Synthesis of 2-thioxoimidazolin-4-one and thiazolo[3,2-*a*]-benzimidazole derivatives from substituted maleimides

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Abstract
We describe here a hetero Michael-type reaction, involving maleimides and 2-cyanoacetichydrazide or 2-mercaptobenzimidazole, followed by an opening cyclization reaction with isothiocyanates. This reaction allows the preparation of new 2-thioxoimidazolidin-4-one and thiazolo[3,2-a]benzimidazole derivatives depending on the nucleophile used.

Keywords: Thioxoimidazolin-4-one, hetero Michael reaction, thiazolobenzimidazoles, maleimide

Introduction

2-thioxoimidazolin-4-one (thiohydantoins) framework is often encountered in compounds dealing with biological activity. As examples, thiohydantoin **1** is an efficient inhibitor of muscle and liver glycogen phosphorylases[1] and has also showed herbicidal activity by inhibition of purine biosynthesis.[2] Substituted 4-methylene-2-thiohydantoins **2** have displayed Cycline Dependant Kinases (CDK) inhibition in a micromolar range[3a] or antileishmanial activity[3b] whereas compounds **3** are Fatty Acid Amide Hydrolase (FAAH) inhibitors[4] and compounds **4** are claimed to be active for treatment of hormone refractory prostate cancer.[5]

So, it is not surprising if a lot of patents have described the use of this attractive skeleton for a range of activity which cover from compounds for biological use[6] till fire retardants materials.[7] Besides conventional methods used for their synthesis, solid phase,[8] use of ionic liquids[9] and microwaves-assisted approaches have been published.[10] On the other hand, the benzimidazole structure is also a scaffold often endowed with different types of biological activities including

antitumor,[11] antimicrobial[12] or antiviral[13] properties. Thiazole nucleus fused with a benzimidazole skeleton, namely thiazolobenzimidazoles, have been reported to exhibit biological properties too, such as anti-HIV[14] or anti-microbial[15] agents. We wish to report here the synthesis of new 2-thioxoimidazolin-4-one and thiazolobenzimidazoles derivatives by hetero Michael reactions on *N*-substituted maleimides.

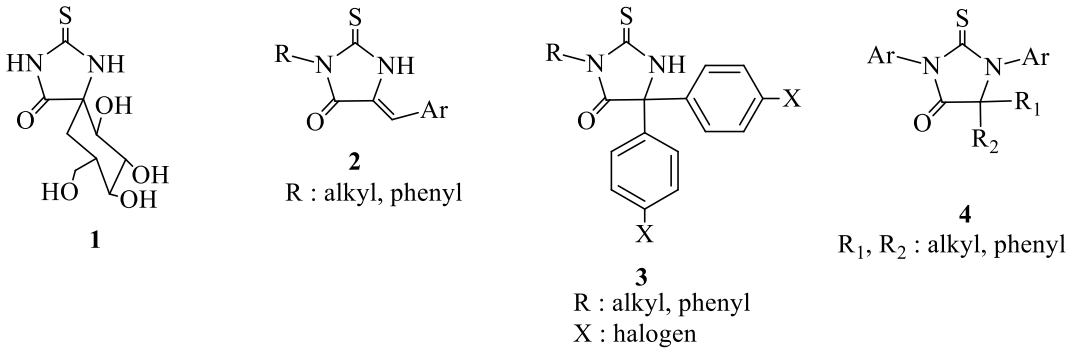
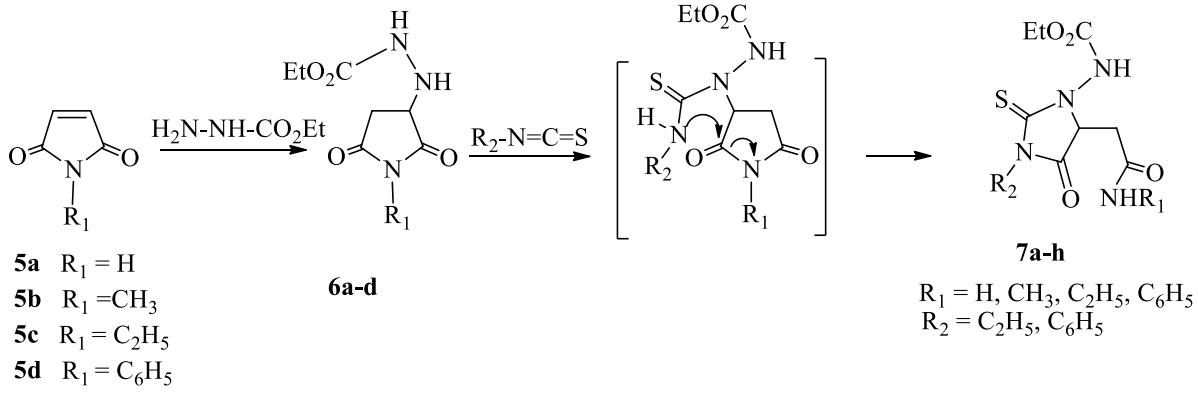


Figure 1. Thiohydantoins with described biological activities.

Results and Discussion

2-Thioxoimidazolin-4-one derivatives

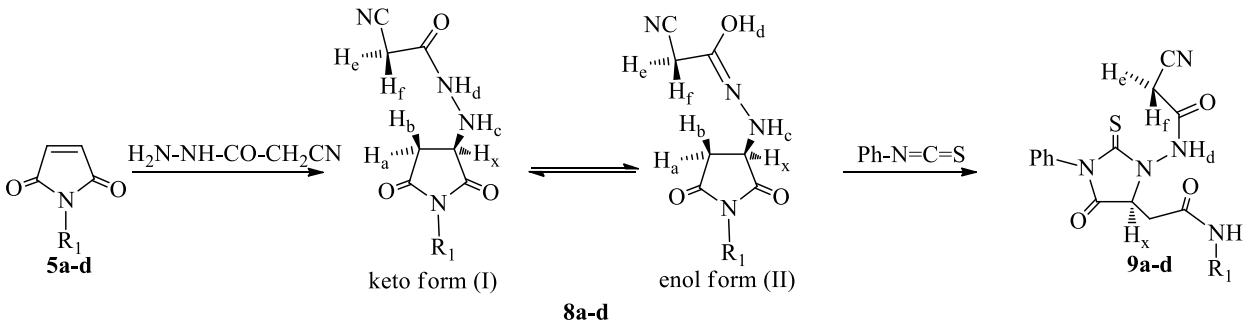
Previous investigations from our laboratory[16] have shown that 2-thioxoimidazolin-4-one derivatives **7** could be easily obtained by Michael addition of 3-ethylhydrazinoacetate on *N*-substituted maleimide **5,** leading to 3,4-dihydro maleimides **6** which reacted smoothly with substituted isothiocyanates to give compounds **7** (Scheme1).



Scheme 1. Synthesis of compounds **7a-h.**

We wish to report here an extension of this methodology using 2-cyanoacetic hydrazide as nucleophile. This compound, by its carbonyl and cyano functions, is enabling to react with bidendate reagents. Moreover, the active hydrogen of this molecule can also take part in a wide range of condensation and substitutions reactions.[17]

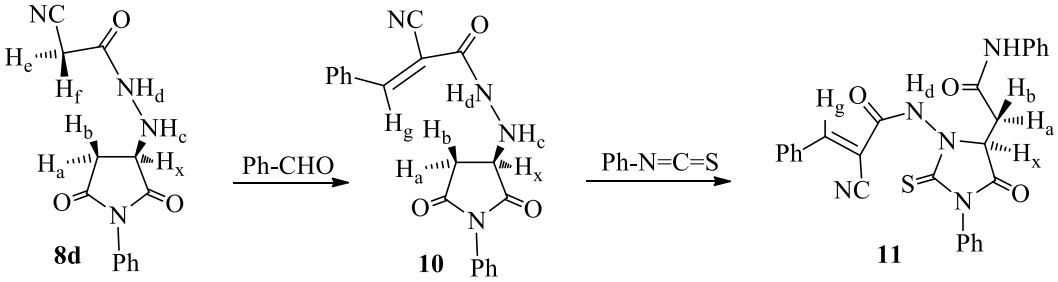
Thus, condensation of maleimide **5a-d** with 2-cyanoacetic hydrazide in refluxing ethanol led to compounds **8a-d** in fair to good yields. Spectral data (^{1}H and ^{13}C NMR) were in complete accordance with the proposed structures and showed that these compounds existed under a tautomeric equilibrium between the keto (I) and enol (II) form in an average ratio of 3/1. For example concerning succinimide **8d**, protons of CH_2-CH fragment showed characteristic patterns of an ABX system (Scheme 2).



Scheme 2. Preparation of 2-thioxoimidazolidines **9a-d**.

The chemical shift observed for the doublet of doublet corresponding to proton H_a was δ= 2.69 ppm (J = 4 and 18 Hz) in the form (I) while it was δ= 2.85 ppm (J = 5 and 18 Hz) in the form (II). For proton H_b, the observed chemical shift was δ= 3.05 ppm (J = 8 and 18 Hz) in form (I) and 2.95 ppm (J = 8 and 18 Hz) in form (II). Same observations could also be made on protons H_e and H_f. In form (I) H_e and H_f give two doublets respectively at 3.62 (H_e) and 3.67 (H_f) ppm (J = 18 Hz), while in form (II) the signals corresponding to these protons was shifted to 3.90 (H_e) and 4.08 (H_f) ppm (J = 19 Hz). As described previously, condensation of succinimides **8a-d** with phenylisothiocyanate furnished the corresponding 2-thioxoimidazolidines **9a-d** resulting of the opening-recyclization reaction. For these compounds **9**, it should be noted that no tautomeric form was observed, contrary to compounds **8**. Here too, the structures of these new compounds were confirmed by careful examination of spectral data, showing mainly in the IR spectra a band around ν = 1500 cm^{-1} and in the ^{13}C NMR spectra a signal at 184 ppm attributed to the thiocarbonyl group.

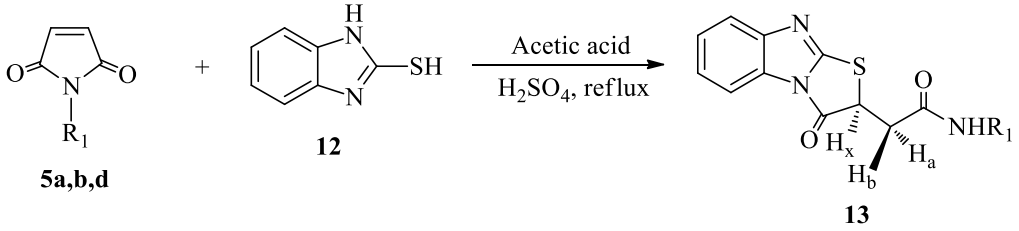
Next, we envisaged to test the reactivity of the 2-cyanoacetic appendage. So, Knoevenagel condensation of compound **8d** with benzaldehyde in refluxing ethanol containing a catalytic amount of piperidine[18] resulted in the formation of benzylidene **10** which reacted smoothly with phenylisothiocyanate to furnish the 2-thioxoimidazolidine derivative **11** in good yield (Scheme 3), the structure of which was in accordance with all spectral data.



Scheme 3. Synthesis of compound **11.**

Thiazolo[3,2-a]benzimidazole derivatives

Finally we envisaged to test the reactivity of other nucleophiles on hetero Michael addition to maleimide and for this purpose we tried the addition of 2-mercaptobenzimidazole **12**. This latter was chosen as this framework is endowed with a lot of biological activities.[11,13] Several methods have been developed for the synthesis of thiazolo[3,2-a]framework using the nucleophilicity of the thiol function of 2-mercaptobenzimidazole.[19] A recent work has also described the synthesis of target molecule by opening thiiranes with 2-chlorobenzimidazole.[20] Thus maleimides **1a,b,d** reacted with **12** in refluxing acetic acid in presence of concentrated sulphuric acid to afford in each case the corresponding thiazolobenzimidazole **13a,b,d** in average yields (Scheme 4).



Scheme 4. Synthesis of thiazolobenzimidazole **13a,b,d**.

Formation of compounds **13** resulted from initial attack of the mercapto group on the double bond of maleimide followed, as described previously, by ring opening of the maleimide by the amino group of the benzimidazole ring. Spectral data obtained from compounds **13** were in complete accordance with the expected thiazolobenzimidazole structures: in ^{1}H NMR spectrum of each derivative, together with the expected signals, one can noticed the presence of three new signals at around 2.95, 3.30-4.95 and 11.30 ppm, due respectively to CH, CH_2 and NH_2 protons. Moreover in ^{13}C NMR spectrum, signals at 38.6, 62.4 and 177.9 ppm were assigned to CH, CH_2 and C=O carbons beside all others carbons at the expected regions.

In conclusion, we have described new 2-thioxoimidazolidine and new thiazolo[3,2-*a*]-benzimidazole derivatives. The use of 2-cyanoacetic hydrazide as nucleophile in the hetero-

Michael reaction on maleimide, followed by the reaction with isothiocyanates, has permitted an entry to polyfunctionalized heterocyclic structures due to its intrinsic reactivity. The extension of this methodology, together with the use of the variety of reactions which could be realized[21] starting from this brick, is actually under progress.

Experimental Section

General. Unless otherwise specified, reagents were obtained from commercial suppliers. Solvents were dried and freshly distilled following the usual procedures. Product organic solutions were dried over sodium sulfate prior to evaporation of the solvents under reduced pressure on a rotatory evaporator. Thin layer chromatography was performed on TLC precoated aluminium backed silica plates and spots were visualized using UV light (254 nm) before using ethanolic phosphomolybdic acid solution (heating). Column chromatography was carried out on silica gel (70-230 mesh).Melting points were measured in open capillary tubes on a BÜCHI B-540 apparatus. ^{1}H and ^{13}C NMR spectra were measured at 400.13 and 100.61 MHz respectively using TMS as internal reference. Chemicals shifts are reported in ppm relative to TMS. Signals are quoted s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) and coupling constant (J) values are given in Hz. Infrared spectra were recorded on a Shimadzu FTIR 8400s spectrophotometer. High Resolution Electro Spray Impact Mass Spectra (HR-ESI-MS) were obtained from the *Centre Régional de Mesures Physiques de l'Université Blaise Pascal (Clermont II), France.* Elemental analyses (C, H, O, N) were performed at the *Centre de Microanalyses du CNRS, Lyon, France.*

General procedure for preparation of compounds (8)

A mixture of cyanoacetic acid hydrazide (1 equivalent) and the corresponding maleimide **5a-d** (1 equivalent) in ethanol was refluxed for 12 hours. After cooling the precipitate was filtered and the resulting solid was crystallized from methanol.

2-Cyano-*N'*-(2,5-dioxopyrrolidin-3-yl)acetohydrazide (8a). Yield 52%; white solid; mp 102-103 °C, IR (KBr, ν cm^{-1})) 3348 (m), 3282 (w), 3194 (m), 3136 (w), 2260 (m), 1703 (s), 1685 (s), 1622 (m); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.25 (1H, br s, NH (I, II)), 9.68 (1H, d, ^{3}J = 5.5 Hz, H_d(I)), 9.07 (1H, s, H_d(II)), 5.67 (1H, d, ^{3}J = 3.5 Hz, H_c(II)), 5,64 (1H, t, ^{3}J = 4.5 Hz, H_c(I)), 4.05-3.95 (3H, m, H_x(I, II) and H_f(II)), 3.86 (1H, d, ^{2}J = 19.0 Hz, H_e(II)), 3.63 (1H, d, ^{2}J = 18.0 Hz, H_f(I)), 3.58 (1H, d, ^{2}J = 18.0 Hz, H_e(I)), 2.80 (1H, dd, ^{2}J = 18.0, ^{3}J = 8.0 Hz, H_b(I)), 2.77 (1H, dd, ^{2}J = 18.0, ^{3}J = 8.0 Hz, H_b(II)), 2.65 (1H, dd, ^{2}J = 18.0, ^{3}J = 5.0 Hz, H_a(II)), 2.43 (1H, dd, ^{2}J = 18.0, ^{3}J = 4.0 Hz, H_a(I)); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.0 (C=O imide, I), 177.8 (C=O imide, II), 176.8 (C=O imide, II), 176.6 (C=O imide, I), 167.4 (C=O amide, I), 162.0 (C(OH)=N, II), 116.2 (CN, II), 115.8 (CN, I), 58.9 (CH_x, II), 58.3 (CH_x, I), 34.9 (CH_aH_b, I), 34.2 (CH_aH_b,II), 23.7 (CH_eH_f, I), 23.6 (CH_eH_f, II); HRMS *m/z* calcd. for $C_7H_8N4O_3Na$ $(M+Na)^+$:

219.0491, found : 219.0494; Anal. Calcd. for $C_7H_8N_4O_3$: C, 42.86; H, 4.11; N, 28.56; O, 24.47. Found: C, 42.75; H, 4.25; N, 28.65; O, 24.59.

2-Cyano-*N'*-(1-methyl-2,5-dioxopyrrolidin-3-yl)acetohydrazide (8b). Yield 56%; white solid; mp 121-122 °C, IR (KBr, ν cm^{-1}) 3348 (w), 3308 (m), 3198 (w), 2258 (m), 1786 (w), 1705 (s), 1654 (s); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.69 (1H, d, ^3J = 5.5 Hz, H_d(I)), 9.29 (1H, br s, H_d(II)), 5.78 (2H, m, H_c(I, II)), 4.08-3.99 (2H, m, H_x(I, II)), 3.98 (1H, d, ^2J = 18.0 Hz, H_f(II)), 3.87 (1H, d, ^2J = 18.0 Hz, H_e(II)), 3.63 (1H, d, ^2J = 18.0 Hz, H_e(I)), 3.58 (1H, d, ^2J = 18.0 Hz, H_f(I)), 2.87-2.75 (8H, m, H_b(I), H_b(II), CH_3 (I, II)), 2.67 (1H, dd, ^2J = 18.0, ^3J = 4.0 Hz, H_a(II)), 2.54 (1H, dd, ^2J = 18.0 ^3J = 4.0 Hz, H_a(I)); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 176.5 (C=O imide, II), 176.3 (C=O imide, I), 175.5 (C=O imide, I), 175.3 (C=O imide, II), 162.0 (C=O amide, I), 161.9 (C(OH)=N, II), 116.0 (CN, I), 115.8 (CN, II), 57.7 (CH_x, I), 57.2 (CH_x, II), 33.7 (CH_aH_b, I), 33.0 (CH_aH_b, II), 24.3 (CH_eH_f, II), 24.2 (CH_eH_f, I), 23.7 (CH_3, II), 23.5 (CH_3, I); HRMS *m/z* calcd. for $C_8H_{10}N_4O_3Na$ $(M+Na)^+$: 233.0651, found : 233.0651; Anal. Calcd. for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.80; N, 26.66; O, 22.84. Found: C, 45.49; H, 4.88; N, 26.41; O, 22.78.

2-Cyano-*N'*-(1-ethyl-2,5-dioxopyrrolidin-3-yl)acetohydrazide (8c). Yield 44%; white solid; mp 99-100 °C, IR (KBr, ν cm^{-1}) 3348 (w), 3306 (m) , 3267(m), 2258 (m), 1774 (s), 1701 (s), 1624 (m); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.78 (1H, br s, H_d(I)), 9.22 (1H, br s, H_d(II)), 5.79 (2H, m, H_c(I, II)), 4.20 (1H, dd, ^3J = 8.0 and 4.0 Hz, H_x(II)), 4.15 (1H, dd, ^3J = 8.0 and 4.0 Hz, H_x(I)), 3.90 (1H, d, ^2J = 18.0 Hz, H_f(II)), 3.85 (1H, d, ^2J = 18.0 Hz, H_e(II)), 3.65 (1H, d, ^2J = 18.0 Hz, H_f(I)), 3.58 (1H, d, ^2J = 18.0 Hz, H_e(I)), 3.40 (4H, q, ^3J = 7.0 Hz, CH_2(I, II)), 2.82 (1H, dd, ^2J = 18.0, ^3J = 8.0 Hz, H_b(I)), 2.80 (1H, dd, ^2J = 18.0, ^3J = 8.0 Hz, H_b(II)), 2.64 (1H, dd, ^2J = 18.0, ^3J = 4.0 Hz, H_a(II)), 2.40 (1H, dd, ^2J = 18.0, ^3J = 4.0 Hz, H_a(I)), 1.02 (6H, t, ^3J = 7.0 Hz, CH_3(I, II)); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 176.2 (C=O imide, II), 176.0 (C=O imide, I), 175.2 (C=O imide, I), 175.1 (C=O imide, II), 167.3 (C=O amide, I), 162.0 (C(OH)=N, II), 116.4 (CN, II), 115.8 (CN, I), 57.7 (CH_x, II), 57.1 (CH_x, I), 33.8 (CH_2, I, II), 33.0 (CH_aH_b, II), 32.8 (CH_aH_b, I), 23.7 (CH_eH_f, I), 23.5 (CH_eH_f, II), 12.6 (CH_3, I, II); HRMS *m/z* calcd. for $C_9H_{12}N_4O_3Na$ $(M+Na)^+$: 247.0808, found : 247.0807; Anal. Calcd. for $C_9H_{12}N_4O_3$: C, 48.21; H, 5.39; N, 24.99; O, 21.41. Found: C, 48.37; H, 5.43; N, 25.07; O, 21.13.

2-Cyano-*N'*-(2,5-dioxo-1-phenylpyrrolidin-3-yl)acetohydrazide (8d). Yield 55%; white solid; mp 179-180 °C, IR (KBr, ν cm^{-1}) 3483 (m), 3288 (m), 3211 (m), 2258 (m), 1784 (s), 1710 (s), 1680 (s); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.77 (1H, d, ^3J = 5.0 Hz, H_d(I)), 9.17 (1H, br s, H_d(II)), 7.53-7.25 (10H, m, $H_{arom.}$ (I, II)), 5.88 (2H, m, H_c(I, II)), 4.20 (1H, dd, ^3J = 8.0 and 4.0 Hz, H_x(II)), 4.17 (1H, dd, ^3J = 8.0 and 4.0 Hz, H_x(I)), 3.90 (1H, d, ^2J = 19.0 Hz, H_f(II)), 3.87 (1H, d, ^2J = 19.0 Hz, H_e(II)), 3.67 (1H, d, ^2J = 18.0 Hz, H_f(I)), 3.62 (1H, d, ^2J = 18.0 Hz, H_e(I)), 3.05 (1H, dd, ^2J = 18.0, ^3J = 8.0 Hz, H_b(I)), 3.00 (1H, dd, ^2J = 18.0, ^3J = 8.0 Hz, H_b(II)), 2.85 (1H, dd, ^2J = 18.0, ^3J = 4.0 Hz, H_a(II)), 2.69 (1H, dd, ^2J = 18.0, ^3J = 4.0 Hz, H_a(I)); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 175.7 (C=O imide, II), 175.4 (C=O imide, I), 174.6 (C=O imide, I), 174.4 (C=O imide, II), 167.4 (C(OH)=N, II), 162.1 (C=O amide, I), 132.2 (C*ipso*, I), 132.1 (C*ipso*, II), 128.9 ($CH_{arom.}$, II), 128.8 ($CH_{arom.}$, I), 128.3 ($CH_{arom.}$, II), 128.2 ($CH_{arom.}$, I), 127.0 ($CH_{arom.}$, I), 126.9 ($CH_{arom.}$, II), 116.4 (CN, I), 115.8 (CN, II), 57.9 (CH_x, II), 57.4 (CH_x, I), 34.0

(CH_aH_b, I), 33.4 (CH_aH_b, II), 23.8 (CH_eH_f, I), 23.5 (CH_eH_f, II); HRMS *m/z* calcd. for $C_{13}H_{12}N_4O_3Na$ $(M+Na)^+$: 295.0811, found : 295.0807; Anal. Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58; O, 17.63. Found: C, 57.25; H, 4.46; N, 20.29; O, 17.87.

General procedure for preparation of compounds 9

To a solution of compounds **8a-d** (10 mmol) in ethanol (20 mL) was added phenyl isothiocyanate (10 mmol). The resulting mixture was brought to reflux for 12 hours. The solid obtained after cooling was filtered and crystallized from ethanol to give compounds **9a-d**.

***N*-[5-(2-Amino-2-oxoethyl)-4-oxo-3-phenyl-2-thioxoimidazolidin-1-yl]-2-cyanoacetamide (9a).** Yield 57%; white solid; mp 158-160 °C; IR (KBr, ν cm^{-1}) 3340 (m), 3284 (m), 2262 (m), 1710 (m), 1697 (s), 1670 (s), 1512 (m); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.25 (1H, s, H_d), 7.56 (2H, s, NH_2), 7.60-7.35 (m, 5H, $H_{arom.}$), 4.67 (1H, t, ^3J = 4.0 Hz, H_x), 3.89 (1H, d, ^2J = 18.0 Hz, H_e), 3.85 (1H, d, ^2J = 18.0 Hz, H_f), 2.87 (2H, d, ^3J = 4.0 Hz, H_a, H_b); ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.2 (C=S), 171.5 (NH_2C=O), 169.7 (C=O thioimidazole), 162.2 (NNHC=O), 133.8 (C*ipso*), 128.9($CH_{arom.}$), 128.8 ($CH_{arom.}$), 128.5 ($CH_{arom.}$), 115.1 (CN), 59.5 (CH_x), 34.9 (CH_aH_b), 23.9 (CH_eH_f); HRMS *m/z* calcd. for $C_{14}H_{13}N_5O_3S$ $(M+H)^+$: 332.0824, found : 332.0817; Anal. Calcd. for $C_{14}H_{13}N_5O_3S$: C, 50.75; H, 3.95; N, 21.14; O, 14.49; S, 9.68. Found: C, 50.84; H, 4.09; N, 21.35; O, 14.98; S, 9.74.

2-Cyano-*N*-{5-[2-(methylamino)-2-oxoethyl]-4-oxo-3-phenyl-2-thioxoimidazolidin-1-yl}acetamide (9b). Yield 66%; white solid; mp 222-224 °C, IR (KBr, ν cm^{-1}) 3379 (m), 3286 (w), 2260(m), 1766 (s), 1654 (s), 1500 (m); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (1H, s, H_d), 8.05 (1H, q, ^3J = 4.5 Hz, NH), 7.65-7.35 (5H, m, $H_{arom.}$), 4.75 (1H, t, ^3J = 4.0 Hz, H_x), 3.95 (1H, d, ^2J = 18.0 Hz, H_e), 3.88 (1H, d, ^2J = 18.0 Hz, H_f), 2.93 (2H, d, ^3J = 4.0 Hz, H_a, H_b), 2.65 (3H, d, *J* = 4.5 Hz, NCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.1 (C=S), 171.3 (NH(CH_3)C=O), 167.8 (C=O thioimidazole), 162.1 (NNHC=O), 133.7 (C*ipso*), 128.8 ($CH_{arom.}$), 128.7 ($CH_{arom.}$), 128.4 ($CH_{arom.}$), 115.0 (CN), 59.5 (CH_x), 33.3 (CH_aH_b), 25.5 (NCH_3), 23.8 (CH_eH_f); HRMS *m/z* calcd. for $C_{15}H_{16}N_5O_3S$ $(M+H)^+$: 346.0971, found : 346.0974; Anal. Calcd. for $C_{15}H_{15}N_5O_3S$: C, 52.16; H, 4.38; N, 20.28; O, 13.90; S, 9.28. Found: C, 51.95; H, 4.29; N, 20.37; O, 14.24; S, 9.15.

2-Cyano-*N*-{5-[2-(ethylamino)-2-oxoethyl]-4-oxo-3-phenyl-2-thioxoimidazolidin-1-yl}acetamide (9c). Yield 53%; white solid; mp 145-146 °C, IR (KBr, ν cm^{-1}) 3369 (m), 3169 (w), 2258 (m), 1766 (s), 1708 (s), 1647 (s), 1500 (m); ^{1}H NMR(400MHz, DMSO-d_6) δ 11.20 (1H, s, H_d), 8.05 (1H, t, ^3J = 4.5 Hz, NHC_2H_5), 7.60-7.30 (5H, m, $H_{arom.}$), 4.75 (1H, t, ^3J = 4.0 Hz, H_x), 3.89 (1H,d, ^2J = 18.0 Hz, H_e), 3.85 (1H, d, ^2J = 18.0 Hz, H_f), 3.10 (2H, m, NCH_2), 2.86 (2H, d, ^3J = 4.0 Hz, H_a, H_b), 1.00 (3H, t, ^3J = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.1 (C=S), 171.4 (NH(C_2H_5)C=O), 167.1 (C=O thioimidazole), 162.2 (NNHC=O), 133.8 (C*ipso*), 128.9 ($CH_{arom.}$), 128.8 ($CH_{arom.}$), 128.5 ($CH_{arom.}$), 115.1 (CN), 59.6 (CH_x), 33.5 (CH_aH_b), 33.1 (NCH_2), 23.9 (CH_eH_f), 14.5 (CH_3); HRMS *m/z* calcd. for $C_{16}H_{18}N_5O_3S$ $(M+H)^+$: 360.3541, found : 360.3543; Anal. Calcd. for $C_{20}H_{17}N_5O_3S$: C, 53.47; H, 4.77; N, 19.49; O, 13.35; S, 8.92. Found: C, 52.70; H, 4.73; N, 19.53; O, 13.82; S, 8.73.

***N*-[5-[2-Anilino-2-oxoethyl)-4-oxo-3-phenyl-2-thioxoimidazolidin-1-yl]-2-cyanoacetamide) (9d).** Yield 57%; white solid; mp 258-259 °C; IR (KBr, ν cm^{-1}) 3335 (m), 3190 (m), 2260 (m), 1763 (s), 1710 (s), 1668 (s), 1502 (m); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.29 (1H, s, H_d), 10.20 (1H, s, NHPh)), 7.60–7.45 (4H, m, $H_{arom.}$), 7.50 (1H, tt, ^3J = 7.0 Hz, ^4J = 1.5 Hz, $H_{arom.}$), 7.40-7.30 (4H, m, $H_{arom.}$), 7.05 (1H, tt, ^3J = 7.5 Hz, ^4J = 1.0 Hz, $H_{arom.}$), 4.81 (1H, dd, ^3J = 4.0 Hz and 3.5 Hz, H_x), 3.90 (1H, d, ^2J = 18.0 Hz, H_e), 3.85 (1H, d, ^2J = 18.0 Hz, H_f), 3.17 (1H, dd, ^2J = 18.0 Hz, ^3J = 3.5 Hz, H_a), 3.13 (1H, dd, ^2J = 18.0 Hz, ^3J = 4.0 Hz, H_b); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 183.1 (C=S), 171.3 (NH(Ph)C=O), 166.6 (C=O thioimidazole), 162.3 (NNHC=O), 138.7 (C*ipso*), 133.7 (C*ipso*), 129.0 ($CH_{arom.}$), 128.8 ($CH_{arom.}$), 128.7 ($CH_{arom.}$), 128.5 ($CH_{arom.}$), 123.4 ($CH_{arom.}$), 119.1 ($CH_{arom.}$), 115.1 (CN), 59.5 (CH_x), 34.5 (CH_aH_b), 23.9 (CH_eH_f); HRMS *m/z* calcd. for $C_{20}H_{18}N_5O_3S$ $(M+H)^+$: 408.1131, found : 408.1130; Anal. Calcd. for $C_{20}H_{17}N_5O_3S$: C, 58.96; H, 4.21; N, 17.19; O, 11.78; S, 7.87. Found: C, 58.83; H, 4.26; N, 17.14; O, 12.03; S, 7.36

2-Cyano-*N*′(2,5-dioxo-1-phenylpyrrolidin-3-yl)-3-phenylacrylo hydrazide (10). To a solution of **8d** (1 mmol) in ethanol (20 mL) containing a catalytic amount of piperidine, benzaldehyde (10 mmol) was added. The reaction mixture was heated at reflux for 12 hours. The resulting solid formed was collected by filtration. Yield 58%; yellow solid; mp 163-165 °C; IR (KBr, ν cm^{-1}) 3298 (w), 3059 (w), 1780 (s), 1708 (s), 1651 (m), 1604 (m); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.25 (1H, br s, H_d), 8.16 (1H, s, H_g), 7.95 (2H, m, $H_{arom.}$), 7.65-7.55 (3H, m, $H_{arom.}$), 7.50 (2H, t, ^3J = 7.5 Hz, $H_{arom.}$), 7.30 (2H, d, ^3J = 7.5 Hz, $H_{arom.}$), 6.09 (1H, br s, H_c); 4.28 (1H, dd, ^3J = 8.5 and 4.0 Hz, H_x), 3.10 (1H, dd, ^2J = 18.0, ^3J = 8.5 Hz, H_a), 2.80 (1H, dd, ^2J = 18.0, ^3J = 4.0 Hz, H_b); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 175.3 (C=O imide), 174.7 (C=O imide), 161.0 (NNHC=O), 150.8 (CH=C), 132.4 (C*ipso*), 132.2 (C*ipso*), 131.8 ($CH_{arom.}$), 130.0 ($CH_{arom.}$), 129.2 ($CH_{arom.}$), 128.9 ($CH_{arom.}$), 128.5 ($CH_{arom.}$), 126.9 ($CH_{arom.}$), 115.8 (CN), 104.8 (C=CH), 57.3 (CH_x), 34.4 (CH_aH_b); HRMS *m/z* calcd. for $C_{20}H_{16}N_4O_3$: 383.1106, found : 383.1120.

***N*-(4-(2-Anilino-2-oxoethyl)-5-oxo-1-phenyl-2-thioxopyrrolidin-3-yl)-2-cyano-3-phenyl-acrylamide (11).** A solution of compound **10** (1 mmol.) in ethanol (20 mL) was refluxed with a large excess of phenyl isothiocyanate during 5 hours. The yellow solid formed is collected by filtration. Yield 45%; yellow solid; mp 216-218 °C; IR (KBr, ν cm^{-1}) 3258 (w), 3129 (w), 2220 (m), 1753 (s), 1686 (s), 1647 (m), 1595 (m), 1271 (w); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.62 (1H, s, H_d), 10.19 (1H, s, NHPh), 8.32 (1H, s, H_g), 7.95 (2H, d, ^3J = 6.5 Hz, $H_{arom.}$), 7.65-7.55 (7H, m, $H_{arom.}$), 7.50 (1H, t, ^3J = 7.0 Hz, $H_{arom.}$), 7.45 (2H, d, ^3J = 7.5 Hz, $H_{arom.}$), 7.35 (2H, t, ^3J = 7.5 Hz, $H_{arom.}$), 7.05 (1H, t, ^3J = 7.5 Hz, $H_{arom.}$), 4.87 (1H, t, ^3J = 4.0 Hz, H_x), 3.20 (2H, dd, ^2J = 17.9 Hz, ^3J = 4.0 Hz, H_a); 3.17 (1H, dd, ^2J = 17.9, ^3J = 4.0 Hz, H_b); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 184.7 (C=S), 170.0 (C=O thioimidazole), 166.0 (C=O amide), 160.7 (NNHC=O), 153.1 (CH=C), 138.8 (C*ipso*), 133.7 (C*ipso*), 131.3 (C*ipso*), 130.2 ($CH_{arom.}$), 129.3 ($CH_{arom.}$), 128.9 ($CH_{arom.}$), 128.8 ($CH_{arom.}$), 128.7 ($CH_{arom.}$), 128.6 ($CH_{arom.}$), 128.4 ($CH_{arom.}$), 123.2 ($CH_{arom.}$), 119.0($CH_{arom.}$), 115.3 (CN), 103.3 (C=CH), 59.9 (CH_x), 35.0 (CH_aH_b); HRMS *m/z* calcd. for $C_{27}H_{22}N_5O_3S$ $(M+H)^+$: 496.1443, found : 496.1448.

General procedure for preparation of compounds 13

To a mixture of 2-mercapto benzimidazoles **12** (1 mmol), appropriate substituted maleimide **5** (1.1 mmol) and sulphuric acid (1.1 mmol) was added glacial acetic acid (5 mL). The resulting solution was heated under reflux for 10 hours. After cooling, the solution was treated with NH_4OH until neutralization. The resulting solid formed was collected by filtration, washed several times with water, dried and crystallized from ethanol to give the corresponding compounds **13a-d**.

2-(3-Oxo-2,3-dihydro[1,3]thiazolo[3,2-*a*]benzimidazol-2-yl) acetamide (13a). Yield 43%; white solid; mp 190-192 °C, IR (KBr, ν cm^{-1}) 3227 (w), 1780 (s), 1708 (s); ^{1}H NMR (400MHz, DMSO-d_6) δ 12.70 (1H, s, NH), 11.50 (1H, s, NH), 7.42 (2H, m, $H_{arom.}$), 7.25 (2H, m, $H_{arom.}$), 4.73 (1H, dd, ^3J = 9.5 and 5.5 Hz, H_x), 3.23 (1H, dd, ^2J = 18.0 Hz, ^3J = 9.5 Hz, H_a), 2.95 (1H, dd, ^2J = 18, ^3J = 5.5 Hz, H_b); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.4 (C=O amide), 176.3 (C=O thioimidazole), 147.5 (C=N), 143.4 (C_{ipso}), 135.1 (C_{ipso}), 121.9 ($CH_{arom.}$), 121.2 ($CH_{arom.}$), 117.5 ($CH_{arom.}$), 110.5 ($CH_{arom.}$), 42.6 (CH_x), 37.5 (CH_aH_b); HRMS *m/z* calcd. for $C_{11}H_{10}N_3O_2S$ $(M+H)^+$: 248.0504, found : 248.0494; Anal. Calcd. for $C_{11}H_9N_3O_2S$: C, 53.43; H, 3.67; N, 16.99; O, 12.94; S, 12.97. Found: C, 53.04; H, 3.75; N, 16.80; O, 13.08; S, 12.88.

***N*-Methyl-2-(3-oxo-2,3-dihydro[1,3]thiazolo[3,2-*a*]benzimidazol-2-yl) acetamide (13b).** Yield 46%; white solid; mp 156-157 °C, IR (KBr, ν cm^{-1}) 3195 (m), 1766 (s), 1697 (s); ^{1}H NMR (400MHz, DMSO-d_6) δ 12.61 (1H, br s, NH), 7.40 (2H, m, $H_{arom.}$), 7.30 (2H, m, $H_{arom.}$), 4.76 (1H, dd, ^3J = 9.5 and 5.0 Hz, H_x), 3.31 (1H, dd, ^2J = 18.0 Hz, ^3J = 9.5 Hz, H_a), 2.90 (1H, dd, ^2J = 18.0 Hz, ^3J = 5.0 Hz, H_b), 2.85 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.4 (C=O amide), 175.2 (C=O thioimidazole), 147.6 (C=N), 134.5 (C_{ipso}), 132.1 (C_{ipso}), 122.2 ($CH_{arom.}$), 109.4 ($CH_{arom.}$), 41.2 (CH_x), 36.5 (CH_aH_b), 24.9 (CH_3); HRMS *m/z* calcd. for $C_{12}H_{12}N_3O_2S$ $(M+H)^+$: 262.2805, found : 262.2803; Anal. Calcd. for $C_{12}H_{11}N_3O_2S$: C, 55.16; H, 4.24; N, 16.08; O, 12.25; S, 12.27. Found: C, 54.59; H, 4.23; N, 15.92; O, 12.64; S, 12.60.

2-(3-Oxo-2,3-dihydro[1,3]thiazolo[3,2-*a*]benzimidazol-2-yl)-*N*-phenylacetamide (13d). Yield 42%; white solid; mp 258-260 °C, IR (KBr, ν cm^{-1}) 3169 (m), 1751 (s), 1668 (s); ^{1}H NMR (400MHz, DMSO-d_6) δ 12.63 (1H, □□s, NH), 7.56-7.13 (9H, m, $H_{arom.}$), 4.86 (1H, dd, ^3J = 9.5 and 5.0 Hz, H_x), 3.46 (1H, dd, ^2J = 18.0 Hz, ^3J = 9.5 Hz, H_a), 3.09 (1H, dd, ^2J = 18.0 Hz, ^3J = 5.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.5 (C=O amide), 174.2 (C=O thioimidazole), 148.9 (C=N), 138.9 (C_{ipso}), 138.5 (C_{ipso}), 130.8 (C_{ipso}), 128.7 ($CH_{arom.}$), 124.4 ($CH_{arom.}$), 123.2 ($CH_{arom.}$), 121.6 ($CH_{arom.}$), 115.4 ($CH_{arom.}$), 41.4 (CH_x), 36.6 (CH_aH_b); HRMS *m/z* calcd. for $C_{17}H_{14}N_3O_2S$ $(M+H)^+$: 324.0813, found : 324.0807; Anal. Calcd. for $C_{17}H_{13}N_3O_2S$: C, 48.45; H, 3.59; N, 9.97; O, 22.78; S, 15.22. Found: C, 48.05; H, 3.61; N, 9.94; O, 22.82; S, 15.53.

References

1. He, S.; Kuang, R.; Venkatamaran, R.; Tu, J.; Truong, T. M.; Chan, H. T.; Groutas, W. *Bioorg. Med. Chem.* **2000**, *8*, 1713.

2. Fuentes, J.; Salameh, B. A. B.; Pradera, A.; Fernandez de Cordoba, F. J.; Gash, G. *Tetrahedron* **2006**, *62*, 97 and references cited therein.
3. (a) Roue, N.; Bergman, J *Tetrahedron* **1999**, *55*, 14729. (b) Cherouvrier, J. R.; Carreaux, F.; Bazureau, J. P. *Tetrahedron Lett.* **2002**, *43*, 8745. Renault, S.; Bertrand, S.; Carreaux, F.; Bazureau, J. P. *J. Comb. Chem.* **2007**, *9*, 935. (c) Porwal, S.; Chauhan, S. S.; Chauhan, P. M. S.; Shakya, N.; Verma, A.; Gupta, S. *J. Med. Chem.* **2009**, *52*, 5793.
4. Muccioli, G. G.; Fazio, N.; Sciba, G. K. E.; Poppitz, W.; Cannata, F.; Poupaert, J. H.; Wouters, J.; Lambert, D. M. *J. Med. Chem.* **2006**, *49*, 417.
5. Sawyers, C.; Jung, M. E.; Chen, C. D.; Ouk, S.; Welsbie, D.; Tran, C.; Wongvipat, J.; Yoo, D. WO 2006 124118.
6. Claussner, A.; Goubet, F.; Teutsch, J. G. WO 1997 19064. Thurieau, C.; Poitout, L. WO 2001 09090. Binet, J.; Boubia, B.; Chaput, E.; Edgar, A.; Ou, K.; Ratel, P.; Samreth, S.; Thomas, D. WO 2004 031160. Wan, Y.; Pan, S.; Zhang, G.; Wang, X.; Xie, Y. F.; Jiang, J.; Phillips, D.; Yang, Y. WO 2009 123948.
7. Lewalter, J.; Rottmaier, L.; Merten, R.; Dunwald, W.; Schulte, B. EP 1980 0013727.
8. Bélai, I. *Tetrahedron Lett*. **2003**, *44*, 7475. Severinsen, R.; Lau, J. F.; Bondensgaard, K.; Hansen, B. S.; Begtrup, M.; Ankersen, M. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 317.
9. Maiti, B.; Chanda, K.; Sun, C. M. *Org. Lett*. **2009**, *11*, 4826.
10. Lin, M. –L.; Sun, C. –M. *Tetrahedron Lett*. **2003**, *44*, 8739.
11. White, A. W.; Curtin, N. I.; Eastman, B. W.; Golding, B. T.; Hostomsky, Z.; Kyle, S.; Li, J.; Maegley, K. A.; Skalitzky, D. J.; Webber, S. E.; Yu, X. H.; Griffin, R. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2433.
12. Ates-Alagoz, Z.; Yildiz, S.; Buyukbingol, E. *Chemotherapy* **2007**, *53*, 110.
13. Hong, S. Y.; Kwal, K. W.; Ryu, C. K.; Kang, S. J.; Chung, K. H. *Bioorg. Med. Chem. Lett.* **2008**, *16*, 644.
14. Grimaudo, S.; Raimondi, M. V.; Capone, F.; Chimirri, A.; Poretto, F.; Monforte, A. M.; Simoni, D.; Tolomeo, M. *Eur. J. Cancer* **2001**, *37*, 122.
15. Hamdy, N. A.; Abdel-Aziz, H. A.; Farag, A. M.; Fakhr, I. M. I. *Monatsh. Chem.* **2007,** *138*, 1001.
16. Bouzroura, S.; Hammal, L.; Nedjar-Kolli, B.; Balegroune, F.; Hamadène, M.; Poulain, S. *Synth. Commun*. **2007**, *38*, 448.
17. Bondock, S.; Tarhoni, A. E-G.; Fadda, A. A. *Arkivoc* **2006**, *(ix)*, 113.
18. Dyachenko, V.; Dyachenko, V. D.; Rusanov, B. E. *Russ. J. Org. Chem*. **2007**, *43*, 83. Mohareb, R. M.; Aziz, S. A.; Abdel-Sayed, N. I.; El-Banna, A. H. *J. Chem. Research (M)* **1999**, 101.
19. Alper, A. E.; Taurins, A. *Can. J. Chem.* **1967**, *45*, 2903-2912. Hayashibe, S.; Kamikubo, T.; Tsukamoto, S. –I.; Sakamoto, S. *Heterocycles* **2004**, *62*, 815.
20. Khaliullin, F. A.; Klen, E. E. *Chem. Heterocycl. Comp*. **2009**, *45*, 876 and references cited therein.
21. Fadda, A. A.; Bondock, S.; Rabie, R.; Etman, H. A. *Turk. J. Chem*. **2008**, *32*, 259.