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Synthesis and characterization of novel thiazole derivatives of disubstituted N-arylmaleimides

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ABSTRACT

*The compound **1** was reacted with bromine in DMF to obtained dibromosuccinimides **2**.The compound **2** react with morpholine followed dehydrohalogenation to obtained monobromo compound, **3**throughcommon enaminone intermediate. Vilsmeier Haack formylation of **3** afforded compound **4**with good yield. Thus condensation of 1-(4-chlorophenyl)-2,5-dihydro-2,5-dioxo-4-(dialkyl-1-yl)-1Hpyrrole-3-carbaldehyde **4**with thiosemicarbazide in ethanol in presence of acetic acid furnished compound **5**with 88% yield. The compound **5** react with substituted phenacyl bromide **6 a-g** to obtained thiazole derivative of disubstituted N-arylmaleimides **7 a-g**.All the synthesized compounds were well characterized by IR, NMR and elemental analysis given in experimental section.*

Keywords: Malieimide, Morpholine, Thiosemicarbazone, phenacyl bromide and Thiazole.

INTRODUCTION

Herein we reported the synthesis of Thiazole derivatives of disubstituted N-arylmaleimides. Maleimide and its derivatives are synthesizes from maleic anhydride and amines followed by dehydration. 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 [3-6]. Maleimides shows a wide range of biological activities such as antibacterial [7-8] and antifungal [9], antiprotozoal [10], antiangiogenic [11], analgesic [12], antitress agents [13], cytotoxic, DNA binding and apoptoticinducing activity.[14] A biological property of these compounds includes angiogenesis inhibition[15], protein kinase inhibition [16], ant proliferative activity [17], and antimicrobial [18]and antifungal[19] properties.

Thiosemicarbazones are a class of compounds obtained by condensation of thiosemicarbazide with suitable aldehydes or ketones. Thiosemicarbazides is valuable building blocks for the synthesis of five-membered heterocycles[20]. Thiosemicarbanzones have received considerable attention because of their pharmacological

activities. They have numerous biological activities, e.g. anticarcinogenic, antibacterial, anti-HIV, anticancer, fungicides, antiviral, antifungal, antitumor [21], etc

Thiazole is aromatic, heterocyclic organic compound featuring both a nitrogen atom and sulfur atom as part of the aromatic five-membered ring. Thiazole and related compounds are called 1, 3-azoles (nitrogen and one other heteroatom in a five-membered ring). Thiazoles are important class of heterocyclic compounds, found in many potent biologically active molecules such as Sulfathiazole (antimicrobial drug), Abafungin (antifungal drug) with trade name Abasol cream, Ritonavir (antiretroviral drug) and Bleomycine and Tiazofurin (antineoplastic drug) [22].

It has been noticed continuously over the years that interesting biological activities [23]were associated with thiazole derivatives. Recently the applications of thiazoles were found in drug development for the treatment of allergies [24], inflammation [25], hypertension [26] bacterial [27], HIV infections [28], hypnotics [29],and schizophrenia [30] and more recently for the treatment of pain [31] as fibrinogen receptor antagonists with antithrombotic activity [32] and as new inhibitors of bacterial DNA gyrase B [33].

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 [34], fungicidal [35], HIV infection [36], mental retardation in children, age related and neurodegenerative brain damage (Alzheimeris disease, Parkinsonism disease) [37].

MATERIALS AND METHODS

Melting points were determined on a Gallenkamp melting point apparatus, Mod.MFB-595 in open capillary tube and are uncorrected. FT-IR spectra were recorded on Schimadzu 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 analyzer 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. Microwave assisted synthesis was carried out in an Emery synthesizer single wave microwave cavity producing controlled irradiation at 2450 MHz, the temp was measured with IR sensor on the outside of reaction vessels. 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.

Experimental:

General procedure for synthesis of1-(4-chlorophenyl)-3-morpholino-1H-pyrrole-2,5-dione(3):

1-(4-chlorophenyl)-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 25^0C 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** [38].

To a solution of trans-3, 4-dibromo-1-(4-chlorophenyl) pyrrolidine-2,5-dione**,2** (0.01 mol) in DMF (10 mL), piperidine, morpholine and pyrrolidine (0.03 mol) was added drop wise at 10^0C and stirred for 30min. The reaction mixture was poured over crushed ice. The golden yellow solid separated out was filtered and recrystallized from aqueous ethanol to obtained compound **3**

M.P.:136-138^{o}C, Yield (%):86, (1.51g), Colour: Yellow solid. The structure of compound **2** established on the basis of spectral and analytical data found as per literature[38].

General procedure for synthesis of 1-(4-chlorophenyl)-2,5-dihydro-4-morpholino-2,5-dioxo-1H-pyrrole-3-carbaldehyde(4):

Vilsmeier Haack adduct prepared from DMF (0.012 mol)and $POCl_3$ (0.05 mol) at 0 ^{0}C was added to a solution of **3**(0.01 mol)in 2 mL DMF, reaction mixture was then stirred at 0-5 ^{0}C for30 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**.M.P.:178-180, Yield (%):78, (1.50 g), Colour: Golden Yellow solid. The structure of compound **2** established on the basis of spectral and analytical data found as per literature [39].

General procedure for synthesis of (1E)-1-((1-(4-chlorophenyl)-2,5-dihydro-4-morpholino-2,5-dioxo-1H-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 50^0C for 20 min. The orange solid separate out, the solid separated was collected and then filtered to afford compounds **5.**

M.P: 158-160^{o}C,Yield(%):88, Colour: Orange solid IR (KBr) (ν):1753, 1699, 3385, 1610, 1276 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ:3.75 (bs, 4H, 2 x CH_2), 4.20 (s, 2H, CH_2), 4.30(s, 2H,CH_2), 3.82 (s, 2H, NH_2), 6.72(S, 1H, =C-H), 7.24-8.10 (m, 4H, Ar-H), 11.20 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ:23.90 (2C'S), 27.58, 27.95, 29.95,61.15, 98.28 127.80 (2C'S), 129.80 (2C'S), 129.95, 133.75, 153.20, 162.5, 163.38, 168.67, 180.56 ppm; MS (70 eV) m/z (%): 393[M^+] and 395[M^{+2}]Analysis Calculated for $C_{16}H_{16}ClN_5O_3S$:Calcd: C(48.79), H(4.09), N(17.18)Found: C(48.52), H(4.36), N(17.46)

General procedure for the preparation of thiazole derivatives of Disubstituted N- aryl maleimides: (7a-g)
The thiosemicarbazone **5**(0.01 mol) in ethanol (10 mL) was stirred for 10 min. To this mixture appropriate phenacyl bromide **6 a-g** (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-g,** and were purified by column chromatography (hexane: ethyl acetate 2:1).

1-((1-(4-chlorophenyl)-2,5-dihydro-4-morpholino-2,5-dioxo-1-phenyl-1H-pyrrol-3-yl)methylene)-(2-(4-(4-p-tolylthiazol-2-yl)hydrazine(7a)
M.P.(^{0}C): 220-222, Yield(%): 76, Colour: Reddish brown Solid; IR (KBr) (ν): 1734, 1695, 3435, 1620 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d^6) δ: 3.10 (s, 3H, CH_3), 3.40 (bs, 4H, 2 x CH_2), 3.80 (s, 4H, 2x CH_2), 7.10(S, 1H, N=C-H), 7.20-8.10 (m, 9H, Ar-H), 11.90 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 23.90, 51.20(2C'S), 75.40(2C'S), 105.40, 123.30(2C'S), 125.50 (2C'S), 127.90(2C'S), 130.60(2C'S), 133.50(2C'S), 137.20, 140.5, 144.70, 149.3, 152.8, 160.20, 168.6, 170.7, 173.5 ppm; MS (70 eV) m/z (%):507[M^+] and 509[M^{+2}]; Analysis Calculated for $C_{25}H_{22}ClN_5O_3S$: Calcd: C(59.11), H(4.37), N(13.79); Found: C(58.83), H(4.62), N(13.79).

1-((1-(4-chlorophenyl)-2,5-dihydro-4-morpholino-2,5-dioxo-1-phenyl-1H-pyrrol-3-yl)methylene)-(2-(4-(4-methoxyphenyl)thiazol-2-yl)-hydrazine (7b)
M.P.(^{0}C): 190-192, Yield(%): 80, Colour: Reddish brown Solid; IR (KBr) (ν): 1730, 1712, 3368, 1615 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d^6) δ: 3.60 (bs, 4H, 2 x CH_2), 3.75 (s, 4H, 2x CH_2), 3.90(s 3H, OCH_3), 6.90-8.0 (m, 9H, Ar-H), 8.20(s,1H, N=C-H), 11.81 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 24.39, 50.50(2C'S), 76.60(2C'S), 107.4, 121.50(2C'S), 125.56 (2C'S), 128.40(2C'S), 131.10(2C'S), 132.80(2C'S), 137.20, 141.40, 144.80, 150.9, 152.5, 161.50, 167.2, 170.6, 173.8 ppm; MS (70 eV) m/z (%):523[M^+] and 525[M^{+2}]; Analysis Calculated for $C_{25}H_{22}ClN_5O_4S$: Calcd: C(57.30), H(4.23), N(13.37) ;Found: C(57.04), H(4.50), N(13.60).

1-((1-(4-chlorophenyl)-2,5-dihydro-4-morpholino-2,5-dioxo-1-phenyl-1H-pyrrol-3-yl)methylene)-(2-(4-(4-flurophenyl)thiazol-2-yl)-hydrazine(7c)
M.P.(^{0}C): 218-220, Yield(%): 86, Colour: Reddish brown Solid; IR (KBr) (ν): 1758, 1787, 3394, 1612 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 3.31 (bs, 4H, 2 x CH_2), 3.65 (s, 2H, CH_2), 3.80(s, 2H, CH_2), 6.12(s,1H, N=C-H), 6.80-8.50 (m, 9H, Ar-H), , 11.91 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 25.20, 52.10(2C'S), 75.10(2C'S), 108.7, 121.60(2C'S), 123.70, 128.50(2C'S), 130.60(2C'S), 131.40(2C'S), 135.90, 141.7, 144.9, 151.7, 153.5, 161.40, 168.7, 172.3, 173.7 ppm; MS (70 eV) m/z (%): 511[M^{+1}], 513[M^{+2}]Analysis Calculated for $C_{24}H_{19}ClFN_5O_3S$: Calcd: C(56.31), H(3.74), N(13.37) ; Found: C(56.07), H(4.02), N(13.94)

1-((1-(4-chlorophenyl)-2,5-dihydro-4-morpholino-2,5-dioxo-1-phenyl-1H-pyrrol-3-yl)methylene)-(2-(4-(4-chlorophenyl)thiazol-2-yl)-hydrazine(7d)
M.P.(^{0}C): 224-226, Yield(%): 87, Colour: Reddish brown Solid; IR (KBr) (ν): 1755, 1773, 3358, 1614 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 3.20 (bs, 4H, 2 x CH_2), 3.50 (s, 2H, CH_2), 3.80(s, 2H, CH_2), 6.30(s,1H, N=C-H), 6.70-8.30 (m, 9H, Ar-H), , 11.70 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 23.50, 50.30(2C'S), 75.10(2C'S), 108.50, 121.70(2C'S), 124.30, 128.20(2C'S), 133.50(2C'S), 131.50(2C'S), 135.70, 141.4, 145.8, 151.5, 153.6, 162.40, 167.80, 171.50, 173.60 ppm; MS (70 eV) m/z (%): 527[M^{+1}], 529[M^{+2}]Analysis Calculated for $C_{24}H_{19}Cl_2N_5O_3S$: Calcd: C(54.55), H(3.62), N(13.25) ; Found: C(54.28), H(3.88), N(13.53)

1-((1-(4-chlorophenyl)-2,5-dihydro-4-morpholino-2,5-dioxo-1-phenyl-1H-pyrrol-3-yl)methylene)-(2-(4-(4-bromophenyl)thiazol-2-yl)-hydrazine(7e)

M.P.(^{0}C): 231-233, Yield(%): 90, Colour: Reddish brown Solid; IR (KBr) (ν): 1735, 1781, 3388, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 3.35 (bs, 4H, 2 x CH_2), 3.70 (s, 2H, CH_2), 3.85(s, 2H, CH_2), 6.10(s,1H, N=C-H), 6.90-8.40 (m, 9H, Ar-H), , 11.80 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 23.70, 50.20(2C'S), 75.30(2C'S), 108.3, 120.90(2C'S), 124.30, 128.60(2C'S), 130.80(2C'S), 131.80(2C'S), 136.90, 141.5, 145.5, 150.6, 152.9, 161.80, 168.3, 171.7, 173.5 ppm; MS (70 eV) m/z (%): 571[M^{+1}], 573[M^{+2}]Analysis Calculated for $C_{24}H_{19}BrClN_5O_3S$: Calcd: C(50.32), H(3.34), N(12.23) ; Found: C(50.07), H(3.60), N(12.51)

1-((1-(4-chlorophenyl)-2,5-dihydro-4-morpholino-2,5-dioxo-1-phenyl-1H-pyrrol-3-yl)methylene)-(2-(4-(4-nitrophenyl)thiazol-2-yl)-hydrazine(7f)

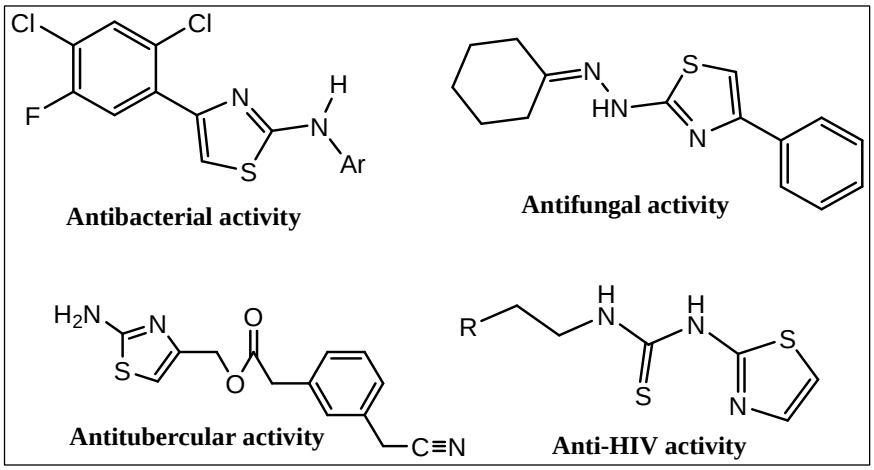
M.P.(^{0}C): 240-242, Yield(%): 83, Colour: Reddish brown Solid; IR (KBr) (ν): 1730, 1710, 3378, 1610, 1355 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.40 (bs, 4H, 2 x CH_2), 3.53 (s, 2H, CH_2), 3.80 (s, 2H, CH_2), 6.90-8.40 (m, 9H, Ar-H), 8.60(s, 1H, N=C-H), 12.20 (bs, 1H, N-H) ppm ; ^{13}C NMR ($CDCl_3$) δ: 23.20, 27.40(2C'S), 49.50(2C'S), 98.3, 105.80, 121.30(2C'S), 123.10(2C'S), 125.6, 127.50(2C'S), 129.70(2C'S), 134.40(2C'S), 142.10, 153.50(2C'S), 161.60, 163.90, 176.20, ppm; MS (70 eV) m/z (%): 538[M^{+1}], 540[M^{+2}];Analysis Calculated for $C_{24}H_{19}ClN_6O_5S$:Calcd: C(53.48), H(3.55), N(15.59) ;Found: C(53.22), H(3.78), N(15.85)

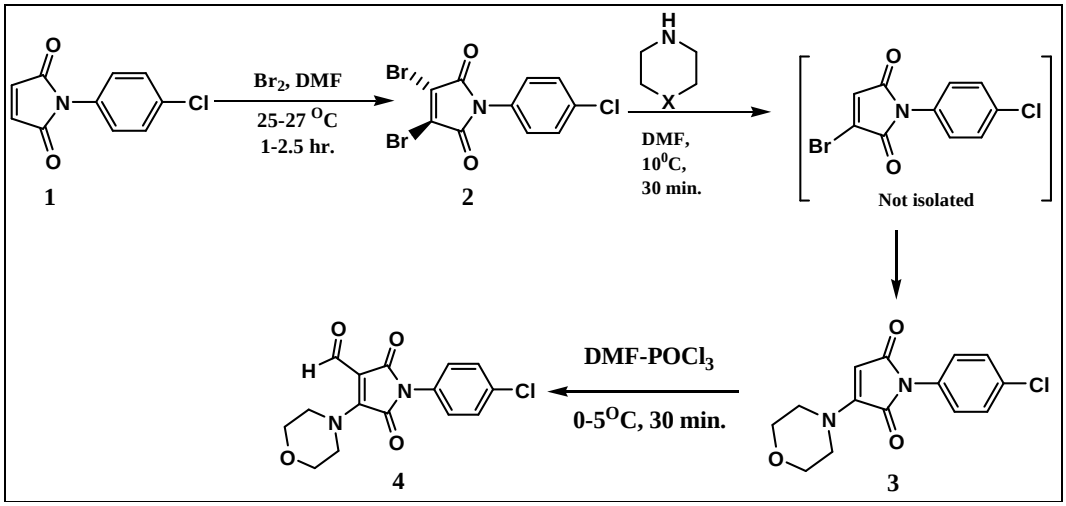
1-((1-(4-chlorophenyl)-2,5-dihydro-4-morpholino-2,5-dioxo-1-phenyl-1H-pyrrol-3-yl)methylene)-(2-(4-(4-2H-chromen-2-one)thiazol-2-yl)-hydrazine(7g)

M.P.(^{0}C): 210-212, Yield(%): 80, Colour: Brown Solid; IR (KBr) (ν): 1733, 1720 1751, ,3398, 1612, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.42 (bs, 4H, 2 x CH_2), 3.51 (s, 2H, CH_2), 3.70 (s, 2H, CH_2), 6.10(s, 1H,Ar-H), 6.50(s,1H, Ar-H), 6.80-7.50 (m, 10H, Ar-H), 8.20(s, 1H, N=C-H), 11.90 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 23.80, 27.80(2C'S), 53.10(2C'S), 97.40, 114.74, 119.10, 122.65(2C'S), 124.40(2C'S), 126.10, 127.10(2C'S), 129.30(2C'S), 136.20, 140.30(2C'S), 142.55, 151.20(2C'S), 161.40, 166.35, 173.20, 180.40, ppm; MS (70 eV) m/z (%): 577[M^{+1}], 579[M^{+2}];Analysis Calculated for $C_{27}H_{24}ClN_5O_5S$:Calcd: C(58.18), H(4.18), N(12.12) ;Found: C(57.85), H(4.43), N(12.44)

RESULTS AND DISCUSSION

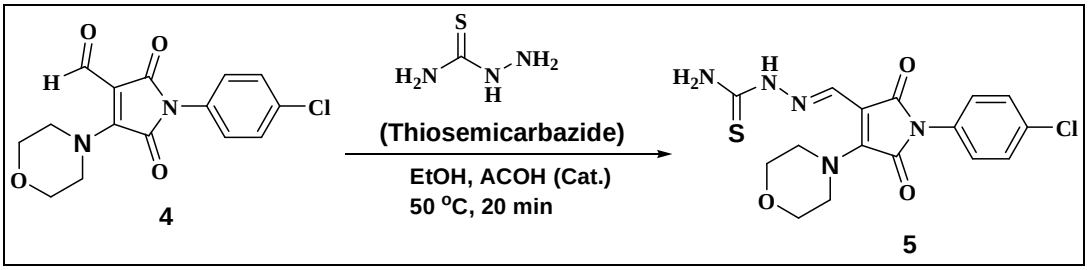
The compound **1** were reacted with bromine in DMF at 25-27 ^{0}C for 1- 2.5 hrs afforded the dibromosuccinimides**2**.The compound **2** was reacted with morpholine as a base followed dehydrohalogenation afforded monobromo compound; instead, complex mixtures of with unreacted dibromosccinimide**3**were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





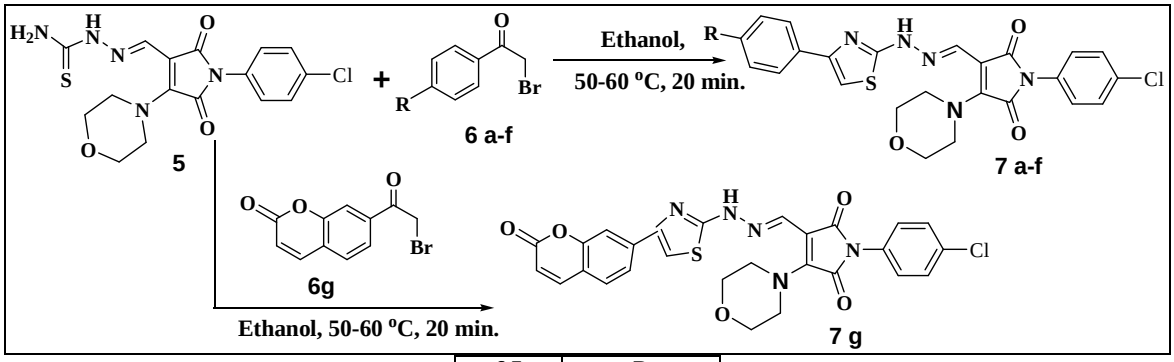
Scheme1Synthesis of2,5-dihydro-4-morpholino-2,5-dioxo-1-phenyl-1H-pyrrole-3-carbaldehyde (4)

Thus condensation of 1-(4-chlorophenyl)-2,5-dihydro-2,5-dioxo-4-(piperidin-1-yl)-1Hpyrrole-3-carbaldehyde **4** with thiosemicarbazide in ethanol in presence of acetic acid at50^{0}C furnished orange colour solid **5** with 88% yield.**(Scheme2).**



Scheme 2 Synthesis (1E)-1-((1-(4-chlorophenyl)-2,5-dihydro-4-morpholino-2,5-dioxo-1H-pyrrol-3-yl)methylene)thiosemicarbazide(5)

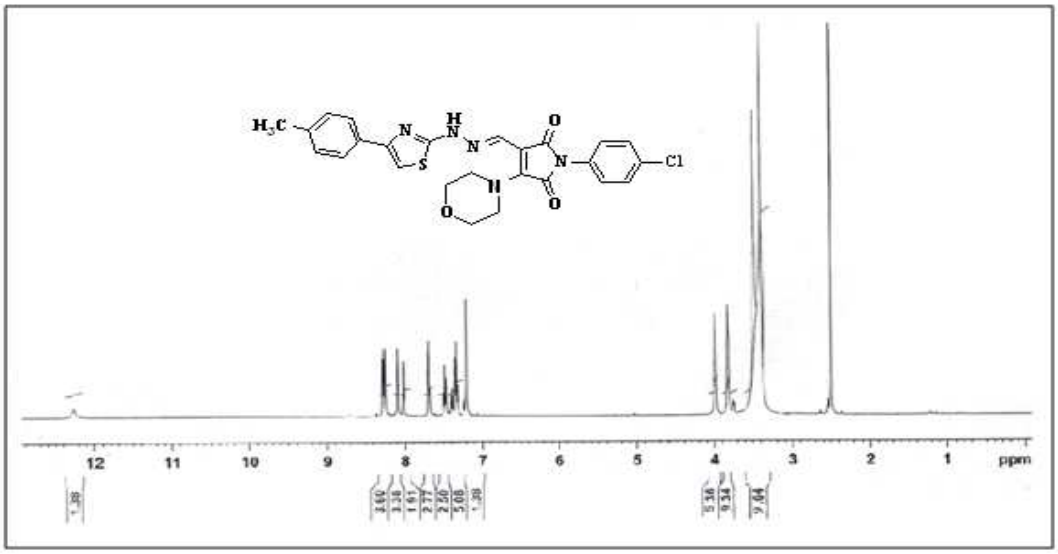
The compound **5** react with substituted phenacyl bromide **6 a-g**to obtained thiazole derivative of disubstituted N-arylmaleimides**7 a-g**.**(Scheme 3).**



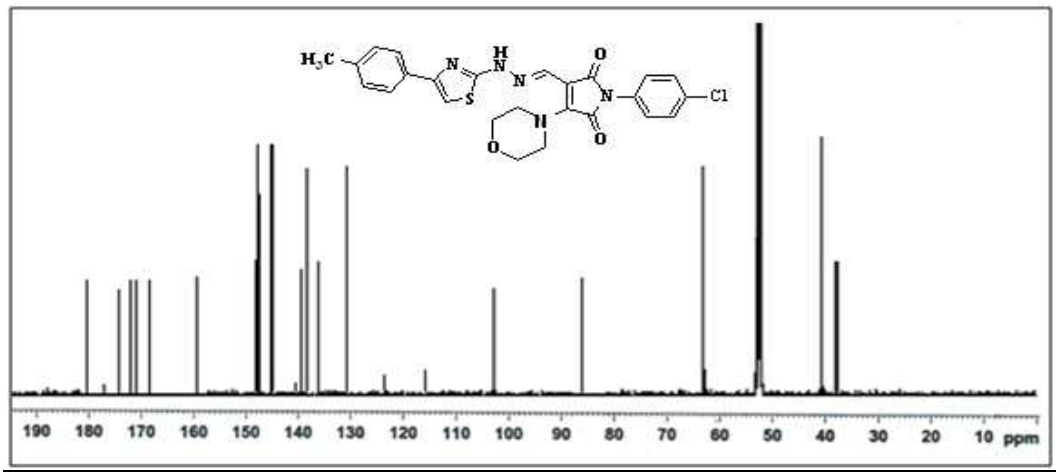
6,7	R
a	CH_3
b	OCH_3
c	F
d	Cl
e	Br
f	NO_2

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

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



[1]H NMR spectrum of 1-((1-(4-chlorophenyl)-2,5-dihydro-4-morpholino-2,5-dioxo-1-phenyl-1H-pyrrol-3-yl)methylene)-(2-(4-(4-p-tolylthiazol-2-yl)hydrazine, 7a



[13]C NMR spectrum of 1-((1-(4-chlorophenyl)-2,5-dihydro-4-morpholino-2,5-dioxo-1-phenyl-1H-pyrrol-3-yl) methylene)-(2-(4-(4-p-tolylthiazol-2-yl) hydrazine, 7a

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 are clean, easy operational & simplicity of reaction. Here we described the synthesis of thiosemicarbazide derivatives of 1-chlorophenyl-4-dialkylamino-3-carbaldehyde-N-arylmaleimides**4**by nucleophilic condensation of trans-3,4-dibromo-1-(4-chlorophenyl)pyrrolidine-2,5-dione,**3** with thiosemicarbazideto obtained thiosemicarbazone **5**with good yield. The compound **5** were further react with substituted phenacyl bromide **6 a-g** to obtained compound **7 a-g.**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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