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SYNTHESIS, STRUCTURE AND TRANSFORMATIONS OF 2-IMINOIMIDAZOLIDINES INTO NOVEL FUSED HETEROCYCLIC RING SYSTEMS

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Abstract – Reaction of 2-chloro-4,5-dihydroimidazole (**1**) with 2-aminobenzylamines (**2a-d**) afforded 2-[(imidazolidin-2-ylideneamino)methyl]-anilines (**3a-d**) which upon treatment with carbon disulfide gave 2,3-dihydro-12*H*-imidazo[2',1':4,5][1,3,5]thiadiazino[2,3-*b*]quinazolin-5-thiones (**4a-d**) and 3,4-dihydro-1*H*-quinazolin-2-thiones (**5a-c**). Analogous reaction of **1** with 2-aminobenzyl alcohol (**6**) led to the formation of [2-(4,5-dihydro-1*H*-imidazol-2-ylamino)phenyl]methanol hydrochloride (**7**) which was transformed into 1-(4*H*-3,1-benzoxazin-2-yl)imidazolidin-2-thione (**8**).

INTRODUCTION

Various fused heterocyclic ring systems containing 2-imidazoline moiety have been shown in Figure 1, which act as I_2 receptors ligands (structure **A**[1]), appetite depressants and cocaine abuse therapeutics (structure **B**[2]), blockers of K_{ATP}-dependant channels (structure **C**[3]) as well as potential anticancer agents (structure **D**[4]).

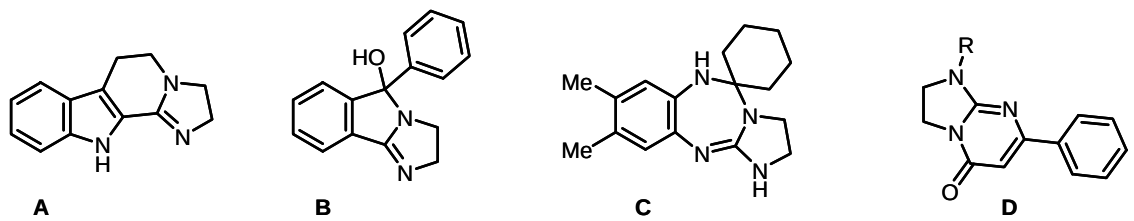


Figure 1

In our recent review article[5] we have shown that 2-chloro-4,5-dihydroimidazole (**1**) is a versatile substrate

for the synthesis of novel fused heterocyclic ring systems incorporating 2-imidazoline moiety. Now, as a part of our ongoing research program[6] we have explored the reactions of **1** with anilines bearing aminomethyl or hydroxymethyl group at position 2.

RESULTS AND DISCUSSION

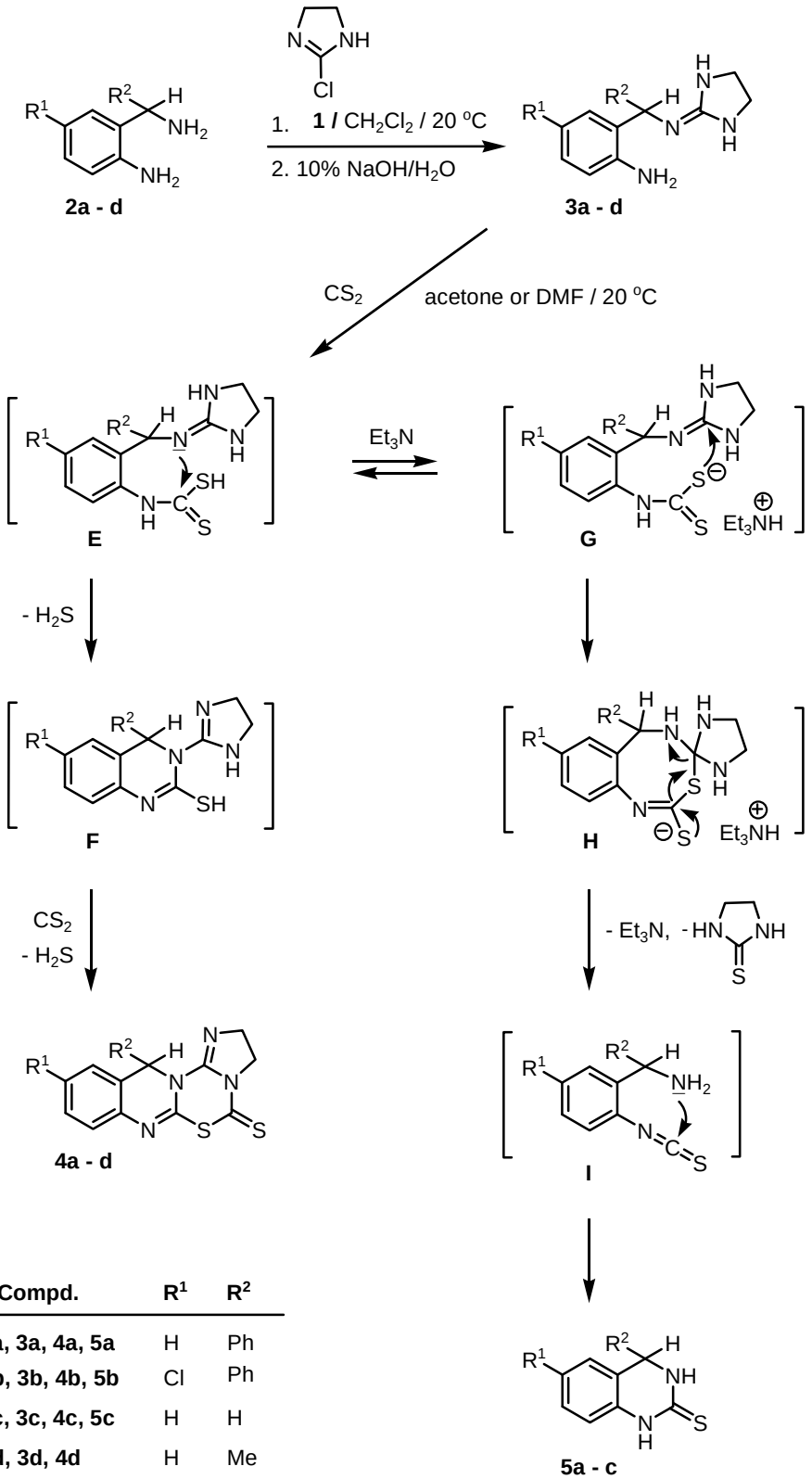
Preparation of 2-(2-aminophenylimino)imidazolidines can be achieved by *N*-heteroalkylation reaction of *o*-phenylenediamines with 2-chloro-4,5-dihydroimidazole (**1**).[7] We found, however, that when 2-aminobenzylamines (**2a-d**) were treated with compound (**1**) in dichloromethane at ambient temperature, the *N*-heteroalkylation reaction of aliphatic amine group took place leading to 2-[(imidazolidin-2-ylideneamino)methyl]anilines **(3a-d)** as shown in Scheme 1. The preferential susceptibility of the aliphatic amine group to the electrophilic attack of **1** was confirmed by X-Ray diffraction analysis of **3a** (Figure 2).

Compounds **(3a-d**) were further subjected to the reaction with carbon disulfide as depicted in Scheme 1. Thus, the treatment of **3a-c** with an excess of carbon disulfide in anhydrous acetone at ambient temperature, in the presence of triethylamine gave rise to the formation of a mixture of 2,3-dihydro-12*H*-imidazo[2',1':4,5][1,3,5]thiadiazino[2,3-*b*]quinazolin-5-thiones (**4a-c**) and 3,4-dihydro-1*H*-quinazolin-2-thiones (**5a-c**) which could be separated owing to a considerable difference in their solubility in hot methanol. However, when compound (**3d**) was used as a substrate, the reaction carried out in DMF solution gave the product (**4d**) as the sole product which could be isolated from the reaction mixture (Scheme 1). Although the expected 4-methyl-3,4-dihydro-1*H*-quinazolin-2-thione[8] was not separated but traces of this compound were detected by means of NMR spectrum of crude product.

The mechanism of the reaction pathway was not investigated but it can be explained as follows. First, initially formed dithiocarbamic acid (**E**) resulting from the addition of the 2-iminoimidazolidine (**3**) to carbon disulfide undergoes a cyclocondensation with evolution of H_2S giving rise to the formation of dihydroquinazoline derivative (**F**), which in turn, reacts with a second molecule of carbon disulfide to afford the corresponding imidazo[2',1':4,5][1,3,5]thiadiazino[2,3-*b*]quinazolin-5-thione (**4**)**.** Alternatively, in the presence of Et_3N, the adduct (**E**) may form triethylammonium dithiocarbamate (**G**), which undergoes intramolecular ring closure to give the intermediate (**H**), which then decomposes with simultaneous loss of imidazolidine-2-thione leading to isothiocyanate (**I**). An intramolecular nucleophilic attack of the nitrogen atom of the amine group at the isothiocyanate group in **I** gives the final product (**5**). Although imidazolidine-2-thione was not separated from the reaction mixture, this side product was identified by NMR evidence in ca 5% yield.

It should be mentioned that compounds (**5a-c**) were previously obtained by Spindler and Kempter,[8] and Liu[9] by the reaction of **2** with carbon disulfide. On the other hand, the imidazo[2',1':4,5][1,3,5]thiadiazino-

[2,3-*b*]quinazolin-5-thione ring system like as the compound (**4**) has not been described previously in chemical literature.



Compd.	R^1	R^2
2a, 3a, 4a, 5a	H	Ph
2b, 3b, 4b, 5b	Cl	Ph
2c, 3c, 4c, 5c	H	H
2d, 3d, 4d	H	Me

Scheme 1

The structures of newly prepared compounds were confirmed by elemental analysis, IR and NMR spectroscopic data, MS spectrometry as well as X-Ray structure analysis of **4b** (Figure 3).

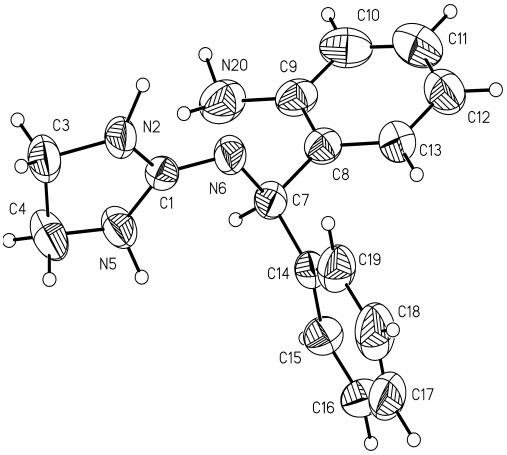


Figure 2. ORTEP drawing of **3a** with atom labelling. Displacement ellipsoids were drawn at 40% probability level.

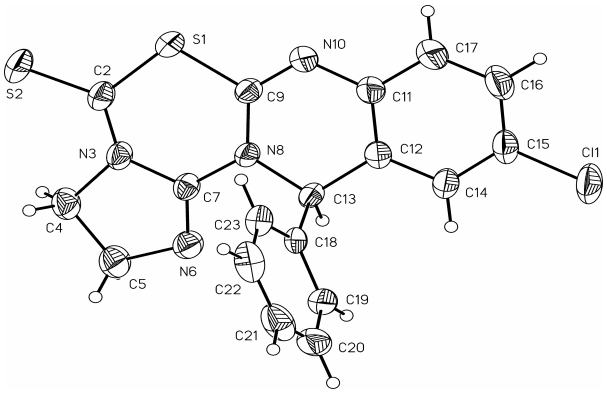
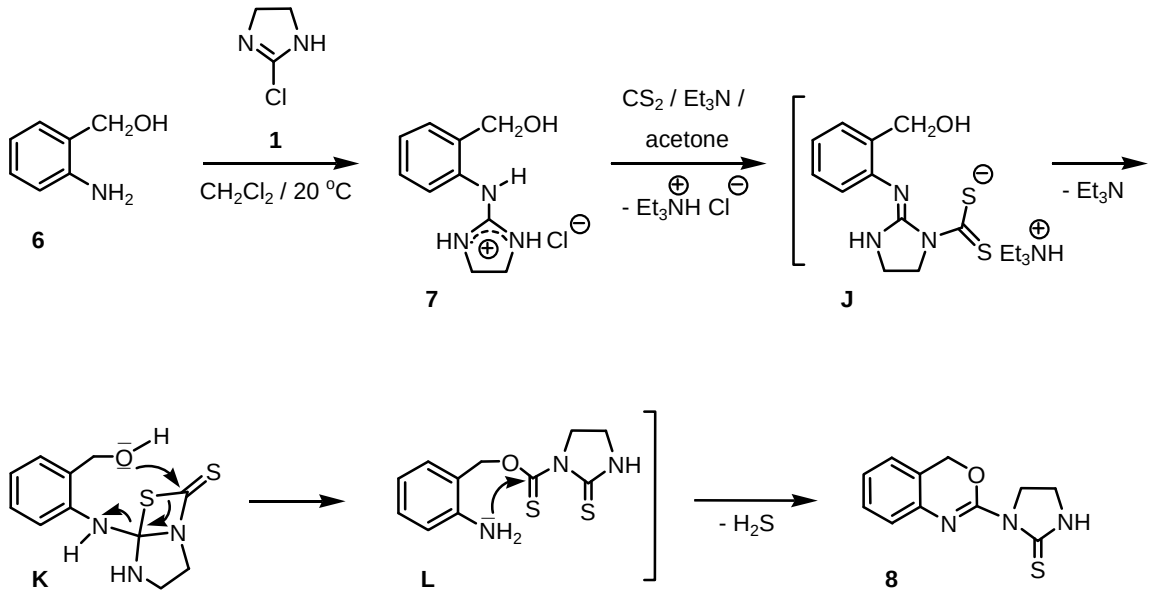


Figure 3. ORTEP drawing of **4b** with atom labeling. Displacement ellipsoids were drawn at 50% probability level.

As depicted in Scheme 2, the reaction of 2-chloro-4,5-dihydroimidazole (**1**) with 2-aminobenzyl alcohol (**6**) took a different course and [2-(4,5-dihydro-1*H*-imidazol-2-ylamino)phenyl]methanol hydrochloride (**7**) was obtained in 50% yield as a result of *N*-heteroalkylation of the aromatic amino group. Then, upon treatment of **7** with an excess carbon disulfide in the presence of 2 fold excess of triethylamine in anhydrous acetone at ambient temperature 1-(4*H*-3,1-benzoxazin-2-yl)imidazolidin-2-thione (**8**) was obtained in 55% yield based on **7**.

A possible mechanism for this reaction is outlined in Scheme 2. We assume, that the reaction mechanism involves the initial formation of the dithiocarbamate (**J**), which undergoes an intramolecular nucleophilic addition reaction giving rise to the unstable thiazetidine (**K**). The later intermediate undergoes further

rearrangement upon nucleophilic attack of the hydroxyl group at the carbon atom of the thiazetidine ring to give thiocarbamate derivative (**L**)**.** This process is completed by an intramolecular cyclocondensation with evolution of H_2S leading to the formation of the final 3,1-benzoxazine (**8)**. Structures of the compounds (**7** and **8**) were confirmed by elemental analyses as well as IR and NMR spectroscopic data.

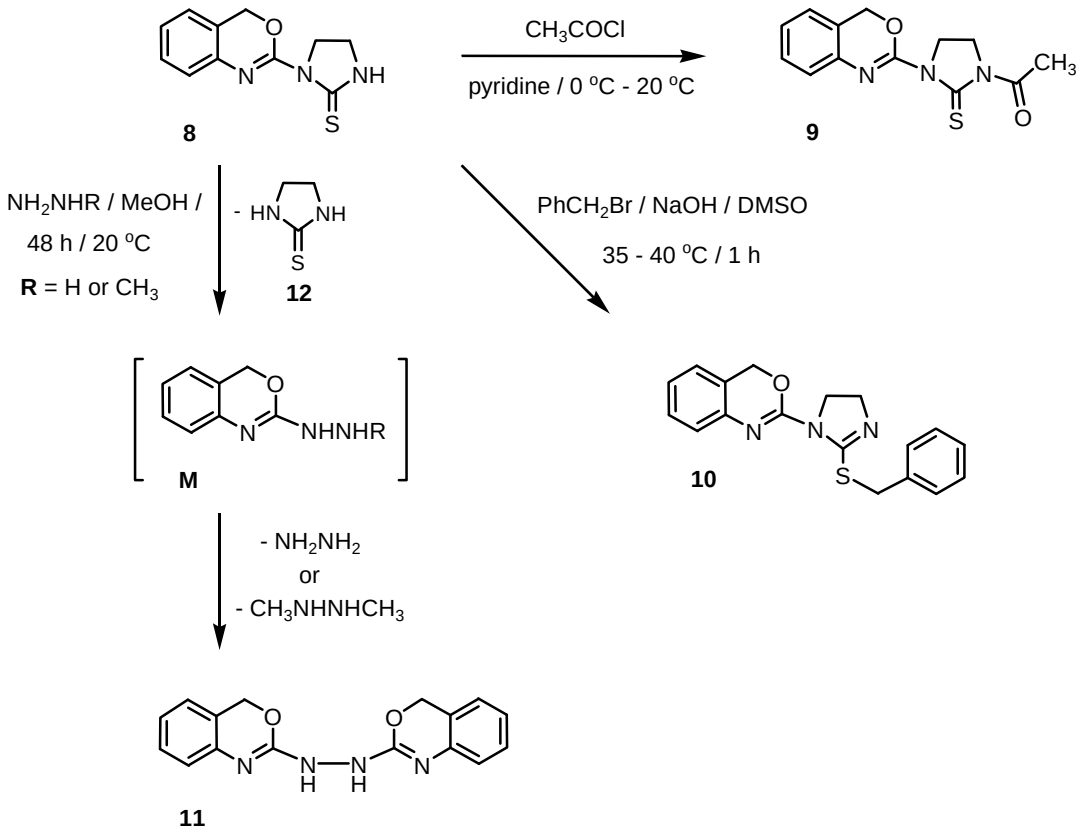


Scheme 2

It is well known that compounds containing 3,1-benzoxazine moiety may act as inhibitors of human chymase, human leukocyte elastase (HLE), human cathepsin G,[10] tissue factor/factor VIIa-induced coagulation,[11] HIV-1 reverse transcriptase[12] as well as antimycobacterial agents,[13] neuropeptide Y5 antagonists for the treatment of obesity[14] or progesterone receptors modulators.[15]

It should also be pointed out that the product obtained **8** represents a new type of 3,1-benzoxazine derivatives functionalized with 2-imidazolidinethione moiety at position 2. Therefore, to examine synthetic potential of **8**, we performed some representative reactions as shown in Scheme 3. As expected, treatment of **8** with acetyl chloride afforded corresponding amide (**9)** in 40 % yield. On the other hand, the reaction of **8** with benzyl bromide in the presence of NaOH led to the formation of the *S*-benzyl derivative (**10**) in 53% yield, structure of which was confirmed by single crystal X-Ray analysis (Figure 4). We have further found that the reaction of **8** with 2 fold excess of hydrazine hydrate or methylhydrazine, carried out in anhydrous methanol at ambient temperature gave the hydrazine derivative (**11)** in 40% and 23% yield, respectively (Scheme 3). Apparently, the nucleophilic displacement of the imidazolidin-2-thione (**12**) in **8** gives mono-substituted hydrazine (**M**), which subsequently undergoes a condensation reaction to give bi-substituted hydrazine (**11**) with simultaneous elimination of hydrazine.

In this context it should be pointed out that an analogous transformation of 2-pyridylcarboxamidrazone into 1,2-bis-(2-pyridylformidoyl)hydrazine in ethanol solution was described previously.[16] Structures of the compounds (**9-11**) were confirmed by elemental analyses, IR and NMR spectroscopic data as well as MS spectrometry (see Experimental).



Scheme 3

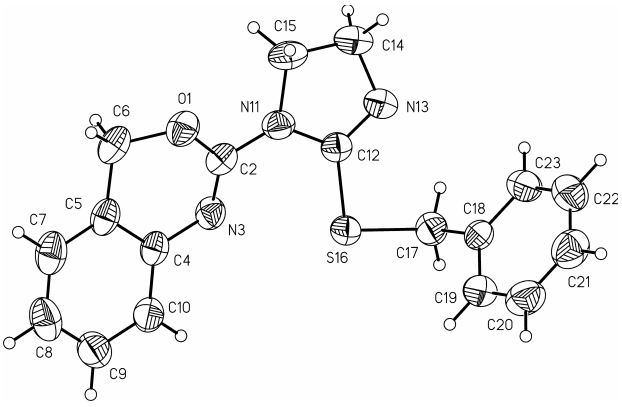


Figure 4. ORTEP drawing of **10** with atom labelling. Displacement ellipsoids were drawn at 50% probability level.

Samples of the compounds (**4b-d** and **8-9, 11**) were submitted to the US National Cancer Institute (Bethesda) for screening against human tumour cell lines. The results of biological tests will be published elsewhere.

EXPERIMENTAL

Melting points 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 were recorded on a Finningan MAT 95 spectrometer at 70 eV. The starting 2-chloro-4,5-dihydroimidazole (**1**) and 2-aminobenzylamines (**2a-b, d**) were prepared according to procedures described previously.[17-19]

Preparation of 4-R^1-2-[(imidazolidin-2-ylideneamino)phenylmethyl]anilines (3a-b). To a solution of **1** (2.5 g, 24 mmol) in CH_2Cl_2 (30 mL) the appropriate 2-aminobenzhydrylamine (**2a-b**) (16 mmol) was added and the reaction mixture was stirred at rt for 12 h. The solid that precipitated was collected by filtration, washed with CH_2Cl_2 (15 mL), dried and suspended in water (1:10). The resulting suspension 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.

2-[(Imidazolidin-2-ylideneamino)phenylmethyl]aniline (**3a**): mp 189-190 °C (acetonitrile); yield 44%. IR (KBr): 3390, 3255, 3150, 3030, 2945, 2840, 1660, 1620, 1490, 1450, 1260 (cm^{-1}). ^{1}H NMR (DMSO-d_6) δ 3.28 (br s, 4H, 2xCH_2), 5.26 (s, 2H, NH_2), 5.85 (br s, 1H, NH), 6.42-6.44 (m, 1H, ArH), 6.57-6.58 (m, 2H, ArH), 6.74 (br s, 1H, NH), 6.87-6.9 (m, 1H, ArH), 7.14-7.21 (m, 1H, ArH), 7.27-7.3 (m, 6H, 5H Ph, CH-Ph). ^{13}C NMR (DMSO-d_6) δ 46.27 (C-4, C-5 imidaz.), 57.07 (CH), 115.5, 115.98, 126.45, 127.33, 127.43, 128.10, 128.29, 128.46, 143.93, 146.71 (12 C aromat.), 160.99 (C=N)*. *Anal.* Calcd for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04. Found: C, 72.01; H, 6.53; N, 21.27.

4-Chloro-2-[(imidazolidin-2-ylideneamino)phenylmethyl]aniline (**3b**): mp 193-194 °C (acetone); yield 40%. IR (KBr): 3410, 3275, 3030, 2945, 2840, 1665, 1620, 1485, 1260 (cm^{-1}). ^{1}H NMR (DMSO-d_6) δ 3.28 (br s, 4H, 2xCH_2), 5.42 (s, 2H, NH_2), 5.74 (br s, 2H, 2xNH), 6.43-6.62 (m, 1H, ArH), 6.79-6.92 (m, 2H, ArH), 7.19-7.29 (m, 6H, 5H Ph, CH-Ph). *Anal.* Calcd for $C_{16}H_{17}N_4Cl$: C, 63.89; H, 5.70; N, 18.63. Found: C, 64.02; H, 5.52; N, 18.32.

Preparation of 2-[(imidazolidin-2-ylideneamino)alkyl]anilines (3c-d). To a solution of **1** (2.5 g, 24 mmol) in CH_2Cl_2 (30 mL) the appropriate 2-aminobenzylamine (**2c-d**) (16 mmol) was added and the reaction suspension was stirred at rt for 12 h. Then the suspension was extracted with water (45 mL) and

the aqueous layer was made alkaline with 10% aqueous NaOH solution (pH 10) and extracted with CH_2Cl_2 (50 mL). The organic layer was dried over $MgSO_4$, evaporated under vacuum and the viscous residue was treated with acetone (25 mL). The precipitate thus obtained was collected by filtration, washed with acetone, dried and purified by crystallization from acetonitrile.

The following compounds were obtained according to the above procedure.

2-[(Imidazolidin-2-ylideneamino)methyl]aniline (**3c**): mp 206-208 °C; yield 32%. IR (KBr): 3425, 3000, 3250-2750 (ν max 3130, 3055, 2930, 2824), 1675, 1625, 1495, 1300 (cm^{-1}). ^1H NMR (DMSO-d_6) δ 3.57 (s, 4H, 2xCH_2), 4.24 (s, 2H, CH_2), 5.12 (s, 2H, NH_2), 6.51-6.54 (m, 1H, ArH), 6.65-6.67 (m, 1H, ArH), 6.98-7.05 (m, 2H, ArH), 8.57 (br s, 2H, 2xNH). ^{13}C NMR (DMSO-d_6) δ 43.18, (C-4, C-5 imidaz.), 43.26 (CH_2), 115.82, 116.69, 120.46, 129.18, 129.26, 147.01 (6 C aromat.), 160.21 (C=N). *Anal.* Calcd for $C_{10}H_{14}N_4$: C, 63.13; H, 7.42; N, 29.45. Found: C, 63.42; H, 7.15; N, 29.11.

2-[1-(Imidazolidin-2-ylideneamino)ethyl]aniline (**3d**): mp 199-200 °C; yield 29%. IR (KBr): 3350, 3320, 3175, 3065, 3035, 2970, 1660, 1600, 1495, 1445, 1285 (cm^{-1}). ^1H NMR (DMSO-d_6) δ 1.36 (d, J = 6.35 Hz, 3H, CH_3), 3.55 (s, 4H, 2xCH_2), 4.25-4.89 (m, 1H, CH-CH_3), 5.0 (br s, 2H, NH_2), 6.58-6.61 (m, 1H, ArH), 6.65-6.68 (m, 1H, ArH), 6.97-6.99 (m, 1H, ArH), 7.31-7.5 (m, 1H, ArH), 8.76 (br s, 2H, 2xNH). *Anal.* Calcd for $C_{11}H_{16}N_4$: C, 64.68; H, 7.89; N, 27.43. Found: C, 64.43; H, 8.12; N, 27.27.

Preparation of 10-R^1-12-R^2-2,3-dihydro-12*H*-imidazo[2',1':4,5][1,3,5]thiadiazino[2,3-*b*]quinazolin-5-thiones (4a-c) and 6-R^1-4-R^2-3,4-dihydro-1*H*-quinazolin-2-thiones (5a-c). To a mixture of the appropriate 2-[(imidazolidin-2-ylideneamino)methyl]aniline (**3a-c)** (2.2 mmol) in anhydrous acetone (10 mL) and carbon disulfide (1.45 g, 1.15 mL, 19 mmol) was added dropwise Et_3N (0.22 g, 0.3 mL, 2.2 mmol). The resulting suspension 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 residue was triturated with water (20 mL). The precipitate thus obtained was filtered off, washed with water, dried and treated with hot methanol (1:25). The insoluble solid was separated by suction (the filtrate denoted as **"T"** was stored for further workup), washed with hot methanol (3x3 mL) and dried.

The following compounds were obtained according to the above procedure.

12-Phenyl-2,3-dihydro-12*H*-imidazo[2',1':4,5][1,3,5]thiadiazino[2,3-*b*]quinazolin-5-thione (**4a**): mp 259-262 °C; yield 30%. IR (KBr): 3070, 3030, 3015, 2925, 1645, 1605, 1585, 1560, 1420, 1370 (cm^{-1}). ^1H NMR (DMSO-d_6) δ 3.75-3.8 (m, 2H, CH_2), 4.15-4.2 (m, 1H, CH_2), 4.27-4.33 (m, 1H, CH_2), 6.7 (s, 1H, CH-Ph), 7.15-7.16 (m, 2H, ArH), 7.24-7.29 (m, 3H, ArH), 7.31-7.36 (m, 5H, Ph). *Anal.* Calcd for $C_{18}H_{14}N_4S_2$: C, 61.69; H, 4.02; N, 15.98. Found: C, 61.73; H, 3.92; N, 15.74.

10-Chloro-12-phenyl-2,3-dihydro-12*H*-imidazo[2',1':4,5][1,3,5]thiadiazino[2,3-*b*]quinazolin-5-thione (**4b**): mp 231-234 °C; yield 25%. IR (KBr): 3065, 3030, 2945, 2880, 1645, 1605, 1580, 1560, 1420, 1385 (cm^{-1}). ^1H NMR (DMSO-d_6) δ 3.77-3.83 (m, 2H, CH_2), 4.14-4.2 (m, 1H, CH_2), 4.27-4.32 (m, 1H, CH_2),

6.73 (s, 1H, CH-Ph), 7.17 (d, *J* = 8.79 Hz, 1H, ArH), 7.26-7.31 (m, 2H, ArH), 7.33-7.38 (m, 4H, ArH), 7.44-7.47 (m, 1H, ArH). ^{13}C NMR (DMSO-d_6) δ 49.8, 53.55 (C-4, C-5 imidaz.), 59.43 (CH), 126.8 (two overlapping signals), 127.03, 127.31, 127.92, 129.09, 129.54, 129.76, 131.35 (two overlapping signals), 137.28, 142.35 (12 C aromat.), 145.56 (C=N), 147.11 (C=N), 180.64 (C=S). MS (70 eV) m/z: 383.9 (M^+). *Anal*. Calcd for $C_{18}H_{13}N_4ClS_2$: C, 56.17; H, 3.40; N, 14.41. Found: C, 56.21; H, 3.27; N, 14.11

2,3-Dihydro-12*H*-imidazo[2',1':4,5][1,3,5]thiadiazino[2,3-*b*]quinazolin-5-thione (**4c**): mp 202-204 °C; yield 30%. IR (KBr): 3030, 2960, 2925, 2870, 1650, 1610, 1575, 1435, 1390 (cm^{-1}). ^{1}H NMR (DMSO-d_6) δ 3.75-3.95 (m, 2H, CH_2), 4.20-4.38 (m, 2H, CH_2), 5.01 (s, 2H, CH_2), 6.93-7.09 (m, 1H, ArH), 7.1-7.28 (m, 3H, ArH). *Anal.* Calcd for $C_{12}H_{10}N_4S_2$: C, 52.53; H, 3.67; N, 20.42. Found: C, 52.67; H, 3.34; N, 20.13.

The filtrate denoted as "**T**" was cooled to 0 °C and the precipitate thus obtained was separated by suction, washed with methanol (2 mL), dried and purified by crystallization from suitable solvent.

The following compounds were obtained according above procedure.

4-Phenyl-3,4-dihydro-1*H*-quinazolin-2-thione (**5a**): mp 228-230 °C (ethanol) (ref.,[8] mp 230 °C); yield 30%. IR (KBr): 3225, 3065, 3025, 1565, 1490 (cm^{-1}). ^{1}H NMR (DMSO-d_6) δ 5.64 (d, *J* = 2.65 Hz, 1H, CH-Ph), 6.95-7.06 (m, 2H, ArH), 7.18-7.25 (m, 2H, ArH), 7.28-7.42 (m, 5H, Ph), 9.25 (s, 1H, NH), 10.71 (s, 1H, NH)*. *Anal.* Calcd for $C_{14}H_{12}N_2S_2$: C, 69.97; H, 5.03; N, 11.65. Found: C, 69.64; H, 5.32; N, 11.42.

6-Chloro-4-phenyl-3,4-dihydro-1*H*-quinazolin-2-thione (**5b**): mp 221-224 °C (propan-1-ol), (ref.,[8] mp 223-226 °C); yield 43%. IR (KBr): 3210, 3110, 2980, 1570, 1510, 1485 (cm^{-1}). ^{1}H NMR (DMSO-d_6) δ 5.62 (d, *J* = 2.44 Hz, 1H, CH-Ph), 7.01 (d, *J* = 8.30 Hz, 1H, ArH), 7.24-7.28 (m, 5H, Ph), 7.35-7.38 (m, 2H, ArH), 9.31 (s, 1H, NH), 10.79 (s, 1H, NH). *Anal.* Calcd for $C_{14}H_{11}N_2ClS$: C, 61.20; H, 4.03; N, 11.30. Found: C, 61.47; H, 4.32; N, 11.23.

3,4-Dihydro-1*H*-quinazolin-2-thione (**5c**): mp 212-214 °C (ethanol) (ref.,[9] mp 211-212 °C); yield 37%. IR (KBr): 3195, 3135, 2990, 1590, 1225 (cm^{-1}). ^{1}H NMR (DMSO-d_6) δ 4.33 (s, 2H, CH_2), 6.9-6.95 (m, 2H, ArH), 7.06-7.07 (m, 1H, ArH), 7.12-7.15 (m, 1H, ArH), 8.58 (s, 1H, NH), 10.35 (s, 1H, NH). *Anal*. Calcd for $C_8H_8N_2S$: C, 53.33; H, 4.47; N, 15.54. Found: C, 53.58; H, 4.21; N, 15.30.

12-Methyl-2,3-dihydro-12*H*-imidazo[2',1':4,5][1,3,5]thiadiazino[2,3-*b*]quinazolin-5-thione (4d). To a suspension of **3d** (0.44 g, 2.2 mmol) in DMF (10 mL) and carbon disulfide (1.45 g, 1.15 mL, 19 mmol) was added dropwise Et_3N (0.22 g, 0.3 mL, 2.2 mmol). The resulting solution was stirred at rt for 48 h (until H_2S had ceased). Then, the corresponding **4d** was obtained according to the procedure described above for **4a-c**. Yield: 0.2 g (31%), mp 183-186 °C. IR (KBr): 3065, 2925, 2875, 1645, 1605, 1585, 1560, 1425, 1380 (cm^{-1}). ^{1}H NMR (DMSO-d_6) δ 1.39 (d, *J* = 4.62 Hz, 3H, CH_3), 3.8-3.95 (m, 2H, CH_2), 4.17-4.38 (m, 2H, CH_2), 5.68 (q, 1H, CH-CH_3), 7.05-7.24 (m, 4H, ArH)*. *Anal.* Calcd for $C_{13}H_{12}N_4S_2$: C,

54.14; H, 4.19; N, 19.43. Found: C, 54.76; H, 3.91; N, 19.27.

[2-(4,5-Dihydro-1*H*-imidazol-2-ylamino)phenyl]methanol hydrochloride (7). 2-Aminobenzyl alcohol (**6**) (1.5 g, 12.3 mmol) was added to a solution of **1** (1.25 g, 12.3 mmol) in CH_2Cl_2 (30 mL) and the reaction mixture was stirred at rt for 12 h. The precipitated solid was filtered off, washed with CH_2Cl_2 (20 mL), dried and purified by crystallization from acetonitrile to give **7** (1.4 g, 50%), mp 165-166 °C. IR (KBr): 3400-2550 (ν max 3275, 3190, 3010, 2975, 2925, 2885), 1655, 1600 (cm^{-1}). ^{1}H NMR (DMSO-d_6) δ 3.63 (s, 4H, 2xCH_2), 4.53 (s, 2H, CH_2), 5.48 (br s, 1H, OH), 7.25-7.31 (m, 1H, ArH), 7.33-7.42 (m, 2H, ArH), 7.52-7.58 (m, 1H, ArH), 8.2 (br s, 2H, 2x$NH^{\oplus}$), 10.45 (br s, 1H, $NH^{\oplus}$)*. *Anal*. Calcd for $C_{10}H_{13}N_3OCl$: C, 52.78 ; H, 5.76; N, 18.46. Found: C, 52.52; H, 5.83; N, 18.32.

1-(4*H*-3,1-Benzoxazin-2-yl)imidazolidin-2-thione (8). To a mixture of the hydrochloride (**7**) (0.8 g, 3.4 mmol) in anhydrous acetone (15 mL) and carbon disulfide (0.2 mL, 17 mmol) was added dropwise Et_3N (0.68 g, 6.8 mmol). The resulting suspension was stirred at rt for 48 h (until H_2S had ceased). Then the solvent and excess of carbon disulfide were evaporated under reduce pressure, and the residue was treated with water (20 mL). The precipitate thus obtained was filtered off, dried and purified by crystallization from DMF to afford **8.** Yield: 0.44 g (54%), mp 184-186 °C. IR (KBr): 3195, 3040, 2945, 2890, 1620, 1600, 1535, 1415, 1400, 1290 (cm^{-1}). ^{1}H NMR (DMSO-d_6) δ 3.49-3.58 (m, 2H, CH_2), 4.08-4.17 (m, 2H, CH_2), 5.29 (s, 2H, CH_2), 7.01-7.08 (m, 1H, ArH), 7.14-7.2 (m, 2H, ArH), 7.24-7.34 (m, 1H, ArH), 9.42 (s, 1H, NH)*. ^{13}C NMR (DMSO-d_6) δ 41.44, 49.26 (C-4, C-5 imidaz.), 66.82 (CH_2), 122.68, 123.04, 124.61, 125.41, 129.07, 140.47 (6 C aromat.), 151.72 (C=N), 180.4 (C=S)*. *Anal.* Calcd for $C_{11}H_{11}N_3OS$: C, 56.63; H, 11.09; N, 18.01. Found: C, 56.45; H, 11.11; N, 17.82.

1-Acetyl-3-(4*H*-3,1-benzoxazin-2-yl)imidazolidin-2-thione (9). To a solution of **8** (0.4 g, 17 mmol) in pyridine (5 mL) acetyl chloride (0.33 g, 42 mmol) was added at 0 °C. After an exothermic reaction had subside (ca 15 min), the reaction suspension was stirred at rt for 12 h, and then the solvent was distilled off under reduce pressure. The dry residue was treated with water (20 mL) and the resulting mixture was neutralized to pH 7.5 with 5% aqueous Na_2CO_3 solution and stirred at room temperature for 30 min. The product that precipitated was collected by filtration, washed with water, dried and purified by crystallization from isopropanol to give **9** (0.18 g, 40%), mp 143-147 °C. IR (KBr): 3000, 2905, 2860, 1695, 1685, 1625, 1600, 1360, 1270 (cm^{-1}). ^{1}H NMR ($CDCl_3$) δ 2.86 (s, 3H, OCH_3), 4.09 (s, 4H, 2xCH_2), 5.39 (s, 2H, CH_2), 7.05-7.09 (m, 1H, ArH), 7.15-7.2 (m, 2H, ArH), 7.24-7.27 (m, 1H, ArH)*. ^{13}C NMR ($CDCl_3$) δ 27.59 (CH_3), 44.91, 46.21 (C-4, C-5 imidaz.), 68.23 (CH_2), 122.7, 124.46, 126.25, 126.96, 129.6, 140.15 (6 C aromat.), 151.27 (C=N), 172.59 (C=O), 179.17 (C=S)*. *Anal.* Calcd for $C_{13}H_{13}N_3O_2S$: C, 56.71; H, 4.76; N, 15.26. Found: C, 56.46; H, 5.12; N, 15.27.

2-(2-Benzylsulfanyl-4,5-dihydro-1*H*-imidazol-1-yl)-4*H*-3,1-benzoxazine (10). To a solution of **8** (0.8 mmol) and finely powdered NaOH (0.13 g, 3.2 mmol) in DMSO (6 mL) was added dropwise benzyl

bromide (0.15 mL, 1.3 mmol). The resulting suspension was stirred at 35-40 °C for 1 h. Then water (30 mL) was added to the reaction mixture, and the solid was collected by filtration, washed with water, and crystallized from ethanol to give compound (**10**) (0.14 g, 53%), mp 147-150 °C. IR (KBr): 3060, 3025, 2915, 2870, 1630, 1595, 1575, 1415, 1280 (cm^{-1}). ^1H NMR ($CDCl_3$) δ 3.99-4.05 (m, 4H, 2xCH_2), 4.36 (s, 2H, $\underline{CH_2}$Ph), 5.23 (s, 2H, CH_2), 6.93-7.08 (m, 3H, ArH), 7.19-7.39 (m, 6H, ArH)*. *Anal.* Calcd for $C_{18}H_{17}N_3OS$: C, 66.85; H, 5.30; N, 13.49. Found: C, 66.43; H, 5.12; N, 13.27.

***N,N'*-bis-(4*H*-3,1-benzoxazin-2-yl)hydrazine (11). Method A**. A mixture of **8** (1.13 g, 5 mmol) and 98% hydrazine hydrate (0.5 g, 10 mmol, 0.5 mL) in anhydrous methanol (10 mL) was stirred at rt for 48 h. The solid that precipitated was filtered off (the filtrate denoted as "**T**" was stored for further workup) washed with methanol (3x5 mL), dried and crystallized from DMF/methanol to give pure product **11** (0.28 g, 40%), mp 209-210 °C (decomp). IR (KBr): 3305, 1655, 1640, 1595, 1475, 1396, 1030 (cm^{-1}). ^1H NMR (DMSO-d_6) δ 5.07 (s, 4H, 2xCH_2), 6.79-6.99 (m, 2H, ArH), 7.14-7.24 (m, 6H, ArH), 9.44 (s, 2H, 2xNH)*. MS (70 eV) m/z: 294 (M^+). *Anal.* Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.53; H, 5.02; N, 19.35.

The filtrate "**T**" was evaporated under reduced pressure, and the oily residue was treated with acetone (10 mL). The precipitate thus obtained, containing **12** and traces of **11** (^1H NMR evidence), was collected by suction (0.3 g) and recrystallized from isopropanol to give imidazolidin-2-thione (**12**) (0.07 g, 20%), mp 187-189 °C (ref.,[20] mp 196-197 °C).

Method B. A mixture of **8** (0.5 g, 2.1 mmol) and methylhydrazine (0.2 g, 4.4 mmol, 0.24 mL) in anhydrous methanol (10 mL) was stirred at rt for 48 h. Then, the resulting suspension was evaporated to dryness, and the residue was treated with hot methanol (4 mL). The insoluble material was separated by suction (the filtrate denoted as "**T**" was stored for further workup), dried and purified by crystallization from DMF/methanol to give **8** (0.07, 23%), which was identical with the product obtained according to the method A. The filtrate "**T**" was worked up as described in the method A. The crude product (**12**) thus obtained (0.09 g) was not further purified.

X-Ray structure analyses. The diffraction data were collected at room temperature with a KumaCCD diffractometer using graphite monochromated Mo K_α radiation. The intensity data were collected and processed using Oxford Diffraction CrysAlis Software.[21] The structures were solved by direct methods with the program SHELXS-97 and refined by full-matrix least-squares method on F^2 with SHELXL-97.[22]

X-Ray structure analysis of 3a. Crystal data for $C_{16}H_{18}N_4$: triclinic, space group $P\bar{1}$, a= 7.9579(15), b= 8.8528(12), c= 11.3026(17) Å, α= 73.850(13), β= 86.426(14), γ= 68.765(15)°, V= 712.3(2) $Å^3$, Z=2, d_x =1.242 $g.cm^{-3}$, T=293K. Final R indices for 1613 reflections with I>2σ(I) and 200 refined parameters are: R_1=0.0597, wR_2=0.1724 (R_1=0.0826, wR_2=0.1939 for all 2513 data.[23]

X-Ray structure analysis of 4b. Crystal data for $C_{18}H_{13}N_4ClS_2$: triclinic, space group $P\bar{1}$, a= 8.6635(8), b= 9.6065(10), c= 11.8111(9) Å, α= 94.271(7), β= 102.262(7), γ= 115.479(10)°, V= 851.68(14) Å^3, Z=2, d_x =1.501 g.cm^{-3}, T=293K. Final R indices for 2957 reflections with I>2σ(I) and 227 refined parameters are: R_1=0.0408, wR_2=0.1115 (R_1=0.0460, wR_2=0.1166 for all 3428 data).[23]

X-Ray structure analysis of 10. Crystal data for $C_{18}H_{17}N_3OS$: triclinic, space group $P\bar{1}$, a= 7.3689(7), b= 10.1304(11), c= 11.6572(10) Å, α= 105.019(8), β= 95.464(8), γ= 105.781(9)°, V= 795.85(13) Å^3, Z=2, d_x =1.350 g.cm^{-3}, T=293K. Final R indices for 2371 reflections with I>2σ(I) and 473 refined parameters are: R_1=0.0391, wR_2=0.1010 (R_1=0.0450, wR_2=0.1063 for all 2794 data).[23]

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23. CCDC 290745 (compound **3a**), CCDC 290746 (compound **4b**) and CCDC 290747 (compound **10**) contain the supplementary crystallographic data for these compounds. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).