Synthesis and Characterization of Novel Oxazole derivatives of Disubstituted *N*-arylmaleimides

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Abstract

*The compound **1** was reacting with bromine in DMF to obtained dibromosuccinimides **2.** The compound **2** react with morpholine followed dehydrohalogenation to obtain monobromo compound, **3** through common 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)-1H pyrrole-3-carbaldehyde **4** with semicarbazide hydrochloride in ethanol in presence of acetic acid furnished compound **5** with 83% 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, ^{1}NMR ^{13}CNMR and elemental analysis given in experimental section.*

Keywords: Malieimide, Morpholine, Semicarbazone, Phenacyl bromide and Oxazole.

INTRODUCTION

Herein we report the synthesis of oxazole derivatives of disubstituted N-arylmaleimides. Maleimides shows a wide range of biological activities such as antifungal [1], antiprotozoal [2],antiangiogenic [3], antibacterial [4-5] and analgesic [6], antitress agents [7], cytotoxic, DNA binding and apoptotic inducing activity.[8] A biological property of these compounds includes angiogenesis inhibition[9], protein kinase inhibition [10], ant proliferative activity [11]. Maleimide and its derivatives are synthesizes from maleic anhydride and amines followed by dehydration.

Semicarbazone derivatives are prepared via the reaction of aldehydes or ketones with semicarbazide hydrochloride in the presence of an acid or a base as catalyst [12-13].

The derivatives of Oxazole have become increasingly important in the past few years because of their use in intermediates for the preparation of new biological materials. The C-2 and C-4 positions of the oxazoles are crucial for their various biological activities. *N*-substituted oxazoles also participated in variety of intermolecular reactions.The oxazole ring is present in numerous pharmacologically important compounds, including those used as antibiotics [14] and antiproliferative [15]. The wide range of biological activities of oxazoles includes anti-inflammatory [16], analgesic [17] antibacterial, antifungal [18], hypoglycemic [19], antiproliferative [20], anti-tuberculosis [21], muscle relaxant [22] and HIV inhibitor activity[23]. In addition, oxazole derivatives are useful synthetic intermediates and can be used as diversity scaffolds in combinatorial chemistry and also as peptidomimetics [24]

A number of synthetic methods to prepare oxazoles have been reported. The typical procedure for the synthesis of oxazoles involves the reaction of readily available substituted urea derivatives with halogenated alkenes or α-haloketones [25].

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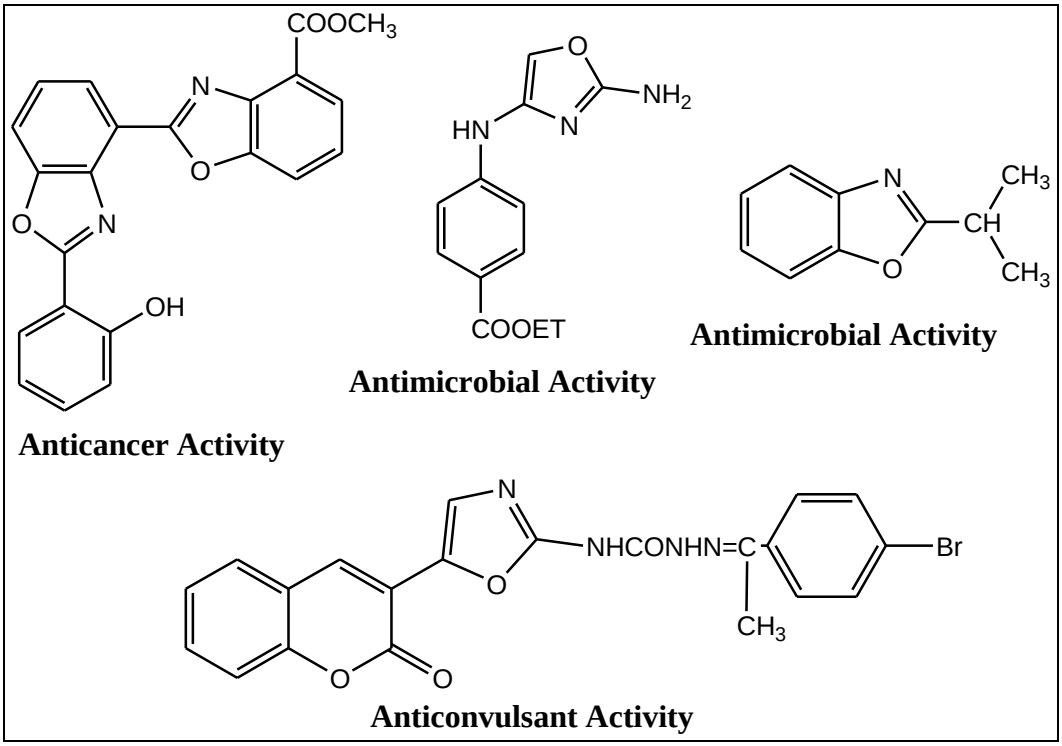
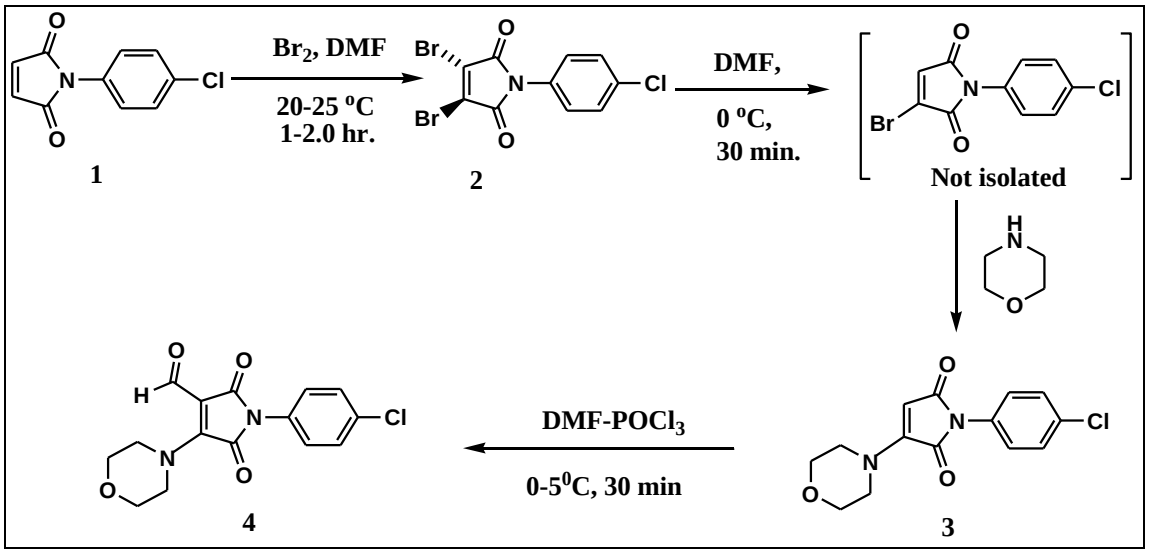


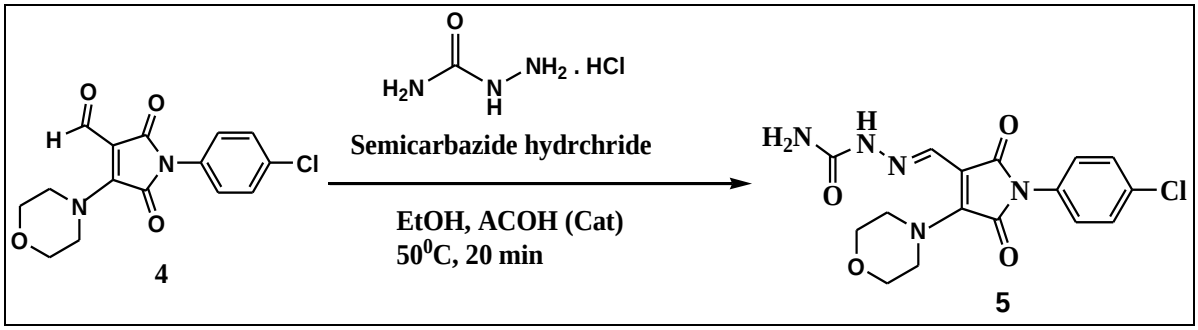
RESULTS AND DISCUSSION

The compound **1** were synthesized [29] and reacted with bromine in DMF at 20-25 ^{0}C for 1-2.0 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^{0}Cfor 5 min. to obtained compound **4**.
Vilsmeier Haack formylation of **3** at 0-5^{0}C afforded compound **4** with good yield. **(Scheme-1)**



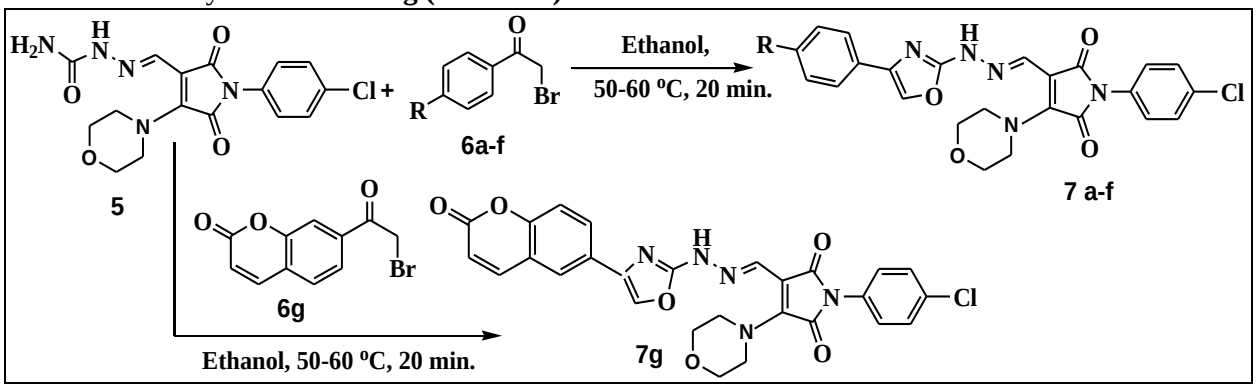
Scheme-1: Synthesis of2,5-dihydro-4-morpholino-2,5-dioxo-1-phenyl-1H-pyrrole-3-carbaldehyde (4)

Thus condensation of 1-(4-chlorophenyl)-2,5-dihydro-2,5-dioxo-4-(piperidin-1-yl)-1Hpyrrole-3-carbaldehyde **4** with semicarbazide hydrochloride in ethanol in presence of acetic acid at50^{0}C for 20 min.furnished orange colour solid **5** with 84 % yield.**(Scheme2).**



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 **5** react with substituted phenacyl bromide **6 a-g** to obtained oxazole derivative of disubstituted Narylmaleimides**7a-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 oxazole derivatives of Disubstituted N- aryl maleimides(7a-g)

EXPERIMENTAL

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 CDCl3and 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. 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.

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 200^{0}C and stirred for 1-2.0 hrs. with constant stirring, white solid were separated was then filtered, washed with cold water, dried and recrystallized using ethanol to obtain compound **2** [27]. To a solution of trans-3, 4-dibromo-1-(4-chlorophenyl) marpholidine-2, 5-dione**,2** (0.01 mol) in DMF (10 mL),

Morpholine (0.03 mol) was added drop wise at 100^{0}C and stirred for 30 min. The reaction mixture was poured on 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 [26].

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 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 [27].

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 hydrochloride (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.**

Spectral Data:

M.P: 150-152^{0}C,Yield(%):82, Colour: Orange solid IR (KBr) (n):1750, 1695, 31245, 1615, 1270 cm-1; 1H NMR (CDCl3) d:3.70 (bs, 4H, 2 x CH2), 4.18 (s, 2H, CH2), 4.31(s, 2H,CH2), 3.84 (s, 2H, NH2), 6.70(S, 1H, =C-H), 7.22- 8.15 (m, 4H, Ar-H), 11.22 (bs, 1H, N-H) ppm; 13C NMR (CDCl3) d:23.87 (2C'S), 26.54, 27.89, 29.85,61.15, 96.28, 127.80 (2C'S), 129.80 (2C'S), 129.95, 133.70, 153.22, 162.41, 164.35, 167.77, 180.45 ppm; MS (70 eV) m/z (%): 395[M+] and 397[M+2]Analysis Calculated for **$C_{16}H_{16}ClN_5O_4$**: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 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 phenacylbromide **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).[28]

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

M.P.(^{0}C): 222-224, Yield(%): 73, Colour: Reddish brown Solid; IR (KBr) (□): 1730, 1690, 3438, 1621 cm-1; ^{1}H NMR (500 MHz, DMSO-d6) □: 3.12 (s, 3H, CH3), 3.41 (bs, 4H, 2 x CH2), 3.83 (s, 4H, 2x CH2), 7.12(S, 1H, N=CH), 7.10-8.20 (m, 9H, Ar-H), 11.92(bs, 1H, N-H) ppm; ^{13}C NMR (CDCl3) □: 23.88, 51.27(2C'S), 75.46(2C'S), 105.45, 123.34(2C'S), 125.51 (2C'S), 127.91(2C'S), 130.65(2C'S), 132.50(2C'S), 134.20, 140.5, 144.70, 149.3, 152.8, 160.20, 168.6, 170.7, 173.5 ppm; MS (70 eV) m/z (%):509[M+] and 511[M+2]; Analysis Calculated for

$C_{25}H_{22}ClN_5O_4$: 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)oxazol-2-yl)-hydrazine (7b)

M.P.(^{0}C): 187-189, Yield(%): 78, Colour: Reddish brown Solid; IR (KBr) (□): 1733, 1714, 3363, 1614 cm-1; ^{1}H NMR (500 MHz, DMSO-d6) □: 3.61 (bs, 4H, 2 x CH2), 3.70(s, 4H, 2x CH2), 3.91(s 3H, OCH3), 6.90-8.0 (m, 9H, Ar-H), 8.21(s,1H, N=C-H), 11.82 (bs, 1H, N-H) ppm; ^{13}C NMR (CDCl3) □: 24.45, 50.52(2C'S), 76.61(2C'S), 107.4, 121.50(2C'S), 125.56 (2C'S), 128.40(2C'S), 131.10(2C'S), 133.80(2C'S), 137.27, 141.41, 144.87, 150.5, 152.4, 161.55, 167.5, 170.7, 173.6 ppm; MS (70 eV) m/z (%):525[M+] and 527[M+2]; Analysis Calculated for $C_{25}H_{22}ClN_5O_5$: 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)oxazol-2-yl)-hydrazine(7c)

M.P.(^{0}C): 214-216, Yield(%): 82, Colour: Reddish brown Solid; IR (KBr) (□): 1754, 1785, 3394, 1615 cm-1; ^{1}HNMR (500 MHz, CDCl3): 3.30 (bs, 4H, 2 x CH2), 3.62 (s, 2H, CH2), 3.81(s, 2H, CH2), 6.14(s,1H, N=C-H), 6.81- 8.55 (m, 9H, Ar-H), , 11.90 (bs, 1H, N-H) ppm; ^{13}C NMR (CDCl3) □: 25.45, 52.17(2C'S), 75.16(2C'S), 108.7, 121.63(2C'S), 123.34, 128.55(2C'S), 130.63(2C'S), 131.44(2C'S), 135.78, 141.56, 143.5, 151.67, 153.56, 160.40, 167.7, 170.3, 172.67 ppm; MS (70 eV) m/z (%): 513[M+1], 515[M+2]Analysis Calculated for $C_{24}H_{19}ClFN_5O4$: Calcd: C(56.36), H(3.73), N(13.40 ; Found: C(56.03), H(4.01), N(13.95)

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

M.P.(^{0}C): 221-223, Yield(%): 81, Colour: Reddish brown Solid; IR (KBr) (□): 1750, 1777, 3353, 1616 cm-1; ^{1}HNMR (300 MHz, CDCl3): 3.22 (bs, 4H, 2 x CH2), 3.51 (s, 2H, CH2), 3.83(s, 2H, CH2), 6.32(s,1H, N=C-H), 6.71- 8.32 (m, 9H, Ar-H), , 11.72 (bs, 1H, N-H) ppm; ^{13}C NMR (CDCl3) □: 23.54, 50.32(2C'S), 75.14(2C'S), 108.55, 121.77(2C'S), 124.36, 128.25(2C'S), 133.55(2C'S), 131.55(2C'S), 135.77, 141.5, 145.8, 151.6, 153.8, 162.46, 167.81, 171.52, 173.61 ppm; MS (70 eV) m/z (%): 529[M+1], 531[M+2]Analysis Calculated for $C_{24}H_{19}Cl_2N_5O_4$: Calcd: C(54.56), H(3.63), N(13.56) ; Found: C(54.23), H(3.80), N(13.58)

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

M.P.(^{0}C): 222-224, Yield(%): 84, Colour: Reddish brown Solid; IR (KBr) (□): 1733, 1784, 3355, 1617 cm-1; ^{1}HNMR (300 MHz, CDCl3): 3.31 (bs, 4H, 2 x CH2), 3.72 (s, 2H, CH2), 3.80(s, 2H, CH2), 6.12(s,1H, N=C-H), 6.90- 8.40 (m, 9H, Ar-H), , 11.82 (bs, 1H, N-H) ppm; ^{13}C NMR (CDCl3) □: 23.74, 50.25(2C'S), 75.34(2C'S), 108.35, 120.91(2C'S), 124.33, 128.66 2C'S), 130.80(2C'S), 131.80(2C'S), 136.91, 141.54, 145.67, 150.6, 152.9, 161.82,
168.55, 171.56, 173.45 ppm; MS (70 eV) m/z (%): 573[M+1], 575[M+2]Analysis Calculated for $C_{24}H_{19}BrClN_5O_4$: Calcd: C(50.35), H(3.36), N(12.21) ; Found: C(50.05), H(3.68), N(12.53)

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

M.P.(^{0}C): 234-236, Yield(%): 82, Colour: Reddish brown Solid; IR (KBr) (□): 1734, 1712, 3371, 1612, 1353 cm-1;^{1}H NMR (300 MHz, CDCl3) □: 3.41 (bs, 4H, 2 x CH2), 3.50 (s, 2H, CH2), 3.81 (s, 2H, CH2), 6.90-8.41(m, 9H, Ar-H), 8.61(s, 1H, N=C-H), 12.21 (bs, 1H, N-H) ppm ; ^{13}C NMR (CDCl3) □: 23.21, 27.45(2C'S), 49.55(2C'S), 98.55, 105.81, 121.33(2C'S), 123.13(2C'S), 125.65, 127.54(2C'S), 129.71(2C'S), 133.40(2C'S), 141.10, 153.55(2C'S),
161.61, 163.92, 176.56, ppm; MS (70 eV) m/z (%): 540[M+1], 542[M+2];Analysis Calculated for $C_{24}H_{19}ClN_6O_6$:Calcd: C(53.42), H(3.58), N(15.57) ;Found: C(53.21), H(3.88), N(15.84)

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

M.P.(^{0}C): 215-217, Yield(%): 77, Colour: Brown Solid; IR (KBr) (□): 1735, 1724 1755, ,3396, 1613, cm-1; ^{1}HNMR (300 MHz, CDCl3) □: 3.41 (bs, 4H, 2 x CH2), 3.52 (s, 2H, CH2), 3.71 (s, 2H, CH2), 6.12(s, 1H,Ar-H), 6.52(s,1H, Ar-H), 6.80-7.55 (m, 10H, Ar-H), 8.21(s, 1H, N=C-H), 11.91 (bs, 1H, N-H) ppm; ^{13}C NMR (CDCl3) □: 23.81, 27.80(2C'S), 53.10(2C'S), 97.41, 114.74, 119.10, 122.64(2C'S), 124.40(2C'S), 126.16, 127.15(2C'S), 129.30(2C'S), 136.25, 140.32(2C'S), 142.56, 151.21(2C'S), 161.42, 166.37, 173.23, 180.41, ppm; MS (70 eV) m/z (%): 579[M+1], 581[M+2];Analysis Calculated for $C_{27}H_{24}ClN_5O_6$:Calcd: C(58.16), H(4.16), N(12.14) ;Found: C(57.87, H(4.43), N(12.42)

CONCLUSION

Here we have designed and synthesized a series of novel semicarbazone 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 semicarbazide derivatives of 1-chlorophenyl-4-dialkylamino-3- Carbaldehyde-N-arylmaleimides **4** by nucleophilic condensation of trans-3,4-dibromo-1-(4-chlorophenyl)marpholidine- 2,5-dione, **3** with semicarbazide hydrochloride 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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