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SYNTHESIS AND CHARACTERIZATION OF NOVEL OXAZOLE DERIVATIVES OF MORPHOLINO 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 by dehydrohalogenation to obtained monobromo compound 3 through common enaminone intermediate. Vilsmeier Haack formylation of compound 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 semicarbazide in ethanol in presence of acetic acid furnished compound 5 with 84% yield. The compound 5 react with substituted phenacyl bromide 6 a-g to obtained oxazole 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: Maleimides, Morpholine, Semicarbazone, Phenacyl bromide and Oxazole.

INTRODUCTION

Herein we reported the synthesis of oxazole derivatives of disubstituted N-arylmaleimides. Maleimide and its derivatives are synthesizing 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] Maleimides shows a wide range of biological activities such as antibacterial[4] and antifungal[5], antiprotozoal[6], antiangiogenic[7], analgesic[12], antistress agents[9], cytotoxic, DNA binding and apoptotic inducing activity.[10] A biological property of these compounds includes angiogenesis inhibition, protein kinase inhibition, ant proliferative activity, antimicrobial and antifungal[11] properties.

Semicarbazone are a class of compounds obtained by condensation of semicarbazide with suitable aldehydes or ketones. Semicarbazide is valuable building blocks for the synthesis of five-membered heterocycles.[12] Semicarbazone 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.[13]

Oxazoles are five membered heterocyclic compounds containing nitrogen and oxygen as hetero atoms. The derivatives of oxazole have become increasingly important in recent year due to their use in intermediate for the preparation of new biological material. The oxazole ring is present in number of pharmacologically important compounds, including antibiotic and proliferative.[14] The wide range of biological activities of oxazole includes antibacterial, antifungal[15], analgesic[16], anti- inflammatory[17], hypoglycemic[18], muscle relaxant[19], anti-tuberculosis[20] and HIV inhibitor activity.[21] In addition, oxazole derivatives are useful synthetic intermediates and can be used as diversity scaffolds in combinatorial chemistry[22] and also as peptidomimetics.[23]

MATERIALS AND METHODS

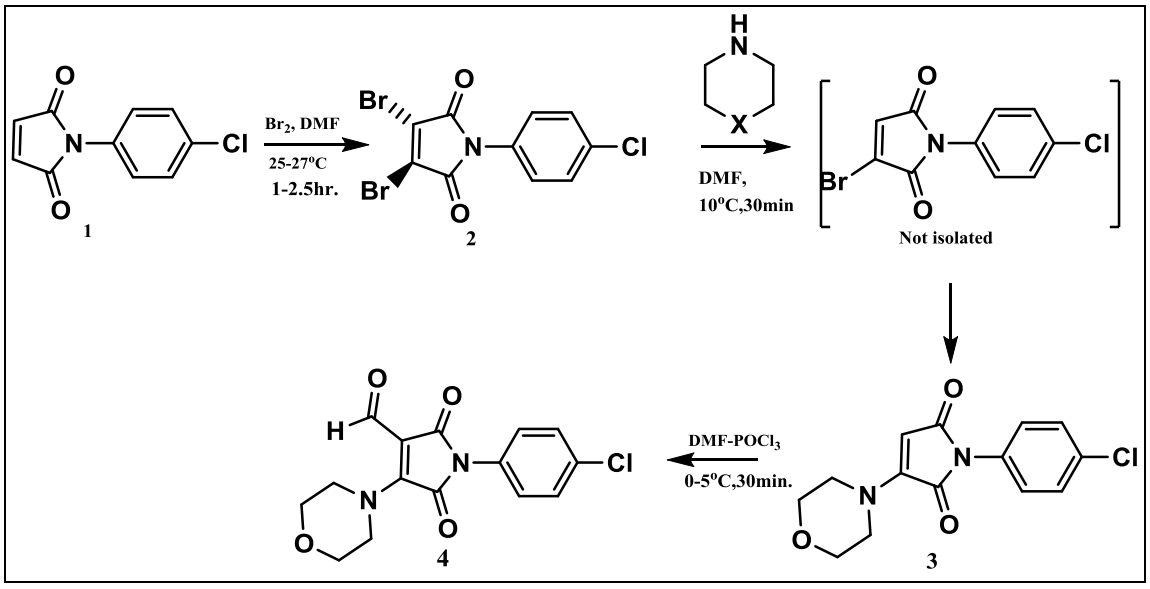
Melting points were determined on a Gallen Kamp melting point apparatus, Mod.MFB-595 in open capillary tube and are uncorrected. FT-IR spectra were recorded on Shimadzu FTIR-408 instrument in KBr pellets. 1H and 13C spectra were recorded on Varian XL 500 spectrometer (500MHz) in $CDCl_3$ and DMSO. Chemical 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. 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.

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 by 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}C for 5 min. to obtained compound 4. Vilsmeier Haack formylation of 3 at 0-5^{o}C afforded compound 4 with good yield, (Scheme-1)

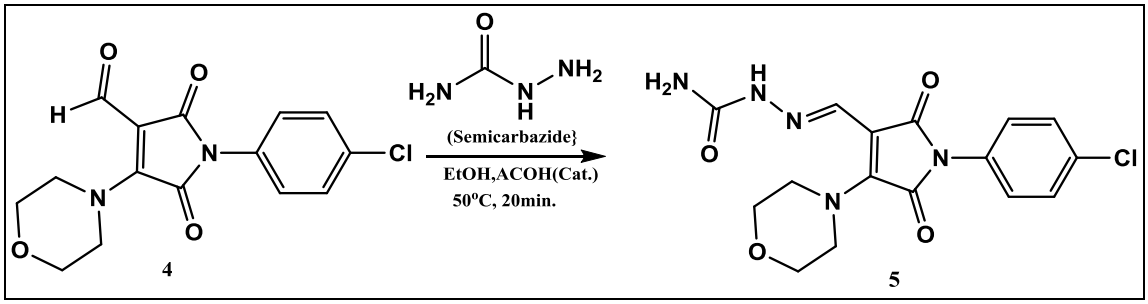
(Scheme-1)



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

Thus, condensation of 2, 5-dihydro-4-morpholino-2, 5-dioxo-1-phenyl-1H-pyrrole-3carbaldehyde 4 with semicarbazide in ethanol in presence of acetic acid at 50°C furnished orange colour solid 5 with 84 % yield. (Scheme 2)

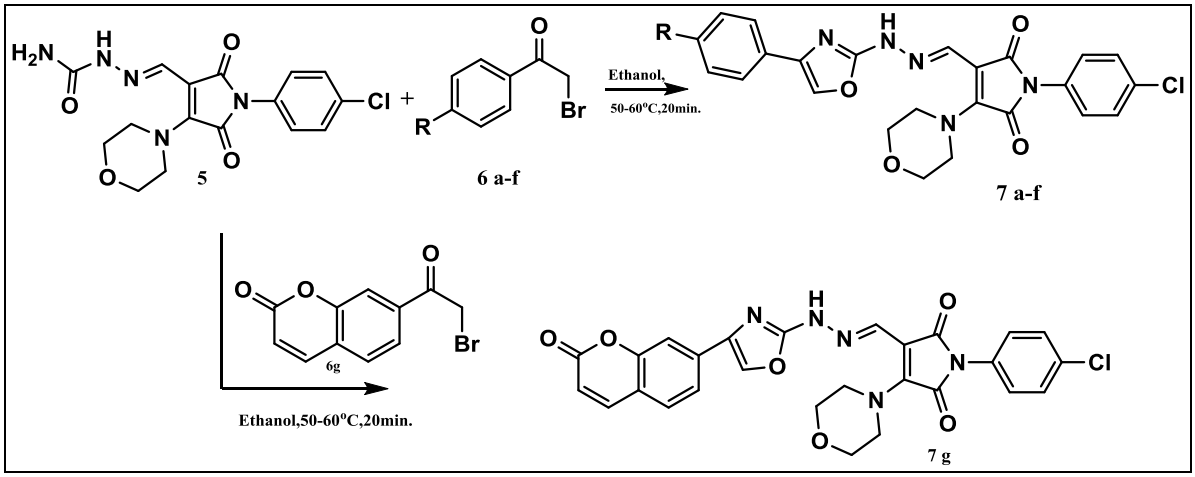
(Scheme 2)



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

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

(Scheme 3)



Scheme 3: Synthesis of oxazole derivatives of Disubstituted N-aryl maleimides (7a-g).

Experimentals

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

General procedure for synthesis of 1-(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 250C 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 obtained compound 2.[24]

To a solution of trans-3, 4-dibromo-1-(4-chlorophenyl) pyrrolidine-2, 5-dione, 2 (0.01 mol) in DMF (10 mL), morpholine (0.03 mol) was added drop wise at 10 ^{0}C and stirred for 30 min. 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.:136-138oC, 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.[24]

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 POCl3 (0.05 mol) at 0 0C was added to a solution of **3** (0.01 mol) in 2 mL DMF, reaction mixture was then stirred at 0-5 0C 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.

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.[25,26]

General procedure for synthesis of (1E)-1-((1-(4-chlorophenyl)-2, 5-dihydro-4-morpholino-2, 5-dioxo-1Hpyrrol-3-yl) methylene) semicarbazide (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 semicarbazide (0.01 mol) was added while stirring. The temperature of reaction mixture was maintained at 50^{0}C for 20 min. The orange solid separate out, the solid separated was collected and then filtered to afford compounds 5.

M.P: 168-170 ^{o}C, Yield (%): 82, Colour: Orange solid IR (KBr) (□): 1751, 1696, 3388, 1615, 1275cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.66 (bs, 6H, 3 x CH_2), 3.40 (s, 2H, CH_2), 3.83 (s, 2H, CH_2), 7.11(S, 1H, =C-H), 7.38-7.53 (dd, 4H, Ar-H), 8.18 (s, 2H, NH_2), 11.41 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 23.80 (2C'S), 27.39, 27.71, 29.70,51.09, 57.77, 97.85, 127.71 (2C'S), 129.23 (2C'S), 129.63, 133.91, 148.06, 160.2, 163.40 169.51,180.12 ppm; MS (m/z%**):** 376 [M^{+}] and 377 [M^{+2}] Analysis Calculated for $C_{17}H_{18}ClN_5O_3$: Calcd: C (54.33), H (4.83), N (18.64); Found: C (54.04), H (5.14), N(18.92)

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

The Semicarbazone 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).

Synthesis of 1-((1-(4-chlorophenyl)-2, 5-dihydro-4-morpholino-2, 5-dioxo-1*H*-pyrrol-3- yl) methylene) -(2-(4-(4-p-tolyloxazol-2-yl) hydrazine, 7a

M.P. (^{o}C): 220-222, Yield (%): 76, Colour: Reddish brown Solid; IR (KBr) (□): 1734, 1695, 3435, 1620 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d^{6}) □: 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 ($CDCl_3$) □: 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 (%):492[M^{+}] and 493[M^{+2}]; Analysis Calculated for $C_{25}H_{22}ClN_5O_4$: Calcd: C(61.04), H(4.51), N(14.24); Found: C(60.75), H(4.77), N(14.52).

Synthesis of 1-((1-(4-chlorophenyl)-2, 5-dihydro-4-morpholino-2, 5-dioxo-1*H*-pyrrol-3-yl) methylene) -(2-(4-(4-methoxyphenyl) oxazol-2-yl)-hydrazine, 7b

M.P .(^{o}C): 190-192, Yield (%): 80, Colour: Reddish brown Solid; IR (KBr) (□): 1730, 1712, 3368, 1615 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d^{6}) □: 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}CNMR($CDCl_3$) □: 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 (%):508[M^{+}] and 509[M^{+2}];

Analysis Calculated for $C_{25}H_{22}ClN_5O_5$: Calcd: C(59.12), H(4.37), N(13.79) ;Found: C(59.29), H(4.64), N(14.07).

Synthesis of 1-((1-(4-chlorophenyl)-2, 5-dihydro-4-morpholino-2, 5-dioxo-1*H*-pyrrol-3-yl) methylene) -(2-(4-(4-flurophenyl) oxazol-2-yl)-hydrazine, 7c

M.P. (^oC): 220-222, Yield (%): 84, Colour: Reddish brown Solid; IR (KBr) (□): 1735, 1781, 3388, 1610 cm^{-1}; ^1H 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 ($CDCl_3$) □: 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 (%): 503[M^{+1}], 505[M^{+2}] Analysis Calculated for $C_{24}H_{19}FClN_5O_4$: Calcd: C(51.77), H(3.44), N(12.58) ; Found: C(51.50), H(4.75), N(12.86).

Synthesis of 1-((1-(4-chlorophenyl)-2, 5-dihydro-4-morpholino-2, 5-dioxo-1*H*-pyrrol-3-yl) methylene) -(2-(4-(4-chlorophenyl) oxazol-2-yl)-hydrazine, 7d

M.P. (^oC): 228-230, Yield (%): 82, Colour: Reddish brown Solid; IR (KBr) (□): 1735, 1781, 3388, 1610 cm^{-1}; ^1H 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 ($CDCl_3$) □: 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 (%): 520[M^{+1}], 522[M^{+2}] Analysis Calculated for $C_{24}H_{19}Cl_2N_5O_4$: Calcd: C(51.77), H(3.44), N(12.58) ; Found: C(51.50), H(4.75), N(12.86).

Synthesis of 1-((1-(4-chlorophenyl)-2, 5-dihydro-4-morpholino-2, 5-dioxo-1*H*-pyrrol-3-yl) methylene) -(2-(4-(4-bromophenyl) oxazol-2-yl)-hydrazine, 7e

M.P. (^oC): 231-233, Yield (%): 88, Colour: Reddish brown Solid; IR (KBr) (□): 1735, 1781, 3388, 1610 cm^{-1}; ^1H 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 ($CDCl_3$) □: 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 (%): 566[M^{+1}], 568[M^{+2}] Analysis Calculated for $C_{24}H_{19}BrClN_5O_4$: Calcd: C(51.77), H(3.44), N(12.58) ; Found: C(51.50), H(4.75), N(12.86).

Synthesis of 1-((1-(4-chlorophenyl)-2, 5-dihydro-4-morpholino-2, 5-dioxo-1*H*-pyrrol-3-yl) methylene) -(2-(4-(4-nitrophenyl) oxazol-2-yl)-hydrazine, 7f

M.P.(^{o}C): 240-242, Yield (%): 83, Colour: Reddish brown Solid; IR (KBr) (□): 1730, 1710, 3378, 1610, 1355 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □: 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 ($CDCl_3$) □: 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 (%): 523[M^{+1}], 524[M^{+2}]; Analysis Calculated for $C_{24}H_{19}ClN_6O_6$:Calcd: C(55.13), H(3.66), N(16.07) ;Found: C(5484), H(3.94), N(16.29).

Synthesis of 1-((1-(4-chlorophenyl)-2, 5-dihydro-4-morpholino-2, 5-dioxo-1*H*-pyrrol-3- yl) methylene) -(2-(4-(4-2H-chromen-2-one) oxazol-2-yl)-hydrazine, 7g

M.P. (^{0}C): 210-212, Yield (%): 80, Colour: Brown Solid; IR (KBr) (□): 1733, 1720 1751, ,3398, 1612, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □: 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 ($CDCl_3$) □: 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 (%): 562[M^{+1}], 563[M^{+2}]; Analysis Calculated for $C_{27}H_{20}ClN_5O_6$:Calcd: C(59.84), H(4.30), N(12.46) ;Found: C(59.50), H(4.55), N(12.73).

CONCLUSIONS

Herein we have designed and synthesized a series of novel Semicarbazone 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 semicarbazide derivatives of 1-chlorophenyl-4-dialkylamino-3-carbaldehyde-N-arylmaleimides 4 by nucleophilic condensation of trans-3,4-dibromo-1-(4-chlorophenyl) morpholino- 2,5-dione, 3 with semicarbazide to obtained Semicarbazone 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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