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Phenylimidazoles Scaffolds as Potent Anticancer Agents (Part I)

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ABSTRACT

Objective: Novel anticancer agents were designed to be synthesized comprising the essential features for anticancer activity considering Leucettamine B as a lead compound. **Method:** 3-Phenyl-2-thioxoimidazolidin-4-one **1** has been utilized for synthesis of various fused pyrrolo[1,2-e]imidazole **4, 8a,b, 11, 14, 16, 18, 20, 21, 23, 25** analogues through different chemical reactions. **Results**: Structures of these compounds were confirmed by spectral and elemental analyses Thirteen of the newly synthesized compounds were selected by the NCI – Maryland-U.S.A. and were tested for their anticancer activity in an initial single high dose in the full NCI 60 cell line panel. **Conclusion:** 5-amino-2,3,7,7a-tetrahydro-7-(4-methoxyphenyl)-1-oxo-2-phenyl-3-thioxo-1H-pyrrolo[1,2-e]imidazole-6-carbonitrile; **4**, 1-(7-(4-chlorophenyl)-3,7-dihydro-1,5-dihydroxy-2-phenyl-3-thioxo-2H-pyrrolo[1,2-e]imidazol-6yl) ethenone; **21**, were found to possess very selective potent anticancer activity against certain cancer cell lines.

Keywords: *Anticancer; Pyrrolo[1,2-e]imidazole; Leucettamine.*

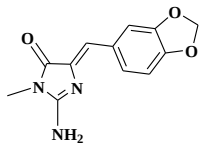
INTRODUCTION

2-Thioxoimidazolidin-4-one and its derivatives comprise a class of heterocyclic compounds of valuable importance due to its broad-spectrum pharmacological properties as; hypolipidemic [1], anticancer [2,3], antiviral [4,5], antituberculosis[6], antimicrobial (antifungal and antibacterial) [7], anti-ulcer and anti-inflammatory agents[8].

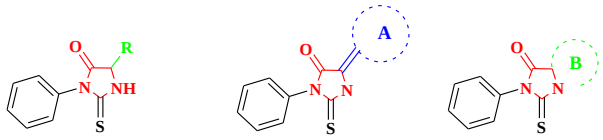
Leucettamine B is a tyrosine-regulated kinase 1A (Dyrk1A) inhibitor, that was isolated from a marine sponge. However, tyrosine-regulated kinase 1A (Dyrk1A) has gathered much interest as a pharmacological target in malignant brain tumors. Since the etiology of brain tumor is multi-factorial, further protein kinases, such as Clk1 and CK2, were proposed to contribute in the pathogenesis of the cancer.[9]

It is worth mentioning that. Marino, M. et al [9] indicated the essential presence of 2-aminoimidazolidine carbonyl oxygen for the activity of Leucettamine B derivatives.

Therefore, it was designed to synthesize novel anticancer agents comprising the essential features for anticancer activity considering Leucettamine B as a lead compound. 3-Phenyl-2-thioxoimidazolidin-4-one **1**, was utilized as building units to synthesize various innovative agents prone to combat cancer.



Leucettamine B



MATERIAL AND METHODS

Part 1-Chemistry

All melting points were determined in open glass capillaries on Electro thermal LA 9000 SERIS and are uncorrected. IR spectra were recorded, for potassium bromide discs, on Nikolet IR 200 FT IR spectrophotometer at pharmaceutical analytical unit, Faculty of pharmacy, Al-Azhar University, and the values are represented in cm-1. **^{1}H NMR** spectra were determined on Varian Gemini EM-400 MHz, NMR spectrometer at laboratories of nuclear magnatic resonance, Chemical Warefare Department, Ministery of Defense. DMSO-d_6 was used as solvent; chemical shifts were measured in δ ppm, relative to TMS as an internal standard. Mass spectra were carried out using a Schimadzu GC/ MS-QP-5050A mass spectrometer at 70 ev at Regional Center for Mycology and biotechnology, Al-Azhar University. Elemental analyses were performed on Elementar Vario EI III CHN analyzer at Micro-analytical, Regional Center for Mycology and biotechnology, Al-Azhar University. Progress of the reactions were monitored by thin-layer chromatography (TLC) on silica gel sheets (60 GF 254, Merk), the spots were visualized by exposure to UV-lamp at λ 254 and 365 nm for few seconds.

3-phenyl-2-thioxoimidazolidin-4-one; 1

Reddish brown powder; yield 1.8 g (78 %); m.p.: 240-242[10]

IR (KBr, cm^{-1}): 3321 (NH); 3032, 3012 (CH-aromatic); 2920, 2850 (CH-aliphatic); 1678 (C=O); 1604, 1554 (C=C); 1512, 1411, 1246, 1049 (I, II, III, IV bands of N-C=S). **Anal. form:** $C_{20}H_{16}N_4O_2S$. **Calcd. (%):** C, 56.23; H, 4.19; N, 14.57; O, 8.32; S, 16.68. **Found (%):** C, 56.49; H, 4.57; N, 14.81; S, 16.49.

2-(4-methoxybenzylidene)malononitrile; 2

Straw yellow crystals; yield 1.4 g (76 %); m.p.: 114-116 [11].

2-((4-Methoxyphenyl)(5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)methyl)malononitrile; 3

An equimolar mixture of 3-phenyl-2-thioxoimidazolidin-4-one **1** (0.38 g, 2 mmol.) and 2-(4-methoxybenzylidene)malononitrile **2** (0.37 g, 2 mmol.) was heated under reflux in dimethylformamide (20 mL) containing triethyl amine (0.20 g, 0.26 mL, 2 mmol.) for 25 hours. The reaction mixture was then poured onto ice cold water, and the precipitated solid was filtered, dried and crystallized from dioxane.

Brown powder, **yield**; 0.56 g (75 %), **m.p.;** 230-232 °C. **IR (KBr, cm^{-1}):** 3113 (NH); 3100 (CH-aromatic); 2974 (CH-aliphatic); 2322 (C≡N); 1716 (C=O); 1627, 1593 (C=C); 1327 (C=S); 1400, 1300, 1249, 1022 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-*d6*, δ ppm):** 3.77-3.80 (m, 2H, CH-$(CN)_2$ & CH-C_6H_5-OCH_3); 3.84 (s, 3H, OCH_3); 3.89 (d, 1H, *J*= 6 Hz, imidazole-C_5-H); 7.00 (d, 2H, *J*=8.8 Hz, 4-OCH_3-C_6H_4-$C_{3,5}$-H); 7.68 (d, 2H, *J*=8.8 Hz, 4-OCH_3-C_6H_5-$C_{2,6}$-H); 8.30-8.60 (m, 5H, N-C_6H_5-$C_{2,3,4,5,6}$-H); 11.88 (s, 1H, imidazole-NH, D_2O exchangeable).). **C^{13} NMR (DMSO-*d6*, δ ppm):** 22.64 (CH-$(CN)_2$); 33.40 (CH-C_6H_5-OCH_3); 55.49 (OCH_3); 55.79 (imidazole-C_5); 114.79 (4-OCH_3-C_6H_4-C_3); 114.86 (4-OCH_3-C_6H_4-C_5); 114.93 (two cyan-C); 126.63 (N-C_6H_5-$C_{2,6}$); 127.01 (N-C_6H_5-C_4); 127.25 (4-OCH_3-C_6H_4-$C_{2,6}$); 129.76 (N-C_6H_5-$C_{3,5}$); 130.11 (N-C_6H_5-C_1); 130.36 (4-OCH_3-C_6H_4-C_1); 156.30 (4-OCH_3-C_6H_4-C_4); 160.89 (imidazole-C_4); 161.73 (imidazole-C_2). **Anal. form:** ($C_{20}H_{16}N_4O_2S$). **Calcd. (%):** C, 63.81; H, 4.28; N, 14.88; S, 8.52. **Found (%):** C, 64.07; H, 4.41; N, 15.25; S, 8.46.

5-amino-3,7-dihydro-1-hydroxy-7-(4-methoxyphenyl)-2-phenyl-3-thioxo-2H-pyrrolo[1,2-e]imidazole-6-carbonitrile; 4

Compound **3** (0.38 g, 1 mmol.) was heated under reflux in pyridine (3 mL) for 6 hours. The reaction mixture was then poured onto ice cold water, and the precipitated solid was filtered, dried and crystallized from dioxane.

Yellow powder, **yield**; 0.42 g (56 %), **m.p**.; >360 °C. **IR (KBr, cm^{-1}):** 3394 (OH tautomer); 3317, 3221 (NH_2); 3074, 3043 (CH-aromatic); 2974 (CH-aliphatic); 2206 (C≡N); 1660 (C=O); 1635, 1585 (C=C); 1508, 1427, 1275, 1184 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-*d6*, δ ppm):** 3.33 (s, 3H, OCH_3, under DMSO); 4.14 (s, 1H, pyrroloimidazole-C_7-H); 7.27-7.33 (m, 1H, N-C_6H_5-C_4-H); 7.39 (d, 2H, *J*=7.2 Hz, 4-OCH_3-C_6H_4-$C_{3,5}$-H); 7.44-7.52 (m, 2H, N-C_6H_4- $C_{3,5}$-H); 7.86 (d, 2H, *J*=7.2 Hz, 4-OCH_3-C_6H_5-$C_{2,6}$-H); 8.00-8.01 (m, 2H, N-C_6H_5-$C_{2,6}$-H); 9.62 (s, 2H, NH_2, D_2O exchangeable); 10.10 (s, 1H, OH, D_2O exchangeable). **C^{13} NMR (DMSO-*d6*, δ ppm):** 34.60

(pyrroloimidazole-C_7); 56.39 (OCH_3 & pyrroloimidazole-C_6); 77.33 (pyrroloimidazole-C_{7a}); 114.38 (4-OCH_3-C_6H_4-C_3); 115.26 (4-OCH_3-C_6H_4-C_5); 115.68 (cyan-C); 124.59 (N-C_6H_5-$C_{2,6}$); 128.62 (N-C_6H_5-C_4); 129.22 (N-C_6H_5-$C_{3,5}$); 131.76 (4-OCH_3-C_6H_4-$C_{2,6}$); 132.25 (N-C_6H_5-C_1); 132.52 (4-OCH_3-C_6H_4-C_1); 160.93 (pyrroloimidazole-C_1); 164.81 (4-OCH_3-C_6H_4-C_4); 166.16 (pyrroloimidazole-C_5); 179.86 (pyrroloimidazole-C_3). **MS:** m/z (%): 377 (M+1, 19.33); 97 (43.30); 69 (100). **Anal. form:** ($C_{20}H_{16}N_4O_2S$). **Calcd. (%):** C, 63.81; H, 4.28; N, 14.88; O, 8.50; S, 8.52. **Found (%):** C, 63.75; H, 4.34; N, 15.01; S, 8.60.

Ethyl 3-(4-chlorophenyl)-2-cyanoacrylate; 5

Straw yellow crystals; yield 1.9 g (81 %); m.p.: 88-90 [12]

Ethyl 2-cyano-5-phenylpenta-2,4-dienoate; 6

Yellow crystals; yield 1.7 g (75 %); m.p.: 114-115 [13]

Ethyl 3-(4-chlorophenyl)-2-cyano-3-(5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)propanoate; 7a, and (4)-ethyl 2-cyano-3-(5-oxo-1-(penta-1,3-dien-3-yl)-2-thioxoimidazolidin-4-yl)-5-phenylpent-4-enoate; 7 b

An equimolar mixture of 3-phenyl-2-thioxoimidazolidin-4-one **1** (0.38 g, 2 mmol.) and ethyl 3-(4-chlorophenyl)-2-cyanoacrylate **5** (0.47 g, 2 mmol.) or ethyl 2-cyano-5-phenylpenta-2,4-dienoate **6** (0.92 g, 2 mmol.) was heated under reflux in dimethylformamide (20 mL) containing piperidine (0.09 g, 0.10 mL, 1 mmol.) for 25 hours. The reaction mixture was then poured onto ice cold water, and the precipitated solid was filtered, dried and crystallized from dioxane.

Ethyl 3-(4-chlorophenyl)-2-cyano-3-(5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)propanoate; 7a

Greyish white powder, **yield;** 0.75 g (88%), **m.p.;** 220-222 °C. **IR (KBr, cm^{-1}):** 3170 (NH); 3109, 2974 (CH-aromatic); 2939, 2885 (CH-aliphatic); 2287 (C≡N); 1750, 1724 (C=O); 1627, 1566 (C=C); 1462, 1211, 1165, 1022 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-*d6*, δ ppm):** 1.84-1.86 (m, 3H, OCH_2-CH_3); 2.87 (s, 1H, imidazole-C_5-H); 3.79-3.81 (m, 1H, CH-CN); 3.86-4.00 (m, 2H, OCH_2-CH_3); 7.00 (d, 2H, *J*=8.8 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.68 (d, 2H, *J*=8.8 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.69-7.73 (m, 5H, N-C_6H_5-$C_{2,3,4,5,6}$-H); 11.89 (s, 1H, NH, D_2O exchangeable). **C^{13} NMR (DMSO-*d6*, δ ppm):** 22.07 (CH_3); 22.64 (CH-4-Cl-C_6H_4) 33.40 (CH.CN); 44.17 (CH_2); 55.49 (imidazole-C_5); 115.29 (CN); 120.62 (N-C_6H_5-$C_{2,6}$); 126.63 (N-C_6H_5-C_4); 129.26 (4-Cl-C_6H_4-$C_{2,6}$); 129.76 (4-Cl-C_6H_4-$C_{3,5}$); 130.11 (N-C_6H_5-$C_{3,5}$); 130.36 (4-Cl-C_6H_4-$C_{3,5}$); 130.43 (N-C_6H_5-C_1); 131.61 (4-Cl-C_6H_5-C_4); 132.25 (4-Cl-C_6H_5-C_1); 160.89 (C=O); 161.73 (imidazole-C_4); 162.01 (imidazole-C_2). **MS:** m/z (%): 428 (M +1, 16.81); 421 (40.05); 367 (100). **Anal. form:** ($C_{21}H_{18}ClN_3O_3S$). **Calcd. (%):** C, 58.94; H, 4.24; N, 9.82; S, 7.49. **Found (%):** C, 58.71; H, 4.38; N, 10.06; S, 7.62.

Ethyl 2-cyano-3-(5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)-5-phenylpent-4-enoate; 7b

Faint yellow powder; yield 0.72 g (86 %) m.p. 128 °C. **IR (KBr, cm^{-1}):** 3167 (NH); 3032 (CH-aromatic); 2939, 2762 (CH-aliphatic); 2198 (C≡N); 1716 (C=O); 1608, 1593 (C=C); 1319 (C=S); 1489, 1404, 1249, 1087 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-d6, δ ppm):** 2.32-2.38 (m, 3H, OCH_2- CH_3); 2.71-2.73 (m, 1H, CH-CH=CH-ph); 3.78-3.82 (m, 1H, CH-CN); 3.86 (s, 1H, imidazole-C_5-H); 3.87-4.00 (m, 2H, OCH_2-CH_3); 7.00 (d, 1H, J=8.8 Hz, CH=CH-ph); 7.04 (d, 1H, J=8.8 Hz, CH=CH-ph); 7.55-7.63 (m, 5H, C_6H_5-$C_{2,3,4,5,6}$-H); 7.64-7.70 (m, 3H, N-C_6H_5-C $_{3,4,5}$-H); 7.77 (d, 2H, J= 8.8 Hz, N-C_6H_5-$C_{2,6}$-H); 11.86 (s, 1H, NH, D_2O exchangeable). **C^{13} NMR (DMSO-*d6*, δ ppm):** 14.91 (CH_3); 34.60 (CH(CN) & (CH-CH=CH); 55.73 (CH_2); 55.96 (imidazole-C_5); 114.68 (CN); 115.22 (N-C_6H_5-$C_{2,6}$); 122.65 (N-C_6H_5-C_4); 122.91 (CH=CH-ph); 123.43 (C_6H_5-$C_{2,6}$); 125.56 (C_6H_5-C_4); 125.98 (C_6H_5-$C_{3,5}$); 126.21 (N-C_6H_5-$C_{3,5}$); 132.15 (CH=CH-ph); 135.03 (N-C_6H_5-C_1); 136.49 (C_6H_5-C_1); 161.19 (C=O); 162.25 (imidazole-C_4); 166.44 (imidazole-C_2). **Anal. Form:** $C_{23}H_{21}N_3O_3S$. **Calcd. (%):** C, 65.85; H, 5.05; N, 10.02; O, 11.44; S, 7.64. **Found (%):** C, 65.76; H, 5.19; N, 10.38; S, 7.58.

7-(4-Chlorophenyl)-2,3,5,7a-tetrahydro-1,5-dioxo-2-phenyl-3-thioxo-1H-pyrrolo[1,2-e]imidazole-6-carbonitrile; 8a and 2,3,5,7a-tetrahydro-1,5-dioxo-2-phenyl-7-styryl-3-thioxo-1H-pyrrolo[1,2-e]imidazole-6-carbonitrile; 8b

Ethyl 3-(4-chlorophenyl)-2-cyano-3-(5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)propanoate **7a** (0.85 g, 2 mmol.) or ethyl 2-cyano-3-(5-oxo-1-(penta-1,3-dien-3-yl)-2-thioxoimidazolidin-4-yl)-5-phenylpent-4-enoate **7b** (0.84 g, 1 mmol.) was heated under reflux in pyridine (3 mL) for 6 hours. The reaction mixture was then poured onto ice cold water, and the precipitated solid was filtered, dried and crystallized from dioxane.

7-(4-Chlorophenyl)-2,3,5,7a-tetrahydro-1,5-dioxo-2-phenyl-3-thioxo-1H-pyrrolo[1,2-e]imidazole-6-carbonitrile; 8a

Yellow powder; yield 0.62 g (73 %) m.p.>360 °C. **IR (KBr, cm^{-1}):** 3095 (CH-aromatic); 2991 (CH-aliphatic); 2224 (C≡N); 1725 (C=O); 1613, 1589 (C=C); 1492, 1364, 1288, 1081 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-d6, δ ppm):** 3.87 (s, 1H, pyrroloimidazole-C_{7a}-H); 7.17 (d, 2H, J=8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.96 (d, 2H, J=8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 8.33-8.40 (m, 5H, N-C_6H_5-$C_{2,3,4,5,6}$-H). **MS:** m/z (%): 379 ($M^{+\cdot}$, 9.93); 293 (46.49); 264 (100). **Anal. Form:** $C_{19}H_{10}ClN_3O_2S$. **Calcd. (%):** C, 60.08; H, 2.65; Cl, 9.33;

N, 11.06; O, 8.42; S, 8.44. **Found (%):** C, 60.24; H, 2.83; N, 11.28; S, 8.38.

2,3,5,7a-Tetrahydro-1,5-dioxo-2-phenyl-7-styryl-3-thioxo-1H-pyrrolo[1,2-e]imidazole-6-carbonitrile; 8b

Brown powder; yield 0.75 g (88 %) m.p.>360 °C. **IR (KBr, cm^{-1}):** 3096, 3073, 3037 (CH-aromatic); 2955, 2903 (CH-aliphatic); 2224 (C≡N); 1724 (C=O); 1612, 1589 (C=C); 1492, 1264, 1201, 1081 (I, II, III, IV bands of N-C=S). **MS:** m/z (%): 371 ($M^{+\cdot}$, 38.73); 360 (84.83); 309 (71.43); 96 (100). **Anal. form:** $C_{21}H_{13}N_3O_2S$. **Calcd. (%):** C, 67.91; H, 3.53; N, 11.31; O, 8.62; S, 8.63. **Found (%):** C, 68.07; H, 3.69; N, 11.57; S, 8.79.

Cinnamoyl chloride; 9

Pale yellow crystals; yield 0.29 g (86 %); m.p. 35-37 ^{0}C as reported.[14]

3-phenyl-5-(3-phenylacryloyl)-2-thioxoimidazolidin-4-one; 10

An equimolar mixture of cinnamoyl chloride **9** (0.33 g, 2 mmol.) and 3-phenyl-2-thioxoimidazolidin-4-one **1** (0.38 g, 2 mmol.) was heated under reflux in toluene (20 mL) containing triethylamine (0.20 g, 0.26 mL, 2 mmol.) for 5 hours. The reaction mixture was then poured onto ice cold water and the precipitated product was filtered, crystallized with ethanol and dried.

Brown powder, **yield;** 0.60 g (93 %), **m.p.;** 278-280 °C. **IR (KBr, cm^{-1}):** 3178 (NH); 3000, 2974 (CH-aromatic); 2939, 2881 (CH-aliphatic); 1716 (C=O); 1604, 1566 (C=C); 1508, 1327, 1249, 1022 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-*d6*, δ ppm):** 3.86 (s, 1H, imidazole-C_5-H); 7.00 (d, 1H, *J*=8.8 Hz, CH=CH-C_6H_5); 7.51 (d, 2H, *J*=8.8 Hz, CH=CH-C_6H_5); 7.64-7.67 (m, 5H, N-C_6H_5-$C_{2,3,4,5,6}$-H); 8.28-8.44 (m, 5H, C_6H_5-$C_{2,3,4,5,6}$-H); 11.89 (s, 1H, imidazole-NH, D_2O exchangeable). **C^{13} NMR (DMSO-*d6*, δ ppm):** 77.33 (imidazole-C_5); 118.09 (N-C_6H_5-$C_{2,6}$); 118.22 (N-C_6H_5-C_4); 118.48 (CH=CH-ph); 121.08 (C_6H_5-$C_{2,6}$); 128.67 (C_6H_5-C_4); 128.78 (C_6H_5-$C_{3,5}$); 129.23 (N-C_6H_5-$C_{3,5}$); 131.76 (C_6H_5-C_1); 132.25 (N-C_6H_5-C_1); 134.15 (CH=CH-ph); 166.18 (imidazole-C_4); 179.87 (imidazole-C_2); 191.36 (C=O). **Anal. form:** ($C_{18}H_{14}N_2O_2S$). **Calcd. (%):** C, 67.06; H, 4.38; N, 8.69; S, 9.95. **Found (%):** C, 66.89; H, 4.46; N, 8.90; S, 10.02.

2,3-dihydro-2,5-diphenyl-3-thioxo-7aH-pyrrolo[1,2-e]imidazole-1,7-dione; 11

Method A:

3-Phenyl-5-(3-phenylacryloyl)-2-thioxoimidazolidin-4-one **10** (0.64 g, 2 mmol.) was heated under reflux in pyridine (3 mL) for 2 hours. The reaction mixture was then poured onto ice cold water, and the precipitated solid was filtered, dried and crystallized from dioxane.

Method B:

An equimolar mixture of cinnamoyl chloride **9** (0.33 g, 2 mmol.) and 3-phenyl-2-thioxoimidazolidin-4-one **1** (0.38 g, 2 mmol.) in toluene (10 mL) \ pyridine (10 mL) mixture for 9 hours. The reaction mixture was then poured into ice cold water and the precipitated product was filtered, crystallized from dioxane and dried.

Black powder; yield 0.58 g (91 %) m.p.>360 °C. **IR (KBr, cm^{-1}):** 3000, 2974 (CH-aromatic); 2939, 2855 (CH-aliphatic); 1724 (C=O); 1600, 1554 (C=C); 1508, 1327, 1249, 1022 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-*d6*, δ ppm):** 3.85 (s, 1H, pyrroloimidazole-C_{7a}-H); 7.12-7.15 (m, 5H, C_6H_5-$C_{2,3,4,5,6}$-H); 8.05-8.08 (m, 5H, N-C_6H_5-$C_{2,3,4,5,6}$-H); 8.29 (s, 1H, pyrroloimidazole-C_6-H). **C^{13} NMR (DMSO-*d6*, δ ppm):** 70.54 (pyrroloimidazole-C_{7a}); 95.41 (pyrroloimidazole-C_6); 128.62 (N-C_6H_5-$C_{2,6}$); 128.78 (N-C_6H_5-C_4); 128.93 (C_6H_5-$C_{2,6}$); 129.16 (C_6H_5-C_4); 129.23 (C_6H_5-$C_{3,5}$); 131.46 (N-C_6H_5-$C_{3,5}$); 131.75 (C_6H_5-C_1); 132.25 (N-C_6H_5-C_1); 152.10 (pyrroloimidazole-C_5); 153.30 (pyrroloimidazole-C_1); 153.33 (pyrroloimidazole-C_3); 166.44 (pyrroloimidazole-C_7). **MS:** m/z (%): 323 (M+3, 7.51); 322 (M+2, 3.96); 320 ($M^{+\cdot}$, 3.95); 148 (100). **Anal. form:** ($C_{18}H_{12}N_2O_2S$). **Calcd. (%):** C, 67.48; H, 3.78; N, 8.74; S, 10.01. **Found (%):** C, 67.32; H, 4.50; N, 8.87; S, 10.03.

2-(ethoxymethylene)malononitrile; 12

Light brown crystals; yield 1.4 g (71 %); m.p.: 66-68 [15]

2-[(5-Oxo-1-phenyl-2-thioxoimidazolidin-4-yl)methylene]malononitrile; 13

An equimolar mixture of 3-phenyl-2-thioxoimidazolidin-4-one **1** (0.38 g, 2 mmol.) and 2-(ethoxymethylene)malononitrile **12** (0.24 g, 2 mmol.) was heated under reflux in dimethylformamide (20 mL) containing triethylamine (0.20 g, 0.26 mL, 2 mmol.) for 25 hours. The reaction mixture was then poured onto ice cold water and the precipitated product was filtered, washed with ethanol, dried and crystallized from acetone.

Brown powder, **yield;** 0.48 g (89 %), **m.p.;** 158-160 °C. **IR (KBr, cm^{-1}):** 3282, 3182 (NH); 3101, 2970 (CH-aromatic); 2827 (CH-aliphatic); 2225 (C≡N); 1708 (C=O); 1624, 1504 (C=C); 1504, 1411, 1296, 1041 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-*d6*, δ ppm):** 3.79-3.86 (m, 1H, imidazole-C_5-H); 7.00 (d, 2H, J= 8.8 Hz, N-C_6H_5-$C_{2,6}$-H); 7.66-7.70 (m, 1H, N-C_6H_5-C_4-H); 7.93 (s, 1H, arylidene-CH); 8.31-8.32 (m, 2H, N-C_6H_5-$C_{3,5}$-H); 11.77 (s, 1H, NH, D_2O exchangeable). **C^{13} NMR (DMSO-*d6*, δ ppm):** 55.79 (imidazole-C_5); 110 ($(CN)_2$-C); 114.79 (two-cyan-C); 127.26 (N-C_6H_5-$C_{2,6}$); 129.75 (N-C_6H_5-$C_{3,4,5}$); 132.15 (N-C_6H_5-C_1); 156.27 (C=C-$(CN)_2$); 169.23 (imidazole-C_4); 173.87 (imidazole-C_2). **Anal. form:** ($C_{13}H_8N_4OS$). **Calcd. (%):** C, 58.20; H, 3.01; N, 20.88; 11.95. **Found (%):** C, 58.43; H, 2.89; N, 21.15; S, 12.08.

5-Amino-2,3-dihydro-1-oxo-2-phenyl-3-thioxo-1H-pyrrolo[1,2-e]imidazole-6-carbonitrile; 14

2-[(5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)methylene]malononitrile **13** (0.54 g, 2 mmol.) was heated under reflux in pyridine (3 mL) for 6 hours. The reaction mixture was then poured onto ice cold water, and the precipitated solid was filtered, dried and crystallized from dioxane.

Yellow crystal, **yield;** 0.40 g (74 %), **m.p.;** 293-295 °C. **IR (KBr, cm^{-1}):** 3317, 3222 (NH_2); 3045, 2918 (CH-aromatic); 2208 (C≡N); 1680 (C=O); 1641 (C=N); 1586 (C=C); 1428 (C=S); 1511, 1428, 1259, 1071 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-*d6*, δ ppm):** 3.78 (s, ½ H, pyrroloimidazole-C_{7a}-H tautomer); 4.11 (s, 1H, pyrroloimidazole-C_7-H); 7.10-7.14 (m, 1H, N-C_6H_5-C_4-H); 7.93-7.96 (m, 2H, N-C_6H_5-$C_{2,6}$-H); 8.04-8.05 (m, 2H, N-C_6H_5-$C_{3,5}$-H); 9.45 (s, 1H, NH_2, D_2O exchangeable); 9.97 (s, ½ H, NH tautomer, D_2O exchangeable). **MS:** m/z (%): 269 (M+1, 1.87); 114 (100). **Anal. form:** ($C_{13}H_8N_4OS$). **Calcd. (%):** C, 58.20; H, 3.01; N, 20.88; S, 11.95. **Found (%):** C, 58.12; H, 3.17; N, 21.15; S, 11.79.

Diethyl 2-[(5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)methylene]malonate;15

An equimolar mixture of 3-phenyl-2-thioxoimidazolidin-4-one **1** (0.38 g, 2 mmol.) and diethyl 2-(ethoxymethylene)malonate (0.44 g, 0.41 mL, 2 mmol.) was heated under reflux in dimethylformamide (20 mL) containing triethylamine (0.20 g, 0.26 mL, 2 mmol.) for 25 hours. The reaction mixture was then poured onto ice cold water and the precipitated product was filtered, washed with ethanol crystallized from dioxane and dried.

Grey powder, **yield;** 0.60 g (83 %), **m.p.;** 253-255 °C. **IR (KBr, cm^{-1}):** 3444 (NH); 2969 (CH-aromatic); 2852, 2781 (CH-aliphatic); 1720 (C=O); 1633 (C=N); 1600 (C=C); 1508, 1429, 1248, 1022 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-*d6*, δ ppm):** 1.04 (t, 6H, *J*= 7.2 Hz, two (OCH_2-$\underline{CH_3}$)); 3.54-3.56 (m, 1H, imidazole-C_5-H); 3.78-3.86 (m, 1H, $\underline{CH}$=C($COOC_2H_5$)$_2$); 4.42-4.50 (m, 4H, two ($O\underline{CH_2}$-CH_3)); 7.01 (d, 2H, *J*= 8.6 Hz, N-C_6H_5-$C_{2,6}$-H); 7.68 (d, 1H, *J*= 8.6 Hz, N-C_6H_5-$C_{3,5}$-H); 8.31-8.32 (m, 2H, N-C_6H_5-C_4-H); 11.75 (s, 1H, imidazole-NH, D_2O exchangeable). **C^{13} NMR (DMSO-*d6*, δ ppm):** 14.91 (Two CH_3); 44.24 (imidazole-C_5); 62.30 (Two CH_2); 118.09 (N-C_6H_5-$C_{2,6}$); 118.22 (N-C_6H_5-C_4); 118.48 ($\underline{C}$=C($COOC_2H_5$)$_2$); 121.08 (N-C_6H_5-$C_{3,5}$); 128.87 (N-C_6H_5-C_1); 145.72 (C=$\underline{C}$($COOC_2H_5$)$_2$); 164.21 (Two C=O); 166.81 (imidazole-C_4); 166.83 (imidazole-C_2). **Anal. form:** ($C_{17}H_{18}N_2O_5S$). **Calcd. (%):** C, 56.34; H, 5.01; N, 7.73; S, 8.85. **Found (%):** 56.49; H, 5.12; N, 7.95; S, 8.91.

Ethyl 2,3,5,7a-tetrahydro-1,5-dioxo-2-phenyl-3-thioxo-1H-pyrrolo[1,2-e]imidazole-6-carboxylate; 16

Diethyl 2-[(5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)methylene]malonate **15** (0.72 g, 2 mmol.) was fused in pyridine (3 mL) for 6 hours. The reaction mixture was then poured into ice cooled water, and the precipitated solid was filtered, dried and crystallized from dioxane/ acetone.

Yellow crystals, **yield;** 0.50 g (79 %), **m.p.;** >360 °C. **IR (KBr, cm^{-1}):** 3008, 2974 (CH-aromatic); 2939, 2885 (CH-aliphatic); 1724, 1700 (C=O); 1597,1566 (C=C); 1508, 1396, 1249, 1022 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-*d6*, δ ppm):** 1.29 (t, 3H, *J*= 7.2 Hz, OCH_2-$\underline{CH_3}$); 4.28-4.33 (m, 4H, $O\underline{CH_2}$-CH_3 & pyrroloimidazole-$C_{7,7a}$-H); 7.66-7.68 (m, 1H, N-C_6H_5-C_4-H); 8.06 (d, 2H, *J*= 8.4 Hz, N-C_6H_5-$C_{2,6}$-H); 8.39-8.40 (m, 2H, N-C_6H_5-$C_{3,5}$-H). **C^{13} NMR (DMSO-*d6*, δ ppm):** 14.53 (CH_3); 54.87 (pyrroloimidazole-C_{7a}); 61.78 (CH_2); 113.87 (N-C_6H_4-$C_{2,6}$); 115.17 (N-C_6H_4-C_4); 124.39 (pyrroloimidazole-C_6); 129.05 (N-C_6H_4-$C_{3,5}$); 133.47 (N-C_6H_5-C_1); 133.56 (pyrroloimidazole-C_7); 164.68 (C=O); 166.78 (pyrroloimidazole-C_1); 168.44 (pyrroloimidazole-C_5); 170.75 (pyrroloimidazole-C_3). **Anal. form:** $C_{15}H_{12}N_2O_4S$. **Calcd. (%):** C, 56.95; H, 3.82; N, 8.86; S, 10.14. **Found (%):** C, 57.12; H, 3.96; N, 9.03; S, 10.37.

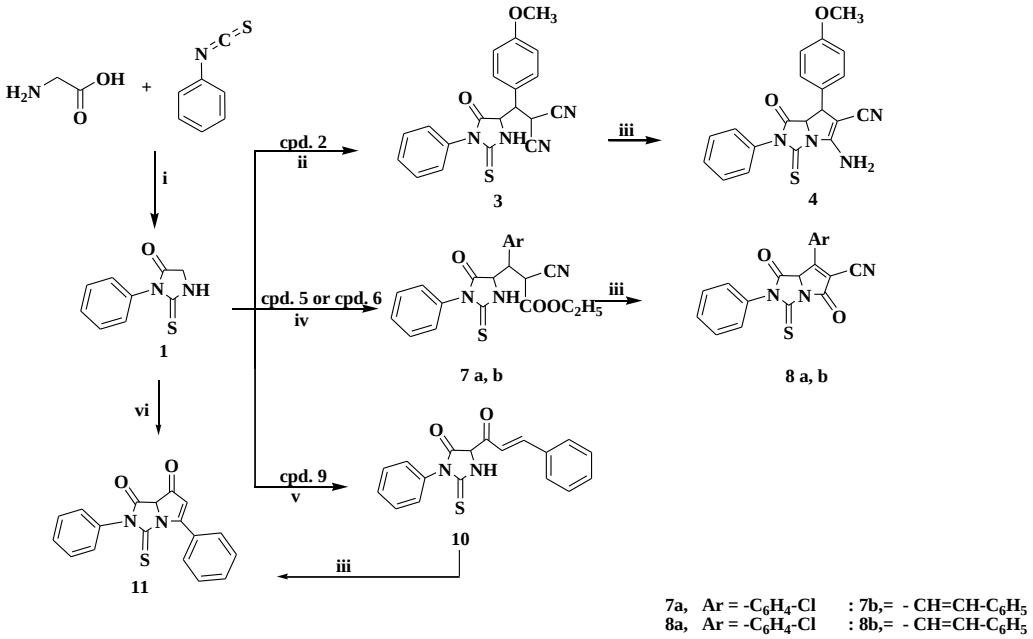
7- Dimethyl 2-(5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)fumarate; 17

An equimolar mixture of 3-phenyl-2-thioxoimidazolidin-4-one **1** (0.38 g, 2 mmol.) and dimethyl acetylene dicarboxylate (0.28 g, 0.24 ml, 2 mmol.) in dimethylformamide (20 mL) containing triethylamine (0.20 g, 0.26 mL, 2 mmol.) for 25 hours. The reaction mixture was then poured into ice cooled water and the precipitated product was filtered, washed with ethanol and dried.

Black powder; yield 0.50 g (75 %) m.p. 190-192 °C. **IR (KBr, cm^{-1}):** 3127 (NH); 3069, 2982 (CH-aromatic); 2921, 2845 (CH-aliphatic); 1741, 1699 (C=O); 1632 (C=N); 1583 (C=C); 1512, 1414, 1217, 1087 (I, II, III, IV bands of N-C=S). **MS:** m/z (%): 335 (M+1, 54.52); 334 ($M^{\cdot+}$, 47.18); 275 (42.66); 135 (100). **Anal. form:** $C_{15}H_{14}N_2O_5S$. **Calcd. (%):** C, 53.88; H, 4.22; N, 8.38; O, 23.93; S, 9.59. **Found (%):** C, 54.06; H, 4.39; N, 8.62; S, 9.63.

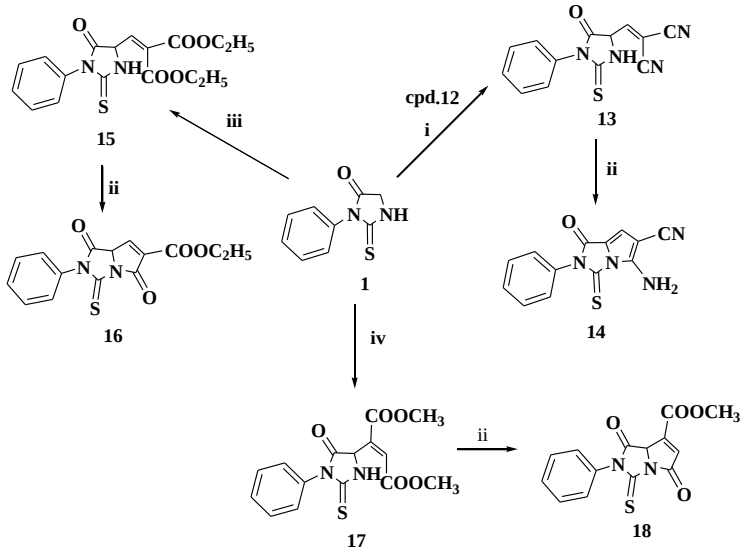
Methyl 2,3,5,7a-tetrahydro-1,5-dioxo-2-phenyl-3-thioxo-1H-pyrrolo[1,2-e]imidazole-7-carboxylate; 18

Dimethyl 2-(5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)fumarate **17** (0.66 g, 2 mmol.) was heated under reflux in pyridine (3 mL) for 6 hours. The reaction mixture was then poured onto ice cold water, and the precipitated solid was filtered, dried and crystallized from dioxane/ acetone.



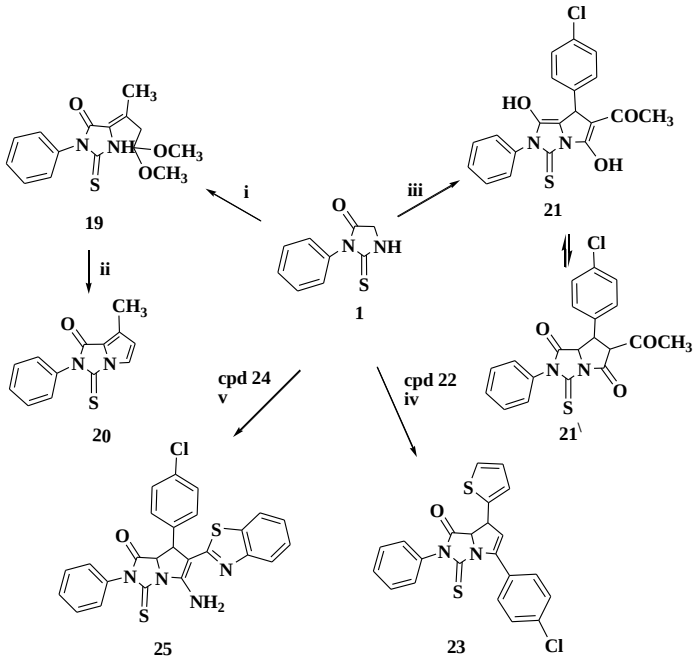
Reagents and conditions: (i) Pyridine / 30% NaOH/ reflux; **(ii)** 2-(4-methoxybenzylidene)malononitrile **2** / DMF/ TEA/ reflux; **(iii)** Pyridine/ reflux **(iv)** Ethyl 3-(4-chlorophenyl)-2-cyanoacrylate **5** or ethyl 2-cyano-5-phenylpenta-2,4-dienoate **6**/ DMF/ Pip./ reflux; **(v)** Cinnamoyl chloride 9/ toluene/ TEA/ reflux; **(vi)** Toluene/ pyridine/ reflux.

Scheme I



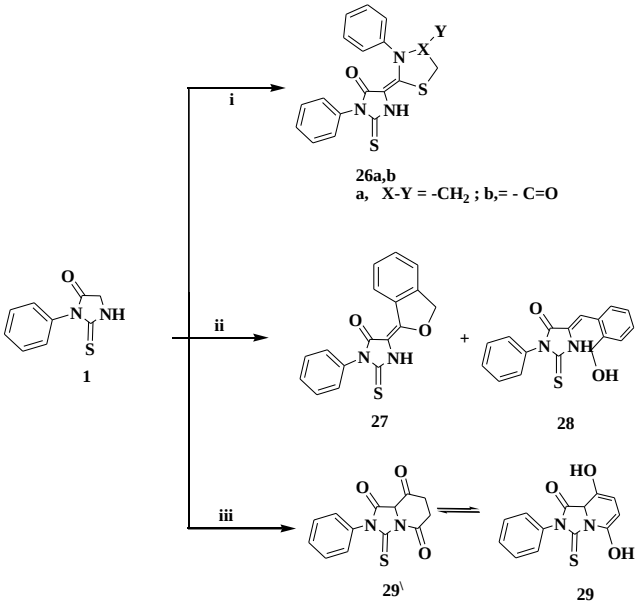
Reagents and conditions: (i) 2-(Ethoxymethylene)malononitrile **12**/ DMF/ TEA./ reflux; **(ii**) pyridine/ reflux **(iii)** Diethyl 2-(ethoxymethylene)malonate/ DMF/TEA/ reflux; **(iv)** DMAD/ DMF/TEA/ reflux.

SchemeII



Reagents and conditions: (i) acetyl acetaldehyde dimethylacetal/ DMF/ Pip./ reflux; **(ii)** pyridine/ reflux; **(iii)** Ethylacetoacetate / 4-chlorobenzaldehyde/ DMF/Pyridine/ reflux; **(vi)**1-(4-chlorophenyl)-3-(thiophen-2-yl) prop-2-en-1-one **22**/ DMF/ pyridine/ reflux;**(v)** 2-(Benzo[d]thiazol-2-yl)acetonitrile **24** / DMF/ pyridine/ reflux.

SchemeIII



Reagents and conditions: (i) Phenyl isothiocyanate/ KOH/ DMF/ 0-5^{O}C/ 1,2-dichloroethane or chloroacetyl chloride; **(ii)** Isobenzofuran-1(3*H*)-one/ dioxane/ pyridine/ reflux; **(iii)** Succinic anhydride/DMF/Pyridine/ reflux.

Scheme IV

Brown powder, **yield;** 0.48 g (80 %), **m.p.;** >360 °C. **IR (KBr, cm^{-1}):** 2974, 2939 (CH-aromatic); 2885, 2762 (CH-aliphatic); 1724, 1710 (C=O); 1627 (C=N); 1600, 1566 (C=C); 1508, 1300, 1249, 1022 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-*d6*, δ ppm):** 3.87 (s, 4H, COO$\underline{CH_3}$ & pyrroloimidazole-C_{7a}-H); 7.15-7.19 (m, 2H, N-C_6H_5-C_4-H & pyrroloimidazole-C_6-H); 7.94-7.98 (m, 2H, N-C_6H_5-$C_{3,5}$-H); 8.37-8.38 (m, 2H, N-C_6H_5-$C_{2,6}$-H). **C^{13} NMR (DMSO-*d6*, δ ppm):** 55.79 (OCH_3); 57.61 (pyrroloimidazole-C_{7a}); 114.79 (N-C_6H_4-$C_{2,6}$); 116.35 (N-C_6H_4-C_4); 123.21 (N-C_6H_4-$C_{3,5}$); 125.19 (pyrroloimidazole-C_6); 127.25 (N-C_6H_5-C_1); 129.76 (pyrroloimidazole-C_7); 154.78 (C=O); 156.14 (pyrroloimidazole-C_1); 161.73 (pyrroloimidazole-C_5); 175.63 (pyrroloimidazole-C_3). **Anal. form:** ($C_{14}H_{10}N_2O_4S$). **Calcd. (%):** C, 55.62; H, 3.33; N, 9.27; S, 10.61. **Found (%):** C, 55.89; H, 3.47; N, 9.62; S, 10.83.

5-(4,4-Dimethoxybutan-2-ylidene)-3-phenyl-2-thioxoimidazolidin-4-one; 19

An equimolar mixture of compound **1** (0.38 g, 2 mmol.) and acetyl acetaldehyde dimethyl acetal (0.26 g, 0.26 mL, 2 mmol.) was heated under reflux in dimethyl formamide (20 mL) containing piperidine (0.17 g, 0.20 mL, 2 mmol.) for 25 hours. The reaction mixture was then poured onto ice cold water and the precipitated product was filtered, crystallized from ethanol and dried.

Grey powder, **yield;** 0.41 g (67 %), **m.p.;** 125 °C. **IR (KBr, cm^{-1}):** 3178 (NH); 3000, 2974 (CH-aromatic); 2939, 2885 (CH-aliphatic); 1724 (C=O); 1627 (C=N); 1604 (C=C); 1508, 1327, 1161, 1103 (I, II, III, IV bands of N-C=S); 1249, 1022 (C-O-C). **^{1}H NMR (DMSO-*d6*, δ ppm):** 2.71 (s, 2H, $\underline{CH_2}$-CH$(OCH_3)_2$); 2.87 (s, 3H, $\underline{CH_3}$); 3.79 (s, 6H, two (OCH_3)); 3.86 (s, 1H, $\underline{CH}$-$(OCH_3)_2$); 6.98-7.01 (m, 1H, N-C_6H_5-C_4-H); 7.68 (d, 2H, *J*= 8.8 Hz, N-C_6H_5-$C_{2,6}$-H); 8.31-8.32 (m, 2H, N-C_6H_5-$C_{3,5}$-H); 11.88 (s, 1H, imidazole-NH, D_2O exchangeable). **C^{13} NMR (DMSO-*d6*, δ ppm):** 21.29 (CH_3); 33.39 ($\underline{CH_2}$-CH$(OCH_3)_2$); 55.79 (Two OCH_3); 110.00 (CH_2-$\underline{CH}(OCH_3)_2$); 112.52 (N-C_6H_5-C_4); 114.79 (N-C_6H_5-$C_{2,6}$); 127.25 ($\underline{C}$-CH3); 129.42 (N-C_6H_5-$C_{3,5}$); 129.68 (N-C_6H_5-C_1); 129.76 (imidazole-C_5); 156.29 (imidazole-C_4); 161.73 (imidazole-C_2). **Anal. form:** ($C_{15}H_{18}N_2O_3S$). **Calcd. (%):** C, 58.80; H, 5.92; N, 9.14; S, 10.47. **Found (%):** C, 59.07; H, 6.11; N, 9.38; S, 10.71.

2,3-Dihydro-7-methyl-2-phenyl-3-thioxopyrrolo[1,2-e]imidazol-1-one; 20

5-(4,4-Dimethoxybutan-2-ylidene)-3-phenyl-2-thioxoimidazolidin-4-one **19** (0.62 g, 2 mmol.) was fused in pyridine (3 mL) for 6 hours. The reaction mixture was then poured onto ice cooled water, and the precipitated solid was filtered, dried and crystallized from dioxane.

Reddish brown powder, **yield;** 0.39 g (81 %), **m.p.;** 225-230 °C. **IR (KBr, cm^{-1}):** 3050, 2974 (CH-aromatic); 2800 (CH-aliphatic); 1724 (C=O); 1603 (C=C); 1509 1420, 1327, 1024 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-$_{d6}$, δ ppm):** 3.13 (s, 3H, $\underline{CH_3}$); 6.94-6.96 (m, 2H, pyrrolimidazole-$C_{5,6}$-H); 7.85-7.89 (m, 3H, N-C_6H_5-$C_{2,4,6}$-H); 8.28-8.29 (m, 1H, N-C_6H_5-$C_{3,5}$-H). **Anal. form:** ($C_{13}H_{10}N_2OS$). **Calcd. (%):** C, 64.44; H, 4.16; N, 11.56; S, 13.23. **Found (%):** C, 64.71; H, 4.28; N, 11.81; S, 13.32.

1-(7-(4-Chlorophenyl)-3,7-dihydro-1,5-dihydroxy-2-phenyl-3-thioxo-2H-pyrrolo[1,2-e]imidazol-6-yl)ethenone; 21

A solution of 3-phenyl-2-thioxoimidazolidin-4-one **1** (0.38 g, 2 mmol.) in dimethylformamide (10 mL) was added to a solution of ethyl acetoacetate (0.16 g, 0.16 mL, 2 mmol.) and 4-chlorobenzaldehyde (0.28 g, 2 mmol.) in pyridine (10 mL) at 20 °C. The reaction mixture was then heated under reflux for 20 hours. The reaction mixture was then poured onto ice cold water, and the precipitated solid was filtered, recrystallized with dioxane and dried.

Yellow powder, **yield**; 0.35 g (44 %), **m.p.**; 158-160 °C. **IR (KBr, cm^{-1}):** 3429 (br. OH tautomer); 3097, 2997 (CH-aromatic); 2897 (CH-aliphatic); 1666 (C=O); 1612, 1573 (C=C); 1527, 1346, 1273, 1122 (I, II, III, IV bands of N-C=S). **MS:** m/z (%): 398 ($M^{+\cdot}$, 13.74); 153 (100). **Anal. form:** ($C_{20}H_{15}ClN_2O_3S$). **Calcd. (%):** C, 60.22; H, 3.79; S, 8.04. **Found (%):** C, 60.45; H, 3.90; N, 7.18; S, 8.17.

1-(4-Chlorophenyl)-3-(thiophen-2-yl)prop-2-en-1-one; 22

Yellow powder, yield 0.43 g (86%), m.p. 123-125 ^{0}C [16].

5-(4-Chlorophenyl)-2,3,7,7a-tetrahydro-2-phenyl-7-(thiophen-2-yl)-3-thioxopyrrolo[1,2-e]imidazol-1-one; 23

A solution of 3-phenyl-2-thioxoimidazolidin-4-one **1** (0.38 g, 2 mmol.) in dimethylformamide (10 mL) was added to a solution of 1-(4-chlorophenyl)-3-(thiophen-2-yl)prop-2-en-1-one **22** (0.50 g, 2 mmol.) in pyridine (10 mL) at 20 °C. The reaction mixture was then heated under reflux for 20 hours, the reaction mixture was then poured onto ice cold water, and the precipitated solid was filtered, washed with ethanol and dried.

White crystals, **yield;** 0.55 g (65 %), **m.p.**; 167-170 °C. **IR (KBr, cm^{-1}):** 3050, 2974 (CH-aromatic); 2881 (CH-aliphatic); 1724 (C=O); 1627 (C=N); 1593, 1566 (C=C); 1508, 1327, 1161, 1091 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-*d6*, δ ppm):** 2.50-2.53 (m, 1H, pyrroloimidazole-C_7-H); 3.75-3.79 (m, 1H, pyrroloimidazole-C_{7a}-H); 3.85-3.87 (m, 1H, pyrroloimidazole-C_6-H); 6.99-7.04 (m, 2H, thiophene-

C_4-H); 7.18 (t, 1H, *J*= 8.4 Hz, N-C_6H_5-C_4-H); 7.51-7.56 (m, 1H, thiophene-C_3-H); 7.61 (d, 2H, *J*= 8.6 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.67 (d, 2H, *J*= 8.4 Hz, N-C_6H_5-$C_{2,6}$-H); 7.78-7.81 (m, 2H, N-C_6H_5-$C_{3,5}$-H); 7.89-7.93 (m, 1H, thiophene-C_5-H); 8.10 (d, 2H, J= 8.6 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H). **C^{13} NMR (DMSO-*d6*, δ ppm):** 42.38 (pyrroloimidazole-C_7); 56.39 (pyrroloimidazole-C_{7a}); 110.42 (pyrroloimidazole-C_6); 114.92 (N-C_6H_5-$C_{2,6}$); 115.68 (N-C_6H_5-$C_{3,4,5}$); 124.59 (thiophen-C_2); 128.62 (thiophen-$C_{3,4}$); 129.23 (4-Cl-C_6H_4-$C_{2,6}$); 129.27 (4-Cl-C_6H_4-$C_{3,5}$); 131.76 (4-Cl-C_6H_4-C_4); 132.26 (4-Cl-C_6H_4-C_1); 132.83 (N-C_6H_5-C_1); 134.17 (thiophen-C_5); 148.36 (pyrroloimidazole-C_5); 166.16 (pyrroloimidazole-C_3); 167.16 (pyrroloimidazole-C_1). **Anal. form:** ($C_{22}H_{15}ClN_2OS_2$). **Calcd. (%):** C, 62.47; H, 3.57; N, 6.62; S, 15.16. **Found (%):** C, 62.70; H, 3.68; N, 6.89; S, 15.08.

3.1.24. 2-(Benzo[d]thiazol-2-yl)acetonitrile; 24

Shinny yellow powder, yield 1 g (57 %), m.p. 103-104 ^{0}C. [17]

5-Amino-6-(benzo[d]thiazol-2-yl)-7-(4-chlorophenyl)-2,3,7,7a-tetrahydro-2-phenyl-3-thioxopyrrolo[1,2-e]imidazol-1-one; 25

A solution of 3-phenyl-2-thioxoimidazolidin-4-one **1** (0.38 g, 2 mmol.) in dimethylformamide (10 mL) was added to a solution of 2-(benzo[d]thiazol-2-yl)acetonitrile **24** (0.34 g, 2 mmol.) in 4-chlorobenzaldehyde (0.28 g, 2 mmol.) in pyridine (10 mL) at 20 °C. The reaction mixture was heated under reflux for 20 hours. The reaction mixture was then poured onto ice cold water, and the precipitated solid was filtered, washed with boiling ethanol and dried.

Brown powder, **yield;** 0.51 g (52 %), **m.p.**; >360 °C. **IR (KBr, cm^{-1}):** 3394, 3350 (NH_2); 3000, 2962 (CH-aromatic); 2904 (CH-aliphatic); 1705 (C=O); 1612, 1585 (C=C); 1512, 1303, 1246, 1033 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-*d6*, δ ppm):** 3.60-3.85 (m, 2H, pyrroloimidazole-$C_{7,7a}$-H); 4.39 (s, ½ H, pyrroloimidazole-C_6-H tautomer); 5.41 (s, 2H, NH_2, D_2O exchangeable); 6.06-6.20 (m, 1H, N-C_6H_5-C_4-H); 6.50 (t, 2H, J= 7.4 Hz, N-C_6H_5-$C_{3,5}$-H); 6.53 (d, 2H, *J*= 7.4 Hz, N-C_6H_5-$C_{2,6}$-H); 6.74-7.15 (m, 1H, benzothiazole-C_5-H); 7.20-7.32 (m, 1H, benzothiazole-C_6-H); 7.35-7.50 (m, 1H, benzothiazole-C_4-H); 7.79 (d, 1H, *J*= 8.4 Hz, benzothiazole-C_7-H); 7.86 (d, 2H, *J*= 8.8 Hz, 4-Cl-C_6H_5-$C_{3,5}$-H); 8.09 (d, 2H, *J*= 8.8 Hz, 4-Cl-C_6H_5-$C_{2,6}$-H); 8.98 (s, ½ H, NH tautomer, D_2O exchangeable). **C^{13} NMR (DMSO-*d6*, δ ppm):** 42.38 (pyrroloimidazole-C_7); 56.39 (pyrroloimidazole-C_{7a}); 107.22 (pyrroloimidazole-C_6); 110.41 (N-C_6H_5-$C_{2,6}$); 128.62 (benzothiazole-$C_{3,6}$); 128.78 (benzothiazole-C_4); 128.93 (benzothiazole-C_5); 129.16 (N-C_6H_5-C_4); 129.23 (N-C_6H_5-$C_{3,5}$); 131.46 (4-Cl-C_6H_4-$C_{3,5}$); 131.75 (4-Cl-C_6H_4-$C_{2,6}$); 132.25 (4-Cl-C_6H_4-C_4); 132.52 (benzothiazole-C_2); 133.22 (N-C_6H_5-C_1); 134.16 (4-Cl-C_6H_4-C_1); 156.11 (pyrroloimidazole-C_5); 165.87 (benzothiazole-C_9); 166.16 (pyrroloimidazole-C_3); 179.86 (pyrroloimidazole-C_1). **Anal. form:** ($C_{25}H_{17}ClN_4OS_2$). **Calcd. (%):** C, 61.40; H, 3.50; Cl, 7.25; N, 11.46; S, 13.11. **Found (%):** C, 61.73; H, 3.62; N, 11.65; S, 13.20.

3-Phenyl-5-(3-phenylthiazolidin-2-ylidene)-2-thioxoimidazolidin-4-one; 26a and 5-(4-oxo-3-phenylthiazolidin-2-ylidene)-3-phenyl-2-thioxoimidazolidin-4-one; 26b

To a well-stirred and ice-cooled suspension of finely powdered potassium hydroxide (0.22 g, 4 mmol.) and 3-phenyl-2-thioxoimidazolidin-4-one **1** (0.38 g, 2 mmol.) in dimethylformamide (10 mL), phenyl isothiocyanate (0.27 g, 0.24 mL, 2 mmol.) was added portion wise. After complete addition, stirring was continued at room temperature for 3 hours. The reaction mixture was cooled to 0-5 ^{0}C, treated with 1,2-dichloroethane (0.20 g, 0.16 mL, 2 mmol.), or chloroacetyl chloride (0.22 g, 0.16 mL, 2 mmol.) then stirred at room temperature for additional 6 hours. The reaction mixture was then poured into ice-cooled water and the precipitated product was filtered, washed with water, crystallized from dioxane and dried to afford compounds **26a** and **26b**; respectively.

3-Phenyl-5-(3-phenylthiazolidin-2-ylidene)-2-thioxoimidazolidin-4-one; 26a

White powder, **yield;** 0.30 g (42 %), **m.p.**; 268-270 °C. **IR (KBr, cm^{-1}):** 3178 (NH); 3000, 2974 (CH-aromatic); 2885, 2762 (CH-aliphatic); 1716 (C=O); 1627 (C=N); 1600, 1566 (C=C); 1508, 1419, 1249, 1022 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-*d6*, δ ppm):** 2.71 (s, 2H, thiazolidine-C_4-H); 2.87 (s, 2H, thiazolidine-C_5-H); 6.97-7.15 (m, 2H, two N-C_6H_5-C_4-H); 7.49-7.80 (m, 4H, two N-C_6H_5-$C_{2,6}$-H); 8.25-8.40 (m, 4H, two N-C_6H_5-$C_{3,5}$-H); 11.88 (s, 1H, NH, D_2O exchangeable). **C^{13} NMR (DMSO-*d6*, δ ppm):** 29.24 (thiazolidine-C_5); 49.56 (thiazolidine-C_5); 110.40 (imidazole-C_4); 114.79 (thiazolidine-N-C_6H_5-$C_{2,6}$); 114.86 (thiazolidine-N-C_6H_5-C_4); 114.93 (N-C_6H_5-$C_{2,6}$); 115.29 (N-C_6H_5-C_4); 126.63 ((N-C_6H_5-$C_{3,5}$); 127.01 (thiazolidine-N-C_6H_5-$C_{3,5}$); 129.13 (N-C_6H_5-C_1); 129.26 (thiazolidine-C_2); 133.95 (thiazolidine-N-C_6H_5-C_1); 172.63 (imidazole-C_4); 174.00 (imidazole-C_2). **Anal. form:** **(**$C_{18}H_{15}N_3OS_2$). **Calcd. (%):** C, 61.16; H, 4.28; N, 11.89; S, 18.14. **Found (%):** C, 61.39; H, 4.05; N, 12.13; S, 18.31.

5-(4-Oxo-3-Phenylthiazolidin-2-ylidene)-3-phenyl-2-thioxoimidazolidin-4-one; 26b

Light grey powder, **yield;** 0.48 g (66 %), **m.p.**; >360 °C. **IR (KBr, cm^{-1}):** 3151, 3113 (NH); 3088, 3012 (CH-aromatic); 2951, 2885 (CH-aliphatic); 1751, 1724 (C=O); 1597 (C=C); 1510, 1396, 1269, 1072 (I, II, III,

IV bands of N-C=S). **MS:** m/z (%): 367 ($M^{+\cdot}$, 25.42); 102 (100). **Anal. form:** ($C_{18}H_{13}N_3O_2S_2$). **Calcd. (%):** C, 58.84; H, 3.57; N, 11.44; S, 17.45. **Found (%):** C, 59.12; H, 3.69; N, 11.68; S, 17.69.

5-(Isobenzofuran-3(1H)-ylidene)-3-phenyl-2-thioxoimidazolidin-4-one; 27
and 5-(2-(Hydroxymethyl)benzylidene)-3-phenyl-2-thioxoimidazolidin-4-one; 28

A solution of 3-phenyl-2-thioxoimidazolidin-4-one **1** (0.38 g, 2 mmol.) in dioxane (10 mL) was added to a solution of isobenzofuran-1(*3H*)-one (0.27 g, 2 mmol.) in pyridine (10 mL) at 20 °C. The reaction mixture was heated under reflux for 10 hrs. then left to attain the room temperature and the obtained crystals was filtered, washed with ethanol, dried and recrystallized from ethanol to yield two products. The insoluble product in boiling ethanol was filtered to give compound **27**, while the filtrate was concentrated and allowed to cool, the formed crystals were filtered and dried to obtain compound **28**.

5-(Isobenzofuran-3(*1H*)-ylidene)-3-phenyl-2-thioxoimidazolidin-4-one; 27

Pale yellow crystals, **yield;** 0.18 g (29 %), **m.p.**; >360 °C. **IR (KBr, cm^{-1}):** 3178 (NH); 3008, 2974 (CH-aromatic); 2885 (CH-aliphatic); 1724 (C=O); 1627 (C=N); 1604, 1566 (C=C); 1508, 1300, 1249, 1022 (I, II, III, IV bands of N-C=S); 1249, 1103 (C-O-C). **^{1}H NMR (DMSO-*d6*, δ ppm):** 3.86 (s, 2H, isobenzofuran-C_7-H); 6.96 (d, 1H, J= 8.6 Hz, isobenzofuran-C_6-H); 7.19 (t, 1H, J= 8.8 Hz, N-C_6H_5-C_4-H); 7.61 (d, 2H, J= 8.8 Hz, N-C_6H_5-$C_{2,6}$-H); 7.64-7.72 (m, 1H, isobenzofuran-C_5-H); 7.78-7.81 (m, 1H, isobenzofurane-C_4-H); 8.10 (d, 1H, J= 8.6 Hz, isobenzofuran-C_3-H); 8.29-8.32 (m, 2H, J= 8.8 Hz, N-C_6H_5-$C_{3,5}$-H); 11.88 (s, 1H, imidazole-NH, D_2O exchangeable). **Anal. form:** ($C_{17}H_{12}N_2O_2S$). **Calcd. (%):** C, 66.22; H, 3.92; N, 9.08; S, 10.40. **Found (%):** C, 66.05; H, 4.16; N, 9.27; S, 10.53.

5-(2-(Hydroxymethyl)benzylidene)-3-phenyl-2-thioxoimidazolidin-4-one; 28

Yellow powder, **yield;** 0.20 g (32 %), **m.p.**; 260-262 °C. **IR (KBr, cm^{-1}):** 3383 (OH); 3286 (NH); 3055, 3032 (CH-aromatic); 2831 (CH-aliphatic); 1651 (C=O); 1593 (C=N); 1543 (C=C); 1543, 1315, 1296, 1026 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-*d6*, δ ppm):** 3.55 (s, 2H, $\underline{CH_2}$OH); 5.11 (s, 1H, OH, D_2O exchangeable); 6.90-7.10 (m, 4H, N-C_6H_5-$C_{2,4,6}$-H & $\underline{CH}$-benzylidene); 7.61-7.67 (m, 4H, N-C_6H_5-$C_{3,5}$-H & C_6H_4-$C_{5,6}$); 8.30-8.32 (m, 2H, C_6H_4-$C_{3,4}$-H); 11.85 (s, 1H, imidazole-NH, D_2O exchangeable). **C^{13} NMR (DMSO-*d6*, δ ppm):** 55.80 ($\underline{CH_2}$OH); 114.80 (benzylidene-C); 114.92 (N-C_6H_5-$C_{2,6}$); 115.68 (N-C_6H_5-C_4); 124.59 (C_6H_4-C_6); 128.62(C_6H_4-C_3); 129.23(C_6H_4-C_5); 129.27 (C_6H_4-C_4); 129.75 (N-C_6H_5-$C_{3,5}$); 131.76 (N-C_6H_5-C_1); 132.26 (C_6H_4-C_1); 132.83 (C_6H_4-C_2); 134.17 (imidazole C_5); 169.24 (imidazole-C_4); 173.88 (imidazole-C_2). **Anal. form:** ($C_{17}H_{14}N_2O_2S$). **Calcd. (%):** C, 65.79; H, 4.55; N, 9.03; S, 10.33. **Found (%):** C, 65.98; H, 4.13; N, 9.36; S, 10.67.

2,3-dihydro-5,8-dihydroxy-2-phenyl-3-thioxoimidazo[1,5-a]pyridin-1(8aH)-one; 29

A solution of 3-phenyl-2-thioxoimidazolidin-4-one **1** (0.38 g, 2 mmol.) in dimethylformamide (10 mL) was added to a solution of succinic anhydride (0.20 g, 2 mmol.) in pyridine (10 mL) at 20 °C. The reaction mixture was heated under reflux for 10 hours. The reaction mixture was allowed to attain room temperature poured onto ice-cold water and the obtained precipitate was filtered, washed with ethanol, dried and crystallized from dioxane.

Colourless needle crystals, yield; 0.34 g (62 %), m.p.; >360 °C. **IR (KBr, cm^{-1}):** 3400 (br. OH tautomer); 3062, 3032 (CH-aromatic); 2927 (CH-aliphatic); 1716 (C=O); 1604 (C=C); 1508, 1388, 1246, 1029 (I, II, III, IV bands of N-C=S). **^{1}H NMR (DMSO-*d6*, δ ppm):** 2.91 (s, 1H, imidazopyridine-C_{8a}-H); 3.20-3.50 (s, 1H, imidazopyridine-$C_{6,7}$-H tautomer); 7.15 (s, 1H, imidazopyridine-C_7-H); 7.19 (s, 1H, imidazopyridine-C_6-H); 7.30-7.48 (m, 1H, N-C_6H_5-C_4-H); 7.68 (d, 2H, *J*= 8 Hz, N-C_6H_5-$C_{2,6}$-H); 8.15-8.17 (m, 2H, N-C_6H_5-$C_{3,5}$-H); 13.71 (s, 1H, two OH tautomer, D_2O exchangeable). **Anal. form:** ($C_{13}H_{10}N_2O_3S$). **Calcd. (%):** C, 56.92; H, 3.67; N, 10.21; S, 11.69. **Found (%):** C, 56.71; H, 3.89; N, 10.49; S, 11.58.

Part 2- Biology

Development therapeutic program (DTP), division of cancer treatment and diagnosis (DCTD), national cancer institute (NCI), Bethesda, Maryland, USA has adopted an in-vitro model consisting of 60 human tumor cell lines for primary anticancer screening [18]. Screening utilizes 60 different human tumor cell lines, representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney.

It is a unique screen in that the complexity of a 60 cell line dose response produced by a given compound results in a biological response pattern which can be utilized in pattern recognition algorithms (COMPARE program).

Screening is a two-stage process, beginning with evaluation of all compounds against the 60 cell lines at single dose level of 10 μ mol.

The output from the single 60 cell panel screen is reported as a mean graph and is available for analysis by the COMPARE program.

Compounds which inhibit growth by more than 50% in a threshold number of cell lines was determined by comparison with historical NCI 60 cell and in–vivo data (COMPARE Prog), were selected for 5-dose assay.

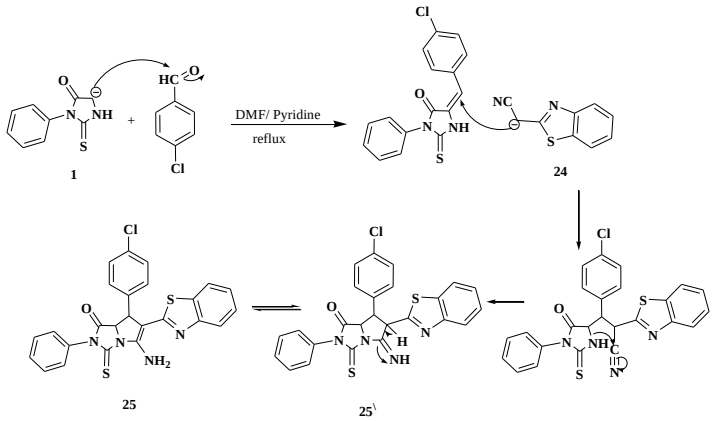


Figure 1. Proposed mechanism of synthesis of compound 25

Mean graph is a mean of presenting the in-vitro test results to emphasize differential effects of test compounds on various human tumor cell lines. It plots the growth relative to no drug control and relative to time zero number of cells. Thus, it detects both growth inhibition (values between 0-100) and lethality (values less than 0) i.e a value of 40 means 60% growth inhibition while value of -40 means 40% lethality. The mean is the average of growth across the tested cell lines, while delta is the maximum difference from the mean.

Cell suspensions which were diluted according to the particular cell type and the expected target cell density were added into micro titer plates. Inoculates were allowed a pre-incubation period of 24 hrs at 37 ^{0}C for stabilization. Test compounds were then added at a single concentration (10 µmole) and culture were incubated for 48 hrs at 37^0 C in 5% CO_2 atmosphere and 100% relative humidity. [18]

Sulforhodamine B (SRB) protein assay was used to estimate cell viability or growth. SRB is a bright pink anionic dye that, in dilute acetic acid, would bind to the basic amino acids. This reagent gives the best combination of stain intensity, single-to-noise ratio and linearity with cell number.

A plate reader was used to read the optical densities and microcomputer preceded the optical densities into special concentration parameters. Results of each compound were reported as a mean graph of the percent growth of treated cells relative to untreated control cell.

RESULTS AND DISCUSSION

Part 1-Chemistry

Literature survey revealed that pyrrole ring was widely reported as potent anticancer agent [19-22]. So novel pyrrolo[1,2-e]imidazole-6-carbonitrile **4** was obtained by refluxing 3-phenyl-2-thioxoimidazolidin-4-one **1** with 2-(4-methoxybenzylidene)malononitrile **2** which yielded the open chain derivative **3** which was fused in pyridine to give the target compound **4**. **(Scheme I).** **^{1}H NMR** spectrum of compound **4** displayed a singlet at δ 4.14 ppm corresponding to pyrrolimdazole C_7 proton. In addition to two deuterium oxide exchangeable singlets at δ 9.62 ppm and 10.10 ppm corresponding to amino and hydroxyl protons; respectively. Also the target compounds pyrrolo[1,2-e]imidazole-6-carbonitrile; **8a** and **8b** derivatives were synthetized through refluxing 3-phenyl-2-thioxoimidazolidin-4-one **1** with ethyl 3-(4-chlorophenyl)-2-cyanoacrylate **5** or ethyl 2-cyano-5-phenylpenta-2,4-dienoate **6** in dimethyl formamide containing catalytic amount of piperidine to yield the open chain 2-thioxoimidazolidine derivatives **7a** or **7b** which upon refluxing in pyridine gives the target pyrrolo[1,2-e]imidazole derivatives **8a** and **8b;** respectively. **^{1}H NMR** spectra of compound **7a** displayed two multiplets at δ 1.84-1.86 and 3.86-4.00 ppm corresponding to the ethoxy ester protons and a singlet at δ 2.87 ppm corresponding to imidazole C_5 proton. As well as deuterium oxide exchangeable singlet at δ 11.89 ppm attributed to imidazole-NH proton.

^{1}H NMR spectra of compounds **8a** revealed a singlet at δ 3.87 ppm due to pyrroloimdazole C_{7a} proton. Other protons appeared at their expected chemical shift.

The target 3-phenyl-5-(3-phenylacryloyl)-2-thioxoimidazolidin-4-one **10** was prepared through refluxing 3-phenyl-2-thioxoimidazolidin-4-one **1** with cinnamoyl chloride **9** in toluene containing catalytic amount of triethylamine. The reaction was suggested to proceed first through nucleophilic attack of the active methylene function on the acid chloride moiety of cinnamoyl chloride **9** with subsequent elimination of hydrochloride molecule to yield the α, β-unsaturated carbonyl compound **10** followed by refluxing compound **10** in toluene / pyridine mixture 1:1 to enhance intermolecular addition of NH function on the double

bond of the α, β-unsaturated carbonyl side chain to yield the desired product **11**.

^{1}H NMR spectrum of compound **11** revealed a singlet at δ 3.85 and 8.29 ppm due to pyrroloimidazole C_{7a} and pyrroloimidazole C_6 protons; respectively.

Moreover, the reaction of compound **1** with 2-(ethoxymethylene)malononitrile **12** in dimethyl formamide containing catalytic amount of triethyl amine yielded the open chain 2-thioxoimidazolidine derivative **13** which upon refluxing in pyridine to give the target compound **14 (scheme II)**.

^{1}H NMR spectrum of compound **14** revealed two singlets at δ 3.78 and 4.11 ppm due to pyrroloimidazole C_{7a} tautomer and pyrroloimidazole C_7 proton. As well as two deuterium oxide exchangeable singlets at δ 9.45 and 9.97 ppm attributed to amino-NH_2 proton and NH tautomer; respectively.

Our scope was extended to study the effect of various substituents in the pyrroloimidazole ring system. So, compound **1** was reacted diethyl ethoxymethylenemalonate in dimethyl formamide containing catalytic amount of triethyl amine yield the open chain 2-thioxoimidazolidine derivative **15** which upon refluxing in pyridine give the target compound **16.** The reaction of ethoxymethylenemalonic acid esters was indicated to proceed through nucleophilic substitution of the ethoxy group by the active methylene proton and elimination of ethanol molecule followed by intramolecular cyclization with subsequent elimination of a second ethanol molecule to furnish the target compound**. ^{1}H NMR** spectrum of compound **16** revealed triplet at 1.29 due to methyl ester proton and multiplet attributed to at δ 4.28-4.33 ppm due to pyrroloimidazole C_{7a}, pyrroloimidazole C_7 and ethyl ester protons.

Compound **1** was reacted with dimethyl acetylenedicarboxylate in dimethyl formamide containing catalytic amount of triethyl amine to yield the open chain 2-thioxoimidazolidine derivatives **17** which upon refluxing in pyridine give the target compounds **18.**

The reaction of compound **1** with acetyl acetaldehyde dimethyl acetal in dimethyl formamide containing catalytic amount of piperidine yielded the open chain 2-thioxoimidazolidine derivative **19** which upon refluxing in pyridine gives the target compound **20 (scheme III)**. **^{1}H NMR** spectrum of compound **19** displayed a singlet at δ 2.71 ppm corresponding to $\underline{CH_2}$-CH $(OCH_3)_2$ protons in addition to two singlets at δ 2.87, 3.79 ppm corresponding to methyl protons and methoxy six protons; respectively. As well as a deuterium oxide exchangeable singlet at δ 11.88 ppm attributed to imidazole-NH proton. While **^{1}H NMR** spectrum of compound **20** revealeda singlet at 3.13 ppm due to methyl protons as well as multiplet at δ 6.94-6.96 ppm due to pyrroloimidazole $C_{5,6}$ proton.

However, the reaction of of compound **1** with ethyl acetoacetate and 4- chlorobenzaldehyde in dimethyl formamide/ pyridine mixture yielded the cyclic thioxopyrrolo[1,2-e]imidazole derivative **21**.

Compound 1 and 1-(4-chlorophenyl)-3-(thiophen-2-yl)prop-2-en-1-one **22** were reacted to afford the target compound **23 (Scheme III)**.

^{1}H NMR spectrum of compound **23** displayed three multplets at δ 2.50-2.53 ppm, 3.75-3.79 ppm and 3.85-3.87 ppm corresponding to pyrroloimidazole C_7, pyrroloimidazole C_{7a} and pyrroloimidazole C_6 protons; respectively.

Compound **1**, 2-(benzo[d]thiazol-2-yl)acetonitrile **24** and 4- chlorobenzaldehyde were heated under reflux in dimethylformamide pyridine mixture to give the target compound **25**. The postulated reaction mechanism for synthesis of compound **25** is illustrated as follows analogous to the reported mechanism [23]:

^{1}H NMR spectrum of compound **25** displayed multiplet at δ 3.60-3.85 ppm corresponding to pyrroloimidazole C_7 and pyrroloimidazole C_{7a} protons. In addition to singlet at 4.39 ppm due to pyrroloimidazole C_6 tautomer as well as two deuterium oxide exchangeable singlets at δ 5.14, 8.98 ppm attributed to amino NH_2 protons and NH tautomer; respectively. Other protons appeared at their expected chemical shift. Compound **1** was also reacted with with phenyl isothiocyanate in the presence of finely powdered potassium hydroxide and dimethyl formamide that was followed by addition of 1,2-dichloroethane or chloroacetyl chloride to afford compounds **26a** and **26b**; respectively **(Scheme IV)**. **^{1}H NMR** spectrum of compound **26a** displayed two singlets at δ 2.71 and 2.87 ppm corresponding to thaizolidine C_4 and thiazolidine C_5 protons; respectively. As well as deuterium oxide exchangeable singlet at δ 11.88 ppm attributed to imidazole-NH proton. Moreover, the reaction of 3-phenyl-2-thioxoimidazolidin-4-one **1** was with isobenzofuran-1(3H)-one in pyridine/ dioxane mixture compounds **27** and **28** were obtained. **^{1}H NMR** spectrum of compound **27** displayed a singlet at δ 3.86 ppm corresponding to isobenzofuran-C_7 proton in addition to deuterium oxide exchangeable singlet at δ 11.88 attributed to imidazole-NH proton. While **^{1}H NMR** spectrum of compound **28** revealed a singlet at δ 3.55 ppm attributed $\underline{CH_2}$OH protons and two deuterium oxide exchangeable singlets at δ 5.11 and 11.85 ppm due to hydroxyl proton and imidazole-NH proton; respectively. While, the thioxoimidazo[1,5-a]pyridin-1-one derivative **29** was synthetized through refluxing 3-phenyl-2-thioxoimidazolidin-4-one **1** with succinic anhydride in dimethyl formamide pyridine mixture. **^{1}H NMR** spectrum of compound **29** displayed three singlets at δ 2.91, 7.15 and 7.19 ppm corresponding to imidazopyridine C_{8a}, imidazopyridine C_7 and imidazopyridine C_6 protons: respectively.

Table 1. The mean growth inhibition percent, delta values and the percent growth inhibition against some subpanel cell lines of selected compounds of scheme I& II.

Comp. No. (NCI No.)	Mean growth percent (Delta)	Panel Subpanel cell line (Growth inhibition percent)
4 (806568)	**96.31 (72.48)**	**Non-Small cell lung cancer:** EKVX (42.92), NCI-H226 (23.02). **CNS Cancer:** SF268 (10.61), SF539 (11.96). **Melanoma:** SK-MEL-5 (13.47), UACC-62 (63.31). **Renal Cancer:** SN12C (16.67), TK-10(11.24), UO-31(20.03). **Prostate Cancer:** DU-145 (11.37). **Breast Cancer:** HS 578T (76.17).
8a (806569)	**99.60 (20.51)**	**Non-Small cell lung cancer:** HOP-92 (20.21), NCI-H226 (13.88). **CNS Cancer:** SNB-75 (11.67). **Renal Cancer:** 786-0 (12.35), A498 (19.02), UO-31(10.52).
8b (806570)	**102.75 (17.34)**	**Non-Small cell lung cancer:** NCI-H522 (14.59). **Melanoma:** SK-MEL-2 (9.11). **Renal Cancer:** UO-31(13.92).
11 (806571)	**102 (13.28)**	**CNS Cancer:** SF-539 (10.62). **Renal Cancer:** A498 (5.97), UO-31(8.66).
14 (806572)	**102.63 (10.44)**	**Leukemia:** RPMI (7.23). **Non-Small cell lung cancer:** NCI-H226 (7.81). **CNS Cancer:** SF-295 (7.5). **Breast Cancer:** BT-549 (5.74).
16 (806573)	**102.92 (20.25)**	**Non-Small cell lung cancer: NCI**-H226 (17.33), NCI-H23 (8.02). **Melanoma:** LOXIMVI (9.22). **Renal Cancer:** CAKI-1 (6.72), UO-31(15.80).
18 (806574)	**102.29 (14.45)**	**CNS Cancer:** SNB-75 (6.5). **Renal Cancer:** CAKI-1 (7.07), RXF 393 (6.17), UO-31 (12.16).

Table 2. The mean growth percent, delta values and the percent growth of some subpanel cell lines of selected compounds of scheme III.

Comp. No. (NCI No.)	Mean growth percent (Delta)	Panel Subpanel cell line (Growth inhibition percent)
20 (806575)	**103.08 (18.29)**	**Leukemia:** MOLT-4 (11.33). **Non-Small cell lung cancer:** NCI-H23 (9.25). **Melanoma:** UACC-62 (6.83). **Renal Cancer:** UO-31 (15.21).
21 (806593)	**92.52 (91.84)**	**Non-Small cell lung cancer:** HOP-92 (8.69), NCI-H226 (25.49), NCI-H23 (11.78), NCI-H460 (13.23). **Melanoma**: LOXIMVI (9.82), MALME-3M (11.88), SK-MEL-5 (8.38), UACC-62 (11.97). **Ovarian Cancer:** IGROV1 (13.24), OVCAR-4(9.22), SK-OV-3 (11.97). **Renal Cancer:** A498 (18.12), CAKI-1 (17.10), RXF 393 (9.57), UO-31 (33.16). **Prostate Cancer:** PC-3 (13.35). **Breast Cancer:** MCF7 (34.77), MDA-MB-231/ATCC (9.63), HS 578T (11.11), T-47D (16.95), BT-549 (11.38), MDA –MB-468 (99.32).
23 (806576)	**99.36 (27.29)**	**Non-Small cell lung cancer:** NCI-H226 (13.17). **Melanoma:** UACC-62 (11.21). **Renal Cancer:** A498 (11.41), CAKI-1 (8.74), UO-31 (29.66). **Prostate Cancer:** PC-3 (14.32). **Breast Cancer:** MDA-MB-231/ATCC (13.67), BT-549 (7.61), MDA –MB-468 (20.29).
25 (806577)	**101.62 (19.98)**	**Leukemia:** MOLT-4 (11.71). **Non-Small cell lung cancer:** NCI-H226 (8.37). **Melanoma:** UACC-62 (5.93). **Renal Cancer:** UO-31(8.36). **Non-Small cell lung cancer:** HOP-92 (6.95), NCI-H522 (7.96).
27 (806592)	**101.68 (20.00)**	**Renal Cancer:** UO-31(18.32). **Prostate Cancer:** PC-3 (5.90). **Breast Cancer:** MDA-MB-231/ATCC (17.97).

28 (806591)	**97.97 (21.01)**	**Non-Small cell lung cancer:** EKVX (10.4), NCI-H226 (11.1), NCI-H23 (14.51), **Colon cancer:** HCT-2998 (12.4). **CNS cancer:** SNB-75 (14.73). **Melanoma**: LOXIMVI (5.38), UACC-62 (8.83). **Ovarian Cancer:** IGROV1 (9.84), OVCAR-4(8.42). **Renal Cancer:** CAKI-1 (11.45), RXF 393 (7.37). **Breast Cancer:** MCF7 (12.09), MDA-MB-231/ATCC (7.48), HS 578T (6.49), BT-549 (8.00), MDA –MB-468 (5.92).

Part 2- Biology

Twelve of the newly synthesized compounds were selected by the National Cancer institute, Bethesda, Maryland, USA, to be evaluated in a single high dose (10 µmole) in the full 60 cell line panel for their anticancer activities. The mean growth inhibition percent, delta values and percent growth inhibition against some subpanel cell lines, of the selected compounds, are presented in **Tables (1-2).**

Eleven compounds **4, 8a, 8b, 11, 14**, **16**, **20, 21, 23** and **25** were selected from schemes **I, II** and **III** by the NCI for the one dose anticancer screening. As noted in the research objectives, that structural modifications to our lead compound Leucettamine B were designed and synthesized in order to obtain more potent anticancer agents. As revealed from the results represented in table **(1)** fusion of different substituted pyrrole rings to the imidazole nucleus lead to variable anticancer activities. Among which compounds **4**, **14** and **25** possessing amino function in 5-position, only compound **4** with cyano and 4-methoxyphenyl groups in positions six and seven; respectively exhibited moderate to strong anticancer activity against certain cell lines namely; Non-Small cell lung cancer EKVX (42.92 %), Melanoma UACC-62 (63.31%) and breast cancer HS 578T (76.17 %).

However, replacement of the 5-amino group in pyrrolo[1,2-e]imidazole system with 5-oxo function as in compounds **8a**, **8b**, **16**, **18** and **21**. In which, compound **8a** bearing 4-chlrophenyl moiety in 7-position and cyano function in 6-position exerted mild anticancer activity against Non-Small cell lung cancer HOP-92 (20.21 %), Renal cancer A498 (19.02 %). However, replacement of 4-chlorophenyl moiety with 7-styryl as in compound **8b** diminished the anticancer activity. While, retaining 4-chlrophenyl group in 7-position and replacing the cyano function by acetyl group in 6-position as in compound **21** led to selective potent anticancer activity against Breast Cancer MDA –MB-468 (99.32 %). As well as moderate activity against non-small cell lung cancer NCI-H226 (25.49 %), Renal cancer UO-31 (33.16 %) and Breast Cancer MCF7 (34.77 %) cell lines.

Moreover, the presence of small aliphatic functions as ethoxy substituent in 6-position, methoxy substituent in 7-position as in compounds **16** and **18**; respectively led to weakly active anticancer compounds except for compound **16** which exhibited mild anticancer activity against non-small cell lung cancer NCI-H226 cell line with inhibition activity of 17.33 %.

It can be noted that, presence of small aliphatic substituent in 6-position is important to maintain the anticancer activity as in compounds **8a**, **16** and **21**, while absence of any substituent in position six diminished the activity as in compound **18**.

However, absence of the 5-oxo function or its replacement by phenyl group as in compound **11** and **20** led to inactive compounds. While replacement of 5-oxo function by 4-chlorophenyl group as in compound **23** led to moderate anticancer activity against Renal Cancer UO-31 (29.66 %) and Breast Cancer MDA –MB-468 (20.29 %) cell lines.

Aligned with the scope of our work in studying structural modification of our lead compound changing the benzo[d][1,3]dioxol-5-yl)methylene substituent by isobenzofuran-3(*1H*)-ylidene and 2-(hydroxymethyl)benzylidene moieties and replacing the 2-amino group with the thioxo function as in compounds **27** and **28**; respectively led to weak anticancer activity except for compound **27** which exhibited mild activity against Renal Cancer UO-31 (18.32 %) and Breast Cancer MDA–MB-231/ATCC (17.97 %) cell lines.

CONCLUSION

Conclusively, an efficient approach for the synthesis of diversly functionalized pyrrolo[1,2-e]imidazole analogs were established with high yield. Twelve of the newly synthesized compounds were selected by the National Cancer Institute, Bethesda, Maryland, USA, to be evaluated for their anticancer activities. Compounds **4** and **21** were identified as the most promising anticancer agents, whereas compound **4** exhibited strong anticancer activity against Melanoma UACC-62 (63.31%) and breast cancer HS 578T (76.17 %). While compound **21** showed selective potent anticancer activity against Breast Cancer MDA –MB-468 (99.32 %).

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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