

Regioselectivity of Electrophilic Attack on 4-Methyl-1-Thioxo-1,2,4,5-Tetrahydro[1,2,4]Triazolo[4,3-A]Quinazolin-5-One Part 2: Reactions on Nitrogen Atom

W. Fathalla¹, M. Čajan^{1,2} and P. Pazdera^{*1}

¹ Department of Organic Chemistry, Faculty of Science, Masaryk University, Brno, Czech Republic.

² Laboratory of Biomolecular Structure and Dynamics, Faculty of Science, Masaryk University, Brno, Czech Republic. Tel.: +420 5 41129305, Fax: +420 5 41211214

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

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Abstract: The regioselectivity on a cyclic thioamide group towards different electrophiles was studied on the model compound 4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one **1**. The examined compound **1** reacts with alkyl halides, amines in the presence of formaldehyde, acyl halides and compounds having activated double bonds to afford the N-substituted derivatives **2**, **3** and **6**. The regioselective reactions on nitrogen atom are due to strong Coulombic attraction. The reaction of **1** with amines in the presence of hydrogen peroxide afforded the aminolysis product **4**. Compounds **1-6** were identified by FTIR, ¹H NMR, ¹³C NMR, and mass spectroscopy.

Keywords: 4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one, regioselective reactions, cyclic thioamides

Introduction

Triazoles and quinazolines and their annelated derivatives exhibit a wide spectrum of biological activities [1,2]. Combining these two structural features in one molecule might produce compounds with promising biological effects [2]. The model compound 4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (**1**) occurs in two tautomeric forms: the thiol **1a** and the thione **1b** having a nucleophilic center either on the sulfur atom or on the nitrogen atom, respectively. This prompted us to study the regioselective reactions on both the sulfur [3] and the nitrogen atoms.

Results and Discussion

In this contribution we report the regioselective reactions on the nitrogen atom of the thioamide moiety of the model compound **1**. The *ab initio* DFT computational studies of the anion formed by the deprotonation of **1** show that the anionic form is completely planar giving an aromaticity for the whole system. The nitrogen atom is a part of extended resonance of electrons through the N-C-N bonds of the triazolo-moiety. These facts were positively confirmed by the calculation of the molecular orbital coefficient of both atoms. The nitrogen atom has a low-energy HOMO while the sulfur atom has a high-energy HOMO. Finally the partial charge distributed on sulfur atom is slightly higher than that of the nitrogen atom (Table 1, 2, 3, Figure 1a, b) [3].

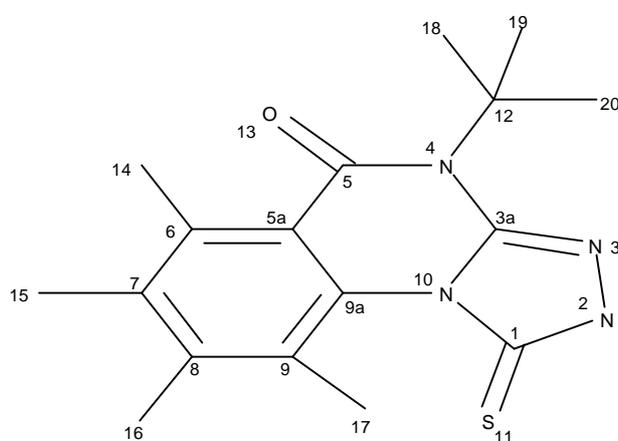


Figure 1a. Numbering of the model compound **1**.

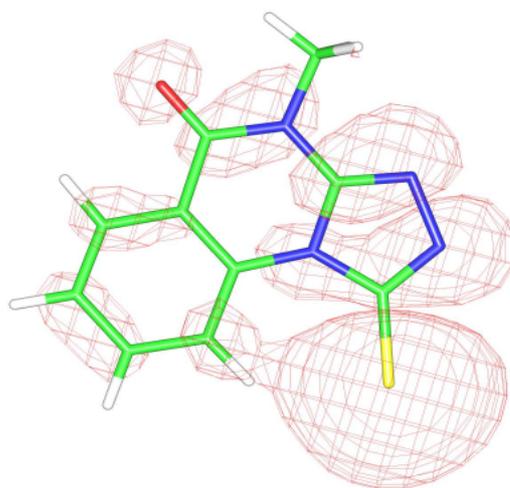


Figure 1b. Graphical representation of HOMO interactions of the anion form of **1**.

Table 1. The molecular orbital coefficients of the anion form of **1**.

HOMO				LUMO			
Atom	orbital	coefficient c	c ²	atom	orbital	coefficient c	c ²
N2	2pz	-0.27819	0.07400	N2	2pz	-0.08124	0.00660
C3a	2pz	0.18864	0.03559	C3a	2pz	0.02391	0.00057
N3	2pz	0.14417	0.02078	N3	2pz	0.03000	0.00090
N4	2pz	-0.10392	0.01080	N4	2pz	-0.19719	0.03888
C9	2pz	0.03267	0.00107	C9	2pz	-0.15622	0.02440
C9a	2pz	-0.00147	0	C9a	2pz	-0.20293	0.04118
C5a	2pz	0.03000	0.00090	C5a	2pz	0.23965	0.05743
C6	2pz	0.03339	0.00111	C6	2pz	-0.23044	0.05310
C5	2pz	-0.05526	0.00305	C5	2pz	0.26747	0.07154
8C	2pz	-0.03229	0.00104	8C	2pz	0.29486	0.08694
O13	2pz	0.07159	0.00513	O13	2pz	-0.21799	0.04752
H17	1s	0.00001	0	H17	1s	-0.00001	0
	2s	-0.00002	0		2s	-0.00003	0
S11	2pz	-0.20707	0.04288	S11	2pz	-0.00784	0
	3pz	0.53525	0.28649		3pz	0.02308	0.00053

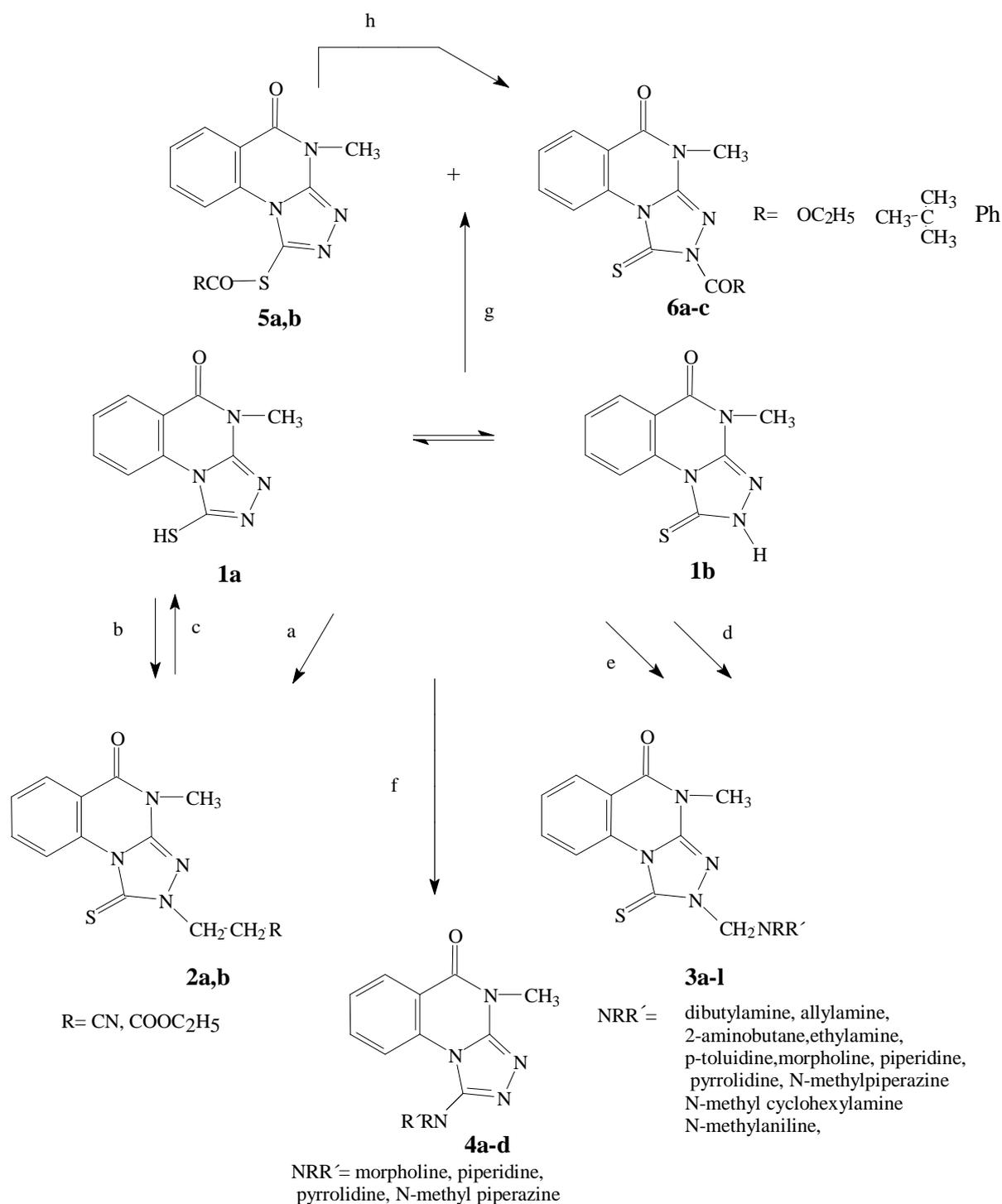
Table 2. The Partial charges of the anion form of **1**.

	Mulliken	ESP		Mulliken	ESP		Mulliken	ESP
1C	0.299805	0.261572	5aC	0.007777	-0.258923	10N	-0.655803	-0.028681
2N	-0.362087	-0.396664	6C	-0.194077	0.065184	11S	-0.494366	-0.641976
3N	-0.439884	-0.414159	7C	-0.135790	-0.263809	12C	-0.313408	-0.191986
3aC	0.724296	0.543478	8C	-0.148125	-0.024285	13O	-0.563195	-0.535417
4N	-0.551258	-0.275745	9C	-0.147373	-0.192450	17H	0.194778	0.138538
5C	0.579318	0.544019	9aC	0.334532	0.113657			

Table 3. Bond orders in the anion form of **1**.

S11-H17	0.13267	N4-C3a	1.09777	C1-N10	0.94453
C9a-N10	1.07074	C3a-N10	1.20156	C1-S11	2.05111
C5a-C5	1.11577	C3a-N3	1.83014		
C5-O13	1.83726	N2-N3	1.07445		
C5-N4	1.19963	C1-N2	1.68059		

The pathway of reactions involving the triazoloquinazoline derivative **1** with electrophiles is dependent on the nature of the electrophile. The greater the charge of the electrophile the higher the hard-hard interactions and the reaction takes place at the nitrogen atom *via* strong Coulombic attraction. On the other hand, once the LUMO of the electrophile is great then the reaction undergo orbital-orbital interactions between the LUMO of the electrophile and the higher HOMO of the ambident nucleophile to produce the *S*-attack [3]. The effect of other factors will be also discussed separately for each reaction.



Scheme 1. Alkylation, Mannich, Michael and aminolysis reactions of model compound **3**.

a: CH₂=CHR, N(C₂H₅)₃, ethanol, 78°C, 3-4h.

b: ClCH₂CH₂R, NaOH, ethanol, 78°C, 3-4h.

c: NaOH, EtOH, H₂O, 78°C, 1h.

d: HNR¹R², CH₂=O, ethanol, 25°C, 1-2h.

e: 4-(morpholinomethyl) morpholine, N(C₂H₅)₃, ethanol, 78°C, 4h.

f: HNR¹R², H₂O₂, 25°C, 2-24h.

g: ClCOR, triethyl amine, benzene, 80°C, 15 min.

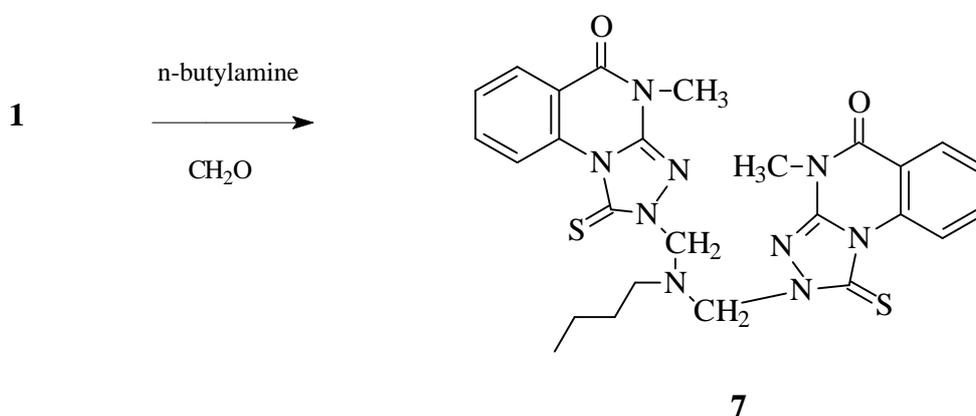
h: CHCl₃, 40°C, 30 min.

The reaction of **1** with activated unsaturated compounds under Michael reaction condition gave the *N*-substituted derivatives **2**. The reaction gave positive results only in the case of acrylonitrile and ethyl acrylate. The presence of the activated C=C double bond conjugated with electron withdrawing nitrile

or ester group evoked an electron deficiency on the C3 carbon atom, consequently giving a partial positive charge on this atom. On the other hand the energy of LUMO π_{2p}^* in both acrylic acid functional derivatives is decreased and the coupling of activated C=C double bond at the nitrogen in **1**. The reaction proceeded *via* strong Coulombic attraction at the hard part of the ambident nucleophile to finally produce the *N*-substituted alkyl derivative **2**. The products formed were also prepared by the reaction of **1** with 3-chloropropionitrile and ethyl-3-chloropropionate [3]. Application of this Michael type of reaction on diethylfumarate, diethylmaleate, diethyl-2-butynedioate, acrylamide and acrylic acid salt was not successful. This is obviously because of the double bond is not sufficiently activated. This might be evidence for the reaction proceeded *via* strong Coulombic attractions, consequently only polarized double bonds are required for such a reaction. The products **2** undergo elimination reaction to give the starting **1** in the presence of ethyl alcohol/ H₂O mixture.

The reaction of **1** with amines in ethyl alcohol in the presence of formaldehyde gave the Mannich reaction products at the nitrogen atom. Before we discuss the reason for the N-contribution in the reaction we must first have a look at the possible reaction mechanisms for such a reaction. The study of the reaction kinetics of products formed by Mannich reaction [4] has led to the following proposals for the mechanisms of this reaction. One is the base catalyzed; the other is the acid catalyzed reaction. Several evidences were introduced to confirm that only the base catalyzed mechanism is involved. The reaction is carried out in a slightly basic medium from excess of the amines used, while no reaction was produced when carried in the presence of few drops of HCl.

The intermediate compound containing two electron withdrawing groups surrounding the methylene group will produce an electron deficiency on the carbon atom and consequently giving a partial positive charge on this carbon making it to some extent as a hard nucleophile. The reaction proceeded *via* strong Coulombic attraction at the hard part of the ambident nucleophile to finally produce the *N*-substituted alkyl derivative **3**. The evidence for the formation of this intermediate and the formation of such a mechanism were given by the reaction of our ambident nucleophile with 4-morpholino(methylmorpholino) that gave the same product as the Mannich type of reaction with morpholine. The Mannich reaction was extended to involve primary, secondary alkyl amines and *p*-toluidine applications. It is noteworthy that all the applied amines gave the mono derived Mannich reaction products **3** except for *n*-butyl amine that gave the bis-triazoloquinazoline derivative **7**.



Scheme 2. Reaction of **1** with *n*-butyl amine and formaldehyde.

The reaction of ambident nucleophile with secondary amines in the presence of H_2O_2 gave the aminolysis product **4** via desulfurization reaction. The reaction proceeds by oxidation of the SH group to form the sulfonic acid derivative **4** which subsequently undergoes elimination reaction via nucleophilic attack by the secondary amines.

The reaction of the acyl halides in presence of benzene and triethyl amine is a kinetically controlled reaction and it is formed via orbital-interactions to give the *S*-acyl product **5**. This product under the effect of prolongation of reaction time or by heating of reaction mixture undergoes trans-acylation reaction to give the thermodynamically controlled *N*-acyl derivative **6**. The trans-acylation reaction proceeded by the formation of the acyl carbocation formed under elevated temperature by the $\text{A}_{\text{B}}1$ mechanism, and is capable of attacking the nitrogen atom to produce the *N*-substituted acyl derivative [3].

Several instrumental techniques were used to elucidate the structures of the *N*- and *S*-substituted derivatives. The infrared spectra generally indicate the absence of the ν_{NH} of compounds **1a-b** and also show the characteristic frequency of the newly formed functional group(s). The mass spectra showed the molecular ion in all examined compounds. It is apparent that the mass spectra do not give reliable evidence to discriminate between the *S*- and *N*- substituted derivatives. The $^1\text{H-NMR}$ spectra provided several pieces of evidence for assigning the structures of the evidences for the *N*- and *S*- products. The $^1\text{H-NMR}$ spectra gave an interesting peak corresponding to H9 at 10.50 ppm in the case of *N*-alkyl **2**, **3** and **7** or *N*-acyl **6** derivatives. This high chemical shift is attributed to high interaction between the thiocarbonyl group and the C9-H9 as shown in Figure 1. This peak was used as an indicator for the *N*-substituted derivatives; the chemical shift for H9 in the case of the *S*-substituted derivatives occurs at 8.2 ppm [3].

The CH_2 group adjacent to the sulfur atom appears at ca. 4.2 ppm [3], while the same group adjacent to nitrogen atom is found at a higher chemical shift ca. 4.6 ppm. The $^{13}\text{C-NMR}$ spectra show a signal at ca 163 ppm due to $\text{C}=\text{S}$ that is associated with the *N*-alkyl **2**, **3** and **7** or *N*-acyl **6** derivatives, while the *S*-alkylation gave chemical shift at ca. 144 ppm for the same carbon C1 (C-S). The CH_2 group adjacent to the sulfur atom in case of the *S*-alkylation appears at ca. 35 ppm, while the *N-CH}_2 appears at ca. 44 ppm.*

Conclusions

The regioselective alkylation reactions of thioamide derivatives with electrophiles could take place at either the sulfur or the nitrogen atoms according to the character of both the thioamide derivative and the applied electrophile.

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. TLC detection was made by Fluotes Universal (Quarzlampen, Hanau) and iodine vapours, respectively. Purity of compounds **1-6** was proved by the elemental analysis on an Erba 1102 instrument. FTIR spectra ($\tilde{\nu}/\text{cm}^{-1}$) were taken on a Genesis (Uni-

cam) spectrometer in potassium bromide pellets. NMR spectra (δ /ppm) were measured on a Bruker Avance DRX-500 spectrometer. Unless stated otherwise, ^1H - and ^{13}C -NMR spectra were measured in CDCl_3 and tetramethylsilane was used as an internal standard. The measured ^{13}C and ^1H NMR spectra were correlated with those obtained by on-line simulation (Advanced Chemistry Development, Inc., Toronto, Canada). Mass spectrometry was measured (electron impact, 70 eV) with FISONS Instruments TRIO 1000 and GC 8000 series.

The theoretical results were obtained using the DFT method on the B3LYP/6-31-G* level [5,6]. Mulliken [7], ESP [8] and NBO [9-11] methods were used to calculate the partial charges and properties of molecular orbitals. Mayer bond orders [12] were calculated on a B3LYP/ii-iglo level using the Demon v.1 program [13]. The starting material **1** is prepared according to [3] from 3-methyl-2-sulfanyl-3,4-dihydroquinazolin-4-one.

3-(4-Methyl-5-oxo-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-2-yl)propane derivatives **2a**, **2b**.

Michael reaction. Method A

To a mixture of triazolo derivative **1** (2.32 g, 0.01 mole) and triethyl amine (2 ml, 0.02 mole) in ethyl alcohol (30 mL, 95 %) the appropriate acrylic acid derivative (0.01 mole) was added. The reaction mixture was heated under reflux for 4-6h, concentrated under reduced pressure. The solid obtained was filtered, and crystallized from ethyl alcohol.

Method B

To a mixture of triazolo derivative **1** (2.32 g, 0.01 mole) and NaOH (0.8 g, 0.02 mole) in ethyl alcohol (30 mL, 95 %) the appropriate alkyl halide (namely ethyl chloropropionate and chloropropionitrile, 0.01 mole) was added. The reaction mixture was heated under reflux for 3-4 h, concentrated under reduced pressure. The solid obtained was filtered, and crystallized from ethyl alcohol.

Ethyl-3-(4-methyl-5-oxo-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-2-yl) propanoate (**2a**).

2.16 g (65%) (Method A, from **1**), 1.43 g (45%) (Method B, from **1**), M.p. 120-121 °C; For $\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}_3\text{S}$ (332.38) calculated: 54.21% C, 4.85% H, 16.86% N, 9.65% S, Found: 54.15% C, 4.76% H, 16.82% N, 9.57% S; FTIR: 1686(C=O), 1725 (C=O ester), 3087, 2977 (CH), 1631 (C=N); ^1H -NMR: 10.33-7.51 (4H, m, ArH), 4.59 (1H, t, NCH_2 , $J=7.1$ Hz), 4.18 (1H, q, OCH_2 , $J=7.1$ Hz), 3.61 (3H, s, NCH_3), 2.93 (2H, t, CH_2CO , $J=7.1$ Hz), 1.29 (3H, t, CH_2CH_3 , $J=7.1$ Hz); ^{13}C -NMR: 170.51 (C=O), 161.72 (C=S), 158.36 (C=O, cyclic amide), 144.36 (C_q), 135.13 (C_q), 134.45 (CH_{Ar}), 129.00 (CH_{Ar}), 127.25 (CH_{Ar}), 116.92 (C_q), 116.55 (CH_{Ar}), 60.96 (NCH_2), 44.32 (OCH_2), 32.23 (CH_2CO), 29.02 (NCH_3), 14.17 (CH_2CH_3).

3-(4-Methyl-5-oxo-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-2-yl) propionitrile (**2b**).

2.13 g (75%) (Method A, from **1**), 1.20g (40%) (Method B, from **1**), M.p. 230-231 °C; For C₁₃H₁₁N₅OS (285.32) calculated: 54.73% C, 3.89% H, 24.55% N, 11.24% S, Found: 54.69% C, 3.71% H, 24.45% N, 11.12% S; FTIR: 1687 (C=O), 2248 (CN), 3005, 2978, 2945 (CH), 1632 (C=N); ¹H-NMR: 10.25-7.58 (4H, m, ArH), 4.59 (2H, t, NCH₂, J= 6.85 Hz), 3.64 (3H, s, NCH₃), 3.03 (2H, t, CH₂CN, J= 6.85 Hz); ¹³C-NMR: 162.20 (C=S), 158.36 (C=O, cyclic amide), 144.76 (C_q), 135.13 (C_q), 134.56 (CH_{Ar}), 129.19 (CH_{Ar}), 127.55 (CH_{Ar}), 116.96 (C_q), 116.32 (CH_{Ar}), 115.23 (CN), 44.14 (NCH₂), 29.10 (NCH₃), 16.09 (CH₂CN); Mass spectrum, m/z (I_r/%) : 286 (18), 285 (100), 245 (34), 232 (29), 199 (3), 174 (5), 162 (12), 144 (8).

Mannich reaction

4-Methyl-2-(R,R'-aminomethyl)-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-ones (**3a-1**)

Method A

To the suspension of triazoloquinazoline **1** (2.32 g, 0.01 mole) in ethyl alcohol (30 mL, 95 %), formaldehyde (30%, 0.9 mL, 0.03mole) the desired amine (0.01 mole) were added dropwise with stirring. The reaction mixture was further stirred for 1-2h. at room temperature, concentrated under reduced pressure and cooled. The solid obtained was filtered and crystallized from ethyl alcohol.

Method B

To a mixture of triazolo derivative **1** (2.32 g, 0.01 mole) and triethyl amine (2 mL, 0.02 mole) in ethyl alcohol (30 mL, 95 %) the 4-(morpholinomethyl)morpholine (1.86 g, 0.01 mole) was added. The reaction mixture was heated under reflux for 3h, concentrated under reduced pressure. The solid obtained was filtered, and crystallized from ethyl alcohol.

4-Methyl-2-morpholinomethyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (**3a**).

1.88 g (57%) (A, from **1**), 1.49g (45%) (B, from **1**), M.p. 185-186 °C; For C₁₅H₁₇N₅O₂S (331.39) calculated: 54.37% C, 5.17% H, 21.13% N, 9.67% S, Found: 54.23% C, 5.08% H, 20.98% N, 9.56% S; FTIR: 1688 (C=O), 2973, 2956 (CH), 1630 (C=N); ¹H-NMR: 10.40-7.56 (4H, m, ArH), 5.22 (2H, s, NCH₂N), 3.71 (4H, t, 2OCH₂, J= 4.68 Hz), 3.64 (3H, s, NCH₃), 2.89 (4H, t, 2NCH₂, J= 4.68 Hz); ¹³C-NMR: 164.07 (C=S), 158.63 (C=O, cyclic amide), 144.53 (C_q), 135.44 (C_q), 134.59 (CH_{Ar}), 129.32 (CH_{Ar}), 127.52 (CH_{Ar}), 117.23 (C_q), 116.70 (CH_{Ar}), 69.26 (NCH₂N), 67.12 (OCH₂), 51.13 (NCH₂), 29.31 (NCH₃).

4-Methyl-2-piperidinomethyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (**3b**).

1.68 g (51%), M.p. 210-211 °C; For C₁₆H₁₉N₅OS (329.42) calculated: 58.30% C, 5.81% H, 21.26% N, 9.73% S, Found: 58.22% C, 5.88% H, 20.70% N, 9.65% S; FTIR: 1682 (C=O), 2932 (CH), 1629

(C=N); $^1\text{H-NMR}$: 10.42-7.52 (4H, m, ArH), 5.22 (2H, s, NCH_2N), 3.64 (3H, s, NCH_3), 2.82 (4H, t, 2NCH_2 , $J = 5.35$ Hz), 1.62-1.57 (4H, m, $2\text{NCH}_2\text{CH}_2$), 1.42-1.37 (2H, m, $2\text{NCH}_2\text{CH}_2\text{CH}_2$); $^{13}\text{C-NMR}$: 163.82 (C=S), 158.68 (C=O, cyclic amide), 144.31 (C_q), 135.52 (C_q), 134.50 (CH_{Ar}), 129.22 (CH_{Ar}), 127.38 (CH_{Ar}), 117.22 (C_q), 116.71 (CH_{Ar}), 70.24 (NCH_2N), 52.15 (NCH_2), 29.29 (NCH_3), 26.21 (NCH_2CH_2), 24.03 ($\text{NCH}_2\text{CH}_2\text{CH}_2$).

4-Methyl-2-pyrrolidinomethyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (**3c**).

1.92 g (61%), M.p. 196-197 °C; For $\text{C}_{15}\text{H}_{17}\text{N}_5\text{OS}$ (315.39) calculated: 57.12% C, 5.43% H, 22.21% N, 10.17% S, Found: 57.07% C, 5.21% H, 22.15% N, 9.95% S; FTIR: 1690 (C=O), 2970, 2950 (CH), 1630 (C=N); $^1\text{H-NMR}$: 10.42-7.52 (4H, m, ArH), 5.33 (2H, s, NCH_2N), 3.64 (3H, s, NCH_3), 2.95 (4H, t, 2NCH_2 , $J = 6.31$ Hz), 1.77 (4H, t, $2\text{NCH}_2\text{CH}_2$); $^{13}\text{C-NMR}$: 163.73 (C=S), 158.67 (C=O, cyclic amide), 144.49 (C_q), 135.49 (C_q), 134.55 (CH_{Ar}), 129.22 (CH_{Ar}), 127.40 (CH_{Ar}), 117.21 (C_q), 116.73 (CH_{Ar}), 65.56 (NCH_2N), 50.77 (NCH_2), 29.29 (NCH_3), 24.19 (NCH_2CH_2).

4-Methyl-2-(4-methylpiperazino)methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (**3d**).

1.54 g (45%), M.p. 184-185 °C; For $\text{C}_{16}\text{H}_{20}\text{N}_6\text{OS}$ (344.43) Calculated: 55.79% C, 5.85% H, 24.40% N, 9.31% S, Found: 55.68% C, 5.59% H, 24.34% N, 9.25% S; FTIR: 1693 (C=O), 2934 (CH), 1633 (C=N); $^1\text{H-NMR}$: 10.40-7.54 (4H, m, ArH), 5.24 (2H, s, NCH_2N), 3.62 (3H, s, NCH_3), 2.94 (4H, t, 2NCH_2 , $J = 4.82$ Hz), 2.46 (4H, t, $2\text{NCH}_2\text{CH}_2$, $J = 4.97$ Hz), 2.27 (3H, s, NCH_3); $^{13}\text{C-NMR}$: 164.01 (C=S), 158.64 (C=O, cyclic amide), 144.46 (C_q), 135.52 (C_q), 134.53 (CH_{Ar}), 129.33 (CH_{Ar}), 127.46 (CH_{Ar}), 117.27 (C_q), 116.76 (CH_{Ar}), 69.00 (NCH_2N), 55.26 (NCH_2), 50.58 (CH_2NCH_3), 46.23 (CH_2NCH_3), 29.24 (NCH_3).

2-Cyclohexyl-N-methylaminomethyl-4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (**3e**).

1.78 g (50%), M.p. 141-142 °C; For $\text{C}_{18}\text{H}_{23}\text{N}_5\text{OS}$ (357.47) calculated: 60.48% C, 6.48% H, 19.59% N, 8.97% S, Found: 60.35% C, 6.45% H, 19.57% N, 8.82% S; FTIR: 1689 (C=O), 2947, 2928 (CH), 1628 (C=N); $^1\text{H-NMR}$: 10.43-7.54 (4H, m, ArH), 5.28 (2H, s, NCH_2N), 3.64 (3H, s, NCH_3), 2.72-2.89 (1H, m, NCH), 2.22 (3H, s, NCH_3), 1.91-1.27 (10H, m, 5CH_2); $^{13}\text{C-NMR}$: 163.04 (C=S), 158.74 (C=O, cyclic amide), 144.31 (C_q), 135.57 (C_q), 134.54 (CH_{Ar}), 129.22 (CH_{Ar}), 127.36 (CH_{Ar}), 117.25 (C_q), 116.84 (CH_{Ar}), 67.89 (NCH_2N), 61.07 (NCH), 37.03 (CH_2NCH_3), 30.59 (NCHCH_2), 29.28 (NCH_3), 26.87 (CHCH_2CH_2), 26.01 ($\text{CHCH}_2\text{CH}_2\text{CH}_2$).

4-Methyl-N-methylanilinomethyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (**3f**).

1.40 g (40%), M.p. 178-179 °C; For $\text{C}_{18}\text{H}_{17}\text{N}_5\text{OS}$ (351.43) calculated: 61.52% C, 4.88% H, 19.93% N, 9.12% S, Found: 61.41% C, 4.73% H, 19.57% N, 8.92% S; FTIR: 1690 (C=O), 3045, 3006, 2939 (CH), 1631 (C=N); $^1\text{H-NMR}$: 10.36-6.82 (9H, m, ArH), 5.85 (2H, s, NCH_2N), 3.57 (3H, s, NCH_3), 3.32 (3H, s, NCH_3); $^{13}\text{C-NMR}$: 162.68 (C=S), 158.60 (C=O, cyclic amide), 147.38 (C_q), 144.74 (C_q), 135.40

(C_q), 134.59 (CH_{Ar}), 129.42 (CH_{Ar}), 129.29 (CH_{Ar}), 127.45 (CH_{Ar}), 118.95 (CH_{Ar}), 117.23 (C_q), 116.77 (CH_{Ar}), 113.87 (CH_{Ar}), 65.70 (NCH₂N), 39.67 (CH₂NCH₃), 29.25 (NCH₃).

2-(Dibutylamino)methyl-4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (3g).

2.23 g (60%), M.p. 118-119 °C; For C₁₉H₂₇N₅OS (373.52) calculated: 61.10% C, 7.29% H, 18.75% N, 8.58% S, Found: 59.89% C, 7.18% H, 18.65% N, 8.31% S; FTIR: 1690 (C=O), 2955, 2930, 2870 (CH), 1629 (C=N); ¹H-NMR: 10.45-7.52 (4H, m, ArH), 5.28 (2H, s, NCH₂N), 3.63 (3H, s, NCH₃), 2.77 (4H, t, 2NCH₂, J= 7.27 Hz), 1.48-1.59 (4H, m, 2NCH₂CH₂), 1.21-1.39 (4H, m, 2NCH₂CH₂CH₂), 0.94 (3H, t, 2CH₂CH₃, J= 7.26 Hz); ; ¹³C-NMR: 163.47 (C=S), 158.75 (C=O, cyclic amide), 144.39 (C_q), 135.58 (C_q), 134.50 (CH_{Ar}), 129.24 (CH_{Ar}), 127.35 (CH_{Ar}), 117.25 (C_q), 116.81 (CH_{Ar}), 66.63 (NCH₂N), 52.29 (NCH₂), 30.40 (NCH₂CH₂), 29.24 (NCH₃), 20.63 (NCH₂CH₂CH₂), 14.24 (CH₂CH₃).

2-(Ethylamino)methyl-4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (3h).

1.59 g (55%), M.p. 165-166 °C; For C₁₃H₁₅N₅OS (289.35) calculated: 53.96% C, 5.22% H, 24.20% N, 11.08% S, Found: 53.86% C, 4.97% H, 23.87% N, 10.93% S; FTIR: 1691 (C=O), 2969, 2956 (CH), 1628 (C=N), 3390 (NH) ; ¹H-NMR: 10.38-7.53 (4H, m, ArH), 5.20 (2H, d, NCH₂NH), 3.64 (3H, s, NCH₃), 2.68 (2H, q, NCH₂, J= 7.13 Hz), 1.11 (3H, t, CH₂CH₃, J= 7.13 Hz); ; ¹³C-NMR: 162.81 (C=S), 158.64 (C=O, cyclic amide), 144.51 (C_q), 135.46 (C_q), 134.62 (CH_{Ar}), 129.29 (CH_{Ar}), 127.46 (CH_{Ar}), 117.20 (C_q), 116.77 (CH_{Ar}), 64.16 (NCH₂N), 40.58 (NCH₂), 29.28 (NCH₃), 15.09 (NCH₂CH₃).

2-(Allylamino)methyl-4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (3i).

1.05 g (35%), M.p. 139-140 °C; For C₁₄H₁₅N₅OS (301.37) calculated: 55.80% C, 5.22% H, 23.24% N, 10.64% S, Found: 55.61% C, 4.97% H, 23.12% N, 10.52% S; FTIR: 1691 (C=O), 2973, 2956 (CH), 1629 (C=N), 3340 (NH) ; ¹H-NMR: 10.34-7.54 (4H, m, ArH), 5.93-5.71 (1H, m, CH=CH₂), 5.24 (1H, d, CH=CH₂, J= 10.53 Hz), 5.20 (2H, d, NCH₂NH, J= 2.93 Hz), 5.09 (1H, d, CH=CH₂, J= 10.53 Hz), 3.63 (3H, s, NCH₃), 3.31-3.28 (2H, d, HNCH₂CH, J= 5.84 Hz); ; ¹³C-NMR: 163.82 (C=S), 158.41 (C=O, cyclic amide), 144.31 (C_q), 135.23 (C_q), 135.58 (CH=CH₂) 134.41 (CH_{Ar}), 129.31 (CH_{Ar}), 127.42 (CH_{Ar}), 117.24 (C_q), 116.56 (CH=CH₂), 116.52 (CH_{Ar}), 63.62 (NCH₂N), 48.64 (NCH₂), 29.26 (NCH₃).

2-(sec-Butylamino)methyl-4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (3j).

1.77 g (56%), M.p. 133-134 °C; For C₁₅H₁₉N₅OS (317.41) calculated: 56.76% C, 6.03% H, 22.06% N, 10.10% S, Found: 56.54% C, 5.83% H, 21.86% N, 9.77% S; FTIR: 1690 (C=O), 2965, 2926 (CH), 1627 (C=N), 3365 (NH) ; ¹H-NMR: 10.38-7.54 (4H, m, ArH), 5.22 (2H, d, NCH₂NH, J= 2.93 Hz), 3.64 (3H, s, NCH₃), 2.52-2.63 (1H, m, NCH), 1.58-1.32 (2H, m, NCHCH₂), 1.09 (3H, d, CHCH₃, J= 6.43 Hz), 0.89 (3H, t, CH₂CH₃, J= 7.47 Hz) ; ¹³C-NMR: 162.06 (C=S), 158.67 (C=O, cyclic amide), 144.50 (C_q), 135.50 (C_q), 134.63 (CH_{Ar}), 129.27 (CH_{Ar}), 127.44 (CH_{Ar}), 117.22 (C_q), 116.80 (CH_{Ar}),

62.10 (NCH₂N), 50.37 (NCH), 52.29 (NCH₂), 29.59 (NCHCH₂), 29.23 (NCH₃), 19.58 (CHCH₃), 10.20 (CH₂CH₃).

4-Methyl-1-thioxo-2-(p-toluidinomethyl)-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (3k).

1.77 g (65%), M.p. 171-172 °C; For C₁₈H₁₇N₅OS (351.43) calculated: 61.52% C, 4.88% H, 19.93% N, 9.12% S, Found: 61.42% C, 4.76% H, 19.82% N, 9.01% S; FTIR: 1691 (C=O), 2952, 2928 (CH), 1628 (C=N), 3385 (NH); ¹H-NMR: 10.28-6.84 (8H, m, ArH), 5.64 (2H, d, NCH₂NH), 3.59 (3H, s, NCH₃), 2.21 (3H, s, NCH₃); ¹³C-NMR (CDCl₃): 162.19 (C=S), 158.53 (C=O, cyclic amide), 142.27 (C_q), 135.30 (C_q), 134.57 (CH_{Ar}), 130.02 (CH_{Ar}), 129.26 (CH_{Ar}), 129.13 (C_q), 127.48 (CH_{Ar}), 117.12 (C_q), 116.69 (CH_{Ar}), 114.69 (CH_{Ar}), 58.79 (NCH₂N), 29.23 (NCH₃), 20.60 (PhCH₃).

2-(Diethylamino)methyl-4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (3l).

1.39 g (45%), M.p. 160-161 °C; For C₁₅H₁₉N₅OS (317.41) calculated: 56.76% C, 6.03% H, 22.06% N, 10.10% S, Found: 56.59% C, 5.87% H, 21.91% N, 9.92% S; FTIR: 1689 (C=O), 2985, 2960 (CH), 1630 (C=N); ¹H-NMR: 10.37-7.42 (4H, m, ArH), 5.22 (2H, s, NCH₂N), 3.56 (3H, s, NCH₃), 2.79 (4H, q, 2NCH₂, J= 7.31 Hz), 1.11 (6H, t, 2NCH₂CH₃, J= 7.0 Hz); ¹³C-NMR: 163.46 (C=S), 158.70 (C=O, cyclic amide), 144.46 (C_q), 135.53 (C_q), 134.50 (CH_{Ar}), 129.22 (CH_{Ar}), 127.35 (CH_{Ar}), 117.24 (C_q), 116.77 (CH_{Ar}), 65.63 (NCH₂N), 46.17 (NCH₂), 29.25 (NCH₃), 13.44 (NCH₂CH₃).

2-[Butyl[(4-methyl-5-oxo-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-2-yl)methyl]amino]methyl-4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (7).

1.79 g (32%), M.p. 163-164 °C; For C₂₆H₂₇N₉O₂S₂ (561.68) calculated: 55.60% C, 4.85% H, 22.44% N, 11.42% S, Found: 55.43% C, 4.63% H, 22.39% N, 11.31% S; FTIR: 1691 (C=O), 2952, 2928 (CH), 1627 (C=N); ¹H-NMR: 10.36-7.53 (8H, m, ArH), 5.61 (4H, s, NCH₂N), 3.60 (6H, s, NCH₃), 3.04 (2H, t, NCH₂, J= 7.26 Hz), 1.66-1.57 (2H, m, NCH₂CH₂), 1.35-1.21 (2H, m, NCH₂CH₂CH₂), 0.87 (3H, t, CH₂CH₃, J= 7.25 Hz); ¹³C-NMR: 163.16, 162.73 (C=S), 158.55 (C=O, cyclic amide), 144.56 (C_q), 135.37 (C_q), 134.62 (CH_{Ar}), 129.26 (CH_{Ar}), 127.48 (CH_{Ar}), 117.11 (C_q), 116.6 (CH_{Ar}), 67.00 (NCH₂N), 50.87 (NCH₂), 30.27 (NCH₂CH₂), 29.25 (NCH₃), 20.20 (NCH₂CH₂CH₂), 14.06 (CH₂CH₃).

Aminolysis reaction: General procedure

To the solution of triazoloquinazoline **1** (2.32 g, 0.01 mole) in the appropriate amine (10 mL), 5 drops of hydrogen peroxide were added drop wise during stirring. The reaction mixture was further stirred for 2-24h. At room temperature, to give a white precipitate, filter, wash with H₂O and crystallized from ethyl alcohol.

4-Methyl-1-morpholino-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (**4a**).

1.60 g (56%), M.p. 166-167°C; For C₁₄H₁₅N₅O₂ (285.30) calculated: 58.94% C, 5.30% H, 24.55% N, Found: 58.67% C, 5.21% H, 24.48% N; FTIR: 1686 (C=O), 2983, 2948 (CH), 1611 (C=N); ¹H-NMR: 8.65-7.54 (4H, m, ArH), 4.12 (4H, t, 2OCH₂, J= 4.87 Hz), 3.82 (3H, s, NCH₃), 2.89 (4H, t, 2NCH₂, J= 4.97 Hz); ¹³C-NMR: 158.77 (C=O, cyclic amide), 149.81 (C_q), 144.58 (C_q), 134.59 (CH_{Ar}), 133.96 (C_q), 130.01 (CH_{Ar}), 127.02 (CH_{Ar}), 117.54 (C_q), 116.96 (CH_{Ar}), 67.61 (OCH₂), 51.72 (NCH₂), 29.83 (NCH₃).

4-Methyl-1-piperidino-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (**4b**).

1.33 g (47%), M.p. 158-159°C; For C₁₅H₁₇N₅O (283.33) calculated: 63.59% C, 6.05% H, 24.72% N, Found: 63.45% C, 5.98% H, 24.65% N; FTIR: 1689 (C=O), 2985, 2932 (CH), 1613 (C=N); ¹H-NMR: 8.65-7.54 (4H, m, ArH), 3.82 (3H, s, NCH₃), 3.17 (4H, t, 2NCH₂, J= 5.40 Hz), 1.54-1.68 (4H, m, 2NCH₂CH₂), 1.41-1.29 (2H, m, NCH₂CH₂CH₂); ¹³C-NMR: 158.77 (C=O, cyclic amide), 149.81 (C_q), 144.58 (C_q), 134.59 (CH_{Ar}), 133.96 (C_q), 130.01 (CH_{Ar}), 127.02 (CH_{Ar}), 117.54 (C_q), 116.96 (CH_{Ar}), 57.62 (NCH₂), 29.64 (NCH₃), 27.28 (NCH₂CH₂), 22.58 (NCH₂CH₂CH₂).

4-Methyl-1-pyrrolidino-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (**4c**).

1.31 g (49%), M.p. 163-164°C; For C₁₄H₁₅N₅O (269.305) calculated: 62.44% C, 5.61% H, 26.01% N, Found: 62.23% C, 5.56% H, 26.01% N; FTIR: 1684 (C=O), 2987 (CH), 1611 (C=N); ¹H-NMR: 8.72-7.58 (4H, m, ArH), 3.62 (3H, s, NCH₃), 3.06 (4H, m, 2NCH₂), 1.75-1.68 (4H, m, 2NCH₂CH₂); ¹³C-NMR: 158.37 (C=O, cyclic amide), 149.75 (C_q), 142.89 (C_q), 134.66 (CH_{Ar}), 133.67 (C_q), 128.87 (CH_{Ar}), 126.85 (CH_{Ar}), 117.31 (C_q), 116.59 (CH_{Ar}), 54.45 (NCH₂), 29.13 (NCH₃), 24.36 (NCH₂CH₂).

4-Methyl-1-(4-methylpiperazino)-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (**4d**).

1.33 g (53%), M.p. 167-168°C; For C₁₅H₁₈N₆O (298.35) calculated: 60.39% C, 6.08% H, 28.17% N, Found: 60.21% C, 5.85% H, 27.76% N; FTIR: 1689 (C=O), 2985 (CH), 1613 (C=N); ¹H-NMR: 8.91-7.54 (4H, m, ArH), 3.81 (3H, s, NCH₃), 3.11 (4H, t, 2NCH₂, J= 4.68 Hz), 2.14 (4H, t, 2NCH₂CH₂, J= 4.68 Hz), 2.20 (3H, s, CH₂NCH₃); ¹³C NMR: 159.05 (C=O, cyclic amide), 150.39 (C_q), 143.17 (C_q), 134.87 (CH_{Ar}), 134.40 (C_q), 130.47 (CH_{Ar}), 127.56 (CH_{Ar}), 118.00 (C_q), 117.17 (CH_{Ar}), 56.29 (NCH₂), 56.10 (NCH₂CH₂N), 46.13 (CH₂NCH₃), 29.99 (NCH₃).

Acylation reaction. General procedure

The appropriate acyl chloride (ethyl chloroformate for **5a**, **6a**, pivaloyl chloride for **5b**, **6b** or benzoyl chloride for **6c**) (0.01 mole) was added to a mixture of triazolo derivative **1** (2.32 g, 0.01 mole) and triethyl amine (2 mL, 0.02 mole) solution in benzene (30 mL). The reaction mixture was heated under reflux for 15 min. Concentrated under reduced pressure. The solid obtained was filtered, and crystallized from ethyl alcohol. The obtained product was a mixture of both **5** and **6** and was not further purified. The constitutional isomers purity was determined from the ¹H-NMR spectra. Compounds **5a** and **5b** were not isolated but detected only from the ¹H-NMR spectra, IR spectroscopy and by the com-

parison with the $^1\text{H-NMR}$ spectra of the pure **6a** and **6b**. The chloroform solution of the mixture of **5** and **6** were heated under reflux for 1h. to give the pure N-acyl derivatives **6**.

Ethyl-[(4-methyl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-1-yl)sulfanyl]methanoate (**5a**).

FTIR: 1708 (C=O), 1743 (C=O ester), 3063, 2980 (CH), 1635 (C=N); $^1\text{H-NMR}$: 8,72-7.34 (4H, m, ArH), 4.33 (2H, q, OCH_2 , $J = 7.0$ Hz), 3,82 (3H, s, NCH_3), 1,29 (3H, t, CH_2CH_3 , $J = 7.0$ Hz).

4-Methyl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-1-yl-2,2dimethylpropanethioate (**5b**).

FTIR: 1691(C=O), 1743 (C=O), 3002, 2978 (CH), 1645 (C=N); $^1\text{H-NMR}$: 8,62-7.56 (4H, m, ArH), 3,84 (3H, s, NCH_3), 1,61 (9H, s, $\text{C}(\text{CH}_3)_3$).

Ethyl-4-methyl-5-oxo-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-2-carboxylate (**6a**).

1.64 g (54%), M.p. °C; For $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_3\text{S}$ (304.32) calculated: 51.31% C, 3.97% H, 18.41% N, 10.53% S, Found: 51.21% C, 3.95% H, 18.33% N, 10.42% S; FTIR: 1689 (C=O), 1778 (C=O ester), 3063, 2980 (CH), 1635 (C=N); $^1\text{H-NMR}$: 10.38-7.55 (4H, m, ArH), 4.55 (2H, q, OCH_2 , $J = 7.0$ Hz), 3.66 (3H, s, NCH_3), 1.50 (3H, t, CH_2CH_3 , $J = 7.0$ Hz); $^{13}\text{C-NMR}$: 176.08 (C=O), 164.75 (C=S), 158.48 (C=O, cyclic amide), 149.04 (C_q), 145.01 (C_q), 135.18 (C_q), 134.85 (CH_{Ar}), 129.47 (CH_{Ar}), 127.91 (CH_{Ar}), 117.17 (C_q), 116.55 (CH_{Ar}), 65.30 (OCH_2), 29.36 (NCH_3), 14.14.36 (CH_2CH_3).

2-(2,2-Dimethylpropanoyl)-4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (**6b**).

1.42 g (45%), M.p. °C; For $\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$ (316.38) calculated: 56.95% C, 5.10% H, 17.71% N, 10.13% S, Found: 56.73% C, 4.97% H, 17.65% N, 9.96% S; FTIR: 1691(C=O), 1743 (C=O), 3002, 2978 (CH), 1645 (C=N); $^1\text{H-NMR}$: 10.49-7.56 (4H, m, ArH), 3.67 (3H, s, NCH_3), 1.52 (9H, s, $\text{C}(\text{CH}_3)_3$); $^{13}\text{C-NMR}$: 176.08 (C=O), 164.71 (C=S), 158.65 (C=O, cyclic amide), 143.89 (C_q), 135.20 (C_q), 134.79 (CH_{Ar}), 129.50 (CH_{Ar}), 127.88 (CH_{Ar}), 117.09 (C_q), 116.84 (CH_{Ar}), 29.87 ($\text{C}(\text{CH}_3)_3$), 29.24 (NCH_3), 27.40 ($\text{C}(\text{CH}_3)_3$).

2-Benzoyl-4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-a]quinazolin-5-one (**6c**).

1.17 g (35%), M.p. °C; For $\text{C}_{17}\text{H}_{12}\text{N}_4\text{O}_2\text{S}$ (336.37) calculated: 60.70% C, 3.60% H, 16.66% N, 9.53% S, Found: 60.59% C, 3.45% H, 16.57% N, 9.49% S; FTIR: 1693 (C=O), 1720 (C=O), 2987, 2955 (CH), 1640 (C=N); $^1\text{H-NMR}$: 10.37-7.48 (9H, m, ArH), 3.60 (3H, s, NCH_3); $^{13}\text{C-NMR}$: 166.40 (C=O), 165.04 (C=S), 158.55 (C=O, cyclic amide), 142.41 (C_q), 135.08 (C_q), 134.76 (CH_{Ar}), 134.01 (CH_{Ar}), 131.98 (CH_q), 131.14 (CH_{Ar}), 129.46 (CH_{Ar}), 128.57 (CH_{Ar}), 127.92 (CH_{Ar}), 117.09 (C_q), 116.66 (CH_{Ar}), 29.32 (NCH_3).

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Sample Availability: Samples are available from the authors.