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Synthesis And Characterization Of Novel Thiazole Derivatives Of Pyrrolidino-Disubstituted *N*-Arylmaleimides.

Sunita A. Chaudhari (Patil)[1]*, Vasant M. Patil[2], Sambhaji V. Patil[3], and Vishwanath R. Patil[2]

*[1]Directorate of Forensic Science Laboratory, Vidya Nagari Kalina, Mumbai-400098 to the Government, Home Department, Maharashtra state, India.
[2]Department of Chemistry, University of Mumbai, Kalina Campus, Vidya Nagari, Mumbai- 400098, Maharashtra, India.
[3]Maratha Vidya Prasarak Samaj's Arts, Science and Commerce College, Ozar (Mig), Tal-Niphad, Dist-Nashik, Maharashtra, India

Abstract:
The compound **1** was reacted with bromine in DMF to obtained dibromo succinimide **2**. The compound **2** was reacted with pyrrolidine as a base followed by dehydrohalogenation to obtained monobromo compound **3** through common enaminone intermediate, further compound **3** on Vilsmeier Haack formylation afforded compound **4** with good yield. The condensation of 2,5-dihydro-2,5-dioxo-1-phenyl-4-(pyrrolidin-1-yl)-1*H*-pyrrole-3-carbaldehyde **4** with thiosemicarbazide hydrochloride in ethanol in presence of acetic acid furnished compound **5** with 81 % yield. The compound **5** react with disubstituted phenacyl bromide **6 a-d** to obtained thiazole derivative of Di-substituted *N*-aryl maleimides **7 a-d** with good yield. All the synthesized compounds were well characterised by spectral and analytical techniques.

Keywords: Dibromosccinimide, *N,N*-dimethylamine, Vilsmeier Haack formylation, thiosemicarbazide, Phenacyl bromide.

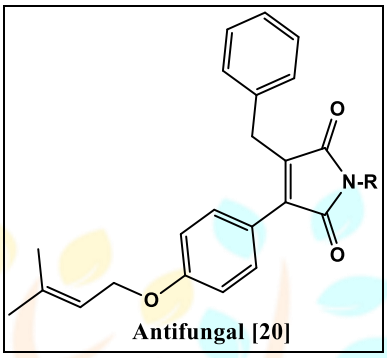
Introduction:

Herein we reported the synthesis of Thiazole derivatives of di-substituted *N*-aryl maleimides.

Maleimides are an important class of substrates for biological and chemical applications. In biological applications they are used as chemical probes of protein structure [1-2], as immunoconjugates for cancer therapy [3-4], Maleimides shows a wide range of biological activities such as antibacterial and antifungal [5], antiprotozoal [6], antiangiogenic [7], analgesic [8], antistress agents [9], cytotoxic, DNA binding activity [10]. These Five-member cyclic N-Aryl imides have attracted the attention of many numbers of groups, as these imides have found numerous applications in biology [11], pharmacology [12], herbicides, pesticides [13], antifungal agent, material science [14], synthetic [15] and polymer chemistry [16].

3 & 4 positions of maleimides:

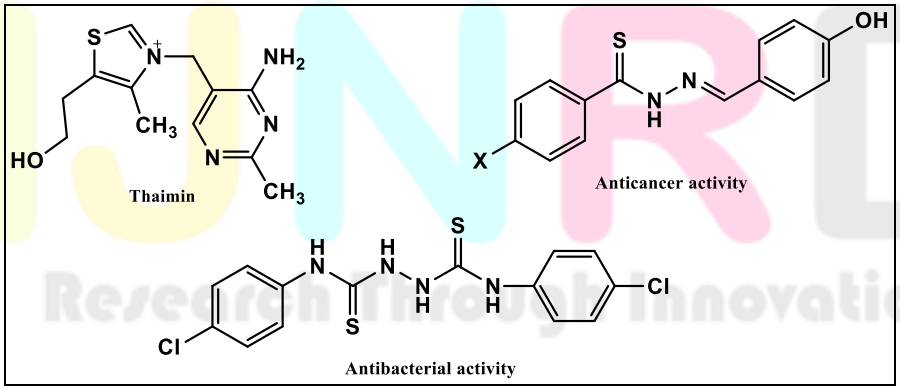
3, 4 substituted maleimides are crucial part for biological activity. Replacement at 3 & 4 position shows medicinally important properties. 3-and/or 4- substituted maleimides exhibits useful biological activities such as antioxidant, antibacterial, antiviral, analgesic, antiplatelet, antimicrobial, and anticancer activities [17]. Therefore, development of versatile methods to functionalized the 3,4-position in maleimide attracts increasing attention in recent year.3,4-position has been reported mainly by arylation or heteroarylation by Heck and Suzuki reaction [18,19] Sortino and co-workers have demonstrated that, substituents on 3 and 4 positions in maleimides show variable effect on activity [20].



Antifungal [20]

Thiosemicarbazones are a class of compounds obtained by condensation of thiosemicarbazide with suitable aldehydes or ketones. Thiosemicarbazide is valuable building blocks for the synthesis of five-membered heterocycles [21]. Thiosemicarbazones have received considerable attention because of their pharmacological activities. They have numerous biological activities, as anticarcinogenic, antibacterial, anti-HIV, anticancer, fungicides, antiviral, antifungal, antitumor activity etc. [22].

Thiazole is aromatic, heterocyclic organic compound featuring both a nitrogen atom and sulphur atom as part of the aromatic five-membered ring. Thiazoles are important class of heterocyclic compounds, found in many potent biologically active molecules such as Sulphathiazole (antimicrobial drug), Abafungin (antifungal drug) with trade name Abasol cream, Ritonavir (antiretroviral drug) and Bleomycin and Tiazofurin (antineoplastic drug) [23]. Thiazole ring system is an important class of compounds in medicinal chemistry. This structure has found applications in drug development for the treatment of cardiotonic [24], fungicidal [25], HIV infection [26], mental retardation in children, age related and neurodegenerative brain damage (Alzheimer's disease, Parkinsonism disease) [27].



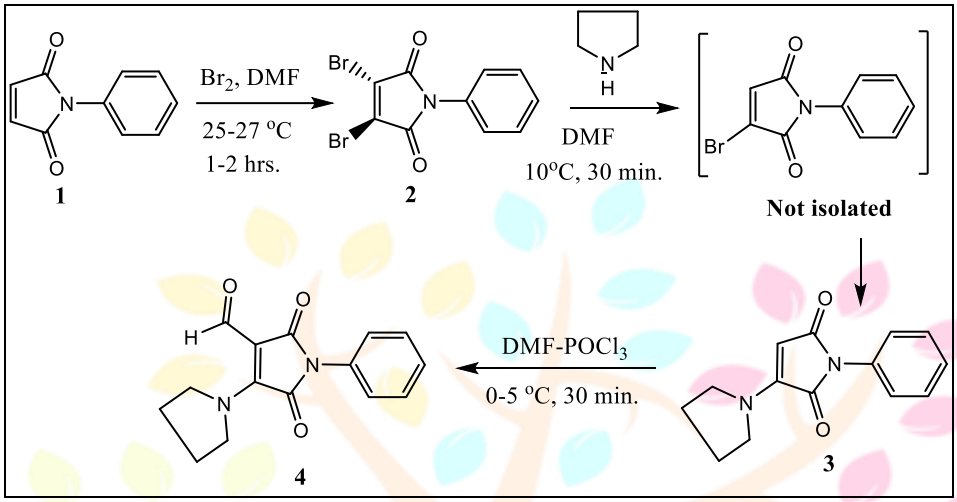
Materials and methods:

Melting points were determined on a Gallen Kamp melting point apparatus, Mod.MFB-595 in open capillary tube and are uncorrected. FT-IR spectra were recorded on Shimadzu FTIR-408 instrument in KBr pellets. ^{1}H and ^{13}C spectra were recorded on Varian XL 500 spectrometer (500MHz) in $CDCl_3$ and DMSO. Chemical shifts are reported in ppm with respect to tetra methyl silane as an internal standard. Elemental analyses were carried out on Hosli CH analyser and are within ± 0.4 of theoretical percentages. The progress of the reaction was monitored by thin layer chromatography (TLC, 0.2 mm silica gel 60 F 254, Merck plates) and visualized using UV light (254 and 366 nm) for detection. All

commercial grade chemicals were purchased from S.D. Fine chemicals India and used without further purification while solvents were purified by standard literature procedures.

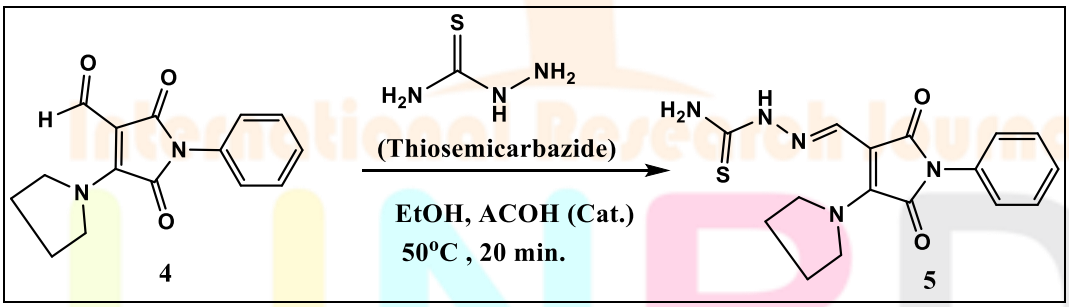
Results and Discussion:

The compound **1** were reacted with bromine in DMF at 25-27 ^{o}C for 1-2.5 hrs. afforded the dibromosuccinimides **2**. The Compound **2** was reacted with pyrrolidine as a base followed dehydrohalogenation afforded monobromo compound; instead, complex mixtures of with unreacted dibromosuccinimides **3** were obtained through common enaminone intermediate. Installation of an ammino functionality at C-3 position in compound **3** should increase nucleophilicity at C-4 position. Compound **3** reacted with bromine in DMF at 0 ^{o}C for 5 min. to obtained compound **4**. Vilsmeier Haack formylation of Compound **3** at 0-5 ^{o}C afforded compound **4** with good yield. **(Scheme-1)**



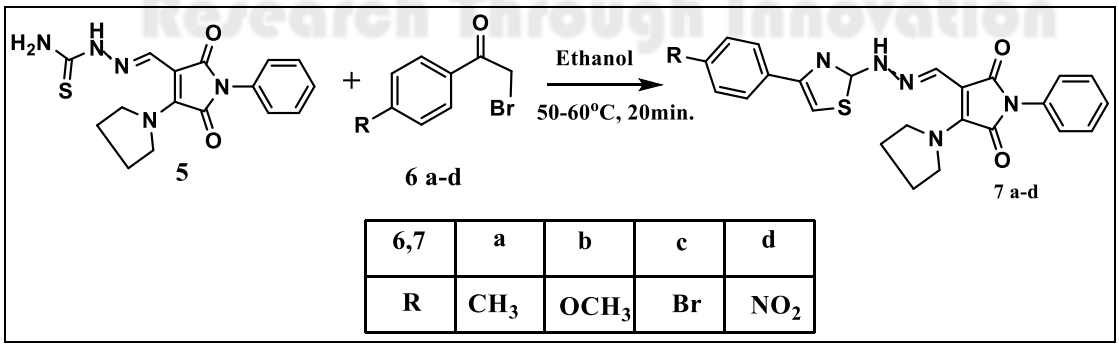
Scheme-1: Synthesis of 2,5-dihydro-2,5-dioxo-1-phenyl-4-(pyrrolidin-1-yl)-1*H*-pyrrole-3-carbaldehyde (4)

Thus, condensation of 2,5-dihydro-2,5-dioxo-1-phenyl-4-(pyrrolidin-1-yl)-1*H*-pyrrole-3-carbaldehyde **4** with thiosemicarbazide in ethanol in presence of acetic acid at 50 ^{o}C furnished orange colour compound **5** with 74 % yield **(Scheme-2).**



Scheme-2: Synthesis of 1-((2,5-dihydro-2,5-dioxo-1-phenyl-4-(pyrrolidin-1-yl)-1*H*-pyrrol-3-yl)-methylene) thiosemicarbazide (5)

The compound **5** reacted with substituted phenacyl bromide **6 a-d** to obtained thiazole derivatives of disubstituted N-arylmaleimides **7 a-d (Scheme-3)**



6,7	a	b	c	d
R	CH_3	OCH_3	Br	NO_2

Scheme-3: Synthesis of thiazole derivatives of Disubstituted N- aryl maleimides: (7a-d)

All the synthesized compounds were well characterized by IR, NMR, Mass Spectroscopy and elemental analysis given in experimental section.

Experimentals:

General procedure for synthesis of 1-phenyl-3-(pyrrolidin-1-yl)-1H-pyrrole-2,5-dione (3):

1-phenyl-1H-pyrrole-2, 5-dione, **1** (0.01 mol) in DMF (8 mL) was vigorously stirred at room temp. The mixture of bromine (0.011 mol) in DMF was added drop wise at 25^{0}C and stirred for 1-2.5 hrs. with constant stirring, white solid separated was then filtered, washed with cold water, dried and recrystallized using ethanol to obtain compound **2** [28].

To a solution of trans-3, 4-dibromo-1-phenyl- pyrrolidin-2,5-dione**, 2** (0.01 mol) in DMF (10 mL), pyrrolidine (0.03 mol) was added drop wise at 10ºC and stirred for 30 min. The reaction mixture was poured over crushed ice. The golden yellow solid separate out was filtered and recrystallized from aqueous ethanol to obtained compound **3**

M.P.:140-142ºC, Yield (%): 80, (1.38g), Colour: Yellow solid. The structure of compound **3** established on the basis of spectral and analytical data found as per literature [28].

General procedure for synthesis of 2,5-dihydro-2,5-dioxo-1-phenyl-4-(pyrrolidin-1-yl)-1*H*-pyrrole-3-carbaldehyde (4):

Vilsmeier Haack adduct prepared from DMF (0.012 mol) and $POCl_3$ (0.05 mol) at 0 ºC was added to a solution of **3** (0.01 mol) in 2 mL DMF, reaction mixture was then stirred at 0-5 ºC for 30 min. The reaction mixture was poured into cold water. The yellow product separated on neutralization with aqueous $NaHCO_3$ solution was filtered, washed with cold water, dried and purified by column chromatography, to obtained compound **4**.[29]

M.P.:180-184ºC, Yield (%):73, (1.42 g), Colour: Golden Yellow solid. The structure of compound **4** established on the basis of spectral and analytical data found as per literature [29].

General procedure for synthesis of 1-((2,5-dihydro-2,5-dioxo-1-phenyl-4-(pyrrolidin-1-yl)-1*H*-pyrrol-3-yl)-methylene) thiosemicarbazide (5):

The compound **4** (0.01 mol) in ethanol (10 mL), catalytic amount of acetic acid was added. The reaction mixture was stirred for 20 min. till we get clear solution. To this mixture thiosemicarbazide (0.01 mol) was added while stirring. The temperature of reaction mixture was maintained at 50ºC for 20 min. The orange solid separate out, the solid separated was collected and then filtered to afford compounds **5.** [30].

M.P: 200-202 ºC, Yield (%): 85, Colour: Orange solid; IR (KBr) (ν): 1755, 1694, 3388, 1608, 1275 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.84 (s, 4H, 2 x CH_2), 1.23 (s, 2H, CH_2), 2.03 (s, 2H, CH_2), 3.99 (s, 2H, NH_2), 6.32 (S, 1H, =C-H), 7.30-8.08 (m, 5H, Ar-H), 11.49 (bs, 1H, N-H) ppm ; ^{13}C NMR ($CDCl_3$) δ: 23.5 (2C'S), 51.7, 52.15, 112,2, 127.5, 122.7(2C'S), 128.5(2C'S), 134.5, 163.2, 158.7, 164.8, 168.8, 182.6 ppm; MS (m/z %): 343[M^+] Analysis Calculated for $C_{16}H_{17}N_5O_3$ **:** Calcd: C (55.96), H (4.99), N (20.39); Found: C (55.70), H (5.23), N (20.68)

General procedure for the preparation of thiazole derivatives of Disubstituted N- aryl maleimides: (7a-d):

The thiosemicarbazone **5** (0.01 mol) in ethanol (10 mL) was stirred for 10 min. To this mixture appropriate phenacyl bromide **6 a-d** (0.01 mol) was added and refluxed at for 20 min. The brown solid separates out, was allowed to cool at room temperature. The solid separated was filtered to afford **7 a-d,** and were purified by column chromatography (Hexane: Ethyl acetate)

Synthesis of 1-((2,5-dihydro-2,5-dioxo-1-phenyl-4-(pyrrolidin-1-yl)-1*H*-pyrrol-3-yl) methylene) -(2-(4-(4-p-tolylthiazol-2-yl) hydrazine, 7a.

M.P.(^{0}C): 180-182, Yield(%): 82, Colour: Reddish brown Solid IR (KBr) (ν): 1735, 1698, 3460, 1610 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d^6) δ: 1.80 (s, 4H, 2 x CH_2), 1.30 (s, 2H, CH_2), 2.03(s, 2H,CH_2), 2.80(s, 3H, CH_3), 6,90(S, 1H, N=C-H), 7.20-8.30 (m,10H, Ar-H), 11.80 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 26.80, 50.35(2C'S), 74.8(2C'S),110.5, 123.70(2C'S), 124.52 (2C'S),

128.90(2C'S), 130.80(2C'S), 132.50(2C'S), 135.70, 141.40, 144.50, 149.8, 154.5, 160.33, 168.7, 171.7, 173.5 ppm;
MS (70 eV) m/z (%): 489[M^+] Analysis Calculated for $C_{25}H_{23}N_5O_2S$: Calcd: C (65.63), H (5.07), N (15.31); Found: C (65.35), H (5.36), N (15.59)

Synthesis of 1-((2,5-dihydro-2,5-dioxo-1-phenyl-4-(pyrrolidin-1-yl)-1*H*-pyrrol-3-yl) methylene) -(2-(4-(4-methoxyphenyl) thiazol-2-yl)-hydrazine, 7b

M.P.(^{0}C): 184-186, Yield (%): 75, Colour: Reddish brown Solid IR (KBr) (ν): 1734, 1715, 3350, 1612 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d^6) δ: 1.78 (s, 4H, 2 x CH_2), 1.45(s, 2H, CH_2), 2.20 (s, 2H, CH_2), 3.90(s 3H, OCH_3), 6.90-8.30 (m, 10H, Ar-H),

8.40(s,1H, N=C-H), 11.80 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 25.10, 50.20(2C'S),

76.20(2C'S),107.5, 121.65(2C'S), 125.50 (2C'S), 128.70(2C'S), 130.50(2C'S),

132.40(2C'S), 136.50, 142.6, 145.5, 150.5, 152.8, 160.50, 168.7, 171.6, 173.4 ppm;
MS (70 eV) m/z (%): 473[M^+] Analysis Calculated for $C_{25}H_{23}N_5O_3S$: Calcd: C(63.41), H (4.90), N (14.79); Found: C (63.13), H (5.18), N (14.09)

Synthesis of 1-((2,5-dihydro-2,5-dioxo-1-phenyl-4-(pyrrolidin-1-yl)-1*H*-pyrrol-3-yl) methylene) -(2-(4-(4-bromophenyl) thiazol-2-yl)-hydrazine, 7c

M.P.(^{0}C): 170-172, Yield(%): 84, Colour: Reddish brown Solid IR (KBr) (ν): 1745, 1710, 3370, 1615 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 1.90 (s, 4H, 2 x CH_2), 1.50 (s, 2H, CH_2), 2.20(s, 2H,CH_2), 6.10(s,1H, N=C-H), 6.90-8.35 (m, 10H, Ar-H), , 12.10 (bs, 1H,
N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 25.50, 50.20(2C'S), 75.20(2C'S), 105.5, 121.60(2C'S), 124.80, 128.50(2C'S), 130.30(2C'S), 132.50(2C'S), 135.50, 143.8, 144.8, 150.8, 152.4, 160.70, 169.2, 171.8, 173.5 ppm; MS (70 eV) m/z (%): 521[M^{+1}], 523[M^{+2}] Analysis Calculated for $C_{24}H_{20}BrN_5O_2S$: Calcd: C(55.18), H(3.86), N(13.41) ;Found: C(54.90), H(4.13), N(13.12).

Synthesis of 1-((2,5-dihydro-2,5-dioxo-1-phenyl-4-(pyrrolidin-1-yl)-1*H*-pyrrol-3-yl) methylene) -(2-(4-(4-nitrophenyl) thiazol-2-yl)-hydrazine, 7d

M.P.(^{0}C): 192-194, Yield (%): 82, Colour: Brown Solid, IR (KBr) (ν): 1740, 1710, 3450, 1612, 1345 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.74 (s, 4H, 2 x CH_2), 1.40(s, 2H, CH_2), 2.20 (s, 2H,CH_2), 6.70-8.20 (m, 10H, Ar-H), 8.30(s, 1H, N=C-H), 12.10 (bs, 1H,
N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 24.50, 26.80(2C'S), 49.80(2C'S), 98.50, 116.80,

156.30, 121.20(2C'S),124.50(2C'S), 126, 127.40(2C'S),129.50(2C'S), 135.20(2C'S),

141.30, 150.50(2C'S), 162.50,165.80, 173.50, ppm; MS (70 eV) m/z (%): 488[M^{+1}]

Analysis Calculated for $C_{24}H_{20}N_6O_4S$: Calcd: C (59.01), H (4.13), N (17.20); found: C (59.28), H (4.40), N (17.48)

Conclusion:

Here we have designed and synthesized a series of novel thiosemicarbazone derivatives of disubstituted *N*-arylmaleimides with excellent yield. The main advantage of our method is clean, easy operational & simplicity of reaction. Here we described the synthesis of thiosemicarbazide derivatives of 2,5-dihydro-2,5-dioxo-1-phenyl-4-(pyrrolidin-1-yl)-1*H*-pyrrole-3-carbaldehyde **4** by nucleophilic condensation of trans-3,4-dibromo-1-(-phenyl) pyrrolidine- 2,5-dione, **3** with thiosemicarbazide to obtained thiosemicarbazone **5** with good yield. The compound **5** were further react with substituted phenacyl bromide **6 a-d** to obtained compound **7 a-d** with good yield. All these synthesized compounds are well

characterized by spectral and analytical method and are new addition to the family of heterocyclic compounds.

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