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Synthesis of novel thiazole derivative of Di-substituted *N*-aryl maleimides and characterized by spectral and analytical techniques

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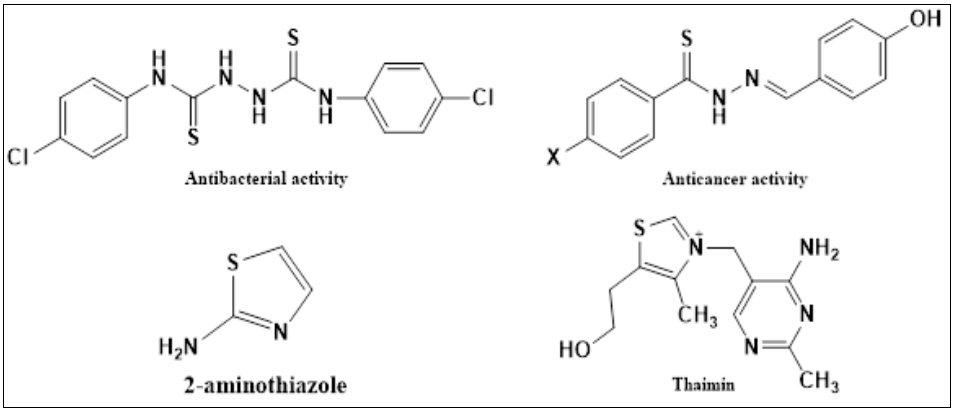
Abstract
The compound 1 was reacted with bromine in DMF to obtain dibromo succinimide 2. Compound 2 was reacted with piperidine as a base followed by dehydrohalogenation to obtained monobromo compound 3 through a common enaminone intermediate, further compound 3 on Vilsmeier Haack formylation afforded compound 4 with good yield. The condensation of 2,5-dihydro-2,5-dioxo-1-phenyl-4-(piperidin-1-yl)-1*H*-pyrrole-3-carbaldehyde 4 with thiosemicarbazide hydrochloride in ethanol in presence of acetic acid furnished compound 5 with 82% yield. The compound 5 react with disubstituted phenacyl bromide 6 a-e to obtained thiazole derivative of Di-substituted *N*-aryl maleimides 7 a-e 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], and as immunoconjugates for cancer therapy [3-4], Maleimides show 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 agents, material science [14], synthetic [15] and polymer chemistry [16]. Thiosemicarbazones are a class of compounds obtained by condensation of thiosemicarbazide with suitable aldehydes or ketones. Thiosemicarbazide is a valuable building block for the synthesis of five-membered heterocycles [17]. 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. [18].
Thiazole is an aromatic, heterocyclic organic compound featuring both a nitrogen atom and a sulphur atom as part of the aromatic five-membered ring. Thiazoles are an 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) [19]. 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 [20], fungicidal [21], HIV infection [22], mental retardation in children, age-related and neurodegenerative brain damage (Alzheimer's disease, Parkinsonism disease) [23].

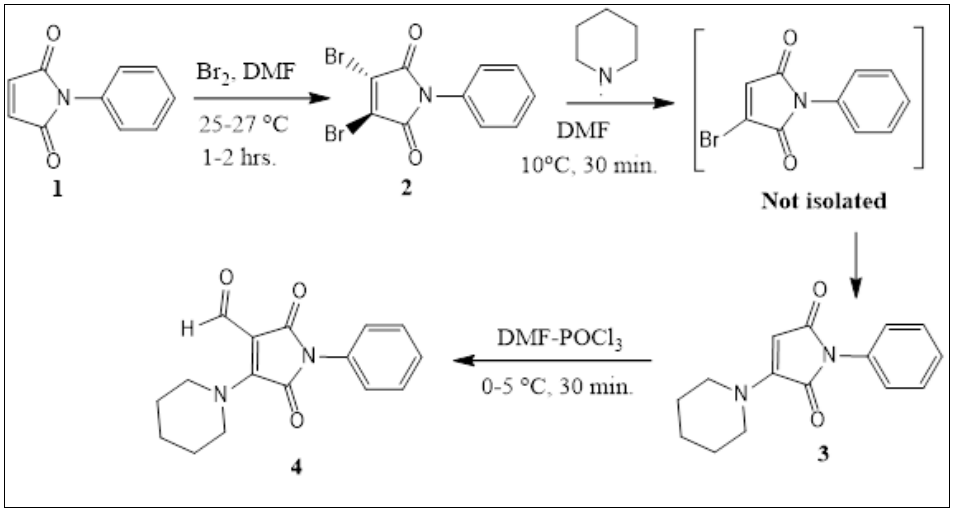


Materials and Methods

Melting points were determined on a Gallen Kamp melting point apparatus, Mod.MFB-595 in an open capillary tube and are uncorrected. FT-IR spectra were recorded on the 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 tetramethyl silane as an internal standard. Elemental analyses were carried out on the 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.

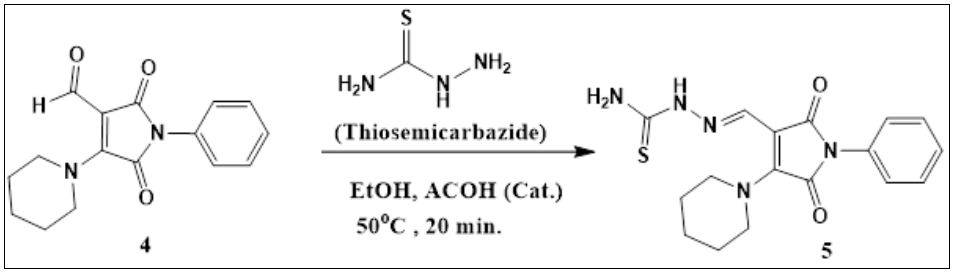
Results and Discussion

Compound 1 was reacted with bromine in DMF at 25-27 °C for 1-2.5 hrs. Afforded the dibromosuccinimides 2. Compound 2 was reacted with piperidine as a base followed by 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 °C for 5 min. to obtain compound 4. Vilsmeier Haack formylation of Compound 3 at 0-5 °C afforded compound 4 with good yield. (Scheme-1).



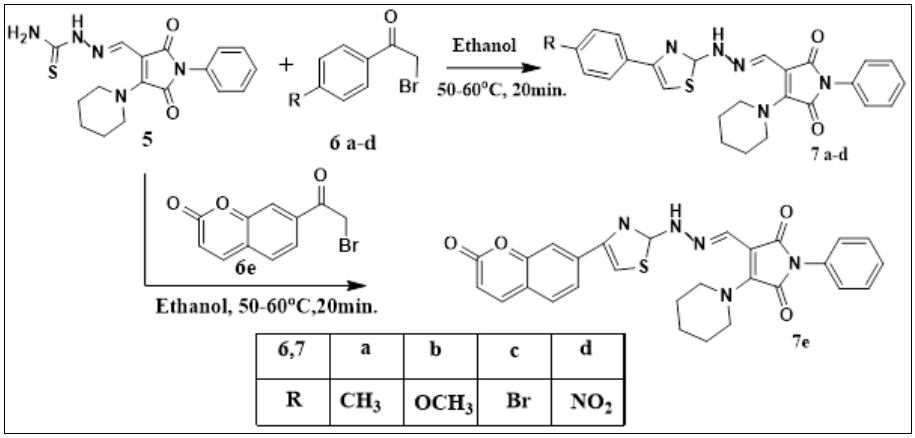
Scheme 1: Synthesis of 2, 5-dihydro-2, 5-dioxo-1-phenyl-4-(piperidin-1-yl)-1*H*-pyrrole-3-carbaldehyde (4)

Thus, condensation of 2,5-dihydro-2,5-dioxo-1-phenyl-4-(piperidine-1-yl)-1 *H*-pyrrole-3-carbaldehyde 4 with thiosemicarbazide in ethanol in presence of acetic acid at 50 °C furnished orange colour compound 5 with 78% yield (Scheme 2).



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

The compound 5 reacted with substituted phenacyl bromide 6 a-e to obtain thiazole derivatives of disubstituted N-aryl maleimides 7 a-e (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-e)

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

Experimentals

General procedure for synthesis of 1-phenyl-3-(piperidin-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 dropwise at 25 °C and stirred for 1-2.5 hrs. with constant stirring, the white solid separated was then filtered, washed with cold water, dried and recrystallized using ethanol to obtain compound 2 [24].

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

M.P.:138-140 ºC, Yield (%): 82, (1.50 g), Colour: Yellow solid. The structure of compound 3 established on the basis of spectral and analytical data found as per literature [24].

General procedure for synthesis of 2,5-dihydro-2,5-dioxo-1-phenyl-4-(piperidin-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 obtain compound 4. [25].

M.P.:176-178 ºC, Yield (%):76, (1.50 g), Colour: Golden Yellow solid. The structure of compound 4 was established on the basis of spectral and analytical data found as per literature [25].

General procedure for synthesis of 1-((2,5-dihydro-2,5-dioxo-1-phenyl-4-(piperidin-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 50 ºC for 20 min. The orange solid separate out, the solid separated was collected and then filtered to afford compounds 5.

M.P: 140-142 ºC, Yield (%): 88, Colour: Orange solid IR (KBr) (ν): 1750, 1698, 3395, 1612, 1276 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.70 (bs, 6H, 3 x CH_2), 2.53 (s, 2H, CH_2), 3.33 (s, 2H, CH_2), 3.83(s, 2H, NH_2), 6.39 (S, 1H, =C-H), 7.20-8.12 (m, 5H, Ar-H), 11.40 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 23.69 (2C'S), 27.39, 27.71, 29.70,51.09, 57.77, 97.81, 127.71 (2C'S), 129.23 (2C'S), 129.63, 133.91, 148.06, 160.2, 163.58, 169.51,182.12 ppm; MS (m/z%): 357 [M^+] Analysis Calculated for $C_{17}H_{19}N_5O_2S$: Calcd: C (57.12), H (5.36), N 19.59); Found: C (56.89), H (5.58), N (19.85).

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

The thiosemicarbazone 5 (0.01 mol) in ethanol (10 mL) was stirred for 10 min. To this mixture appropriate phenacyl bromide 6 a-e (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-e, and were purified by column chromatography (Hexane: Ethyl acetate).

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

M.P: 180-182 ºC, Yield (%): 72, Colour: Reddish brown solid IR (KBr) (ν): 1734, 1695, 3368, 1612 cm^{-1}; ^1H NMR (500 MHz, DMSO-d6) δ: 1.85 (bs, 6H, 3xCH_2), 2.70 (s, 2H, CH_2), 2.85 (s 3H CH_3), 3.85 (s, 2H, CH_2), 6.90-7.85 (m, 10H, Ar-H), 8.20 (s,1H, N=C-H), 11.60 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 25.45, 27.35(2C'S), 47.25 (2C'S), 56.40, 82.34, 105, 126 (2C'S), 132, 134 (2C'S), 137, 142 (2C'S), 144 (2C'S), 148, 149.5, 153, 163.20, 167.60, 173, 176, 181.05 ppm; MS (m/z %) 472 [M^+]; Analysis Calculated for $C_{26}H_{25}N_5O_2S$ Calcd**:** C (66.22), H (5.34), N (14.85); Found: C (65.98), H (5.61), N (15.13).

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

M.P.: 186-188 ºC, Yield (%): 84, Colour: Reddish brown solid IR (KBr) (ν): 1720, 1705, 3370, 1610 cm^{-1}; ^1H NMR (500 MHz, DMSO-d6) δ: 1.80 (bs, 6H, 3xCH_2), 2.88 (s, 2H, CH_2), 3.92 (s 3H, OCH_3), 4.20 (s, 2H, CH_2), 6.85-7.92 (m, 10H, Ar-H), 8.10 (s,1H, N=C-H), 12.20 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 23.36, 26.56 (2C'S), 43.10 (2C'S), 58.40, 60.34, 100, 126.25 (2C'S), 132, 133.20 (2C'S), 136, 140 (2C'S), 142.45 (2C'S), 147, 148.25, 156, 160.80, 162.80, 168, 174.15, 179.40 ppm; MS (70 eV) m/z (%): 488 [M^+] Analysis Calculated for $C_{26}H_{25}N_5O_3S$: Calcd: C (64.05), H (5.17), N (14.36); Found: C (63.77), H (5.33), N (14.11).

Synthesis1-((2, 5-dihydro-2, 5-dioxo-1-phenyl-4-(piperidin-1-yl)-1*H*-pyrrol-yl) methylene) -(2-(4-(4-bromophenyl) thiazol-2-yl)-hydrazine, 7c

M.P.: 170-172 ºC, Yield (%): 87, Colour: Reddish brown solid IR (KBr) (ν): 1735, 1710, 3355, 1610, 825 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.70 (s, 2H, CH_2), 3.91 (s, 2H, CH_2), 4.10 (bs, 6H,3 x CH_2), 8.05 (s, 1H, N=C-H), 7.35-7.80 (m, 10H, Ar-H), 12.10 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 23.10, 26.20 (2C'S), 50 (2C'S), 75.10, 94.50, 125 (2C'S), 130, 133 (2C'S),135, 141 (2C'S), 142 (2C'S), 143, 143.5, 156, 16, 168, 170, 175, 180ppm; MS (70 eV) m/z (%): 536 [M^+] and 538 [M^{+2}] Analysis Calculated for $C_{25}H_{22}BrN_5O_2S$; Calcd: C (55.97), H (4.13), N (13.06); Found: C (54.64), H (4.38), N (13.32)

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

M.P.: 188-190 ºC, Yield (%): 83, Colour: Reddish brown solid IR (KBr) (ν): 1733, 1720, 3348, 1610, 1355 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.78 (s, 2H, CH_2), 2.85 (s, 2H, CH_2), 3.90 (bs, 6H, 3xCH_2), 6.75-8.35 (m, 10H, Ar-H), 8.50 (s, 1H, N=C-H), 12.20 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 24.10, 27.60 (2C'S), 48.20 (2C'S), 98.50, 116.10, 156.20, 120.10 (2C'S), 124 (2C'S), 126, 127.25 (2C'S), 129 (2C'S), 133.10 (2C'S), 140.15, 150.20 (2C'S), 162.10, 164.25, 178.50, ppm; MS (70 eV) m/z (%): 503.13 [M^+]; Analysis Calculated for $C_{25}H_{22}N_6O_4S$; Calcd: C (59.75), H (4.41), N (16.72); Found: C (59.43), H (4.12), N (17.06)

Synthesis of 1-((2,5-dihydro-2,5-dioxo-1-phenyl-4-(piperidin-1-yl)-1*H*-pyrrol-3-yl) methylene) -(2-(4-(4-2H-chromen-2-one) thiazol-2-yl)-hydrazine, 7e

M.P.: 130-132 ºC, Yield(%): 85, Colour: Reddish brown solid IR (KBr) (ν): 1735, 1695, 1745, 3355, 1612, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.93 (s, 2H, CH_2), 2.60 (s, 2H, CH_2), 4.25(bs, 6H, 3xCH_2), 6.10 (s, 1H,Ar-H), 6.40 (s,1H, Ar-H), 7.10-7.60 (m, 9H, Ar-H), 8.20(s, 1H, N=C-H), 10.50 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 23.90, 26.50(2C'S), 50.20(2C'S), 96.25,116.10, 118.30,140.20,157.40,121.20(2C'S), 124(2C'S),126 128.15(2C'S),129.20(2C'S), 135.10,140.15(2C'S),151.10(2C'S), 162.10,164.25, 168 180.10, ppm; MS (70 eV) m/z (%): 526 [M^+] Analysis Calculated for $C_{28}H_{23}N_5O_4S$ Calcd: C(63.99), H(4.41), N(13.33; Found: C(63.71), H(4.68), N(13.61)

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 operation & and simplicity of reaction. Here we described the synthesis of thiosemicarbazide derivatives of 2,5-dihydro-2,5-dioxo-1-phenyl-4-(piperidin-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. Compound 5 was further reacted with substituted phenacyl bromide 6 a-e to obtained compound 7 a-e. All these synthesized compounds are well characterized by spectral and analytical methods and are a new addition to the family of heterocyclic compounds.

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Bait and switch strategy for obtaining catalytic antibodies with acyl-transfer capabilities

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