1-yl)thiazol-5-yl)quinazoline (10a)*

From **4**: NRR = piperidine (0.98 g), RX: phenacyl bromide (0.56 g): yellow crystals (0.79 g, 63%); m.p. 198–199 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (2H, d, $J = 7.59$ Hz, ArH), 8.05 (1H, d, $J = 8.25$ Hz, ArH), 7.65 (2H, d, $J = 8.25$ Hz, ArH), 7.55–7.44 (3H, m, ArH), 7.39 (2H, d, $J = 7.92$ Hz, ArH), 7.15–7.06 (3H, m, ArH), 3.65 (4H, t, $J = 5.36$ Hz, NCH_2), 1.74–1.58 (6H, m, $3CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.55 (C2-thiazole), 162.20 (C2-quinazoline), 160.29 (C_{qAr}), 153.22 (C4-quinazoline), 152.25 (C4-thiazole), 138.43 (C_{qAr}), 135.88 (C_{qAr}), 133.78 (CH_{Ar}), 130.84 (CH_{Ar}), 129.20 (CH_{Ar}), 128.82 (CH_{Ar}), 128.75 (CH_{Ar}), 128.50 (CH_{Ar}), 127.79 (CH_{Ar}), 126.48 (CH_{Ar}), 120.88 (C_{qAr}), 118.19 (C5-thiazole), 49.63 (NCH_2), 25.48 (CH_2), 24.31 (CH_2). Anal. Calcd. for $C_{28}H_{24}N_4S$(448.6): 74.97% C, 5.39% H, 12.49% N; found: 74.95% C, 5.39% H, 12.48% N.

3.4.8. *2-Phenyl-4-(2-(piperidin-1-yl)-4-p-tolylthiazol-5-yl)quinazoline (10b)*

From **4**: NRR = piperidine (0.98 g), RX: 4-methylphenacyl bromide (0.60 g): yellow crystals (0.91 g, 71%); m.p.216–217 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 88.59 (2H, d, $J = 8.04$ Hz, ArH), 8.00 (1H, d, $J = 8.25$ Hz, ArH), 7.74–7.61 (2H, m, ArH), 7.57–7.46 (3H, m, ArH), 7.32 (2H, d, $J = 7.59$ Hz, ArH), 7.16 (1H, t, $J = 7.59$ Hz, ArH), 6.95 (2H, d, $J = 7.59$ Hz, ArH), 3.68 (4H, t, $J = 5.15$ Hz, $2NCH_2$), 2.26 (3H, s, CH_3), 1.87–1.59 (6H, m, $3CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.26 (C2-thiazole), 162.19 (C2-quinazoline), 160.32 (C_{qAr}), 153.03 (C4-quinazoline), 152.25 (C4-thiazole), 138.42 (C_{qAr}), 138.18 (C_{qAr}), 133.49 (CH_{Ar}), 133.20 (C_{qAr}), 130.63 (CH_{Ar}), 129.35 (CH_{Ar}), 129.09 (CH_{Ar}), 128.92 (CH_{Ar}), 128.78 (CH_{Ar}), 128.66 (CH_{Ar}), 127.86 (CH_{Ar}), 126.37 (CH_{Ar}), 121.26 (C_{qAr}), 117.65 (C5-thiazole), 49.62 (NCH_2), 25.49 (CH_2), 24.38 (CH_2), 21.39 (CH_3). Anal. Calcd. for $C_{29}H_{26}N_4S$(462.6): 75.29% C, 5.66% H, 12.11% N; found: 75.17% C, 5.65% H, 12.09% N.

3.4.9. *4-Methoxyphenyl)-2-piperidin-1-yl-1,3-thiazol-5-yl]-2-phenylquinazo-line (10c)*

From **4**: NRR = piperidine (0.98 g), RX: 4-methoxyphenacyl bromide (0.64 g): yellow crystals (0.72 g, 54%); m.p. 178–179 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (2H, d, $J = 8.25$ Hz, ArH), 7.99 (1H, d, $J = 8.15$ Hz, ArH), 7.78–7.65 (2H, m, ArH), 7.58–7.44 (3H, m, ArH), 7.35 (2H, d, $J = 8.58$ Hz, ArH), 7.14 (1H, t, $J = 8.25$ Hz, ArH), 6.65 (2H, d, $J = 8.91$ Hz, ArH), 3.71 (3H, s, OCH_3), 3.66 (4H, t, $J = 5.1$ Hz, $2NCH_2$), 1.78–1.56 (6H, m, $3CH_2$);^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.15 (C2-thiazole), 162.31 (C2-quinazoline), 160.36 (C_{qAr}), 152.79 (C4-quinazoline), 152.25 (C4-thiazole), 138.41 (C_{qAr}), 133.54 (CH_{Ar}), 130.56 (CH_{Ar}), 128.92 (CH_{Ar}), 128.76 (CH_{Ar}), 128.68 (CH_{Ar}), 127.88 (CH_{Ar}), 126.43 (CH_{Ar}), 121.10 (C_{qAr}), 118.27 (C5-thiazole), 113.91 (CH_{Ar}), 55.43 (OCH_3), 49.58 (NCH_2); 25.49 (CH_2), 24.38 (CH_2). Anal.

Calcd. for $C_{29}H_{26}N_4OS$(478.6): 72.78% C, 5.48% H, 11.71% N; found: 72.63% C, 5.41% H, 11.68% N.

3.4.10. *4-[4-(4-Chlorophenyl)-2-piperidin-1-yl-1,3-thiazol-5-yl]-2-phenyl-quinazoline (10d)*

From **4:** NRR = piperidine (0.98 g), RX: 4-chlorophenacyl bromide (0.66 g): yellow crystals (0.89 g, 66%); m.p. 185–186 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (2H, d, J = 8.04 Hz, ArH), 8.02 (1H, d, J = 8.15 Hz, ArH), 7.72 (2H, d, J = 8.15 Hz, ArH), 7.51–7.49 (3H, m, ArH), 7.36 (2H, d, J = 8.25 Hz, ArH), 7.20 (1H, t, J = 8.05 Hz, ArH), 7.09 (2H, d, J = 8.25 Hz, ArH), 3.65 (4H, t, J = 5.35 Hz, $2NCH_2$), 1.75–1.53 (6H, m, $3CH_2$); Anal. Calcd. for $C_{28}H_{23}ClN_4S$ (483.0): 69.62% C, 4.80% H, 11.60% N; found: 69.55% C, 4.73% H, 11.54% N.

3.4.11. *4-(2-(N,N-Dimethylamino-4-phenyl-1,3-thiazol-5-yl)-2-phenylquin-azoline (11a)*

From **5**: NRR = dimethyl amine (0.86 g), RX: phenacyl bromide (0.56 g): yellow crystals (0.46 g, 41%); m.p. 179–180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (2H, d, J = 8.04 Hz, ArH), 8.04 (1H, d, J = 8.25 Hz, ArH), 7.75 (2H, d, J = 8.25 Hz, ArH), 7.54–7.49 (3H, m, ArH), 7.39 (2H, d, J = 8.25 Hz, ArH), 7.19–7.05 (4H, m, ArH), 3.54 (3H, s, CH_3), 3.52 (3H, s, CH_3). Anal. Calcd. for $C_{25}H_{20}N_4S$ (408.52): 73.50% C, 4.93% H, 13.71% N; found: 73.38% C, 4.88% H, 13.54% N.

3.5. *Synthesis of 4-[2-Dialkylamino-4(5H)-oxo-1,3-thiazol-5-yl]-2-phenyl-quinazolin-4(3H)-ylidene 12–14*

General procedure. To a stirred solution of **1** (2.8 mmol) in DMF (30 mL), methyl chloroacetate (0.25 mL, 2.9 mmol) and triethylamine (1 mL, 7 mmol) was added. The reaction mixture was heated at 80 °C for 4 h, the solvent was evaporated under reduced pressure. The solid residue was crystallized from ethanol.

3.5.1. *2-Morpholino-5-(2-phenylquinazolin-4(3H)-ylidene)thiazol-4(5H)-one (12)*

From **1**: NRR = morpholine (0.98 g): yellow crystals (0.41 g, 38%); m.p. 275–276 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 15.67 (1H, bs, N3H. . .O=C), 8.31 (2H, d, J = 7.92 Hz, ArH), 7.96 (1H, d, J = 8.25 Hz, ArH), 7.76–7.66 (2H, m, ArH), 7.69–7.57 (3H, m, ArH), 7.44 (1H, t, J = 7.92 Hz, ArH), 3.58–3.84 (8H, m, $4CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 183.32 (C=O), 173.17 (C2-thiazole), 150.63 (C4-quinazoline), 148.29 (C2-quinazoline), 144.71 (C_{qAr}), 133.46 (CH_{Ar}), 132.85 (C_q), 131.85 (CH_{Ar}), 129.29 (CH_{Ar}), 128.85 (CH_{Ar}), 127.25 (CH_{Ar}), 126.66 (CH_{Ar}),126.06 (CH_{Ar}), 118.71 (C_{qAr}), 92.78 (C5-thiazole), 66.45 (OCH_2), 48.18 (NCH_2). Mass spectrum, m/z (I_r/%): 392.3 (9) M + 2, 391.3 (9) M + 1, 392.3 (65) M+, 304 (3), 278 (7), 251 (22), 250 (100) [2-phenylquinazoline + CS], 231 (11), 230 (9), 206 (8), 205 (15) [2-phenylquinazoline], 195 (3), 171 (4), 121 (6), 112 (8), 104 (16), 103 (19), 77 (3). Anal. Calcd. for $C_{21}H_{18}N_4O_2S$(390.5): 64.60% C, 4.65% H, 14.35% N; found: 64.55% C, 4.63% H, 14.31% N.

3.5.2. *5-(2-Phenylquinazolin-4(3H)-ylidene)-2-(pyrrolidin-1-yl)thiazol-4(5H)-one (13)*

From **2**: NRR = pyrrolidne (0.94 g), yellow crystals (0.55 g, 53%); m.p. 201–202 °C; found: ^{1}H NMR (300 MHz, $CDCl_3$): δ 15.68 (1H, bs, N3H. . .O=C), 8.56 (2H, d, J = 8.15 Hz, ArH), 7.97 (1H, d, J = 8.25 Hz, ArH), 7.69–7.62 (2H, m, ArH), 7.59–7.49 (4H, m, ArH), 3.58–3.84 (8H, m, $4CH_2$); 3.62 (4H, t, J = 5.15 Hz, $2NCH_2$), 2.11 (4H, t, J = 5.15 Hz, CH_2);^{13}C NMR

(75.5 MHz, $CDCl_3$): δ 183.20 (C=O), 169.90 (C2-thiazole), 150.63 (C4-quinazoline), 148.05 (C2-quinazoline), 143.93 (C_{qAr}), 134.51 (CH_{Ar}), 133.17 (C_{qAr}), 131.74 (CH_{Ar}), 129.20 (CH_{Ar}), 128.58 (CH_{Ar}), 127.55 (CH_{Ar}), 127.17 (CH_{Ar}),126.49 (CH_{Ar}), 118.87 (C_{qAr}), 92.78 (C5-thiazole), 50.24 (NCH_2); 25.67 (CH_2). Anal. Calcd. for $C_{21}H_{18}N_4OS$(374.5): 67.36% C, 4.85% H, 14.96% N; found: 67.34% C, 4.84% H, 14.95% N.

3.5.3. *5-(2-Phenylquinazolin-4(3H)-ylidene)-2-(piperidin-1-yl)thiazol-4(5H)-one (14)*

From **4**: NRR = piperidine (0.98 g): yellow crystals (0.70 g, 64%); m.p. 214–215 °C.^{1}H NMR (300 MHz, $CDCl_3$): δ 15.64 (1H, bs, N3H. . .O=C), 8.31–8.27 (2H, m, ArH), 7.94 (1H, $J = 8.25$ Hz, ArH), 7.73–7.66 (2H, m, ArH), 7.59–7.52 (3H, m, ArH), 7.45–7.40 (1H, m, ArH), 3.67 (4H, m, $2NCH_2$), 2.17–1.58 (6H, m, $3CH_2$); Anal. Calcd. for $C_{22}H_{20}N_4OS$(388.5): 68.02% C, 5.19% H, 14.42% N; found: 67.84% C, 5.01% H, 14.34% N.

3.6. *2-Morpholino-5-(2-phenylquinazolin-4-yl)thiazol-4-amine (15)*

General procedure. To a stirred solution of **1** (0.98, 2.8 mmol) in DMF (30 mL), chloroacetonitrile (0.2 mL, 2.9 mmol) and triethylamine (1 mL, 7 mmol) was added. The reaction mixture was heated at 90 °C for 3 h, the solvent was evaporated under reduced pressure. The solid residue was crystallized from ethanol.

Brown crystals (0.74 g, 68%); m.p 188–189 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (2H, d, $J = 8.25$ Hz,), 8.28 (1H, d, $J = 8.15$ Hz, NH), 7.98 (1H, $J = 8.25$ Hz, ArH), 7.83–7.66 (3H, m, ArH, NH), 7.51–7.39 (4H, m, ArH), 3.83 (4H, t, $J = 5.28$ Hz, $2OCH_2$), 3.64 (4H, t, $J = 5.28$ Hz, $2NCH_2$), ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.34 (C2-thiazole), 164.07 (C4-thiazole), 160.33 (C2-quinazoline), 159.10 (C_{qAr}), 150.93 (C4-quinazoline), 139.22 (C_{qAr}), 132.66 (CH_{Ar}), 130.22 (CH_{Ar}), 128.79 (CH_{Ar}), 128.70 (CH_{Ar}), 128.44 (CH_{Ar}), 125.77 (CH_{Ar}), 125.64 (CH_{Ar}), 119.29 (C5-thiazole), 66.27 (OCH_2), 48.04 (NCH_2). Mass spectrum, m/z (I_r/%): 391.3 (9) M + 2, 390.3 (22) M + 1, 389.3 (78) M+, 388.2 (100) M − 1, 352.1 (4), 320 (3), 277 (6), 276 (17), 251 (9), 250 (72) [2-phenylquinazoline + CS], 206 (8), 205 (12) [2-phenylquinazoline], 194 (4), 146 (6), 117 (11), 104 (9), 103 (14), 77 (8). Anal. Calcd. for $C_{21}H_{19}N_5OS$(389.13): 64.76% C, 4.92% H, 17.98% N; found: 64.35% C, 4.84% H, 17.91% N.

References

(1) Almeida, T.A.; Rojo, J.; Nieto, P.M.; Pinto, F.M. *Curr. Med. Chem*. **2004,** *11,* 2045.
(2) Myers, A.C.; Goldie, R.G.; Hay, D.W.P.; *Am. J. Respir. Crit. Care Med.* **2005,** *171,* 212.
(3) Salom, N.; Stemmelin, J.; Cohen, C.; Griebel, G. *Pharmacol. Biochem. Behav.* **2006,** *83,* 533.
(4) Spooren, W.; Riemer, C.; Meltzer, H.; *Nat. Rev. Drug Discov.* **2005,** *4,* 967.
(5) Kronenberg, G.; Berger, P.; Tauber, R.F.; Bandelow, B.; *Pharmaco-Psychiatry* **2005,** *38,* 24.
(6) Giardina, G.A.M.; Sarau, H.M.; Farina, C.; Medhurst, A.D.; *J. Med. Chem.* **1996,** *39,* 2281.
(7) Giardina, G.A.M.; Raveglia, L.F.; Grugni, M.; Sarau, H.M.; *J. Med. Chem.* **1999,** *42,* 1053.
(8) Borioni, A.; Mustazza, C.; Sestili, I.; Sbraccia, M.; Turchetto, L.; Rosaria Del Giudice, M. *Arch. Pharm. Chem. Life Sci.* **2007,** *340,* 17.
(9) Fathalla, W.; Marek, J.; Pazdera, P.; *Heterocycl. Commun.* **2002,** *8,* 157.
(10) Fathalla, W.; Čajan, M.; Marek, J.; Pazdera, P.; *J. Heterocycl. Chem.* **2002,** *39,* 1139.
(11) Fathalla, W.; Čajan, M.; Marek, J.; Pazdera, P.; *J. Molecules* **2001,** *6,* 574.
(12) Tietze, L.F.; *Chem. Rev*. **1996,** *96,* 115.
(13) Tietze, L.F.; Beifuss, U.; *Angew. Chem*. **1993,** *105,* 137.
(14) Kristian, P.; Hamulakova, S.; Bernat, J.; Imrich, J.; Voss G.; Bošova, D. *Heterocycles* **1998,** *49,* 197.
(15) Fathalla, W.; Čajan, M.; Marek, J.; Pazdera, P.; *J. Heterocycl. Chem.* **2002,** *39,* 1145.
(16) Ukrainets, I.V.; Tkach, A.A.; Sidorenko, L.V.; Gorokhova, O.V.; *Chemistry of Heterocyclic Compounds* **2006,** *42,* 1301.
(17) Sheldrick, G.M. *Acta Crystallogr. Sect A*. **1990,** *46,* 467.
(18) Sheldrick, G.M. SHELXL93– program for structure refinement. University of Göttingen, Göttingen **1993**.