Access to Novel Imidazo[1,5-a]pyrazine Scaffolds by the Combined Use of a Three-Component Reaction and a Base-Assisted Intramolecular Cyclization

Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID:	OB-ART-03-2014-000676.R1
Article Type:	Paper
Date Submitted by the Author:	29-Apr-2014

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Organic & Biomolecular Chemistry RSCPublishing

ARTICLE

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Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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A novel and practical two-step approach to intriguing class of imidazo[1,5-*a*]pyrazines with exocyclic C=X (X = CH_2, O) bonds is described. The process utilizes a sequential three-component reaction of propargyl amine or aminoester, 1,2-diaza-1,3-dienes and isothiocyanates to furnish functionalized 2-thiohydantoins which are transformed into thiohydantoin-fused tetrahydropyrazines by subsequent regioselective base-promoted cyclization.

Introduction

Among the known members of the azaindolizine family the imidazo[1,5-*a*]pyrazine heterocyclic framework is structural unit found in several natural products, drugs, and drug candidates. For example, the imidazo[1,5-*a*]pyrazine[1] derived structures possess diverse pharmacological properties, such as Factor Xa inhibitors,[2] IGF-IR inhibitors,[3] PDE10 inhibitors,[4] mTORC1/2 inhibitors,[5] ACK1 inhibitors,[6] Smo antagonists,[7] etc. They are also identified to act on a number of targets including the CFR receptor,[8] GABAA receptor,[9] and melanocortin receptor[10]. Recently, compound BMS-279700 was discovered as novel, potent, and orally active Lck inhibitor with excellent in vivo anti-inflammatory activity[11] (Figure 1). Due to resemblance to drug-like molecules, bicyclic skeletons with thiohydantoin and tetrahydropyrazine have a special appeal. However, this heterobicyclic structure as derivatization of a new scaffold[12] obtained from fusion of these two important motifs is much less common. A thorough search of the literature revealed only a single example of such type of imidazo[1,5-*a*]pyrazine (compound **I**, Figure 1).[13]

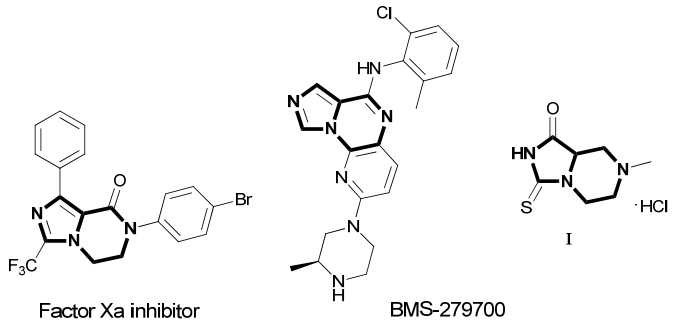
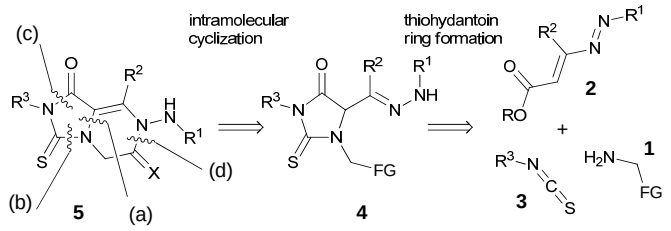


Fig 1 Selected examples of compounds containing imidazo [1,5-*a*]pyrazine skeletons

In the field of multicomponent reactions (MCRs),[14] sequential multiple bond-forming transformations (MBFTs)[15] represent undoubtedly a well-suited tool for lead compound discovery and optimization in medicinal chemistry. By virtue of its inherent convergence, simplicity, efficiency, atom economy, shortened reaction times, and complexity-generating power, the MBFTs represent an attractive area in modern organic chemistry. In conjunction of our efforts to explore new multiple bonds forming reaction from 1,2-diaza-1,3-dienes (DDs),[16] herein we would like to report a new synthetic strategy for the efficient construction of potentially biological active bicyclic thiohydantoin-tetrahydropyrazine derivatives by using MCRs/post-functionalization[17] strategy. Recently, our laboratory has developed a robust chemo- and regioselective approach to 2-thiohydantoin or 2-iminothiazolidin-4-one derivatives by sequential three-component reactions involving the combination of a primary amine **1**, a DD **2**, and a isothiocyanate **3**.[18] The ready availability of numerous acyclic reagents **1**−**3** allows for the incorporation of various points of functional diversity in the products **4**. Aiming at expanding the scope of this 3CR, we envisaged that an intramolecular cyclization reaction of functionalized 2-thiohydantoin intermediate of the type **4** with a propargylic or ester appendage on the N(1) position would lead to an imidazo[1,5-*a*]pyrazine skeleton **5**. The key cyclization precursor **4** should be accessible from 1-propargylamine **1a** or aminoester **1b**, DD **2**, and isothiocyanate **3** via a sequential one-pot reaction (see retrosynthetic analysis, Scheme 1). Following this designed strategy, overall the transformation should create four C−N bonds (a)-(d) and two new fused heterocyclic rings. Such thiohydantoin-fused tetrahydropyrazine scaffolds could have

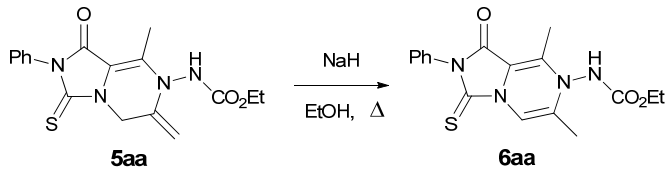
worth in the synthesis of novel screening compounds with lead-like molecular properties.



Scheme 1 Access to thiohydantoin-fused tetrahydropyrazines

Results and discussion

We initiated exploratory study preparing 2-thiohydantoin structure as **4aa** bearing *N*-propargyl appendage that was then subjected to cyclization via an intramolecular hydroamination. Thus, 1-propargylamine **1a** was reacted with **2a** in $CHCl_3$ at room temperature and, subsequently (after the quickly disappearance of the reagents, TLC check) isothiocyanate **3a** was added to furnish 2-thiohydantoin compound **4aa** in 64% yield (entry 1, Table 1). With the required precursor **4aa** in hand, NaH as base was tested to attempt the base-mediated activation of the hydrazonic nitrogen to induce the intramolecular cyclization.[19] Surprisingly, the hydroamination/cyclization of **4aa**-containing unactivated alkyne proceeded well in ethanol at room temperature and the desired bicyclic product **5aa** was obtained in 67% yield (entry 1, Table 1). Notably, only **5aa** with an exocyclic C-C double bond formed via a 6-*exo*-dig ring closing pathway was observed. Despite the importance provided by the intramolecular amines-alkynes cyclization for the construction of azaheterocycles,[20–22] hydroamination reactions of hydrazones are scarce and mostly limited to the formation of five-membered rings. Analogously, reports of similar hydroamination/cyclization to form six-membered *N*-heterocycles having exocyclic olefin are rarely encountered in the literature.[23] In fact, although an exocyclic olefin is preferentially formed through the hydroamination/cyclization process, a more stable endocyclic double bond is then obtained by a spontaneous 1,3-hydrogen shift.[24] In our case, the exclusive formation of **5aa**-*exo* isomer may lie in its rigid conformation, which prevents at room temperature a possible isomerization toward a more strained structure. Only when **5aa** was refluxed in ethanol with the assistance of NaH conversion to **6aa**-*endo* isomer (68% yield) was observed as result of double bond isomerization (Scheme 2).[25]



Scheme 2 Isomerization of **5aa** to **6aa**

Based on these promising results, the scope of this novel two-step synthesis of thiohydantoin-fused tetrahydropyrazines was next examined with different DDs **2a-f**, and isothiocyanates **3a-e** (Table 1). In practice, diversely substituted 2-thiohydantoin intermediates **4aa-ag** (52−82% yield) were prepared earlier by a 3CR and then converted into the corresponding methylidene thiohydantoin-fused tetrahydropyrazines **5aa-ag** (54−93% yield). The reactions were found to be equally effective with both aliphatic and aromatic isothiocyanates even if ethyl isothiocyanate gave lower yields (Table 1, entry 7). Similarly, differently substituted DDs (R^1 = COX; X = OMe, OEt, OBn, O*t*-Bu; R, R^2 = Me, Et) were found to be tolerated. All the thiohydantoin-fused tetrahydropyrazines **5aa-ag** synthesized were characterized by their ^{1}H NMR, ^{13}C NMR and MS data and unambiguously confirmed by X-ray crystal structure analysis of **5ac** (see ORTEP diagram, Figure 2).[26]

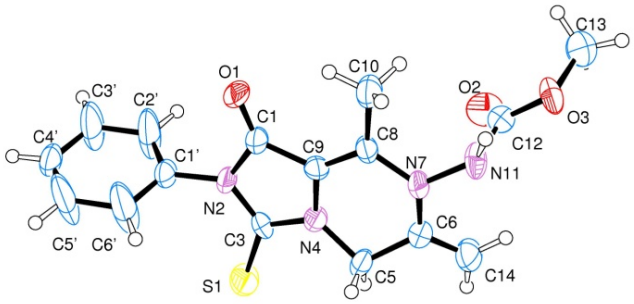
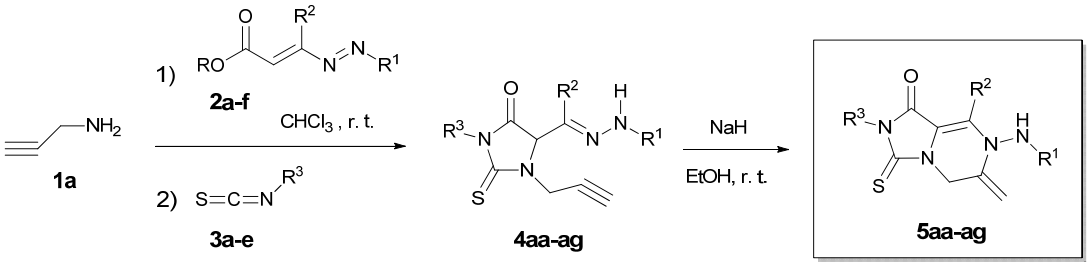


Fig 2 ORTEP representation of **5ac**

With the preparation of variously functionalized 2-thiohydantoin structures **4** in mind, we hypothesized that we could expand the utility of a cyclization approach to the novel thiohydantoin-fused tetrahydropyrazine nucleus by introduction of an acetate appendage on the N(1) position of **4**. For this purpose, the requisite cyclization precursor, was readily synthesized from glycine ethyl ester hydrochloride **1b**, DD **2g** and isothiocyanate **3a** in $CHCl_3$ at room temperature and in the presence of DIPEA. 2-Thiohydantoin compound **4ba** was obtained in 78% yield. Treatment of **4ba** with DIPEA in $CHCl_3$ effected cyclization (in practice a lactamization[27]) within 2 h at reflux to afford the bicyclic product **5ba** in 87% yield (entry 1, Table 2). With the objective of promoting consecutive ring annulation events in a single stroke, we next moved our attention toward a one-pot strategy. Capture of the pendant ester by the in situ generated hydrazone nucleophile would afford a thiohydantoin-fused tetrahydropyrazine **5ba** having an exocyclic C=O bond. Thus, when the formation of functionalized 2-thiohydantoin intermediate **4ba** was complete (TLC check), DIPEA was added to the reaction mixture, and after 4 h at reflux, bicyclic compound **5ba** was obtained in 77% overall yield.[28] Following the same one-pot protocol, combinations of glycine ethyl ester hydrochloride **1b** with different DDs **2b-e,g,h** and isothiocyanates **3a,b,d,f** were next examined. The results are reported in Table 2.

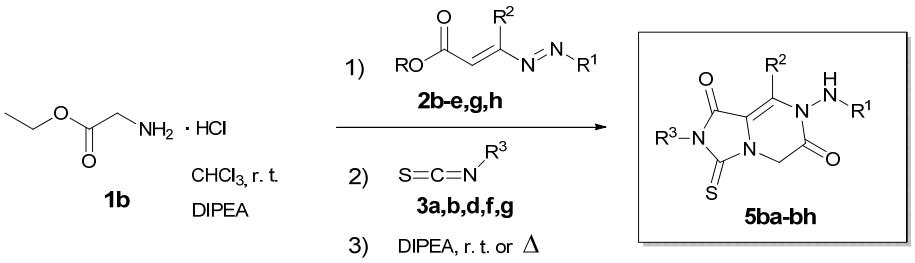
Table 1 Synthetic pathway to thiohydantoin-fused tetrahydropyrazine derivatives **5aa-ag**



Entry		DD **2**				Isothiocyanate **3**	1-Propargyl-2-Thiohydantoin **4**		Thiohydantoin-fused Tetrahydropyrazine **5**	
		R	R^1	R^2		R^3		Yield[a] (%)		Yield[b] (%)
1	**2a**	Et	CO_2Et	Me	**3a**	Ph	**4aa**	64	**5aa**	67
2	**2b**	Me	CO_2Bn	Me	**3a**	Ph	**4ab**	55	**5ab**	76
3	**2c**	Et	CO_2Me	Me	**3a**	Ph	**4ac**	57	**5ac**	58
4	**2d**	Et	CO_2t-Bu	Me	**3b**	4-MeO-Ph	**4ad**	60	**5ad**	78
5	**2e**	Me	CO_2t-Bu	Et	**3c**	Bn	**4ae**	63	**5ae**	93
6	**2f**	Me	CO_2Bn	Et	**3d**	4-Cl-Ph	**4af**	82	**5af**	91
7	**2c**	Et	CO_2Me	Me	**3e**	Et	**4ag**	52	**5ag**	54

[a]Yield of isolated pure product based on DD **1**.
[b]Yield of isolated pure product based on intermediate **4**.

Table 2 One-pot three-component synthesis of thiohydantoin-fused tetrahydropyrazine derivatives **5ba-bh**

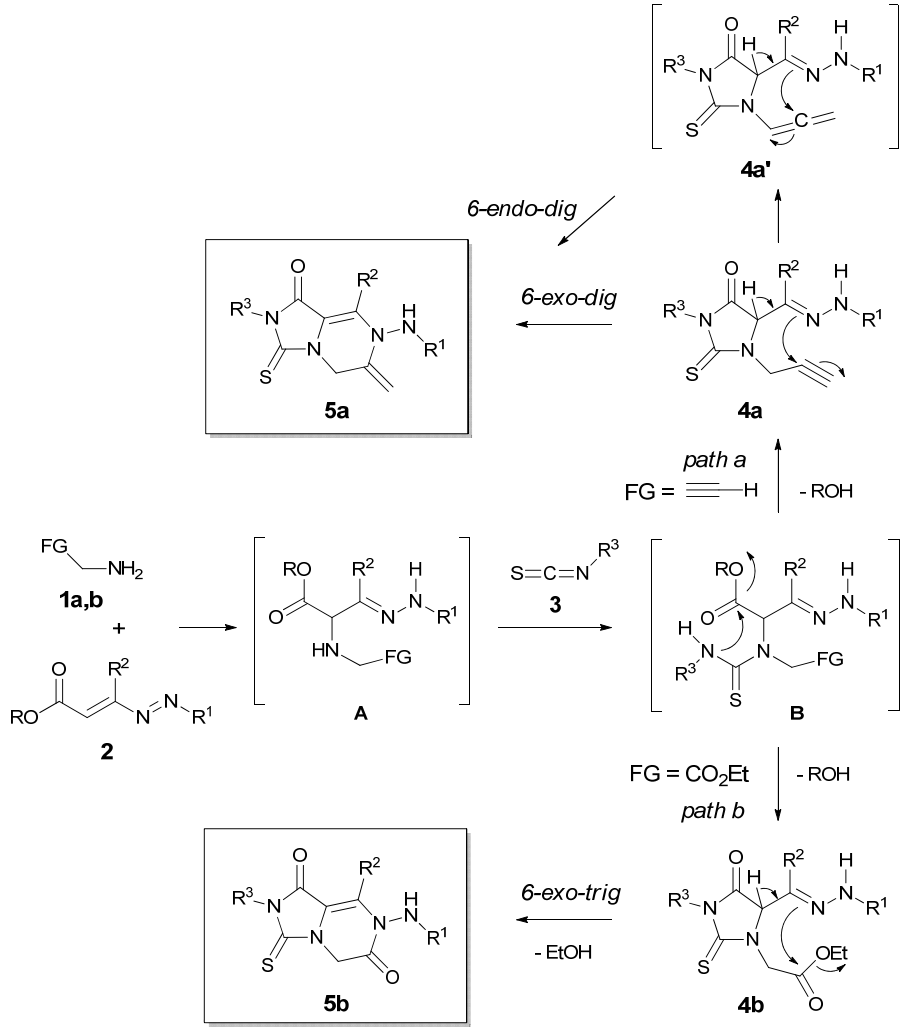


entry		DD **2**				isothiocyanate **3**	thiohydantoin-fused tetrahydropyrazine **5**	
		R	R^1	R^2		R^3		Yield (%)[a]
1	**2g**	Et	CONHPh	Me	**3a**	Ph	**5ba**	77 (87[b])
2	**2c**	Et	CO_2Me	Me	**3f**	4-NO_2-Ph	**5bb**	59
3	**2h**	Me	CO_2Et	Me	**3b**	4-MeO-Ph	**5bc**	61
4	**2b**	Me	CO_2Bn	Me	**3f**	4-NO_2-Ph	**5bd**	65

5	**2c**	Et	CO_2Me	Me	**3a**	Ph	**5be**	78
6	**2e**	Me	CO_2t-Bu	Et	**3a**	Ph	**5bf**	61
7	**2d**	Et	CO_2t-Bu	Me	**3d**	4-Cl-Ph	**5bg**	55
8	**2g**	Et	CONHPh	Me	**3g**	CH_2CO_2Et	**5bh**	30

[a]Yield of isolated pure product based on DD **1**. [b]Yield of isolated pure product based on intermediate **4ba**.

Scheme 3 Mechanism pathways for sequential 3CRs/cyclizations strategy



The reactions proceeded with both aromatic isothiocyanates and differently substituted DDs (R^1 = COX; X = OMe, OEt, OBn, O*t*-Bu, NHPh; R, R^2 = Me, Et) to give a series of new thiohydantoin-fused tetrahydropyrazines in yields ranging from 55% to 78% (Table 2, entries 1–7). Our efforts to include aliphatic isothiocyanates in this transformation have been fruitful only when **3g** was investigated (entry 8, Table 2).

From a mechanistic point of view, the 2-thiohydantoin **4** ring annulation commences from the preliminary aza-Michael addition of amine **1** to DD **2** to generate intermediate **A**, which subsequently reacts with isothiocyanate **3**. Then, an intramolecular ring closure of the hydrazone intermediate **B** produces 2-thiohydantoin **4** (**4a** or **4b**) upon loss of an alcohol molecule. The formation of additional tetrahydropyrazine ring would occur via intramolecular nucleophilic attack of the hydrazonic nitrogen onto the pendant C≡C or C=O system (Scheme 3, *path a* and *path b*, respectively). When 1-propargylamine **1a** is used a NaH-promoted hydroamination leads to product **5a** via a 6-*exo*-dig ring closing process (Scheme 3, *path a*). Alternatively, a pathway that involves NaH-mediated alkyne-allene isomerization followed by 6-*endo*-trig cyclization could also occur. With respect to glycine ethyl ester **1b** as amine component, an intramolecular 6-*exo*-trig cyclization of **4b** via a nucleophilic acyl substitution results in the formation of bicyclic product **5b** (Scheme 3, *path b*). Presumably, the driving force of all these intramolecular cyclizations derives from the appreciable acidity of the proton in the α-position to the C=N hydrazone function which being susceptible to tautomerization under basic conditions allows activation of sp^2 nitrogen towards the ring closure.

Experimental

Materials and methods. All chemicals and solvents were purchased from commercial suppliers and used as received. 1,2-Diaza-1,3-dienes (DDs) were prepared as reported[16a,29] and used as *EE*/*EZ* isomer mixtures. Melting points were determined in open capillary tubes and are uncorrected. FT-IR spectra were obtained as Nujol mulls or neat. Mass spectra (MS) were carried out by electron impact (EI) at an ionizing voltage of 70 eV. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in DMSO-d_6, or in $CDCl_3$ as specified below. For all new compounds the reported chemical shift values are referred to the prevalent stereoisomer. Chemical shifts (δ_H) and (δ_C) are reported in parts per million (ppm), and were referred to solvent signals as follows: δ = 2.50 ppm for proton (middle peak) and δ = 39.50 ppm for carbon in DMSO; δ = 7.26 ppm for proton and δ = 77.00 ppm for carbon (middle peak) in $CDCl_3$. All coupling constant (*J* values) are given in hertz (Hz). The following abbreviations are used to describe peak patterns where appropriate: s, singlet; d, doublet; dd, double-doublet; t, triplet; q, quartet; m, multiplet; br, broad. All the NH exchanged with D_2O. Precoated silica gel plates 0.25 mm were employed for analytical thin layer chromatography and silica gel 35-70 μm for column chromatography. All new compounds showed satisfactory elemental analysis.

General procedure for the one-pot synthesis of 1-propargyl-2-thiohydantoin derivatives 4aa-ag. To a stirred solution of propargylamine **1a** (1 mmol) in $CHCl_3$ (5 mL) DD derivative **2a-f** (1 mmol) was added at room temperature. After the disappearance of the reagents (0.1-8 h) (TLC check), isothiocyanate derivative **3a-e** was added and the reaction mixture was allowed to stand overnight at room temperature for the completion (TLC check). After the removal of the reaction solvent thiohydantoins **4aa-ad** and **4af,ag** were obtained by crystallization from appropriate solvents, whereas **4ae** was achieved after chromatographic purification (cyclohexane/ethyl acetate mixtures) and subsequent crystallization.

Ethyl 2-{1-[5-oxo-1-phenyl-3-(2-propynyl)-2-thioxo-4-imidazolidinyl]ethylidene}-1-hydrazinecarboxylate (4aa). Yield 229.4 mg (64%); white powder; mp 160-162 °C (dec.) (from hot EtOH-EtOAc); IR (Nujol, ν, cm^{-1}) 3277, 3229, 2127, 1760, 1722, 1712; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (t, *J* = 6.8 Hz, 3H), 1.85 (s, 3H), 3.40 (t, ^4J = 2.4 Hz, 1H), 4.15 (q, *J* = 6.8 Hz, 2H), 4.61 (dd, ^2J = 17.6 Hz, ^4J = 2.4 Hz, 1H), 4.67 (dd, ^2J = 17.6 Hz, ^4J = 2.4 Hz, 1H), 5.16 (s, 1H), 7.34 (d, *J* = 6.8 Hz, 2H), 7.44−7.53 (m, 3H), 10.41 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.9, 14.5, 35.3, 60.8, 68.7, 76.0, 76.9, 128.6, 128.7, 128.9, 133.5, 143.4, 153.8, 169.5, 182.1; MS (EI) *m/z* (%) 358 (M^+, 84), 285 (5), 270 (33), 229 (2), 189 (20), 135 (74), 107 (100); Anal. calcd. for $C_{17}H_{18}N_4O_3S$ (358.41) C, 56.97; H, 5.06; N, 15.63; Found C, 57.08; H, 4.93; N, 15.68.

Benzyl 2-{1-[5-oxo-1-phenyl-3-(2-propynyl)-2-thioxo-4-imidazolidinyl]ethylidene}-1-hydrazinecarboxylate (4ab). Yield 231.2 mg (55%); white powder 158 °C (dec.) (from EtOAc-Et_2O-light petroleum ether); IR (Nujol, ν, cm^{-1}) 3263, 3247, 2120, 1752, 1735, 1706, 1673; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.86 (s, 3H), 3.42 (t, ^4J = 2.4 Hz, 1H), 4.61 (dd, ^2J = 17.6 Hz, ^4J = 2.4 Hz, 1H), 4.69 (dd, ^2J = 17.6 Hz, ^4J = 2.4 Hz, 1H), 5.16−5.22 (m, 3H), 7.31−7.55 (m, 10H), 10.57 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.0, 35.3, 66.2, 68.6, 76.1, 76.9, 128.1, 128.4, 128.6, 128.9, 129.0, 133.5, 136.3, 144.0, 153.8, 169.5, 182.1; MS (EI) *m/z* (%) 420 (M^+, 69), 285 (38), 271 (16), 189 (13), 151 (11), 135 (64), 107 (100); Anal. calcd. for $C_{22}H_{20}N_4O_3S$ (420.48) C, 62.84; H, 4.79; N, 13.32; Found C, 62.97; H, 4.68; N, 13.40.

Methyl 2-{1-[5-oxo-1-phenyl-3-(2-propynyl)-2-thioxo-4-imidazolidinyl]ethylidene}-1-hydrazinecarboxylate (4ac). Yield 196.3 mg (57%); white powder 163−164 °C (dec.) (from hot EtOH); IR (Nujol, ν, cm^{-1}) 3323, 3239, 2120, 1757, 1711, 1598; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.84 (s, 3H), 3.41 (s, 1H), 3.70 (s, 3H), 4.63 (s, 2H), 5.15 (s, 1H), 7.33 (d, *J* = 6.8 Hz, 2H), 7.46−7.51 (m, 3H), 10.46 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.0, 35.3, 52.2, 68.8, 76.1, 76.9, 128.7, 129.0, 129.1, 133.5, 143.6, 154.4, 169.6, 182.2; MS (EI) *m/z* (%) 344 (M^+, 40), 312 (9), 270 (15), 230 (11), 189 (100), 135 (25), 115(19); Anal. calcd. for $C_{16}H_{16}N_4O_3S$ (344.39) C, 55.80; H, 4.68; N, 16.27; Found C, 55.68; H, 4.77; N, 16.20.

tert-Butyl 2-{1-[1-(4-methoxyphenyl)-5-oxo-3-(2-propynyl)-2-thioxo-4-imidazolidinyl]ethylidene}-1-hydrazinecarboxylate (4ad). Yield 249.9 mg (60%); white powder 145-147 °C (dec.) (from hot EtOH); IR (Nujol, ν, cm^{-1}) 3325, 3271, 2122, 1752, 1717, 1608; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.47 (s, 9H), 1.82 (s, 3H), 3.40 (s, 1H), 3.80 (s, 3H), 4.57 (d, *J* = 17.6 Hz, 1H), 4.70 (d, *J* = 17.6 Hz, 1H), 5.10 (s, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 10.14 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.0, 28.1, 35.3, 55.4, 68.6, 76.1, 77.0, 79.9, 114.2, 126.0, 129.8, 142.8, 152.8, 159.4, 169.8, 182.5; MS (EI) *m/z* (%) 416 (M^+, 10), 360 (23), 316 (9), 300 (9), 219 (17), 165 (21), 125 (59), 111 (100); Anal. calcd. for $C_{20}H_{24}N_4O_4S$ (416.49) C, 57.68; H, 5.81; N, 13.45; Found C, 57.81; H, 5.67; N, 13.37.

tert-Butyl 2-{1-[1-benzyl-5-oxo-3-(2-propynyl)-2-thioxo-4-imidazolidinyl]propylidene}-1-hydrazinecarboxylate (4ae). Yield 261.1 mg (63%); white powder 142 °C (dec.) (from EtOAc-cyclohexane); IR (Nujol, ν, cm^{-1}) 3246, 2127, 1753, 1724, 1704; ^1H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, J = 7.6 Hz, 3H), 1.45 (s, 9H), 2.04−2.13 (m, 1H), 2.41−2.50 (m, 1H), 3.38 (s, 1H), 4.40 (d, J = 18.0 Hz, 1H), 4.76 (d, J = 18.0 Hz, 1H), 4.91−5.12 (m, 3H), 7.26−7.32 (m, 5H), 10.18 (s, 1H);^{13}C NMR (100 MHz, DMSO-d_6) δ 9.1, 20.5, 28.0, 35.2, 44.7, 66.3, 76.3, 78.2, 79.8, 127.3, 127.4, 127.7, 128.2, 128.3, 135.7, 146.4, 152.7, 170.3, 182.0; MS (EI) *m/z* (%) 414 (M^+, 13), 358 (22), 314 (53), 298 (23), 244 (40), 203 (100), 149 (23), 111 (41); Anal. calcd. for $C_{21}H_{26}N_4O_3S$ (414.52) C, 60.85; H, 6.32; N, 13.52; Found C, 60.71; H, 6.46; N, 13.61.

Benzyl 2-{1-[1-(4-chlorophenyl)-5-oxo-3-(2-propynyl)-2-thioxo-4-imidazolidinyl]propylidene}-1-hydrazinecarboxylate (4af). Yield 384.5 mg (82%); white powder 155−157 °C (dec.) (from CH_2Cl_2); IR (Nujol, ν, cm^{-1}) 3294, 3222, 2130, 1751, 1725; ^1H NMR (400 MHz, DMSO-d_6) δ 0.97 (t, J = 7.2 Hz, 3H), 2.21−2.26 (m, 1H), 2.56−2.61 (m, 1H), 3.43 (t, ^4J = 2.4 Hz 1H), 4.48 (dd, ^2J = 18.0 Hz, ^4J = 2.4 Hz, 1H), 4.82 (dd, ^2J = 18.0 Hz, ^4J = 2.4 Hz, 1H), 5.17−5.20 (m, 3H), 7.34−7.43 (m, 7H), 7.58 (d, J = 8.8 Hz, 2H), 10.64 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 9.5, 20.6, 35.4, 66.3, 76.5, 76.7, 128.2, 128.5, 128.8, 128.9, 129.1, 130.5, 132.3, 133.7, 136.3, 147.8, 153.8, 169.6, 181.7; MS (EI) *m/z* (%) 470 [M^++2, (8)], 468 (23), 333 (18), 169 (12), 149 (46), 121 (100); Anal. calcd. for $C_{23}H_{21}ClN_4O_3S$ (468.96) C, 58.91; H, 4.51; N, 11.95; Found C, 58.83; H, 4.64; N, 12.08.

Methyl 2-{1-[1-ethyl-5-oxo-3-(2-propynyl)-2-thioxo-4-imidazolidinyl]ethylidene}-1-hydrazinecarboxylate (4ag). Yield 154.1 mg (52%); white powder 141−142 °C (from EtOH); IR (Nujol, ν, cm^{-1}) 3289, 3217, 2121, 1740, 1709; ^1H NMR (400 MHz, DMSO-d_6) δ 1.12 (t, J = 7.2 Hz, 3H), 1.69 (s, 3H), 3.34 (s, 1H), 3.69 (s, 3H), 3.75 (q, J = 7.2 Hz, 2H), 4.54 (s, 2H), 4.97 (s, 1H), 10.39 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.7, 12.8, 35.0, 36.8, 52.0, 68.1, 75.8, 76.9, 143.5, 154.3, 169.8, 181.9; MS (EI) *m/z* (%) 296 (M^+, 25), 264 (9), 222 (49), 181 (11), 141 (100), 115 (5); Anal. calcd. for $C_{12}H_{16}N_4O_3S$ (296.35) C, 48.64; H, 5.44; N, 18.91; Found C, 48.76; H, 5.31; N, 18.78.

General procedure for the synthesis of thiohydantoin-fused tetrahydropyrazine derivatives 5aa-ag. To a stirred solution of 2-thiohydantoins **4aa-ag** (1 mmol) in anhydrous EtOH (5 mL), NaH (60% dispersion in mineral oil) (1 eq) was added portionwise at room temperature. The reaction mixture was allowed to stand overnight at room temperature, then the reaction solvent was removed under reduced pressure. The residue was suspended in H_2O and acidified at pH 5 with HCl 2N. The aqueous phase was extracted with EtOAc (3x); the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The organic residue was crystallized from the appropriate solvent or solvent mixture to give pure derivatives **5aa-ag**.

Ethyl N-(8-methyl-6-methylene-1-oxo-2-phenyl-3-thioxo-1,2,3,5,7-hexahydroimidazo[1,5-a]pyrazin-7-yl)carbamate (5aa). Yield 240.1 mg (67%); light yellow powder 183−185 °C (charcoals) (from hot EtOH-EtOAc); IR (Nujol, ν, cm^{-1}) 3261, 1725, 1703, 1695, 1659; ^1H NMR (400 MHz, DMSO-d_6) δ 1.24 (t, J = 6.8 Hz, 3H), 2.31 (s, 3H), 4.17 (q, J = 6.8 Hz, 2H), 4.67−4.80 (m, 4H), 7.33 (d, J = 7.2 Hz, 2H), 7.41−7.51 (m, 3H), 10.29 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.2, 14.4, 44.3, 61.7, 94.8, 106.1, 128.4, 128.7, 133.8, 135.7, 136.0, 155.1, 160.4, 169.3; MS (EI) *m/z* (%) 358 (M^+, 100), 285 (5), 270 (40), 195 (4), 135 (78), 107 (99); Anal. calcd. for $C_{17}H_{18}N_4O_3S$ (358.41) C, 56.97; H, 5.06; N, 15.63; Found C, 56.82; H, 5.14; N, 15.56.

Benzyl N-(8-methyl-6-methylene-1-oxo-2-phenyl-3-thioxo-1,2,3,5,7-hexahydroimidazo[1,5-a]pyrazin-7-yl)carbamate (5ab). Yield 319.5 mg (76%); yellow powder 165 °C (from EtOAc-Et_2O); IR (Nujol, ν, cm^{-1}) 3287, 1721, 1706, 1669, 1640; ^1H NMR (400 MHz, DMSO-d_6) δ 2.29 (s, 3H), 4.67−4.80 (m 4H), 5.20 (s, 2H), 7.32−7.49 (m, 10H), 10.51 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.1, 44.2, 67.0, 94.8, 106.2, 127.9, 128.2, 128.4, 128.5, 128.7, 133.8, 135.6, 135.8, 136.0, 155.0, 160.4, 169.4; MS (EI) *m/z* (%) 420 (M^+, 75), 285 (37), 271 (15), 135 (62), 122 (38), 107 (100); Anal. calcd. for $C_{22}H_{20}N_4O_3S$ (420.48) C, 62.84; H, 4.79; N, 13.32; Found C, 62.71; H, 4.87; N, 13.43.

Methyl N-(8-methyl-6-methylene-1-oxo-2-phenyl-3-thioxo-1,2,3,5,7-hexahydroimidazo[1,5-a]pyrazin-7-yl)carbamate (5ac). Yield 199.7 mg (58%); light orange powder 168 °C (from hot EtOH-EtOAc); IR (Nujol, ν, cm^{-1}) 3269, 1719, 1660, 1646, 1628; ^1H NMR (400 MHz, DMSO-d_6) δ 2.31 (s, 3H), 3.72 (s, 3H), 4.69−4.81 (m, 4H), 7.33 (d, J = 7.2 Hz, 2H), 7.43−7.51 (m, 3H), 10.39 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.1, 44.3, 52.9, 94.9, 106.1, 128.4, 128.7, 133.8, 135.7, 135.9, 155.6, 160.4, 169.4; MS (EI) *m/z* (%) 344 (M^+, 67), 270 (32), 181 (6), 135 (75), 107 (100); Anal. calcd. for $C_{16}H_{16}N_4O_3S$ (344.39) C, 55.80; H, 4.68; N, 16.27; Found C, 55.66; H, 4.79; N, 16.18.

tert-Butyl N-[2-(4-methoxyphenyl)-8-methyl-6-methylene-1-oxo-3-thioxo-1,2,3,5,7-hexahydroimidazo[1,5-a]pyrazin-7-yl]carbamate (5ad). Yield 324.8 mg (78%); light yellow powder 180 °C (charcoals) (from hot EtOH); IR (Nujol, ν, cm^{-1}) 3278, 1747, 1717, 1694, 1653, 1647, 1630; ^1H NMR (400 MHz, DMSO-d_6) δ 1.46 (s, 9H), 2.28 (s, 3H), 3.80 (s, 3H), 4.64−4.77 (m, 4H), 7.02 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 10.05 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.2, 27.9, 44.3, 55.3, 81.1, 94.5, 106.1, 113.9, 126.4, 129.8, 135.8, 136.0, 154.1, 159.0, 160.6, 169.6; MS (EI) *m/z* (%) 416 (M^+, 2), 316 (3), 219 (12), 165 (23), 149 (29), 125 (63), 111 (100); Anal. calcd. for $C_{20}H_{24}N_4O_4S$ (416.49) C, 57.68; H, 5.81; N, 13.45; Found C, 57.55; H, 5.93; N, 13.40.

tert-Butyl N-(2-benzyl-8-ethyl-6-methylene-1-oxo-3-thioxo-1,2,3,5,7-hexahydroimidazo[1,5-a]pyrazin-7-yl)carbamate (5ae). Yield 385.5 mg (93%); light yellow powder 95-97 °C (from EtOH-H_2O); IR (Nujol, ν, cm^{-1}) 3244, 1738, 1723, 1711, 1693, 1642, 1632; ^1H NMR (400 MHz, DMSO-d_6) δ 1.09 (t, J = 7.2 Hz, 3H), 1.43 (s, 9H), 2.46−2.50 (m, 1H), 2.95−3.01 (m, 1H), 4.63−4.75 (m, 4H), 4.94 (s, 2H), 7.25−7.31 (m, 5H), 10.11 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.5, 18.4, 27.9, 43.8, 44.3, 80.9, 94.8, 105.3, 127.3, 127.5, 128.3, 136.0, 136.6, 141.7, 154.2, 160.2, 169.3; MS (EI) *m/z* (%) 414 (M^+, 26), 358 (80), 314 (5), 298 (40), 208 (19), 149 (47), 121 (100); Anal. calcd. for $C_{21}H_{26}N_4O_3S$ (414.52) C, 60.85; H, 6.32; N, 13.52; Found C, 60.76; H, 6.48; N, 13.41.

Benzyl N-[2-(4-chlorophenyl)-8-methyl-6-methylene-1-oxo-3-thioxo-1,2,3,5,7-hexahydroimidazo[1,5-a]pyrazin-7-yl]carbamate (5af). Yield 426.7 mg (91%); orange powder 178−180 °C (dec.) (from hot EtOH-EtOAc); IR (Nujol, ν, cm^{-1}) 3170, 1754, 1745, 1692, 1628; ^1H NMR (400 MHz, DMSO-d_6) δ 1.09 (t, J = 7.2 Hz, 3H), 2.40−2.50 (m, 1H), 2.97−3.07 (m, 1H), 4.65−4.82 (m, 4H), 5.21 (s, 2H), 7.30−7.42 (m, 7H), 7.56 (d, J = 8.4 Hz, 2H), 10.59 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.4, 18.3, 44.3, 67.0, 95.1, 105.6, 127.9, 128.2, 128.5, 128.7, 130.5, 132.6, 133.0, 135.7, 136.0, 141.2, 155.1, 159.7, 169.2; MS (EI) *m/z* (%) 470 [M^+ + 2 (7)], 468 (M^+, 20), 333 (9), 319 (14), 298 (13), 169 (12), 149 (56), 121 (100); Anal. calcd. for $C_{23}H_{21}ClN_4O_3S$ (468.96) C, 58.91; H, 4.51; N, 11.95; Found C, 58.78; H, 4.63; N, 11.84.

Methyl N-(2-ethyl-8-methyl-6-methylene-1-oxo-3-thioxo-1,2,3,5,6,7-hexahydroimidazo[1,5-a]pyrazin-7-yl)carbamate (5ag). Yield 160.0 mg (54%); light orange needles 152−154 °C (from hot EtOH); IR (Nujol, ν, cm^{-1}) 3285, 1712, 1682, 1660, 1643; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.11 (t, J = 6.8 Hz, 3H), 2.26 (s, 3H), 3.63−3.76 (m, 5H), 4.57−4.80 (m, 4H), 10.34 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.2, 13.1, 35.8, 44.2, 53.1, 94.9, 106.3, 135.8, 136.0, 155.7, 160.7, 169.1; MS (EI) *m/z* (%) 296 (M^+, 12), 222 (9),135 (21), 57 (100); Anal. calcd. for $C_{12}H_{16}N_4O_3S$ (296.35) C, 48.64; H, 5.44; N, 18.91; Found C, 48.77; H, 5.36; N, 19.01.

General one-pot three-component procedure for the synthesis of thiohydantoin-fused tetrahydropyrazine derivatives 5ba-bh. To a suspension of glycine ethyl ester hydrochloride **1b** (1 mmol) in $CHCl_3$ (4 mL), DIPEA (1 eq) was added and the suspension was stirred at room temperature for 0.5 h. After this time, DD **2b-e,g,h** (1 mmol) was added portionwise as solid or solved in $CHCl_3$ (2 mL) and the reaction mixture was left at room temperature until the complete disappearance of **2** (0.5-2 h, TLC check). Then, isothiocyanate derivative **3a,b,d,f,g** (0.95 mmol) was added and the reaction mixture was allowed to stand at room temperature (24-48 h). After this time, the reaction mixture was refluxed without (**5bb**,**bd**,**bf**) (4-8 h) or with the addition of DIPEA (**5ba**,**bc**,**be**,**bg**,**bh**) (4-18 h) for the completion. The crude was purified by crystallization obtaining pure **5ba,bb**,**bd**,**be**,**bg** or by coloumn chromatography (cyclohexane/ethyl acetate mixtures) and subsequent crystallization as in the case of **5bc**,**bf,bh**.

Ethyl {5-[N-(anilinocarbonyl))ethanehydrazonoyl]-4-oxo-3-phenyl-2-thioxoimidazolidin-1-yl)}acetate (4ba). Following the same one-pot procedure described above, the reaction was stopped after stirring at room temperature for 24 h once that the isothiocyanate **3a** (1 mmol) was added. After the removal of the solvent under reduced pressure, the crude reaction mixture was crystallized from EtOAc-Et_2O to yield **4ba**.

Yield 353.7 mg (78%); beige powder 153−156 °C (from EtOAc-Et_2O); IR (Nujol, ν, cm^{-1}) 3359, 3208, 1756, 1742, 1713, 1595; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 3H), 2.04 (s, 3H), 4.14 (d, J = 17.2 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 5.00 (d, J = 17.2 Hz, 1H), 5.13 (s, 1H), 7.11 (t, J = 7.2 Hz, 1H), 7.32−7.36 (m, 4H), 7.47−7.52 (m, 5H), 8.09 (s, 1H), 9.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 14.6, 47.1, 62.6, 69.3, 120.1, 124.4, 128.7, 129.6, 129.8, 130.0, 133.5, 137.9, 140.2, 153.3, 167.9, 169.6, 184.4; MS (EI) *m/z* (%) 453 (M^+, 2), 407 (3), 360 (6), 176 (100), 135 (20); Anal. calcd. for $C_{22}H_{23}N_5O_4S$ (453.51) C, 58.26; H, 5.11; N, 15.44; Found C, 58.39; H, 4.99; N, 15.33.

N-(8-Methyl-1,6-dioxo-2-phenyl-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-a]pyrazin-7(1H)-yl)-N′-phenylurea (5ba). To a stirred solution of **4ba** (0.5 mmol) dissolved in $CHCl_3$ (4 mL), a catalytic amount of DIPEA (0.05 mmol) was added and the reaction mixture was refluxed for 4 h. Then, the solvent was removed *in vacuo* and the crude reaction mixture was crystallized to afford the desired compound **5ba**.

Yield 177.3 mg (87% from **4ba**); 156.8 mg (77% from **1a**); beige powder 238−239 °C (from Et_2O-MeOH-light petroleum ether); IR (Nujol, ν, cm^{-1}) 3267, 3138, 3077, 1745, 1713, 1687, 1664, 1599; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.40 (s, 3H), 4.82 (s, 2H), 7.02 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 7.6 Hz, 2H), 7.36 (d, J = 7.6 Hz, 2H), 7.46−7.55 (m, 5H), 8.94 (br s, 1H), 9.38 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.3, 47.8, 109.3, 118.7, 122.7, 128.6, 128.7, 128.8, 128.9, 132.8, 133.2, 138.8, 154.3, 160.5, 161.4, 171.1; MS (EI) *m/z* (%) 407 (M^+, 59), 314 (12), 288 (70), 273 (52), 137 (43), 119 (100); Anal. calcd. for $C_{20}H_{17}N_5O_3S$ (407.45) C, 58.96; H, 4.21; N, 17.19; Found C, 59.09; H, 4.29; N, 17.02.

Methyl [8-methyl-2-(4-nitrophenyl)-1,6-dioxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-a]pyrazin-7(1H)-yl]carbamate (5bb). Yield 231.0 mg (59%); light pink powder 214-218 °C (from hot EtOAc); IR (Nujol, ν, cm^{-1}) 3186, 1765, 1736, 1717, 1678, 1599; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3H), 3.72 (s, 3H), 4.81 (d, J = 18.8 Hz, 1H), 4.87 (d, J = 18.8 Hz, 1H), 7.71 (d, J = 7.2 Hz, 2H), 8.38 (d, J = 7.2 Hz, 2H), 10.31 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.1, 47.7, 53.0, 109.5, 124.1, 129.9, 132.0, 138.7, 147.2, 156.1, 160.0, 160.7, 170.5; MS (EI) *m/z* (%) 391 (M^+, 100), 363 (11), 317 (2), 289 (7), 183 (47), 155 (75), 137 (59), 115 (46), 109 (62); Anal. calcd. for $C_{15}H_{13}N_5O_6S$ (391.36) C, 46.03; H, 3.35; N, 17.89; Found C, 47.15; H, 3.48; N, 17.76.

Ethyl [2-(4-methoxyphenyl)-8-methyl-1,6-dioxo-3-thioxo-2,3,5,6-[1,5-a]pyrazin-7(1H)-yl]carbamate (5bc). Yield 238.1 mg (61%); light yellow powder 126−130 °C (from Et_2O/*n*-pentane); IR (Nujol, ν, cm^{-1}) 3206, 1760, 1720, 1713, 1672, 1667; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.24 (t, J = 6.8 Hz, 3H), 2.32 (s, 3H), 3.80 (s, 3H), 4.16 (q, J = 6.8 Hz, 2H), 4.77 (d, J = 18.8 Hz, 1H), 4.84 (d, J = 18.8 Hz, 1H), 7.05 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 10.24 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.0, 14.3, 47.7, 55.4, 61.8, 109.6, 114.1, 125.7, 129.7, 131.1, 155.6, 159.3, 160.7, 160.8, 172.0; MS (EI) *m/z* (%) 390 (M^+, 100), 344 (6), 196 (8), 165 (39), 137 (43); Anal. calcd. for $C_{17}H_{18}N_4O_5S$ (390.41) C, 52.30; H, 4.65; N, 14.35; Found C, 52.21; H, 4.79; N, 14.42.

Benzyl [8-methyl-2-(4-nitrophenyl)-1,6-dioxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-a]pyrazin-7(1H)-yl]carbamate (5bd). Yield 303.8 mg (65%); light orange powder 229−232 °C (from $CHCl_3$/*n*-pentane); IR (Nujol, ν, cm^{-1}) 3262, 3081, 1772, 1736, 1709, 1688, 1676, 1612, 1595; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3H), 4.82 (d, J = 18.8 Hz, 1H), 4.88 (d, J = 18.8 Hz, 1H), 5.18 (d, J = 12.4 Hz, 1H), 5.23 (d, J = 12.4 Hz, 1H), 7.36−7.42 (m, 5H), 7.72 (d, J = 8.8 Hz, 2H), 8.38 (d, J = 8.8 Hz, 2H), 10.47 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.0, 47.7, 67.1, 109.6, 124.1, 127.9, 128.2, 128.5, 129.9, 131.9, 135.9, 138.7, 147.1, 155.6, 160.0, 160.7, 170.5; MS (EI) *m/z* (%) 467 (M^+, 13), 333 (4), 180 (4), 149 (13), 108 (100); Anal. calcd. for $C_{21}H_{17}N_5O_6S$ (467.45) C, 53.96; H, 3.65; N, 14.98; Found C, 54.10; H, 3.77; N, 14.89.

Methyl (8-methyl-1,6-dioxo-2-phenyl-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-a]pyrazin-7(1H)-yl)carbamate (5be). Yield 270.1 mg (78%); light yellow powder 108−110 °C (from Et_2O-light petroleum ether); IR (Nujol, ν, cm^{-1}) 3282, 1754, 1727, 1685, 1601; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.33 (s, 3H), 3.72 (s, 3H), 4.79 (d, J = 18.8 Hz, 1H), 4.85 (d, J = 18.8 Hz, 1H), 7.34 (d, J = 7.6 Hz, 2H), 7.48−7.54 (m, 3H), 10.29 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.9, 47.7, 52.9, 109.6, 128.5, 128.8, 128.9, 131.3, 133.2, 156.1, 160.5, 160.8, 171.5; MS (EI) *m/z* (%) 346 (M^+, 100), 273 (5), 244 (13), 183 (19), 155 (46), 137 (29); Anal. calcd. for $C_{15}H_{14}N_4O_4S$ (346.36) C, 52.02; H, 4.07; N, 16.18; Found C, 52.19; H, 4.15; N, 16.10.

tert-Butyl (8-ethyl-1,6-dioxo-2-phenyl-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-a]pyrazin-7(1H)-yl)carbamate (5bf). Yield 245.5 mg (61%); light yellow powder 150−155 °C (from EtOAc-light petroleum ether); IR (Nujol, ν, cm^{-1}) 3252, 3052, 1725, 1709, 1672, 1601; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12 (t, J = 7.6 Hz, 3H), 1.46 (s, 9H), 2.56−2.67 (m, 1H), 2.92−3.00 (m, 1H), 4.81 (s, 2H), 7.35 (d, J = 7.2 Hz, 2H), 7.48−7.54 (m, 3H), 10.02 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.2, 18.1, 27.8, 47.6, 81.2, 109.1, 128.6, 128.7, 128.8, 133.2, 136.5, 154.7, 160.1, 161.0, 171.7; MS (EI) *m/z* (%) 402 (M^+, 36), 346 (66), 302 (100), 287 (29), 258

(21), 139 (38), 135 (26), 123 (38); Anal. calcd. for $C_{19}H_{22}N_4O_4S$ (402.47) C, 56.70; H, 5.51; N, 13.92; Found C, 56.58; H, 5.65; N, 14.01.

tert-Butyl [2-(4-chlorophenyl)-8-methyl-1,6-dioxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-a]pyrazin-7(1H)-yl]carbamate (5bg). Yield 232.6 mg (55%); light yellow powder 179-181 °C (from EtOAc); IR (Nujol, ν, cm^{-1}) 3272, 1735, 1725, 1708, 1668; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46 (s, 9H), 2.31 (s, 3H), 4.78 (d, J = 18.8 Hz, 1H), 4.84 (d, J = 18.8 Hz, 1H), 7.40 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 9.98 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.0, 27.8, 47.7, 81.2, 109.5, 129.0, 130.5, 131.8, 132.0, 133.4, 154.5, 160.3, 160.8, 171.2; MS (EI) *m/z* (%) 424 [M^+ + 2 (3)], 422 (M^+, 6), 366 (11), 322 (15), 307 (13), 169 (16), 137 (39), 125 (65), 111 (100); Anal. calcd. for $C_{18}H_{19}ClN_4O_4S$ (422.89) C, 51.12; H, 4.53; N, 13.25; Found C, 51.23; H, 4.41; N, 13.31.

Ethyl 2-(8-methyl-1,6-dioxo-7-(3-phenylureido)-3-thioxo-6,7-dihydroimidazo[1,5-a]pyrazin-2(1H,3H,5H)-yl)acetate (5bh). Yield 125.2 mg (30%); light yellow solid 208-215 °C (from EtOAc-Et_2O); IR (Nujol, ν, cm^{-1}) 3289, 3196, 1746, 1731, 1717, 1671, 1600; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (t, J = 6.8 Hz, 3H), 2.37 (s, 3H), 4.16 (q, J = 6.8 Hz, 2H), 4.59 (s, 2H), 4.79 (s, 2H), 7.01 (t, J = 6.8 Hz, 1H), 7.28 (t, J = 6.8 Hz, 2H), 7.43 (d, J = 6.8 Hz, 2H), 8.86 (br s, 1H), 9.37 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.3, 14.0, 41.9, 47.7, 61.3, 109.2, 118.8, 122.7, 128.7, 133.6, 138.7, 154.3, 160.2, 161.4, 166.8, 172.0; MS (EI) *m/z* (%) 417 (M^+, 62), 298 (62), 283 (26), 152 (37), 137 (100), 119 (94); Anal. calcd. for $C_{18}H_{19}N_5O_5S$ (417.44) C, 51.79; H, 4.59; N, 16.78; Found C, 51.64; H, 4.67; N, 16.69.

Procedure for the conversion of 5aa to 6aa. To a stirred solution of bicyclic compound **5aa** (0.5 mmol) in anhydrous EtOH (5 mL), NaH (60% dispersion in mineral oil) (1 eq) was added portionwise. The reaction mixture was refluxed for 9 h, then the reaction solvent was removed under reduced pressure. The residue was suspended in H_2O and acidified at pH 5 with HCl 2N. The aqueous phase was extracted with CH_2Cl_2 (3x); the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The organic residue was purified after flash chromatography (cyclohexane/ethyl acetate mixtures) to give pure **6aa**.

Methyl (6,8-dimethyl-1-oxo-2-phenyl-3-thioxo-2,3-dihydroimidazo[1,5-a]pyrazin-7(1H)-yl)carbamate (6aa). Yield 117.7 mg (68%); red orange powder 155−156 °C (from hot-ethyl acetate); IR (Nujol, ν, cm^{-1}) 3267, 1697, 1643; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.24 (t, J = 7.2 Hz, 3H), 1.85 (s, 3H), 2.26 (s, 3H), 4.18 (q, J = 7.2 Hz, 2H), 6.92 (s, 1H), 7.31−7.53 (m, 5H), 10.34 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.0, 14.3, 62.1, 107.1, 108.6, 128.4, 128.6, 129.7, 134.0, 144.3, 155.2, 155.8, 158.0; MS (EI) *m/z* (%) 358 (M^+, 36), 285 (8), 270 (18), 150 (30), 135 (100), 123 (24), 107 (88); Anal. calcd. for $C_{16}H_{16}N_4O_3S$ (344.39) C, 55.80; H, 4.68; N, 16.27; Found C, 55.66; H, 4.77; N, 16.34.

Conclusions

In summary, we have developed a novel and practical approach for the construction of lead-like imidazo[1,5-*a*]pyrazine scaffolds. Thus, 2-thiohydantoin derivatives **4** prepared in one-pot sequential three-component reaction of primary amines **1**, 1,2-diaza-1,3-dienes **2**, and isothiocyanates **3**, were converted to thiohydantoin-fused tetrahydropyrazines with an exocyclic C=CH_2 or C=O bond depending on the specific primary amines. This transformation involves a two-step reactions, in which the first step is intermolecular and the second is intramolecular and overall creates four C−N bonds and two new fused heterocyclic rings. In addition, the method benefits from operational simplicity, chemical efficiency, high selectivity, and high molecular complexity and diversity. At present, further exploring are currently underway.

Acknowledgements

Financial support from the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR)-Roma and from the University of Urbino "Carlo Bo" is gratefully acknowledged.

Notes and references

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