Synthesis of some novel Mannich bases bearing pyrazolone moiety

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ABSTRACT

Synthesis of N\(^{1}\)(2-OXO-1-(piperidine-yl methyl) indoline 3-ylidine )-2-(4-(5-oxo-4(2-phenyl hydrazono )-3-trichloromethyl)-4,5-di hydro -1-H pyrazol-1-yl) phenoxy) aceto hydrazide) were synthesis by condensation of 2-(4-(5-oxo-4(2-phenyl hydrazono)-3-(trichloro methyl)-4,5-di hydro -1-H pyrazol-1-yl) phenaxy )N-(2-oxoindoline)-3-ylidine) aceto hydrazide with isatin offered corresponding synthesis of N\(^{1}\)(2-OXO-1-(piperidine-yl methyl) indoline 3-ylidine )-2-(4-(5-oxo-4(2-phenyl hydrazono)-3-chloromethyl)-4,5-di hydro -1-H pyrazol-1-yl) phenoxy) aceto hydrazide) this was subjected manich reaction with cyclic secondary amines such as piparine or morpholine or N-methyl piparine in presence of formaldehyde in DMF to give corresponding manich base synthesis of N\(^{1}\)-2oxo -1-(4-substituted hydrazono)-3-chloromethyl)-4,5-di hydro -1-H pyrazol-1-yl) phenoxy) aceto hydrazide in excellent yield. The structure of these newly synthesis compound were charactrised by H\(^1\)-NMR,C\(^{13}\)-NMR,Mass and IR elemental analysis

Keywords: Pyrazolone, Mannich bases, β-lactam, isatin

INTRODUCTION

Heterocyclic compounds are acquiring more importance in recent years because of their immense biological and pharmacological potency. Various biologically active synthetic compounds have five membered nitrogen containing heterocyclic ring in their structures. Many compounds bearing pyrazoles and their reduced forms pyrazolines constitute an interesting class of heterocycles due to their synthetic versatility and effective biological activities such as antimicrobial [1,2], antiviral [3], anti-inflammatory [4,5], antidepressant [6], antitubercular [7], antiamoebic [8], analgesic [9] activities. Literature survey reveals several synthetic protocols for the synthesis of these compounds and the presence of this core in any molecule plays a key role in enhancing the activity. On the other hand, coumarin and its derivatives represent one of the important class of heterocyclic compounds possessing a wide range of biological activities. These include antibacterial [10], antifungal [11,12], antitumor [13,14], herbicidal, antiinflammatory[15] activities. Coumarins are oxygen containing heterocycles widely distributed in nature. They are also used as additives in food, perfumes, agrochemicals, pharmaceuticals, and in the preparation of insecticides, optical brighteners, dispersed fluorescent and dye lasers.

Chalcones are 1,3-diaryl-2-propen-1-ones are natural or synthetic compounds prepared by claisen-schmidt condensation of aromatic aldehydes with acetophenones in presence of base and alcohol as solvent medium [16,17]. These compounds found application in the synthesis of various heterocyclic compounds. Keeping in view of the above interesting pharmacological features, we hereby report the synthesis and antimicrobial activity of a series of new pyrazoline derivatives.
MATERIALS AND METHODS

All the chemicals were used as received without further purification. Melting points were determined in open capillary tubes in Buchi530 circulating oil apparatus and are not corrected. Reactions were carried out using household micro oven (power consumption 1200 W, microwave frequency 2450 MHz) and monitored by thin layer chromatography (TLC) on silica gel plates (60 F254) visualizing with ultraviolet light or iodine spray. 1H NMR spectra were determined in DMSO-d6 solution on JOEL AL300 Spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane as internal standard and expressed in ppm.
RESULTS AND DISCUSSION

A series of four novel Maniche bases are afford substituted anilene is dissolved. In suitable volume of water. Containing 2.5 - 3.5 equivalence of HCl by the application of heat afford to substituted phenyl diazonium chloride. (a) A is treated of a solution of sodium acetated in presence of ethyl trichloro acet acid ester (B) is obtained. B is condensed with 4 – hydrazenyl phenol and DMF was subjected to formed. 3 –trichloromethyl 4-hydraxy phenyl hydrazono) pyrazoline 5-one (c). compound (c) is stirred at room temperature in presence of anhydrous in K2CO3, chloro ethyl acetate and DMF (1) is formed. compound (1) is amination with hydrazine hydrate in presence of ethanol afford a ethylene 4-(5-oxo phenyl hydrazono) - 3-trichloromethyl -4,5-di hydro – H pyrazol-1-yl) pohenoxy) aceto hydrazide(2). compound 2 is condensed with Isatin in presence of DMF afford to a 2-(4-(5-oxo-4-(2-oxoindoline-3-ylidene) aceto hydrazide (3). compound (3) is reaction with Manich bases formaldehyde and DMF (piparadine ,morpholine ,N-Methyl piparazine to obtained compound (4) is formed. N1-(2-oxo-1-(4-substitud )hydrazono 3-(trichloromethyl) -4,5-dihydro –1-H-pyrazol-1-yl)phenony)aceto hydrazide.

(a) Substituted phenyl diazonium chloride 1

The required primary amine is dissolved in a suitable volume of water containing 2.5 – 3.0 equivalents of hydrochloric acid (or sulphuric acid) by the application of heat if necessary. The solution thus obtained is cooled to 0°C when the amine hydrochloride (or sulphate) usually crystallizes. The temperature is maintained at 0 – 5°C, and the aqueous solution of sodium nitrite is added portion wise till there is free nitrous acid. The solution is tested for the later with an external indicator (moist potassium iodide starch paper). An excess of acid is always maintained to stabilize the diazonium salt, acid is harmful, the concentration of the acid is reduced to optimum value. The similar procedure is adopted for the preparation of other substituted phenyl diazonium chlorides.

(b) Substituted phenyl diazonium ethyl trichloro acet acid ester

A solution of sodium acetate (1.0g) is added to a solution of ethyl trichloro acet acid ester (0.1 mole) in 50 ml of ethanol and the mixture is added to 0°C. To this cold mixture, the corresponding diazonium chloride is added gradually till turbidity is observed. The addition is continued till yellow crystals separated out. These crystals are filtered, washed with water and dried.

(c) 3-methyl-4-(substituted phenyl hydrazono)-pyrozoline-5-one

Condensation of 4-substituted phenyl hydrazono acetooacetic ester (b) and 4-hydraxy phenyl hydrazine (4) in the presence of catalytic amount of dimethyl formamide under microwave irradiation afforded 5. In typical experimental procedure, a mixture of ary hydrazono acet acid ester (3), 4-hydrayzynyl phenol and dimethyl formamide (10 drops) was subjected to microwave irradiation at 150W intermittently at 30 sec intervals for 2 minutes. After complete conversion as indicated by TLC, the reaction mixture was cooled and heated with cold water. The precipitate 5 was filtered recrystalized from ethanol M.P. 159°C, yield 85%. The The mass spectra of 2-(4-(5-oxo-4-(2-phenyl hydrazono)-3-(trichloromethyl)-4,5-dihydro–1-H pyrazol-1-yl)phenoxy)N-(2-oxoindolin)-3-ylidine) aceto hydrazide 10a (R=H) showed molecular ion (M+) peaks at m/z 598.5

1. Synthesis of ethyl 2-(4-(5-oxo phenyl hydrazono)-3-(trichloromethyl)-4,5-dihydro–1-H pyrazol-1-yl) phenoxy) aceto hydrazide

A mixture of synthesis of 1-(4-hydrophenyl)-4-2(phenyl hydrazono)-3-(trichloromethyl)-1H–pyrazol-5(4H)-one 5, anhydrous K2CO3, chloro ethyl acetate and DMF was stirred at room temperature for 8 hours. The reaction mixture was diluted with ice cold water. The separated solid was identified as ethyl 2-(4-(5-oxo-4-(2-phenyl hydrazono)-3-(trichloromethyl)-4,5-dihydro–1-H pyrazol-1-yl)phenoxy)aceto hydrazide 6

2. Synthesis of ethyl 2-(4-(5-oxo phenyl hydrazono)-3-(trichloromethyl)-4,5-dihydro–1-H pyrazol-1-yl)phenoxy)aceto hydrazide 2(a)

The IR(KBr): -3445, 3425, (2 bands) 3305, 1620, 1665, 1460 and 1455 cm-1 due to – NH, >NH and >C = N, cyclic carbonyl and five membered hetero cyclic ring respectively. The 1H NMR (300MHz) spectra of signals 3.95(s, 2H, NC=O), 4.23(s, 2H, NH), 10.97(s, 1H, Ar–NH=N), 6.82–7.93(m, 9H, C6H5 and C3H4), 9.23(s, 1H, C=O–NH). C15H17N3O3 (295.30) mol. formula: C15H17N3O3. Calculated values: C 58.37, H: 5.94, N: 22.70, O: 12.97

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2. Synthesis of ethyl 2-(4-(5-oxo phenyl hydrazono)-3-(trichloro methyl)-4,5-dihydro–Methyl pyrazol–1- yl)phenoxy)acetohydrazide 2(B)

IR(KBr): 3205(-NH), 3170 (Indol -NH), 1602(-c=N), 1656(pyrazoline –C=O), 1700(indole- c=o), 1618(-CO-NH).

Found(%) C: 59.37, H: 6.25, N:21.87, O :12.23

3. Synthesis of ethyl 2-(4-(5-oxo phenyl hydrazono)-3-(trichloro methyl)-4,5-dihydro–Methoxy pyrazol–1- yl)phenoxy)acetohydrazide 2(C)

IR(KBr): 3420, 3400(-NH), 1605(-c=N), 1656(pyrazoline –C=O), 1700(indole- c=o), 87.1(CCl

Found(%) C: 57.85, H:6.18, N:20.20, O:15.35

4. Synthesis of ethyl 2-(4-(5-oxo phenyl hydrazono)-3-(trichloro methyl)-4,5-dihydro–ethoxy pyrazol–1-y l)phenoxy)acetohydrazide 2(d)

IR(KBr): 3425, 3415(-NH), 1615(-C=O) NMR(300MHZ,(CD)SO,TMS);δ=1.78(t, 3H, CH3), 3.20 (q, 2H, –OCH2–), 4.93(s, 2H, O–CH2–CO), 4.18(s, 2H, NH2), 10.96(s, 1H, Ar–NH=N=), 6.89–7.92(m, 8H, C6H4 and C6H3), 9.20(s, 1H, CO–NH) C13 Spectrum of (CDCl3)δ=30.05, 27.74, 24.6, 152.7, 102.0, 32.7, 20.8 (Ar-c), 69.4 (CH2) 155.6(NH-N=C), 205(Pyrazolone-C=O), 92.5(CCl3), 56.3(CCl4), 23.9, 25.5, 46.5, 32.4, 100.4, 155.9 .(Phenoxo) yield 75% M.P. 154-156 Mol.formula C9H7ClN2O3 Calculated values C:55.85, H:5.68, N:19.85, O:15.85 Found(%) C:57.00 H:6.18, N:20.20, 15.35 Found(%): C:57.97, H:6.28, N:20.28, O:15.45

5. Synthesis of ethyl 2-(4-(5-oxo phenyl hydrazono)-3-(trichloro methyl)-4,5-dihydro–choloro pyrazol–1- yl)phenoxy)acetohydrazide 2(e)

IR(KBr): 3435, 3415(-NH), 1615(-C=O) NMR(300MHZ,(CD)SO,TMS);δ=4.89(s, 2H, O–CH2–CO), 4.0(s, 2H, NH2), 10.93(s, 1H, Ar–NH=N=), 6.82–7.96(m, 8H, C6H4 and C6H3), 9.15(s, 1H, CO–NH) C13 Spectrum of (CDCl3)δ=31.05, 26.14, 151.02, 152.03, 32.2(2Ar-c), 136.81(Cl) 255.3(Pyrazolone-C=O), 158.3(Cl), 168.0(C=ONH3H2), 20.27, 36.5, 68.4, 119, 1139(NHPhenoxo) yield 75 M.P.173-174 Mol.formula C9H7ClN2O3 Calculated values:C:53.29, H:5.10, N:20.66, O:11.76, Cl:8.66 Found(%): C:53.39, H:5.19, N:20.76, O:11.86, Cl:8.77

6. Synthesis of ethyl 2-(4-(5-oxo phenyl hydrazono)-3-(trichloromethyl)-4,5-dihydro–bromo pyrazol–1- yl)phenoxy)acetohydrazide 2(f)

IR(KBr): 3444, 3424(-NH), 3290(NH), 1615(C=O)1H NMR(300MHZ,(CD)SO,TMS);δ=4.85(s, 2H, O–CH2–CO), 4.0(s, 2H, NH2), 10.95(s, 1H, Ar–NH=N=), 6.85–7.93(m, 8H, C6H4 and C6H3), 9.18(s, 1H, CO–NH) C13 Spectrum of (CDCl3)δ=20.6, 32.7, 29.4, 58.6(Ar-c), 68.07(-CH2-Cl) 137.7(-NH-N=C) 139.0(Pyrazolone-c=O), 87.1(CCl3), 158.3(CCl4), 168.6(C=ONH3H2), 23.9, 25.5, 46.5, 32.4, 155.9 yield 65 M.P.167-169 Mol. formula C9H7BrN2O3 Calculated values:C:47.98, H:4.60, N:18.07, O:10.78 Found(%): C:48.11, H:4.71, N:18.170.1089


IR(KBr): 3205(NH), 3170(Indol -NH), 1620(c=C=O), 1700(indole- c=O), 1618-(CO-NH) 1H NMR(300MHZ,(CD)SO,TMS);δ=9.28(s, 1H, CO–NH), 10.97(s, 1H, Ar–NH=N=), 10.54(s, 1H, Indole –NH), 4.85(s, 2H, O–CH2–CO), 6.87–7.83(m, 13H, Ar–H), C13 Spectrum of (CDCl3)δ=20.7, 29.4, 32.7, 56.2, 31.3, (Ar-c), 65.6(-CH2-), 153.8(-NH-N=C), 171.1(Pyrazol-c=O), 94.9(CCl3), 155.6(CCl3) C13 Spectrum of (CDCl3)δ=32.8(C=ONH3H2), 21.6, 28.5, 27.7, 119.1, 133.9(Phenoxo), 25.2, 25.7, 126.0, 131.3, 119.0, 139.1156(Indoline-c) yield 70 M.P.172-212 Mol. formula C9H7ClN2O3 Calculated values:C:52.16,H:3.00N:16.34,O:10.62,Cl:17.45 Found(%):C:52.26, H:3.01, N:16.58, O:10.72, Cl:17.58
8. Synthesis 2-[(4-((5-oxo-4-(2-phenyl hydrazono)-3-(trichloro methyl)-4,5-dihydro-1-Methyl pyrazol-1-yl)phenoxo)N-(2-oxoindolin-3-ylidine) aceto hydrazide 3(b)

IR(KBr):3180(-NH),3140(Indol-NH),1600(-C=N),1039(s, 1H, CO–NH), 8.02 (m, 12H, Ar–H), 10.63 (s, 1H, Indole –NH) C 241-243 Mol.formula C 26 H 17 Cl,N O 2 Calculated Values: C:52.41, H:3.43, N:15.28, O:16.38

9. Synthesis 2-[(4-((5-oxo-4-(2-phenyl hydrazono)-3-(trichloro methyl)-4,5-dihydro-1-Methoxy pyrazol-1-yl)phenoxo)N-(2-oxoindolin-3-ylidine) aceto hydrazide 3(c)

IR(KBr):3195(-NH),3150(indole-NH),1505(-C=N),1654(Pyrazoline-C=O),1701(Indole-C=O),1625(-CO-NH), H NMR(300MHZ,(CD) 3 SO,TMS);=δ=9.89, 28(s, 1H, Ar–NH–N=), 3.39(q, 2H, O–CH 3 ), 6.85-7.92(m, 12H, Ar–H), 10.63(s, 1H, Indole –NH) C 223-225 Mol.formula C 26 H 17 Cl,N O 2 Calculated Values: C:52.41, H:3.43, N:15.28, O:16.38

10. Synthesis 2-[(4-((5-oxo-4-(2-phenyl hydrazono)-3-(trichloro methyl)-4,5-dihydro-1-ethoxy pyrazol-1-yl)phenoxo)N-(2-oxoindolin-3-ylidine) aceto hydrazide 3(d)

IR(KBr):3195(-NH),3150(indole-NH),1604(-C=N),1654(Pyrazoline-C=O),1701(Indole-C=O),1624(-CO-NH), H NMR(300MHZ,(CD) 3 SO,TMS);=δ=9.89, 28(s, 1H, Ar–NH–N=), 3.39(q, 2H, O–CH 3 ), 6.85-7.92(m, 12H, Ar–H), 10.63(s, 1H, Indole –NH) C 223-225 Mol.formula C 26 H 17 Cl,N O 2 Calculated Values: C:52.41, H:3.43, N:15.28, O:16.38

15. Synthesis of N'-2-oxo-1-(piperidine-yl methyl) Indole-3-ylidine)-2-(4-(5-oxo-4-(2-phenyl hydrazono)-3-(trichloro methyl)-4,5-dihydro-1-Methoxy pyrazol-1-yl)phenoxy) aceto hydrazide 4(C) yield 70 M.P. 155-158 Mol.formula C₃₁H₂₅ClBrN₂O₄ Found(%): C:55.93, H:4.37, N:15.81, O:9.03, Cl:14.83


17. Synthesis of N'-2-oxo-1-(piperidine-yl methyl) Indole-3-ylidine)-2-(4-(5-oxo-4-(2-phenyl hydrazono)-3-(trichloro methyl)-4,5-dihydro-1-Chloro pyrazol-1-yl)phenoxy) aceto hydrazide 4(e) yield 70 M.P. 158-159 Mol.formula C₃₁H₂₅ClBrN₂O₄ Found(%): C:52.28, H:3.84, N:15.36, O:8.79, Cl:13.58


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morpholine ring), 4.15(s, 2H, N–CH₂–N), 4.78(s, 2H, O–CH₂–CO), 10.95(s, 1H, Ar–NH=H), 8.92(s, 1H, CONH), 6.83–7.76(m, 13H, Ar–H) C¹³ Spectrum of (CDCl₃) δ= 20.08, 23.02, 02101.32, 154, 101.23, 30.65(Arc), 59.13(CH₂), 162(NHN=C) 113(C=ONHNH₂) 15.12, 20.02, 32.03, 40.03(Phenoxy) 21.04, 21.02, 21.03, 19.03, 30.03, 115.02, 143.03, 153(Indoline) 11.02, 20.21, 41.12, 55.51(piperidine) yield 85 M.P. 0°C 159 Mol.formula C₃₂H₃₀C₃N₉O₄ Found(%): C:53.44, H:3.87, N:16.09, O:11.49, Cl:15.02


IR(KBr): -NCH₃(X), 3180(-NH), 1617(-C=N), 1666(Pyrazoline-C=O), 1710(Indole-C=O), 1657(-CONH), 2920(-CH₂), 2.34(s, 3H, N–CH₃), 2.45(t, 4H, –CH₂–N–CH₂– of piperazine ring), 2.53(t, 4H, CH₂–N–CH₂ of piperazine ring), 4.17(s, 2H, N–CH₂–N), 4.81(s, 2H, O–CH₂–CO), 10.93(s, 1H, Ar–NH=H), 8.89(s, 1H, CO–NH), 6.76–7.81(m, 13H, Ar–H) C¹³ Spectrum of (CDCl₃) δ= 20.08, 23.02, 02101.32, 154, 101.23, 30.65(Arc), 59.13(CH₂), 162(NHN=C) 113(C=ONHNH₂) 15.12, 20.02, 32.03, 40.03(Phenoxy) 21.04, 21.02, 21.03, 19.03, 30.03, 115.02, 143.03, 153(Indoline) 11.02, 20.21, 41.12, 55.51(piperidine) yield 80 M.P. 0°C 157 Mol. formula C₃₂H₃₀C₃N₉O₄ Found(%): C:54.16, H:4.23, N:17.23, O:9.06, Cl:14.80

Antibacterial activity by disc diffusion method.

Table 1. Antibacterial activity of synthesized compounds (4a-f)

<table>
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<th>Compound</th>
<th>Compound Zone of inhibition (mm) at 100 µg/ml concentration</th>
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<tr>
<td>4(a)</td>
<td>B.subtilis E.coli P.aeruginosa</td>
</tr>
<tr>
<td>4(b)</td>
<td>11 10 08</td>
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<tr>
<td>4(c)</td>
<td>14 13 13</td>
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<td>4(d)</td>
<td>16 14 14</td>
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<tr>
<td>4(e)</td>
<td>17 16 15</td>
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<tr>
<td>4(f)</td>
<td>10 09 -</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>24 22 22</td>
</tr>
</tbody>
</table>

Comp 4a 4b 4c 4d 4e 4f 4g 4f
R H 4-CH₃ 4-OCH₃ 4-OC₂H₅ 4-CI 4-Br 4-H 4-H
X CH₂ CH₂ CH₂ CH₂ CH₂ CH₂ CH₂ CH₂

CONCLUSION

1) Further more the substitution with phenyl group hahing a chloro group at p-position showed better activities.
2) Pyrazolone and its derivaties were found to play an important role in medicinal chemistry as herbicidal, fungicidal bacterial, antiflammatory.

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