New domino-reaction for the synthesis of N4-(5-aryl-1,3-oxathiol-2-yliden)-2-phenylquinazolin-4-amines and 4-[4-aryl-5-(2-phenylquinazolin-4-yl)-1,3-thiazol-2-yl]morpholine

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New Domino-Reaction for the Synthesis of N^4-(5-Aryl-1,3-oxathiol-2-yliden)-2-phenylquinazolin-4-amines and 4-[4-Aryl-5-(2-phenylquinazolin-4-yl)-1,3-thiazol-2-yl]morpholine

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Dedicated to Professor Jaroslav Jonas on the occasion of his 65th birthday.

-ARTICLE-

The model morpholine-1-carbothioic acid (2-phenyl-3*H*-quinazolin-4-ylidene) amide (**1**) reacts with phenacyl bromides to afford N^4-(5-aryl-1,3-oxathiol-2-yliden)-2-phenylquinazolin-4-amines (**4**) or N^4-(4,5-diphenyl-1,3-oxathiol-2-yliden)-2-phenyl-4-aminoquinazoline (**5**) by a thermodynamically controlled reversible reaction favoring the enolate intermediate, while the 4-[4-aryl-5-(2-phenylquinazolin-4-yl)-1,3-thiazol-2-yl]morpholine (**8**) was produced by a kinetically controlled reaction favoring the C-anion intermediate. ^{1}H nmr, ^{13}C nmr, ir, mass spectroscopy and x-ray identified compounds (**4**), (**5**) and (**8**).

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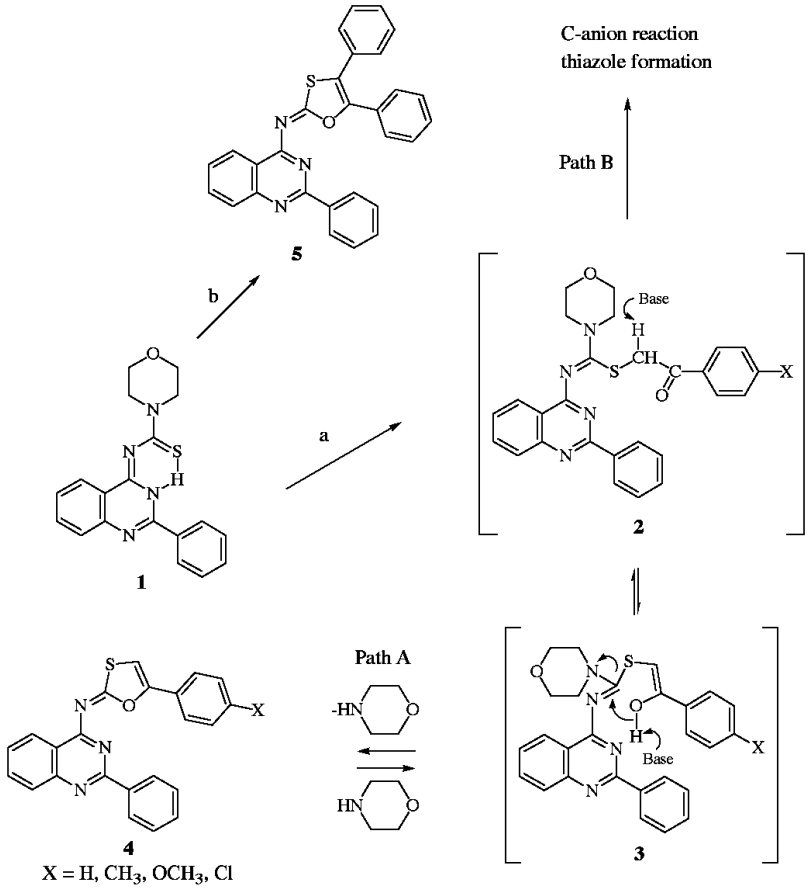
Introduction.

Several research workers have reported sulfur-nitrogen regioselective nucleophilic competitions in the synthesis of heterocyclic compounds by intermolecular and intramolecular cyclization reactions. The change in the reaction condition might favor the *S*-attack or the *N*-attack to afford different cyclic products from the same reaction precursor. It is very well known that thioamides including thioureas are used as precursors for the preparation of a great variety of heterocyclic skeletons such as triazoles,

Scheme 1



The reaction of thiourea (**1**) with phenacyl bromides. a: 4-XPhCOCH$_2$Br, DMF, NEt$_3$ 25 °C, 30 minutes; b: PhCOCHPhBr, DMF, NEt$_3$ 25 °C, 30 minutes.

thiadiazoles, quinazolines, benzothiazines, benzothiadiazocines, benzotriazocines, quinoxalines, thiazines, thiouracils, oxathioles, and thiazoles.

The reactivity of thiourea derivative (**1**), *i. e.* morpholine-1-carbothioic acid (2-phenyl-3*H*-quinazolin-4-ylidene) amide was previously discussed [1,2]. This compound (**1**) was prepared by the reaction of *N*-(2-cyanophenyl)benzimidoyl isothicyanate with morpholine in the course of domino-process as reported [3].

The scope on the structure of quinazoline (**1**) together with results described in paper [1] gave us a satisfactory background for more sophisticated multi-step reactions.

Results and Discussion.

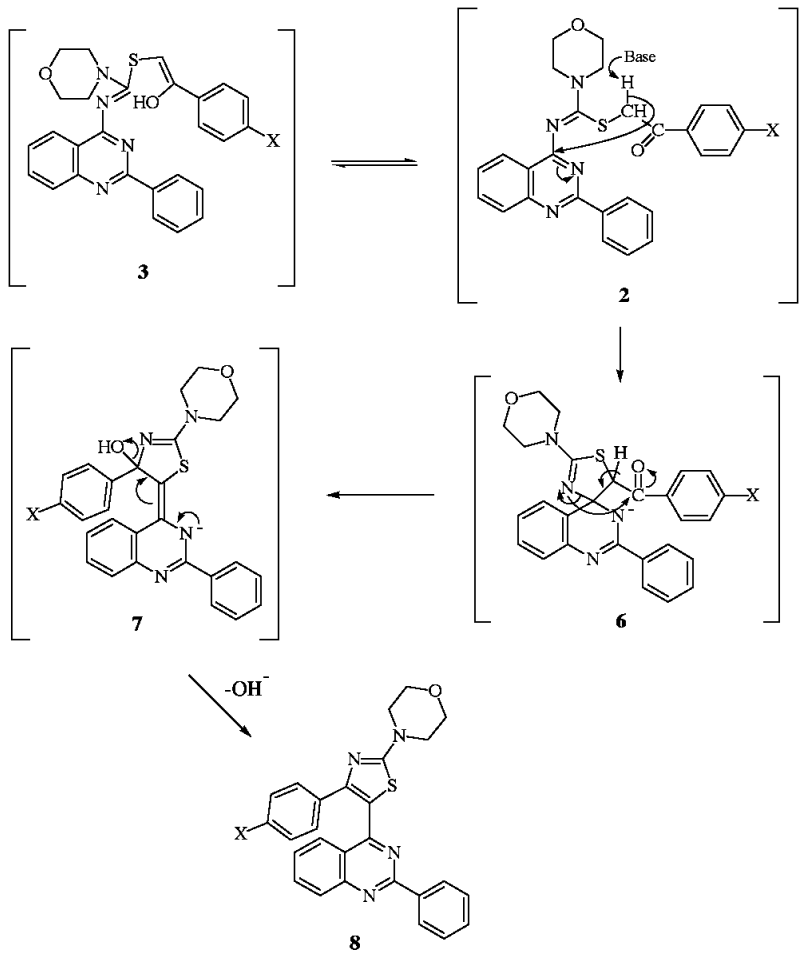
The reaction of (**1**) with alkyl halides containing activated methylene group however gave more complicated but interesting reactions that involve more than one nucleophilic character and more than one electrophilic character in a domino reaction.

The reaction of thiourea (**1**) with 4-X-phenacyl bromides and desyl bromide gave 1,3-oxathiols (**4**) and (**5**), respectively (Scheme 1). The reaction giving (**4**) could be extended to form 1,3-thiazoles (**8**). On the other hand, it is likely that the presence of the second phenyl in (**5**) stabilizes this product (Scheme 1).

Thiourea (**1**) reacts with phenacyl bromide or desyl bromide to give principally isothioureas (**2**). The regioselective *S*-substitution reaction is favored due to orbital-orbital interactions between the LUMO of the electrophile and the higher HOMO of the ambident nucleophile (**1**) to produce the *S*-attack [1,4,5]. This fact was supported by the DFT computational calculations [1].

The isothiourea derivatives (**2**) undergoes an enolisation to give (**3**) [6], followed by a base induced oxygen attack at the imino carbon C12 and the consequent elimination of the morpholino moiety to finally afford the 1,3-oxathioles (**5**) and (**4**), respectively (Scheme 1).

Scheme 2



The reaction pathway for the preparation of 1,3-thiazoles (**8**).

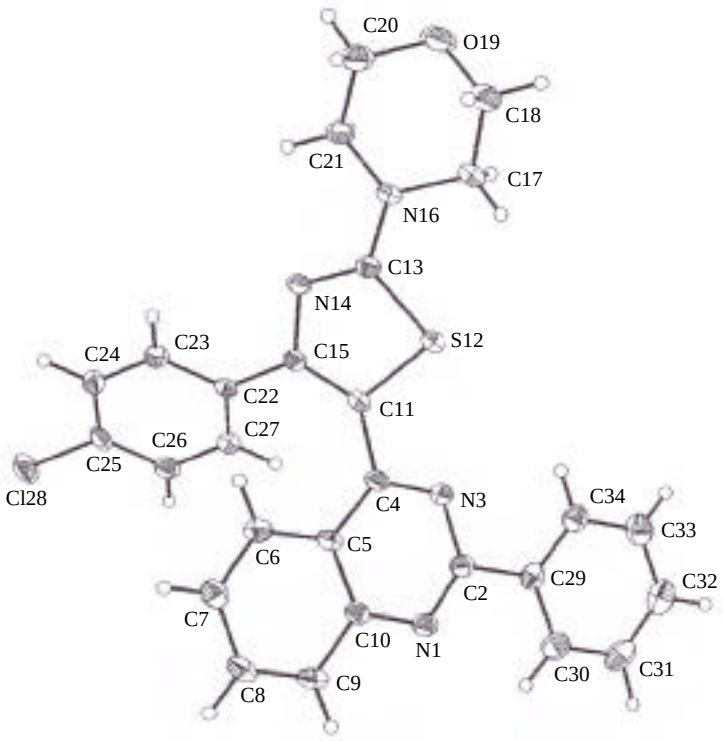


Figure 1. The ORTEP diagram of x-ray structure analysis of 1,3-thiazoles (**8**).

Table 1

The Most Important Interatomic Distances in 1,3-Thiazole(**8d**)

Bond	Bond Length [Å]	Bond	Bond Length [Å]
N1-C2	1.318	C11-S12	1.740
N1-C10	1.361	S12-C13	1.743
C2-N3	1.367	C13-N14	1.301
C2-C29	1.481	C13-N16	1.370
N3-C4	1.321	C5-C10	1.408
C4-C11	1.471	C5-C10	1.408
C4-C5	1.427	N14-C15	1.382

Both tautomers (**2**) and (**3**) were the key intermediates for the explanation of the thiazoles (**8**) and oxathiole (**4**), (**5**) formation.

It should be noted that the reactions of (**1**) with phenacyl bromides giving the isothiourea derivative as an intermediate have two pathways: Path A: a thermodynamically controlled reversible reaction favoring the enolate reaction to afford the oxathiole derivatives (**4**) or (**5**) (Scheme 1). The morpholino moiety eliminated in the former step undergoes addition reaction on the imino carbon attached at position 2 of the oxathiole moiety of compound (**4**) and consequently the enol form (**3**) was

Table 2

The Most Important Bond Angles in 1,3-Thiazole (**8d**)

Angle [∞]	X-ray	Angle [°]	X-ray
N1-C2-C29	118.24	C10-C5-C4	115.60
C2-N1-C10	116.50	C4-C11-S12	116.89
N1-C2-N3	125.88	C11-S12-C13	88.61
C4-N3- C2	117.95	N14-C13-N16	123.28
N3-C4-C5	121.47	N14-C13-S12	115.59
N3-C4-C11	115.10	C13-N14-C15	110.35
C5-C4-C11	123.32	C11-C15-N14	115.82

Table 3

The Most Important Torsion Angles in 1,3-Thiazole (**8d**)

Torsion angle [°]	X-ray	Torsion angle [°]	X-ray
C2-N1-C10-C5	-0.39	N3-C4-C11-S12	-43.52
C2-N1-C10-C9	-179.69	N3-C4-C11-S15	136.60
C10-N1-C2-C29	179	C11-C4-C5-C10	-178.03
N1-C2-C29-C30	3.74	S12-C11-C15-C22	172.63
N1-C2-C29-C30	-174.23	C15-C11-S12-C13	3.39
N1-C2-N3-C4	0.11	C11-S12-C13-N14	-3.21
N3-C2-C29-C30	-176.56	C11-S12-C13-N16	175.25
C2-N3-C4-C5	1.32	S12-C13-N16-C17	17.52
C2-N3-C4-C11	177.54	S12-C13-N16-C15	1.99

reformed (Scheme 1) that might take part in path B; Path B: a kinetically controlled irreversible reaction favoring the C-anion reaction to finally afford the thiazoles (**8**) (Scheme 1 and 2) at the complete consumption of the 1,3-oxathiole intermediate (Figure 1).

The oxo-tautomer (**2**) under the effect of a base induced hydrogen atom abstraction from the methylene group will attack the C4 carbon of the quinazoline ring (the electrophilic character of this carbon was mentioned in the structure characteristics as reported [1]) to give the spiro intermediate (**6**) [7]. Ring opening of the five member ring attached to the quinazoline moiety takes place due to base abstraction of the other methine proton in (**6**), giving a negative charge localized on the nitrogen atom, which enables this nitrogen to attack the carbonyl group to form (**7**). The former step simply represents the spiro-ring opening followed by the thiazole ring closure. The elimination of hydroxyl group will finally give the thiazole derivative (**8**) (Scheme 2). The over all process is accompanied by a base catalyzed reaction and elimination of a water molecule.

Conclusion.

The model thiourea (**1**) react with phenacyl bromides to afford 1,3-oxathioles (**4**), (**5**) and 1,3-thiazoles (**8**) *via* spontaneous domino-reaction. 1,3-Oxathioles (**4**) are formed under reversible thermodynamically controlled reaction, whereas 1,3-thiazoles (**8**) under irreversible kinetically controlled process.

Table 4

Crystal Data and Structure Refinement of(**8d**)

Empirical formula	$C_{27}H_{21}ClN_4OS$
Molecular weight	484.99
Temperature, k	120(2) k
Wavelength, Å	0.71073 Å
Crystal system, space group	Triclinic, P1
Unit cell dimensions	
a, Å; α, °	10.1135 (11) Å, α= 93.073 (8) °
b, Å; β, °	10.9731 (10) Å, β= 113.941 (10) °
c, Å; γ, °	11.4240 (2) Å, γ= 96.918 °
Volume, Å^3	1132.5 (2) Å^3
Z; density calculated mg m^{-3}	2; 1.422 mg m^{-3}
Absorption coefficient, mm^{-1}	0.290 mm^{-1}
F(000)	504
Crystal size, mm	0.30 X 0.20 X 0.20 mm
θ Range for data collection,	3.62- 24.99°
Range of *h, k, l*	*-12< = h< =9, -12< = k< =12, -12< = l< = 13*
Reflections collected	6116
Independent reflections	3864 [R(int) = 0.0346]
Refinement method	full-matrix least-squares on F^2
Data; restraints; parameters	3864 / 0 / 391
Goodness-of-fit on F^2	1.002
Final R indices [I > 2σ(I)]	R1= 0.0380, wR2 = 0.0881
R indices (all data)	R1= 0.0531, wR2 = 0.0961
Largest diff. Peak and hole	0.211 and –0.280 e. Å^{-3}

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). The eluent used was a 20:80 mixture of acetone-benzene, detection was accomplished with a Fluotes universal instrument (Quarzlampen, Hanau) and iodine vapors. The purity of compounds (**4a-d**), (**5**) and (**8a-d**) were proven by their elemental analysis, measured on an Erba 1102 instrument. Ir spectra were taken on a Genesis (Unicam) spectrometer in potassium bromide pellets. Both ^{1}H and ^{13}C nmr spectra were measured on a Bruker Avance DRX-500 spectrometer in deuteriochloroform solutions and tetramethylsilane was used as the internal standard. The measured ^{13}C and ^{1}H nmr data were correlated with those obtained by a simulation (Advanced Chemistry Development, Inc., Toronto, Canada). The x-ray structural data of compound (**8d**) (Table 4) were collected with a KUMA KM-4 kappa four-circle diffractometer. The structure was solved by direct methods using SHELXS86 [8] and refined on F^2 for all reflections using SHELXl93 [9]. 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 (**8c**) and (**8d**) have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 169181 and 170710, respectively. Mass spectrometry was determined (electron impact, 70 eV) with a Fisons TRIO 1000 and GC 8000 series instrument.

N^4-[5-(4-X-phenyl)-1,3-oxathiol-2-yliden]-2-phenylquinazolin-4-amine (**4**).

To a solution of (**1**) (1.0 g, 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 minutes. The solvent was then evaporated under reduced pressure. The oily residue was cooled till solidification and crystallized from ethyl alcohol.

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

Compound **4a** was obtained in 58% yield, 0.63 g; mp 191-192 °C; ir: 3100, 3061, 2844 (CH), 1614(C=N) 1600, 1579, 1546 (C=C) cm^{-1}; ^{1}H nmr: δ 8.72-7.47 (14H, m, ArH), 6.90 (1H, s, C*H*-oxathiole); ^{13}C nmr: δ 161.86 (C_q), 160.17 (C_q), 152.18 (C_q), 148.59 (C_q), 138.89 (C_q), 133.86 (CH_{Ar}), 130.56 (CH_{Ar}), 130.03 (CH_{Ar}), 129.24 (CH_{Ar}), 129.13 (CH_{Ar}), 128.72 (CH_{Ar}), 128.20 (C_q), 127.88 (CH_{Ar}), 126.71 (CH_{Ar}), 125.43 (CH_{Ar}), 125.33 (CH_{Ar}), 120.72 (C_q), 101.39 (CH-oxathiole).

Anal. Calcd. for $C_{23}H_{15}N_3OS$ (381.45): C 72.42; H 3.96; N 11.02; S 8,40. Found: C 72.38; H 3.91; N 10.96; S 8.34.

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

Compound **4b** was obtained in 63% yield, 0.71 g; mp 177-178 °C; ir: 3054, 3027, 2921, 2856 (CH) 1614 (C=N) 1579, 1544 (C=C) cm^{-1}; ^{1}H nmr: δ 8.69-7.24 (13H, m, ArH), 6.79 (1H, s, C*H*-oxathiole), 2.40 (3H, s, CH_3); ^{13}C nmr: δ 161.81 (C_q), 151.95 (C_q), 148.75 (C_q), 140.26 (C_q), 138.74 (C_q), 133.83

(CH_{Ar}), 130.56 (CH_{Ar}), 129.88 (CH_{Ar}), 129.10 (CH_{Ar}), 128.71 (CH_{Ar}), 128.06 (CH_{Ar}), 126.68 (CH_{Ar}), 125.39 (CH_{Ar}), 125.21 (CH_{Ar}), 125.03 (C_q), 120.64 (C_q), 100.35 (CH-oxathiole), 21.65 (CH_3); ms: m/z 395 (M^+) 231, 230, 206, 205 (2-phenylquinazoline), 198, 179, 148, 147, 119, 91 (C_6H_5N), 77 (C_6H_5).

Anal. Calcd. for $C_{24}H_{17}N_3OS$ (395.48): C 72.89; H 4.33; N 10.63; S 8.11. Found: C 72.64; H 4.25; N 10.51; S 8.10.

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

Compound **4c** was obtained in 66% yield, 0.78 g; mp 209-210°C; ir: 3060, 2952, 2923, 2834 (CH), 1614 (C=N) 1581, 1547 (C=C) cm^{-1}; ^1H nmr: δ 8.71-6.91 (13H, m, ArH), 6.73 (1H, s, C*H*-oxathiole), 3.72 (3H, s, OCH_3); ^{13}C nmr: δ 162.04 (C_q), 160.40 (C_q), 152.83 (C_q), 138.24 (C_q), 133.82 (CH_{Ar}), 130.56 (CH_{Ar}), 129.14 (CH_{Ar}), 129.03 (CH_{Ar}), 128.89 (CH_{Ar}), 128.56 (CH_{Ar}), 128.11 (CH_{Ar}), 126.92 (CH_{Ar}), 126.67 (CH_{Ar}), 125.40 (CH_{Ar}), 120.25 (C_q), 117.27 (C_q), 114.65 (CH_{Ar}), 99.07 (CH-oxathiole), 55.64 (OCH_3).

Anal. Calcd. for $C_{24}H_{17}N_3O_2S$ (411.48): C 70.06; H 4.16; N 10.21; S 7.79. Found: C 70.01; H 4.11; N 10.18; S 7.76.

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

Compound **4d** was obtained in 38% yield, 0.45 g; mp 174-175 °C; ir: 3062, 3038, 2864 (CH) 1612 (C=N) 1585, 1548 (C=C) cm^{-1}; ^1H nmr: δ 8.67-7.12 (13H, m, ArH), 6.92 (1H, s, C*H*-oxathiole); ^{13}C nmr: δ 171.72 (C_q), 161.93 (C_q), 148.63 (C_q), 133.98 (CH_{Ar}), 130.71 (CH_{Ar}), 130.01 (CH_{Ar}), 129.20 (CH_{Ar}), 128.73 (CH_{Ar}), 127.82 (CH_{Ar}), 127.74 (C_q), 126.80 (CH_{Ar}), 125.42 (CH_{Ar}), 125.30 (CH_{Ar}), 123.77 (C_q), 120.59 (C_q), 101.47 (CH-oxathiole).

Anal. Calcd. for $C_{23}H_{14}ClN_3OS$(415.90): C 66.42; H 3.39; Cl 8.52; N 10.10; S 7.71. Found: C 66.36; H 3.38; Cl 8.45; N 10.09; S 7.62.

4-(4,5-Diphenyl-1,3-oxathiol-2-yliden)-2-phenylquinazolin-4-amine (**5**).

Compound **5** was obtained in 55% yield, 0.72 g; mp 231-232 °C ; ir: 3058, 2969, 2939, (CH) 1637, 1616 (C=N) 1598, 1577, 1553 (C=C) cm^{-1}; ^1H nmr: δ 8.68-8.63 (2H, m, ArH), 8.06-8.03 (1H, m, ArH), 7.90-7.88 (1H, m, ArH), 7.64-7.42 (12H, m, ArH), 7.39-7.31 (3H, m, ArH); ^{13}C nmr: δ 169.71 (C_q), 161.90 (C_q), 160.20 (C_q), 152.19 (C_q), 142.19 (C_q), 138.91 (C_q), 133.80 (CH_{Ar}), 130.44 (CH_{Ar}), 130.06 (C_q), 129.77 (CH_{Ar}), 129.56 (CH_{Ar}), 129.43 (CH_{Ar}), 129.10 (CH_{Ar}), 128.83 (CH_{Ar}), 128.72 (CH_{Ar}), 128.19 (CH_{Ar}), 127.93 (CH_{Ar}), 126.65 (CH_{Ar}), 125.49 (CH_{Ar}), 120.74 (C_q), 119.04 (C_q); ms: m/z 457 (M^+), 286, 279, 270, 247, 230, 210, 205 (2-phenylquinazoline), 199, 178, 156, 140, 121, 105, 99, 84, 77 (C_6H_5), 72, 58, 57.

Anal. Calcd. for $C_{29}H_{19}N_3OS$ (457.55): C 76.13; H 4.19; N 9.18; S 7.01. Found: C 76.11; H 4.19; N 9.14; S 6.98.

4-[4-(4-Substitutedphenyl)-5-(2-phenylquinazolin-4-yl)-4,5-dihydro-1,3-thiazol-2-yl]-morpholine (**8**).

Procedure A.

To a solution of (**1**) (1.0 g, 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 heated at 80 °C for 4 hours. The solvent was then evaporated under reduced pressure. The oily residue was cooled till solidification and crystallized from ethyl alcohol.

Procedure B.

To the solution of (**4**) (2.8 mmol) in DMF (30 mL) was added (0.6 mL, 7 mmol) morpholine. The reaction mixture heated at 80 °C for 4 hours. The solvent was then evaporated under reduced pressure. The oily residue was cooled till solidification and crystallized from ethyl alcohol.

4-[4-Phenyl-5-(2-phenylquinazolin-4-yl)-1,3-thiazol-2-yl]morpholine (**8a**).

Compound **8a** was obtained in 38% yield, (Procedure A) 0.49 g; (Procedure B) 0.74 g (57%); mp 164-165 °C; ir: 3058, 2971, 2846, (CH), 1614 (C=N) 1558, 1532 (C=C) cm^{-1}; ^1H nmr: δ 8.58- 7.12 (14H, m, ArH), 33.89 (4H, t, $J_{A,B}$= 5.28 Hz, OCH_2), 3.68 (4H, t, $J_{A,B}$= 5.28 Hz, NCH_2); ^{13}C nmr: δ 171.41 (C_q), 161.76 (C_q), 160.37 (C_q), 153.09 (C_q), 152.23 (C_q), 138.17 (C_q), 135.56 (CH_{Ar}), 133.95 (CH_{Ar}), 130.72 (CH_{Ar}), 129.12 (CH_{Ar}), 128.96 (CH_{Ar}), 128.74 (CH_{Ar}), 128.52 (CH_{Ar}), 127.56 (CH_{Ar}), 126.57 (CH_{Ar}), 121.03(C_q), 66.42 (OCH_2), 48.50 (NCH_2); ms m/z 450 (M^+), 408 (M – C_2H_2O), 394, 393, 365 (M – morpholine), 337, 339 (M – (morpholine + NCS)), 307, 305, 261, 225, 205 (2-phenylquinazoline), 190 179, 157, 140, 105, 84, 77, 57.

Anal. Calcd. for $C_{27}H_{22}N_4OS$ (450.55): C 71.98; H 4.92; N 12.44; S 7.12. Found: C 71.92; H 4.90; N 12.37; S 7.05.

4-[4-(4-Methylphenyl)-5-(2-phenylquinazolin-4-yl)-1,3-thiazol-2-yl]morpholine (**8b**).

Compound **8b** ws obtained in 57% yield, (Procedure A) 0.75 g; mp 223-224 °C; ir: 3056, 3025, 2971, 2846 (CH), 1614 (C=N) 1558, 1530 (C=C) cm^{-1}; ^1H nmr: δ 8.59-6.92 (13H, m, ArH), 3.87 (4H, t, $J_{A,B}$= 5.28 Hz, OCH_2), 3.67 (4H, t, $J_{A,B}$= 5.28 Hz, NCH_2), 2.23 (3H, s, CH_3); ^{13}C nmr: δ 171.31 (C_q), 161.94 (C_q), 160.36 (C_q), 153.15 (C_q), 152.21 (C_q), 138.42 (C_q), 138.21 (C_q), 133.71 (CH_{Ar}), 132.75 (C_q), 130.71 (CH_{Ar}), 129.20 (CH_{Ar}), 129.01 (CH_{Ar}), 128.96 (CH_{Ar}), 128.73 (CH_{Ar}), 127.68 (CH_{Ar}), 126.58 (CH_{Ar}), 121.10 (C_q), 117.74 (C_q), 66.44 (OCH_2), 48.50 (NCH_2), 21.45 (CH_3).

Anal. Calcd. for $C_{28}H_{24}N_4OS$ (464.58): C 72.39; H 5.21; N 12.06; S 6.90. Found: C 72.23; H 5.18; N 11.97; S 6.65.

4-[4-(4-Methoxyphenyl)-5-(2-phenylquinazolin-4-yl)-1,3-thiazol-2-yl]morpholine (**8c**).

Compound **8c** was obtained in 46% yield, (Procedure A) 0.63 g; (Procedure B) 0.68 g (49%); mp 216-217 °C; ir: 3064, 2966, 2935, 2844 (CH), 1612 (C=N) 1577, 1558, 1530 (C=C) cm^{-1}; ^1H nmr: δ 8.62-6.59 (13H, m, ArH), 3.89 (4H, t, $J_{A,B}$= 5.29 Hz, OCH_2), 3.72 (3H, s, OCH_3), 3.67 (4H, t, $J_{A,B}$= 5.29 Hz, NCH_2); ^{13}C nmr: δ 173.11 (C_q), 171.28 (C_q), 161.99 (C_q), 160.36 (C_q), 159.82 (C_q), 152.79 (C_q), 152.21 (C_q), 138.19 (C_q), 133.70 (CH_{Ar}), 130.70 (CH_{Ar}), 130.47 (CH_{Ar}), 128.96 (CH_{Ar}), 128.71 (CH_{Ar}), 128.23 (C_q), 127.68 (CH_{Ar}), 126.61 (CH_{Ar}), 120.99 (C_q), 113.92 (CH_{Ar}), 66.41 (OCH_2), 55.40 (OCH_3), 48.46 (NCH_2); ms: m/z 480 (M^+), 479, 423, 422, 394 (M – morpholine), 368 (M – (morpholine + NCS)), 337, 240, 206, 205 (2-phenylquinazoline), 190, 178, 150, 134, 130, 78, 77, 63.

Anal. Calcd. for $C_{28}H_{24}N_4O_2S$ (480.58): C 69.98; H 5.03; N 11.66; S 6.67. Found: C 69.94; H 4.99; N 11.59; S 6.54.

4-[4-(4-Chlorophenyl)-5-(2-phenylquinazolin-4-yl)-1,3-thiazol-2-yl]morpholine (**8d**).

Compound **8d** was obtained in 57% yield, (Procedure A) 0.78 g; mp 194-195 °C; ir: 3061, 2979, 2851 (CH), 1617 (C=N) 1583, 1559, 1531 (C=C) cm^{-1}; ^1H nmr: δ 8.71-7.12 (13H, m, ArH), 3.92 (4H, t, $J_{A,B}$= 5.29 Hz, OCH_2), 3.65 (4H, t, $J_{A,B}$= 5.29 Hz, NCH_2); ^{13}C nmr: δ 171.85 (C_q), 161.63 (C_q), 159.48 (C_q), 154.12 (C_q), 152.19 (C_q), 139.01 (C_q), 138.89 (C_q), 135.34 (CH_{Ar}), 133.71 (CH_{Ar}), 131.56 (C_q), 131.11 (CH_{Ar}), 129.47 (CH_{Ar}), 129.83 (CH_{Ar}), 128.34 (CH_{Ar}), 127.55 (CH_{Ar}), 127.48 (CH_{Ar}), 120..65 (C_q), 118.79 (C_q), 66.53 (OCH_2), 48.49 (NCH_2).

Anal. Calcd. for $C_{27}H_{21}ClN_4OS$(485.00): S 66.87; H 4.36; Cl 7.31; N 11.55; S 6.61. Found: C 66.83; H 4.34; Cl 7.21; N 11.44; S 6.57.

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