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SYNTHESIS OF *N*-IMIDAZOLIDIN-2-YLIDENEHYDRAZONES AND THEIR TRANSFORMATION INTO 5,10,11,12*a*-TETRAHYDRO-6*H*,9*H*-IMIDAZO[2′,1′:3,4][1,2,4]TRIAZOLO[1,5-*c*]QUINAZOLINE-6-THIONES

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Abstract – The reaction of 2-chloro-4,5-dihydroimidazole (**1**) with 2-aminoacetophenone hydrazones (**2a-b**) afforded 1,2,3,5-tetrahydroimidazo-[2,1-*b*]quinazolines (**3a-b**) in contrast to the analogues reaction of **1** with 2-aminobenzophenone hydrazones (**4a-e**), which led to the formation of corresponding *N*-imidazolidin-2-ylidenehydrazones (**5a-e**). Compounds (**5a-d**) were further treated with carbon disulfide to give 5,10,11,12*a*-tetrahydro-6*H*,9*H*-imidazo[2′,1′:3,4][1,2,4]triazolo[1,5-*c*]quinazoline-6-thiones (**6a-d**). The structures of all new compounds obtained were established by elemental analyses and spectroscopic data (IR, NMR) as well as X-ray crystallographic analyses of **5a** and **6a**.

INTRODUCTION

Polycyclic imidazol(in)e-containing derivatives constitute an important class of compounds with interesting biological activities including cyclic AMP phosphodiesterase inhibitors,[1] hypotensive agents,[2] I_2 receptors ligands,[3] appetite depressants and cocaine abuse therapeutics[4] or potential anticancer agents.[5] An illustrative example is the fusion of 1,2,4-triazolo[4,3-*c*]quinazoline (**A**, Figure 1), which exhibited antiproliferative activity,[6] with imidazole giving rise to the formation of antibacterial imidazo[2′,1′:5,1][1,2,4]triazolo[4,3-*c*]quinazolines (**B**[7], Figure 1). As a part of our research program aimed at search for new pharmacophores as chemotherapeutic agents, we have previously described the synthesis of imidazo[2′,1′:4,5][1,3,5]thiadiazino[2,3-*b*]quinazoline-5-thiones (**C**, Figure 1) starting from 2-aminobenzylamines and 2-chloro-4,5-dihydroimidazole.[8] In continuation of these works, the present study deals with the synthesis of *N*-imidazolidin-2-ylidenehydrazones and their transformation into

imidazo[2′,1′:3,4][1,2,4]triazolo[1,5-*c*]quinazoline-6-thiones (**D**, Figure 1) incorporating thioamide functionality, which is often found in the structure of anticancer agents that act as the inducer of DNA cleavage.[9]

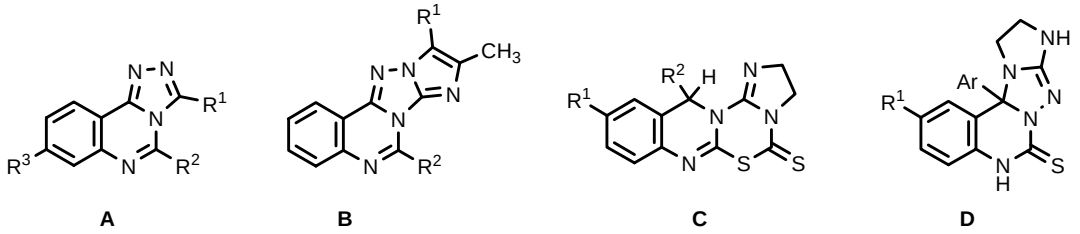
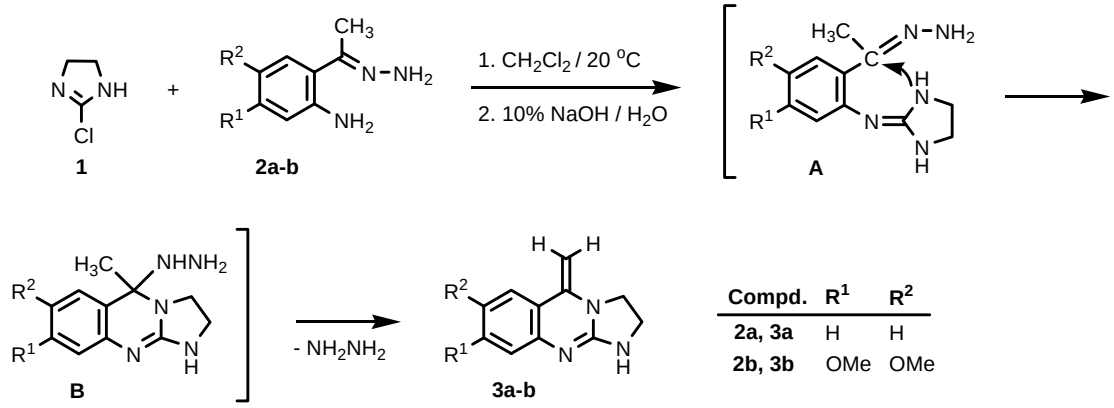


Figure 1

RESULTS AND DISCUSSION

The reaction of 2-chloro-4,5-dihydroimidazole (**1**) with the appropriate 2-aminophenyl ketone hydrazones (**2**) and (**4**) was carried out in dichloromethane at ambient temperature. We found, however, that when 2-aminoacetophenone hydrazones (**2a-b**) were used as substrates the reaction led to the formation of 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolines (**3a-b**) in 25-30% yield (Scheme 1). Apparently, the first step of the reaction sequence is the formation of the hydrazone (**A**), which upon nucleophilic attack of the nitrogen atom of the imidazoline ring at the carbon atom of the imine group undergoes intramolecular ring closure to give imidazo[2,1-*b*]quinazoline derivative (**B**). Loss of the hydrazine molecule from **B** gives rise to the product (**3**).



Compd.	R^1	R^2
2a, 3a	H	H
2b, 3b	OMe	OMe

Scheme 1

It should be mentioned that compounds (**3a-b**) have been obtained previously by the reaction of **1** with the appropriate 2-aminoacetophenones.[10]

As shown in Scheme 2, the reaction of **1** with 2-aminobenzophenone hydrazones (**4a-e**) took a different course and the target 2-aminophenyl ketone *N*-imidazolidin-2-ylidenehydrazones (**5a-e**) were obtained as a result of *N*-heteroalkilation of the hydrazone nitrogen atom. Structure of **5a** was confirmed by X-ray diffraction analysis (Figure 2).[11]

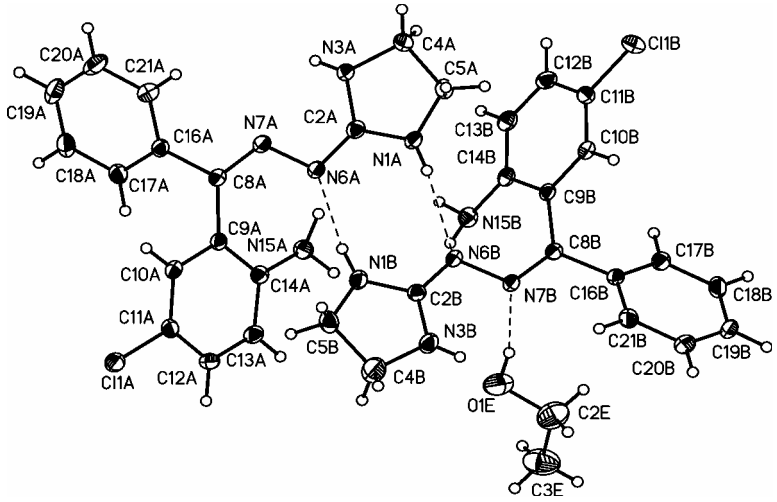


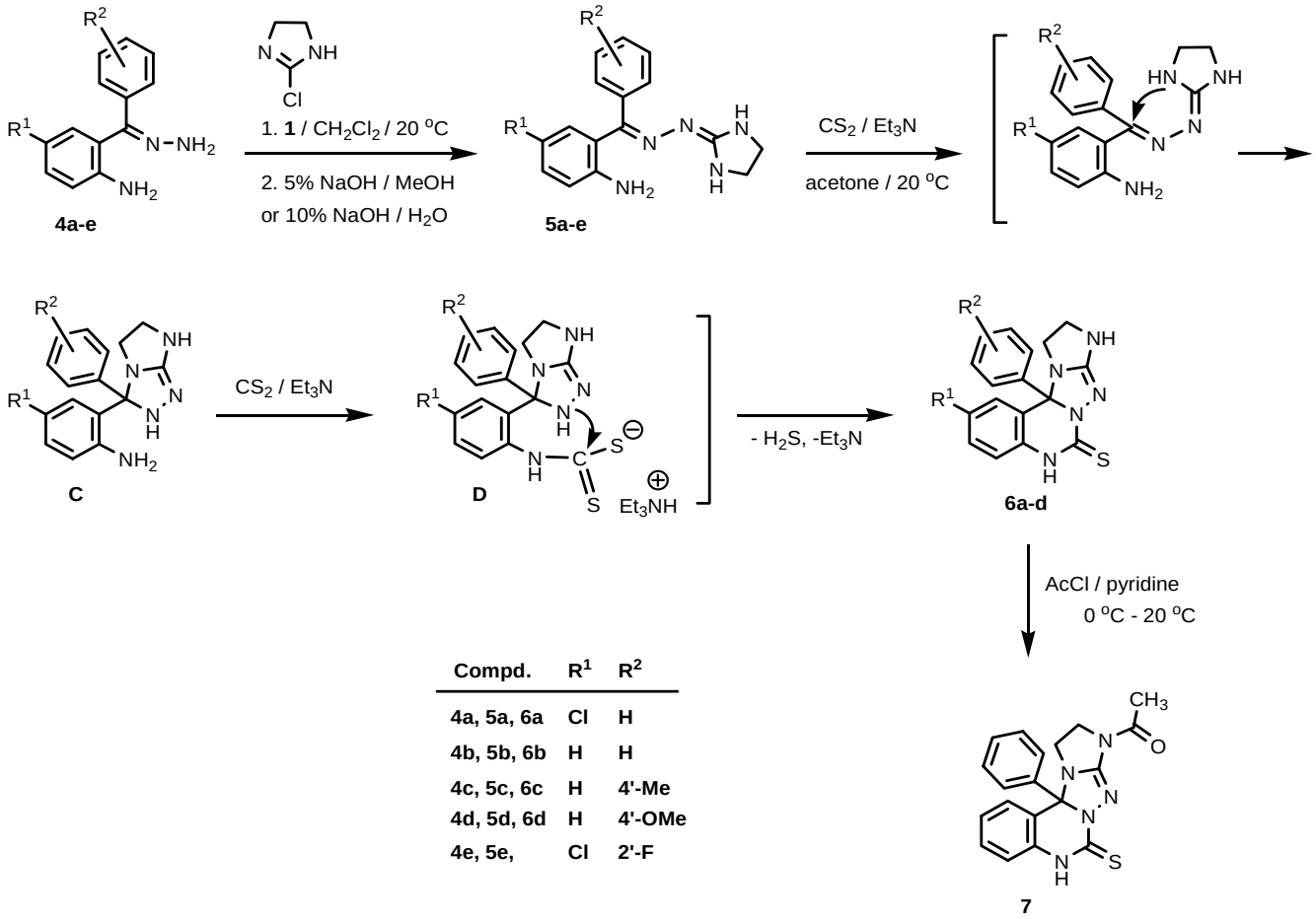
Figure 2. ORTEP drawing of **5a** with labeling scheme and displacement ellipsoids at the 40% probability level (dashed lines show hydrogen bonds).[11]

Then, we have elaborated a method for the preparation of 5,10,11,12*a*-tetrahydro-6*H*,9*H*-imidazo-[2′,1′:3,4][1,2,4]triazolo[1,5-*c*]quinazoline-6-thiones (**6a-d**), which consists in the reaction of **5a-d** with an excess of carbon disulfide in the presence of triethylamine, as depicted in Scheme 2. In general, the reaction of **5** with carbon disulfide was performed in acetone at ambient temperature and gave the desired product (**6**) in 44-58% yield. However, when the compound (**5e**) was used as a substrate, the reaction carried out under different conditions led to the intractable mixtures of products, probably due to the steric hindrance of fluorine atom at the C-2′ position. Although, the expected imidazo[2′,1′:3,4][1,2,4]-triazolo[1,5-*c*]quinazoline-6-thione was not separated from the reaction mixture, traces of this compound were detected by means of NMR spectrum of crude product.

The reaction pathway leading to **6a-d** was not studied in detail, but we presume that the reaction mechanism involves formation of the unstable 2-(5,6,7,7*a*-tetrahydro-3*H*-imidazo[2,1-*c*][1,2,4]-triazol-3-yl)aniline (**C**), which *in situ* reacts with a molecule of carbon disulfide in the presence of triethylamine to give triethylammonium dithiocarbamate (**D**). The latter intermediate undergoes further intramolecular cyclocondensation with evolution of H_2S to afford the final product (**6**).

It should be pointed out that the 5,10,11,12*a*-tetrahydro-6*H*,9*H*-imidazo[2′,1′:3,4][1,2,4]triazolo[1,5-*c*]-quinazoline-6-thione ring system of **6a-d** has not been described previously in the chemical literature.

We have further found, that the acetylation of **6b** with acetyl chloride occurred at the site of the imidazoline nitrogen to give amide (**7**) in 41% yield (Scheme 2).



Compd.	R^1	R^2
4a, 5a, 6a	Cl	H
4b, 5b, 6b	H	H
4c, 5c, 6c	H	4'-Me
4d, 5d, 6d	H	4'-OMe
4e, 5e,	Cl	2'-F

Scheme 2

Structures of the newly prepared compounds were confirmed by elemental analyses, IR and NMR spectroscopic data, MS spectrometry as well as X-ray analysis of **6a** (Figure 3).[11]

In order to rationalize the difference in reactivity of hydrazones (**2**) and (**4**) with 2-chloro-4,5-dihydroimidazole (**1**) we studied the electronic structure of these substrates using *ab initio* 6-31G** calculations.[12] As shown in Figure 4, for both compounds the calculated negative charges and the highest occupied molecular orbital (HOMO) have the highest contribution for N^1 amino nitrogen atoms which should be involved in the reactions with electrophiles. It is therefore clear that the chemical inertness of the amino group in **4** is a consequence of the steric shielding (buttressing effect) provided by the adjacent phenyl ring, which forces electrophile away from the stronger nucleophilic N^1 atom towards the less hindered but also less nucleophilic N^3 nitrogen atom.

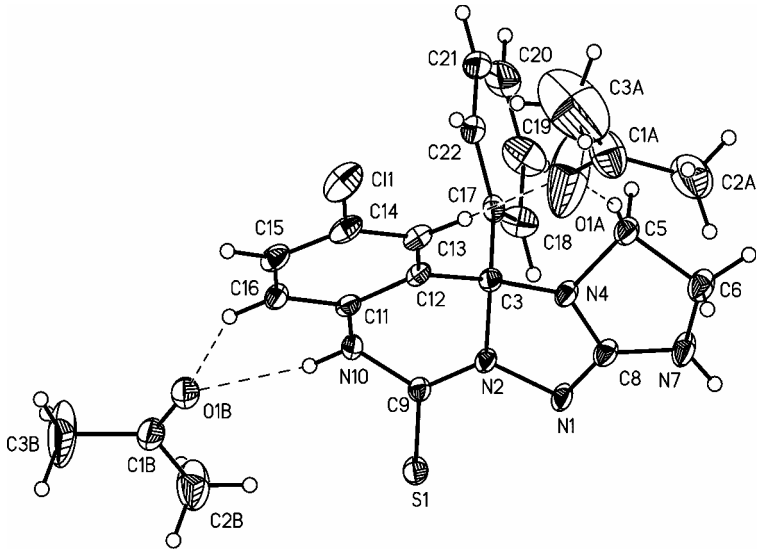
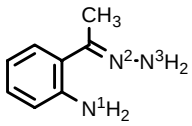
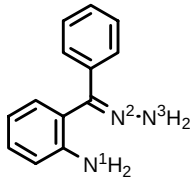


Figure 3. ORTEP drawing of **6a** with labeling scheme and displacement ellipsoids at the 40% probability level (dashed lines show hydrogen bonds and short C-H····O contacts).[11]



2a



4b

	Electrostatic	Mulliken	NPA	HOMO
N^1	-0.897e	-0.744e	-0.900e	0.016a.u.
N^2	-0.740e	-0.532e	-0.742e	0.03a.u.
N^3	-0.373e	-0.350e	-0.304e	0.03a.u.

	Electrostatic	Mulliken	NPA	HOMO
N^1	-0.936e	-0.757e	-0.897e	0.013a.u.
N^2	-0.746e	-0.527e	-0.733e	0.07a.u.
N^3	-0.310e	-0.356e	-0.356e	0.07a.u.

Figure 4. Selected charges from electrostatic potential, charges from Mulliken population analysis, natural atomic charges and absolute values of the HOMO on the electron density isosurface corresponding to the van der Waals surface calculated for hydrazones (**2a**) and (**4b**).[12]

Samples of the compounds (**6a-b**) were submitted to the US National Cancer Institute (Bethesda) for screening against human tumor cell lines. The results of biological tests will be published elsewhere.

EXPERIMENTAL

Melting points (mp) were determined on a Büchi SMP 20 apparatus and are uncorrected. IR spectra (KBr pellets) were measured on a Perkin Elmer 1600 FTIR spectrophotometer. NMR spectra were recorded on

a Varian Gemini 200 or Varian Unity 500 spectrometer at 200 MHz* or 500 MHz for proton and 50 MHz* or 125 MHz for carbon nuclei. Chemical shifts (δ) are expressed in ppm relative to internal tetramethylsilane. MS spectrum was recorded on a Finningan MAT 95 spectrometer at 70 eV. Compounds (**1**), (**2a**), (**4a-b**) and (**4d**) were prepared as previously described.[13,14] The 2-aminophenyl ketone hydrazones have not yet reported such as: 2-amino-4,5-dimethoxyacetophenone hydrazone (**2b**): mp 132-134 °C (EtOH); yield 50%. IR (KBr): 3445, 3390, 3315, 1619, 1595, 1515 (cm^{-1}). ^1H NMR (DMSO-d_6): δ 2.02 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 6.05 (br s, 2H, 2-NH_2), 6.28 (s, 3H, ArH and NH_2), 6.80 (s, 1H, ArH). *Anal.* Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.22; N, 20.08. Found: 57.21; H, 7.58; N, 19.83; 2-amino-4′-methylbenzophenone hydrazone (**4c**): mp 110-112 °C (EtOH); yield 47%. IR (KBr): 3460, 3355, 3335, 1605, 1575, 1448, 1445 (cm^{-1}). ^1H NMR (DMSO-d_6): δ 2.26 (s, 3H, CH_3), 4.66 (s, 2H, 2-NH_2), 6.16 (s, 2H, NH_2), 6.67 (t, J = 6.98 Hz, 1H, Ph), 6.77-6.84 (m, 2H, Ph), 7.08 (d, J = 8.19 Hz, 2H, 4′-MePh), 7.14-7.17 (m, 1H, Ph), 7.25 (d, J = 8.19 Hz, 2H, 4′-MePh).* *Anal.* Calcd for $C_{14}H_{15}N_3$: C, 74.28; H, 6.68; N, 18.56. Found: C, 73.96; H, 6.32; N, 18.45; 2-amino-5-chloro-2′-fluorobenzophenone hydrazone (**4e**): mp 132-135 °C (EtOH); yield 35%. IR (KBr): 3425, 3375, 3320, 1615, 1580, 1448, 1450 (cm^{-1}). ^1H NMR (DMSO-d_6): δ 5.05 (s, 2H, 2-NH_2), 6.61 (s, 2H, NH_2), 6.75 (d, J = 1.95 Hz, 1H, 6-H, 5-ClPh), 6.82 (d, J = 8.79 Hz, 1H, 3-H, 5-ClPh), 7.08-7.18 (m, 3H, 5-ClPh and 2′-FPh), 7.29-7.33 (m, 1H, 2′-FPh), 7.41 (t, J = 7.82 Hz, 1H, 2′-FPh). *Anal.* Calcd for $C_{13}H_{11}ClFN_3$: C, 59.21; H, 4.20; N, 15.93. Found: C, 58.92; H, 4.46; N, 16.21; were obtained in a similar manner according to the procedure described in ref.[14]

Preparation of 7-R^2-8-R^1-5-methylidene-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolines (**3a-b**). To a solution of 2-chloro-4,5-dihydroimidazole (**1**) (2.5 g, 24 mmol) in CH_2Cl_2 (30 mL) the appropriate 2-aminoacetophenone hydrazone (**2a-b**) (24 mmol) was added and the reaction mixture was stirred at rt for 12 h. The solid that precipitated was filtered off, washed with CH_2Cl_2 (20 mL) dried and dissolved in water (1:10). The resulting solution was made alkaline with 10% aqueous NaOH solution (pH 10). The crude product that precipitated was filtered off, washed with water, dried and recrystallized from suitable solvent. The following compounds were obtained according to the above procedure.

5-Methylidene-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (**3a**): mp 194-197 °C (toluene) (ref.,[10] mp 194-197 °C); yield 25%.

7,8-Dimethoxy-5-methylidene-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (**3b**): mp 185-189 °C (dioxane) (ref.,[10] mp 185-189 °C); yield 30%.

2-Amino-5-chlorobenzophenone *N*-imidazolidin-2-ylidenehydrazone (**5a**). To a solution of **1** (2.5 g, 24 mmol) in CH_2Cl_2 (30 mL) 2-amino-5-chlorobenzophenone hydrazone (**4a**) (6.07 g, 24 mmol) was added and the resulting mixture was stirred at rt for 12 h. The solid that precipitated was filtered off,

washed with CH_2Cl_2 and suspended in anhydrous methanol (15 mL). The resulting suspension was made alkaline with 5% methanolic NaOH (15 mL, pH 10), and then the solvent was evaporated under reduced pressure. The solid residue was treated with water (20 mL) and the insoluble product was collected by filtration and purified by crystallization from EtOH to give **5a** (2.0 g, 41%), mp 195-198 °C. IR (KBr): 3415, 3345, 3140, 1625, 1595, 1505, 1485 (cm^{-1}). ^{1}H NMR (DMSO-d_6): δ 3.36-3.38 (m, 2H, CH_2), 3.43-3.46 (m, 2H, CH_2), 4.66 (s, 2H, 2-NH_2), 6.71 (d, $J_{6,4}$ = 2.44 Hz, 1H, 6-H, 5-ClPh), 6.76 (d, $J_{3,4}$ = 8.70 Hz, 1H, 3-H, 5-ClPh), 6.80 (s, 1H, NH), 7.01 (s, 1H, NH), 7.07 (dd, $J_{4,6}$ = 2.44 Hz, $J_{4,3}$ = 8.70 Hz, 1H, 4-H, 5-ClPh), 7.22-7.29 (m, 3H, Ph), 7.52 (d, J = 7.33 Hz, 2H, Ph). ^{13}C NMR (DMSO-d_6): δ 41.95, 42.56 (C-4, C-5 imidaz.), 117.28, 119.49, 126.01, 127.05 (two overlapping signals), 127.71, 127.93, 128.13 (two overlapping signals), 128.82, 139.36, 145.49 (12 C aromat.), 148.3 (C=N), 166.21 (C-2 imidaz.).* *Anal.* Calcd for $C_{16}H_{16}ClN_5$: C, 60.09; H, 5.04; N, 21.90. Found: C, 60.32; H, 4.96; N, 21.72.

Preparation of 2-amino-5-R^1-2′- or 4′-R^2-benzophenone *N*-imidazolidin-2-ylidenehydrazones (**5b-e**). To a solution of **1** (2.5 g, 24 mmol) in CH_2Cl_2 (30 mL) the appropriate hydrazone (**4b-e**) (24 mmol) was added and the reaction suspension was stirred at rt for 12 h. Then the suspension was extracted with water (50 mL) and the aqueous layer was made alkaline with 10% aqueous NaOH solution (pH 10). The precipitate thus obtained was separated by suction, dried and recrystallized from suitable solvent.

The following compounds were obtained according to the above procedure.

2-Aminobenzophenone *N*-imidazolidin-2-ylidenehydrazone (**5b**): mp 187-190 °C (MeCN); yield 30%. IR (KBr): 3430, 3375, 3335, 1635, 1595, 1495, 1485 (cm^{-1}). ^{1}H NMR (DMSO-d_6): δ 3.39-3.47 (m, 4H, 2xCH_2), 4.55 (br s, 2H, 2-NH_2), 6.55-6.63 (m, 1H, ArH), 6.72-6.76 (m, 3H, ArH and 2xNH), 6.96-7.09 (m, 2H, ArH), 7.22-7.26 (m, 3H, Ph), 7.50-7.55 (m, 2H, Ph).* *Anal.* Calcd for $C_{16}H_{17}N_5$: C, 68.79; H, 6.13; N, 25.07. Found: C, 68.63; H, 6.16; N, 25.33.

2-Amino-4′-methylbenzophenone *N*-imidazolidin-2-ylidenehydrazone (**5c**): mp 197-199 °C (EtOH); yield 40%. IR (KBr): 3415, 3280, 3120, 1645, 1605, 1570, 1490 (cm^{-1}). ^{1}H NMR (DMSO-d_6): δ 2.27 (s, 3H, CH_3), 3.39-3.42 (m, 4H, 2xCH_2), 4.53 (br s, 2H, 2-NH_2), 6.53-6.60 (m, 1H, ArH), 6.67-6.74 (m, 3H, ArH), 6.90 (s, 1H, NH), 6.99-7.03 (m, 3H, 4′-MePh and NH), 7.41 (d, J = 8.06 Hz, 2H, 4′-MePh).* *Anal.* Calcd for $C_{17}H_{19}N_5$: C, 69.60; H, 6.53; N, 23.87. Found: C, 69.42; H, 6.32; N, 24.22.

2-Amino-4′-methoxybenzophenone *N*-imidazolidin-2-ylidenehydrazone (**5d**); mp 201-203 °C (EtOH); yield 35%. IR (KBr): 3455, 3360, 3145, 1615, 1565, 1545, 1505 (cm^{-1}). ^{1}H NMR (DMSO-d_6): δ 3.36-3.42 (m, 4H, 2xCH_2), 3.73 (s, 3H, OCH_3), 4.53 (br s, 2H, 2-NH_2), 6.53-6.61 (m, 2H, ArH), 6.71-6.89 (m, 5H, 4′-MeOPh, ArH and 2xNH), 6.99-7.06 (m, 1H, ArH), 7.45 (d, J = 8.79 Hz, 2H, 4′-MeOPh).* ^{13}C NMR (DMSO-d_6): δ 41.93, 42.54 (C-4, C-5 imidaz.), 55.35 (OCH_3), 113.41 (two overlapping signals), 116.02, 116.29, 124.67, 128.23, 128.64 (two overlapping signals), 129.65, 132.80,

146.46, 150.22 (14 C aromat.), 159.21 (C=N), 165.67 (C-2 imidaz.).* *Anal.* Calcd for $C_{17}H_{19}N_5O$: C, 66.0; H, 6.19; N, 22.64. Found: C, 65.67; H, 5.82, N, 22.73.

2-Amino-5-chloro-2′-fluorobenzophenone *N*-imidazolidin-2-ylidenehydrazone (**5e**): mp 200-204 °C (decomp.) (isopropanol); yield 15%. IR (KBr): 3455, 3420, 3285, 3130, 1625, 1600, 1545, 1485 (cm^{-1}). ^{1}H NMR (DMSO-d_6): δ 3.37-3.39 (m, 2H, CH_2), 3.42-3.43 (m, 2H, CH_2). 5.01 (s, 2H, 2-NH_2), 6.62 (d, $J_{6,4}$ = 2.44 Hz, 6-H, 5-ClPh), 6.73 (d, $J_{3,4}$ = 8.30 Hz, 3-H, 5-ClPh), 6.87 (s, 2H, 2xNH), 7.02 (dd, $J_{4,6}$ = 2.44 Hz, $J_{4,3}$ = 8.30 Hz, 4-H, 5-ClPh), 7.05-7.09 (m, 1H, 2′-FPh), 7.17 (t, J = 7.55 Hz, 1H, 2′-FPh), 7.30-7.35 (m, 1H, 2′-FPh), 7.61-7.64 (m, 1H, 2′-FPh). *Anal.* Calcd for $C_{16}H_{15}ClFN_5$: C, 57.92; H, 4.56; N, 21.11. Found: C, 57.53; H, 4.17; N, 20.92.

Preparation of 2-R^1-12*a*-(4′-R^2-phenyl)-5,10,11,12*a*-tetrahydro-6*H*,9*H*-imidazo[2′,1′:3,4][1,2,4]triazolo[1,5-*c*]quinazoline-6-thiones (6a-d). To a suspension of the appropriate *N*-imidazolidin-2-ylidenehydrazone (**5a-d**) (2 mmol) in anhydrous acetone (15 mL) and carbon disulfide (1.34 g, 1.06 mL, 17.6 mmol) was added dropwise triethylamine (0.2 g, 0.28 mL, 2 mmol). The resulting mixture was stirred at rt for 48-72 h (until H_2S had ceased). Then, the solvent and excess of carbon disulfide were evaporated under reduce pressure, and the precipitate thus obtained was mixed with water (30 mL), filtered off, dried and purified by crystallization from the suitable solvent.

The following compounds were obtained according to the above procedure.

2-Chloro-12*a*-phenyl-5,10,11,12*a*-tetrahydro-6*H*,9*H*-imidazo[2′,1′:3,4][1,2,4]triazolo[1,5-*c*]quinazoline-6-thione (**6a**): mp 234-235 °C (decomp.) (EtOH); yield 44%. IR (KBr): 3225, 1665, 1545, 1485, 1460, 1295 (cm^{-1}). ^{1}H NMR (DMSO-d_6): δ 2.62-2.68 (m, 1H, CH_2), 3.67-3.76 (m, 2H, CH_2), 3.89-3.92 (m, 1H, CH_2), 7.08-7.09 (m, 3H, ArH), 7.36-7.43 (m, 4H, ArH), 7.51 (s, 1H, NH), 7.75 (s, 1H, ArH), 10.54 (s, 1H, NHCS). MS (70 eV) m/z: 355.1 (M^+). *Anal.* Calcd for $C_{17}H_{14}ClN_5S$: C, 57.38; H, 3.96; N, 19.68. Found: C, 57.02; H, 3.61; N, 19.34.

12*a*-Phenyl-5,10,11,12*a*-tetrahydro-6*H*,9*H*-imidazo[2′,1′:3,4][1,2,4]triazolo[1,5-*c*]quinazoline-6-thione (**6b**): mp 236-237 °C (decomp.) (DMF/MeOH); yield 53%. IR (KBr): 3180, 1660, 1555, 1485, 1465, 1245 (cm^{-1}). ^{1}H NMR (DMSO-d_6): δ 2.70-2.75 (m, 1H, CH_2), 3.70-3.76 (m, 2H, CH_2), 3.81-3.84 (m, 1H, CH_2), 7.07-7.08 (m, 3H, ArH), 7.19 (t, J = 7.33 Hz, 1H, ArH), 7.32-7.40 (m, 4H, ArH), 7.55 (s, 1H, NH), 7.71 (d, J = 7.81 Hz, 1H, ArH), 10.41 (s, 1H, NHCS). ^{13}C NMR (DMSO-d_6): δ 45.04, 47.63 (C-4, C-5 imidaz.), 84.14 (C-12*a*), 114.78, 122.53, 123.19, 125.10, 127.01 (two overlapping signals), 129.46 (two overlapping signals), 129.81 (two overlapping signals), 135.01, 135.30 (12 C aromat.), 164.03 (C=N), 165.42 (C=S). *Anal.* Calcd for $C_{17}H_{15}N_5S$: C, 63.53; H, 4.70, N, 21.79. Found: C, 63.14; H, 4.41; N, 21.87.

12*a*-(4′-Methylphenyl)-5,10,11,12*a*-tetrahydro-6*H*,9*H*-imidazo[2′,1′:3,4][1,2,4]triazolo[1,5-*c*]quinazoline-6-thione (**6c**): mp 259-260 °C (decomp.) (DMF/MeOH); yield 58%. IR (KBr): 3215, 1665, 1550, 1485, 1465, 1245 (cm^{-1}). ^1H NMR (DMSO-d_6): δ 2.24 (s, 3H, CH_3), 2.61-2.81 (m, 1H, CH_2), 3.68-3.74 (m, 3H, CH_2), 6.92-6.96 (m, 2H, ArH), 7.04-7.16 (m, 4H, ArH), 7.29-7.32 (m, 1H, ArH), 7.49 (s, 1H, NH), 7.65-7.69 (m, 1H, ArH), 10.37 (s, 1H, NHCS).* *Anal*. Calcd for $C_{18}H_{17}N_5S$: C, 64.45; H, 5.11; N, 20.88. Found: C, 64.12; H, 4.89; N, 20.73.

12*a*-(4′-Methoxyphenyl)-5,10,11,12*a*-tetrahydro-6*H*,9*H*-imidazo[2′,1′:3,4][1,2,4]triazolo[1,5-*c*]quinazoline-6-thione (**6d**): mp 240-241 °C (decomp.) (DMF/MeOH); yield 57%. IR (KBr): 3185, 1660, 1545, 1485, 1465, 1255 (cm^{-1}). ^1H NMR (DMSO-d_6): δ 2.73-2.87 (m, 1H, CH_2), 3.51-3.88 (m, 6H, OCH_3 and CH_2), 6.79-6.98 (m, 4H, ArH), 7.05-7.32 (m, 3H, ArH), 7.53 (s, 1H, NH), 7.63-7.66 (m, 1H, ArH), 10.37 (s, 1H, NHCS).* *Anal*. Calcd for $C_{18}H_{17}N_5OS$: C, 61.52; H, 4.87; N, 19.93. Found: C, 61.15; H, 4.51; N, 19.98.

9-Acetyl-12*a*-phenyl-5,10,11,12*a*-tetrahydro-6*H*,9*H*-imidazo[2′,1′:3,4][1,2,4]triazolo[1,5-*c*]quinazoline-6-thione (7). To a mixture of **6b** (0.5 g, 15 mmol) in pyridine (5 mL), acetyl chloride (0.29 g, 0.27 mL, 3.75 mmol) was added at 0 °C. After exothermic reaction had subside (ca 10 min), the reaction suspension was stirred at rt for 12 h, and then the solvent was distilled under reduce pressure. The residue was treated with water (10 mL), and the resulting mixture was neutralized to pH 7-7.5 with 5% aqueous Na_2CO_3 solution and stirred at rt for 20 min. The product that precipitated was filtered off, dried and purified by crystallization from isopropanol to give **7** (0.23 g, 41%), mp 220-221 °C (decomp.). IR (KBr): 3245, 1700, 1635, 1525, 1480, 1320 (cm^{-1}). ^1H NMR (DMSO-d_6): δ 2.45 (s, 3H, CH_3), 2.63-2.88 (m, 1H, CH_2), 3.91-4.18 (m, 2H, CH_2), 4.21-4.25 (m, 1H, CH_2), 7.04-7.53 (m, 8H, ArH), 7.77 (d, J = 6.79 Hz, 1H, ArH), 10.81 (s, 1H, NHCS).* ^{13}C NMR (DMSO-d_6): δ 23.51 (CH_3), 41.96, 49.17 (C-4, C-5 imidaz.), 84.42 (C-12*a*), 114.67, 122.22, 123.28, 124.63, 126.53 (two overlapping signals), 129.32 (two overlapping signals), 129.76, 129.82, 134.02, 134.31 (12 C aromat.), 157.04 (C=O), 167.39 (C=N), 168.18 (C=S).* *Anal.* Calcd for $C_{19}H_{17}N_5OS$: C, 62.79; H, 4.71; N, 19.27. Found: C, 62.55; H, 4.36; N, 19.03.

X-Ray structure analyses. The diffraction data were collected with a KumaCCD diffractometer using graphite monochromated Mo K_α radiation. The intensity data were collected and processed using Oxford Diffraction CrysAlis Software.[15] The crystal structures were solved by direct methods with the program SHELXS-97[16] and refined by full-matrix least-squares method on F^2 with SHELXL-97.[17]

X-Ray structure analysis of 5a. Crystal data for $(C_{16}H_{16}ClN_5)_2 \cdot C_2H_5OH$ obtained by slow evaporation from absolute ethanol: monoclinic, space group C2/c, a = 27.5085(13), b = 12.9559(8), c = 20.5767(11) Å, β = 111.967(5)°, V = 6801.1(7) $Å^3$, Z = 4, d_x = 1.316 $g.cm^{-3}$, μ(Mo K_α) = 0.235 mm^{-1}, T =130K. 21468

data were collected up to $2\theta_{max} = 50°$ for a crystal with dimensions 0.6x0.6x0.5 mm^3 ($R_{int} = 0.0161$, $R_\sigma = 0.0232$). Final R indices for 5228 reflections with $I>2\sigma(I)$ and 427 refined parameters are: $R_1 = 0.0412$, $wR_2 = 0.1129$ ($R_1 = 0.0571$, $wR_2 = 0.1234$ for all 6896).[18]

X-Ray structure analysis of 6a. Crystal data for $C_{17}H_{14}ClN_5S\cdot[(CH_3)_2CO]_2$ obtained by slow evaporation from anhydrous acetone: monoclinic, space group $P2_1/n$, a = 14.9077(13), b = 8.9829(10), c = 18.8199(11) Å, $\beta = 102.118(6)°$, $V = 2464.1(4)$ $Å^3$, $Z = 4$, $d_x = 1.272$ $g.cm^{-3}$, μ(Mo K_α) = 0.268 mm^{-1}, T = 130K. 13898 data were collected up to $2\theta_{max} = 50°$ for a crystal with dimensions 0.6x0.6x0.3 mm^3 ($R_{int} = 0.0174$, $R_\sigma = 0.0204$). Final R indices for 3465 reflections with $I>2\sigma(I)$ and 298 refined parameters are: $R_1 = 0.0448$, $wR_2 = 0.1131$ ($R_1 = 0.0572$, $wR_2 = 0.1214$ for all 4330 data).[18]

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