Synthesis of novel mannich bases containing pyrazolones and indole systems

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ABSTRACT

Novel mannich bases N-(2- ((R) -1- ((Z) -2- (1-((4-methyl piperazin-1-yl) methyl) -2-oxindolin-3-ylidene) hydrazinyl) -1-oxopropan -2-ylamino) -2-oxoethyl) -4-(5–oxo –4-(2-phenyl hydrazono) -3-(trifluoromethyl) -4, 5- dihydro -1H -pyrazol -1-yl) benzamide were synthesized by the condensation reaction between (R)-N-(2-(1-hydrazinyl-1-oxopropan-2-ylamino)-2-oxoethyl) -4-(5-oxy–4-(2-phenyl hydrazono)-3- (trifluoromethyl) -4, 5-dihydro -1H -pyrazol -1-yl) benzamide with isatin afford corresponding N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-(2-oxoindolin-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl)-4-(5–oxo–4-(2-phenylhydrazono)-3-(trifluoromethyl)-4, 5-dihydro-1H-pyrazol-1-yl)benzamide. This was subjected to mannich reaction with cyclic secondary amine such as piperidine/morpholine/N-methyl piperidine in the presence of formaldehyde in DMF to give corresponding mannich base N-(2- ((R) -1- ((Z) -2- (1-((4-methyl piperazin-1-yl) methyl) -2-oxindolin-3-ylidene) hydrazinyl) -1-oxopropan -2-ylamino) -2-oxoethyl) -4-(5–oxo –4-(2-phenyl hydrazono)-3-(trifluoromethyl)-4, 5-dihydro -1H -pyrazol -1-yl) benzamide in excellent yields. The structure of these newly synthesized compounds were characterized by 1H-NMR, Mass, IR & Elemental analysis.

INTRODUCTION

Heterocyclic compounds represents an important class of biologically active molecules specifically, those containing the pyrazolone nucleus have been shown to posses high biological actives such as tranquilizing, muscle relaxant, psycho analeptic, anticonvulsant, antihypertensive, antidepressant activities. The derivatives of pyrazolone are important class of antipyretic and analgesic compounds[1-7].

Medicinal chemists have been designed used pyrazolones extensively as scaffolds from which novel therapeutic agents. This heterocyclic ring system is found in a number of compounds showing analgesic morazone[8] immunosuppressant BTS-71412[9] and anti-inflammatory (aspirin-propyphenazone) activity. Numerous methods for general pyrazolone synthesis have been reported[10].

Some substituted pyrazolines and their derivatives are used as antitumor[11] anti bacterial, antifungal, antiviral, anti parasitic, anti-tubercular and insecticidal agents[12-20]. Some of these compounds have also anti-inflammatory, anti-diabetic, and anesthetic properties [21-25].
MATERIALS AND METHODS

Experimental

All the chemicals were used as received without further purification. Melting points were measured on a gallenkamp electro thermal melting point apparatus and are uncorrected. Reactions were carried out using household micro oven (power consumption 1200w, microwave frequency 2450MHz) and monitored by thin layer chromatography (TLC) on silica gel plates (60F254) visualizing with ultraviolet light or iodine spray. 

**1H NMR spectra were determined in DMSO-d$_6$ solution on JOEL AL300 spectrometers. Proton chemical shifts are relative to tetramethylsilane as internal standard and expressed in ppm.**

**Ethyl 4,4,4-trifluoro-3-oxo-2-(4-phenyl hydrazono) butanoate (42)** was prepared by the procedure described by H.M.W. Alborsky, M.E. Baum$^{24}$. 

**Ethyl 4-(5-oxo-4-(4-phenylhydrazono)-3-(trifluoromethyl)-4, 5-dihydro-1H-pyrazol-1-yl)benzoate 43.**

A mixture of (42) and 4-hydrazone ethyl benzoate and dimethylformamide (10 drops) was subjected to microwave radiation at 150W intermittently at 30 seconds intervals for 2 minutes. after complete conversion as indicated by TLC, the reaction mixture was cooled and treated with cold water. The precipitate Ethyl 4-(5-oxo-4-(2-phenyl hydrazono)-4,5-dihydro-1H-pyrazol-1-yl)benzoate (43) was filtered and recrystallized from ethanol. The yield is 85%.

**4-(5-oxo-4-(4-phenyl hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzoic acid 44.**

The compound (43) was dissolved in THF and treated with aq. 5N NaOH Solution in THF and stirred at room temperature for four hours. The completion of reaction was monitored by TLC, the THF distill out under reduced pressure and acetylated with con.Hcl, separated solid was filtered, washed with Hcl and water to afforded 4-(5-oxo-4-(2-phenyl hydrazono)-4,5-dihydro-1H-pyrazol-1-y)benzoic acid (44) yield 68%, m.p:142$^\circ$C; 

**H-NMR(400MHz, DMSO-d$_6$, δ ppm); 10.56(s, H, Ar-NH-N=), 12.68 (s, 1H, COOH) 6.81-7.88 (M, 9H, for C$_6$H$_5$ and C$_6$H$_4$ of two phenyl group; IR (KBR); δ=1615, 3120, 1682, 1617 cm$^{-1}$ and these are due to C=N, NH, acid carbonyl and cyclic carbonyl in five membered heterocyclic ring respectively Anal. Calcd. for C$_{17}$H$_{11}$F$_3$N$_2$O$_3$ (348.27); C, 58.63; H, 3.18; N, 8.04; found(%); C, 58.59; H, 3.11; N, 8.01

**Synthesis of methyl (2R)-2-(2-aminoacetamido) propanoate hydrochloride 45**

The compound synthesized (2R)-2(2-aminoacetamido) propanoate hydrochloride45 have been characterized by means of their elemental analysis, IR, H NMR and MS data.

The IR (KBr) spectra of methyl (2R)-2-(2-aminoacetamido) propanoate hydrochloride showed absorptions around 3445-3425, (m , -NH$_2$str, Gly ) , 3123(m , -NHstir, amide ), 2954-2925 (m , -CHstr, asym , CH$_3$ and CH$_2$ ) , 2852 (m , -CHstr, sym , CH$_2$ ) , 1748 (S , -C=Ostr , ester ) , 1645 , 1636 (s , C=Ostr, 2$^\circ$amide) 1534 (m , -NHbend , 2$^\circ$amide) , 1272 (s , C-Ostr , ester);

**1H-NMR(200MHz, CDCl$_3$); δ 6.22 (br , s , -NH ) , 4.74-4.69(1H , m , α-H ,Ala) , 3.59 (3H , S , OCH$_3$ ) , 3.49-3.27 (2H , d , CH$_2$ ) , 2.0 (br , s , -NH$_2$ ) , 1.29 – 1.27 (3H , d , β-H’s , Ala) ppm
Synthesis of (R)-methyl 2-(2-(4-(5-oxo-4-(4-phenyl hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamido)acetamido propanoate 46.

Methyl (2R)-2-(2-amino acetamido) propionate hydrochloride (45) was dissolved in chloroform and cooled to 0°C, then add NMM and stirred for 15 min. Then add 4-(5-oxo-4-(2-phenyl hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzoic acid (44a) in CHCl₃, DCC and stirred for 24 h, the reaction was monitored by TLC. After completion of the reaction, washed with CHCl₃, the filtrate was washed with 5% sodium bicarbonate and saturated sodium chloride solution. Further the solvent was distilled under reduced pressure to give crude product, it was filtered, washed with water and recrystallized from ethanol to afforded (R)-N-(2-(1-hydrazinyl-1-oxo propane-2-ylamino)-2-oxo ethyl)-4-(5-oxo-4-(2-phenyl hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide (49). The yield was 60%.

N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-(2-oxoindolin-3-ylidene)hydrazinyl)propane-2-ylamino)-2-oxoethyl)-4-(5-oxo-4-(4-phenylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide 47

A solution of (R)-methyl 2-(2-(4-(5-oxo-4-(2-phenyl hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamido)acetamido propanoate (46) (0.01 M) and hydrazine hydrate (0.015M) in ethanol 20mL was refluxed for 5 hours. The reaction mixture was cooled and poured on to ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afforded compounds (49a-f). IR (KBr); ν=3216, 1615, 1652, 1695cm⁻¹ and these are due to >NH, exo >C=N, cyclic carbonyl in five membered heterocyclic ring, carbonyl group, ester carbonyl group respectively. Anal.Calcd for C₂₃H₂₃FN₉O₇ (647.59); C,55.64; H, 3.65; N, 21.61; found(%);C,55.62; H, 3.65; N, 19.41

N-(2-oxo-2-(( R)-1-oxo-1-((Z)-2-(2-oxoindolin-3-ylidene)hydrazinyl)propionate-2-ylamino)-2-oxoethyl)-4-(5-oxo-4-(4-phenylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide

Equimolar quantities (0.01mol) of Isatin (48) and the corresponding acid hydrazide (47a-f) were dissolved in warm ethanol (40mL) containing DMF (0.5mL). The reaction mixture was refluxed for 1-4 hours and then kept at room temperature overnight. The resulting solid was filtered and washed with ethanol, dried and recrystallized from ethanol to afford compounds (49a-f)

N-(2-oxo-2-(( R)-1-oxo-1-((Z)-2-(2-oxoindolin-3-ylidene)hydrazinyl)propionate-2-ylamino)-2-oxoethyl)-4-(5-oxo-4-(4-p-tolylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide (49b); yield 65%, m.p.230°C; H-NMR(400MHz,DMSO-δ ppm); 1.58 (d, 3H, CH₃), 5.33(q, H, CH₂CH); 10.59(s, H, Ar-NH-N=), 8.03(s,2H,CONH), 8.1(s, H,CONH), 6.78-8.37(m, 12H, for three phenyl groups).

13C-NMR(400MHz,DMSO-δ ppm); C₁-143.1,C₂-113.9,C₃-129.5,C₄-122.4,C₅-113.9,C₆-128.7,C₇-149.3,C₈-157.5,C₉-122.3,C₁₀-143.7,C₁₂-121.7,C₁₃(C₅-129.6),C₁₄-129.8,C₁₅-167.8,C₁₆-43.9,C₁₇-170.7,C₁₈-54.6,C₁₉-175.5,C₂₀-18.2,C₂₁-134.5,C₂₂-168.5,C₂₃-129.4,C₂₄-124.4,C₂₅-131.2,C₂₆-119.4,C₂₇-141.2,C₂₈-117.7; IR (KBr); 3226,3280,1615,1652,1695cm⁻¹; El m/s:m/z; ; Anal.Calcd for C₃₀H₂₃FN₉O (674.596); C,55.64; H, 3.65; N, 19.46; found(%);C,55.60; H, 3.65; N, 19.41

The required isatin(48) was prepared by the procedure described by marvel and heris

Synthesis of N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-(2-oxoindolin-3-ylidene)hydrazinyl)propionate-2-ylamino)-2-oxoethyl)-4-(5-oxo-4-(4-phenylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide 49.

Equimolar quantities (0.01mol) of Isatin (48) and the corresponding acid hydrazide (47a-f) were dissolved in warm ethanol (40mL) containing DMF (0.5mL). The reaction mixture was refluxed for 1-4 hours and then kept at room temperature overnight. The resulting solid was filtered and washed with ethanol, dried and recrystallized from ethanol to afford compounds (49a-f)
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4-(5-oxo-4-(2-(4-methoxyphenyl)hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-(2-oxoindolin-3-ylidene)hydrazinyl)propan-2-ylamino)benzamide 49c: yield 64%, m.p.233°C; H-NMR(400MHz,DMSO-d$_6$ δ ppm): 6.78–8.37 (m, 12H, for three phenyl groups), 3.7 (s, 3H, Ar-OCH$_3$), 8.03 (s, 2H, CONH), 8.1 (s, H, CONH), 7.3 (s, H, CONH), 3.41; N, 18.30; found (%): C, 52.80; H, 3.36; N, 18.30; Anal. Calcd for C$_{31}$H$_{29}$F$_3$N$_6$O$_8$ (677.57); C, 54.95; H, 3.81; N, 18.6; found (%): C, 54.90; H, 3.76; N, 18.2

4-(5-oxo-4-(2-(4-bromophenyl)hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-(2-oxoindolin-3-ylidene)hydrazinyl)propan-2-ylamino)benzamide 49d: yield 63%, m.p.233°C; H-NMR(400MHz,DMSO-d$_6$ δ ppm): 6.78–8.37 (m, 12H, for three phenyl groups), 3.18 (q, 2H, -OCH$_2$CH$_3$), 8.03 (s, 2H, CONH), 8.1 (s, H, CONH), 7.3 (s, H, CONH), 3.41; N, 18.30; found (%): C, 52.8; H, 3.36; N, 18.3; Anal. Calcd for C$_{31}$H$_{29}$F$_3$N$_6$O$_8$ (677.57); C, 54.95; H, 3.81; N, 18.6; found (%): C, 54.90; H, 3.76; N, 18.2

4-(5-oxo-4-(2-(4-ethoxyphenyl)hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-(2-oxoindolin-3-ylidene)hydrazinyl)propan-2-ylamino)benzamide 49e: yield 64%, m.p.233°C; H-NMR(400MHz,DMSO-d$_6$ δ ppm): 6.78–8.37 (m, 12H, for three phenyl groups), 3.7 (s, 3H, Ar-OCH$_3$), 8.03 (s, 2H, CONH), 8.1 (s, H, CONH), 7.3 (s, H, CONH), 3.41; N, 18.30; found (%): C, 52.80; H, 3.36; N, 18.30; Anal. Calcd for C$_{31}$H$_{29}$F$_3$N$_6$O$_8$ (677.57); C, 54.95; H, 3.81; N, 18.6; found (%): C, 54.90; H, 3.76; N, 18.2

Synthesis of N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-(2-oxo-1-((R)-1-piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl)-5-(5-oxo-4-(4-phenylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide 50: A mixture of 49a (0.1 mol), piperidine (0.15 mol) and water (20mL) was stirred to obtain a clear solution, to this solution, HCHO (0.05mol) and DMF were added in ice cold condition and stirred for 2 hr in an ice-bath and left...
N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-oxo-1-(piperidin-1-ylmethyl)indolon-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl)-4-(4-phenylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide (50a) obtained as yellow orange crystals, yield 68%, m.p. 158°C. 1H-NMR(400MHz,DMSO-d6, δ ppm): 1.82(d, 3H, CH3), 2.58(m, 6H(CH3)3 of piperidine ring), 2.19(t, 4H –CH2-N-CH3 of piperidinering), 4.38(s, 2H, -N-CH3), 5.05(q, 2H, H-CH2), 7.11(s, 3H, CONH), 7.31-8.02(m, 12H, for three phenyl groups), 13C-NMR(400MHz,DMSO-d6, δ ppm): C1=143.0,C2=139.3,C6=122.4,C7=113.9,C8=128.7,C9=149.3,C10=157.5,C11=122.3,C12=134.7; IR (KBr disc cm−1):3420,1618,1653,1751,1683; EI ms:m/z; Anal.Calcd. for C31H28Cl2F12N10O3; C, 57.82; H, 4.8; N, 18.07; found (%); C, 57.31; H, 4.2; N, 17.1.

N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-oxo-1-(piperidin-1-ylmethyl)indolon-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl)-4-(4-phenylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide (50b) obtained as yellow orange crystals, yield 71%, m.p. 162°C. 1H-NMR(400MHz,DMSO-d6, δ ppm): 2.04(d, 3H, CH3), 5.06(q, 2H, H-CH2), and 13C-NMR(400MHz,DMSO-d6, δ ppm): C1=143.3,C2=114.1,C6=122.4,C7=128.7,C8=119.6,C9=159.4,C10=122.5,C11=143.9,C12=121.6,C13=129.8,C14=129.9,C15=167.9,C16=43.6,C17=170.6,C18=54.8,C19=175.6,C20=183.4,C21=134.6,C22=168.6,C23=129.5,C24=124.6,C25=131.5,C26=119.5,C27=141.3,C28=117.4, C29=75.6,C30=54.5; C31=1765.24; IR (KBr disc cm−1):3140,1616,1650,1748,1868; El ms:m/z; Anal.Calcd. for C33H33F3N10O3 (785.75); C, 58.7; H, 4.9; N, 18.46; found (%); C, 58.52; H, 4.3; N, 18.4.

N-(2-oxo-2-((Z)-1-oxo-1-((Z)-2-oxo-1-(piperidin-1-ylmethyl)indolon-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl)-4-(4-(2-(4-chlorophenyl)hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-oxo-1-(piperidin-1-ylmethyl)indolon-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl)benzamide (50c) obtained as yellow crystals, yield 64%, m.p. 172°C. 1H-NMR(400MHz,DMSO-d6, δ ppm): 1.87(d, 3H, CH3), 2.56(m, 6H(CH3)3 of piperidine ring), 2.19(t, 4H –CH2-N-CH3 of piperidinering), 4.48(s, 2H, -N-CH3), 5.08(q, 2H, H-CH2), 7.10(s, 3H, CONH), 7.20-7.58(m, 12H, for three phenyl groups), 13C-NMR(400MHz,DMSO-d6, δ ppm): C1=143.2,C2=114.3,C6=122.4,C7=128.7,C8=119.6,C9=159.4,C10=122.5,C11=143.9,C12=121.6,C13=129.8,C14=129.9,C15=167.9,C16=43.6,C17=170.6,C18=54.8,C19=175.6,C20=183.4,C21=134.6,C22=168.6,C23=129.5,C24=124.6,C25=131.5,C26=119.5,C27=141.3,C28=117.4, C29=75.6,C30=54.5; C31=175.6; IR (KBr disc cm−1);3140,1614,1653,1742,1868; El ms:m/z; Anal.Calcd. for C33H33F3N10O3 (774.75); C, 57.36; H, 4.8; N, 18.07; found (%); C, 57.82; H, 4.2; N, 18.02.
Table 1. Analytical data of the compounds 50a-f

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N-(2-((R)-1-((Z)-2-(1-methylpyrazin-1-yl)methyl)-2-oxoindolin-3-ylidene)hydrazinyl)-1-oxopropan-2-ylamino)-2-oxoethyl-4-(5-oxo-4-(4-phenylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide50i: obtained as orange crystals; yield 604%, m.p.159°C, 3.52(t, 4H, CH₂ –O-CH₂ of morpholine ring), 2.45(t, 4H, -CH₂ –N-CH₂ of morpholine ring), 2.41(s, 2H, -N-CH₂-N-), 5.09(q, 2H, CH₂CH₂), 8.03(s, 2H, CONH), 7.10(s, 1H, CONH) 10.65(s, 1H, Ar-NH-N=), 6.66-8.12(m, 12H, for three phenyl groups); ¹³C-NMR(400MHz,DMSO-d₆, δ ppm): C₁-143.4, C₂-114.2, C₃-129.8, C₄-122.9, C₅-114.4, C₆-128.9, C₇-149.9, C₈-157.9, C₉-122.9, C₁₀-143.9, C₁₁-121.9, C₁₂-129.6, C₁₃-129.8, C₁₄-128.9, C₁₅-134.8, C₁₆-143.8, C₁₇-175.6, C₁₈-134.8, C₁₉-126.8, C₂₀-129.5, C₂₁-124.4, C₂₂-131.4, C₂₃-119.6, C₂₄-141.4, C₂₅-117.7 C₂₆-75.9, C₂₇-73.6 C₂₈-54.7, C₂₉-26.4; IR (KBr disc cm⁻¹)3142,1616,1657,1733,1684; El ms/m/z; Anal.Calcd. for C₉H₆F₃N₃O₆ Br (788.733); C,54.8, H, 4.4, N, 19.5; found(%);C,54.2; H, 4.1; N, 19.1;
The development of carbon − nitrogen bond formation was described in all the steps of our synthetic sequence. The reaction conditions and good yield procedure. Compound 49 was allowed to undergo the manich reaction with different secondary amines namely piperidine, morpholine and N-methyl piperazine and formaldehyde in absolute ethanol to give compounds 50a-h respectively. The IR spectrum of 50 revealed the appearance of bands corresponding to the characteristic of 3150(NH), 1618(C=N), 1633(Pyrazoline C=O), 1741(Indole C=O), 1710(CONH). The appearance of a signal at δ 4.38 due to (N-CH2) shown 1341,1618,1658,1740,1868; EI ms:m/z; Anal.Calcd.for C30H30F3N1O6 (759.74); C,56.2; H, 4.7; N, 20.28; found(%);C,56.0; H, 4.2; N, 20.23;

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<td>N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl)benzamide (50b)</td>
<td>05</td>
<td>06</td>
<td>05</td>
<td>07</td>
</tr>
<tr>
<td>3</td>
<td>4-(4-(2-(4-hydroxyphenyl)hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrrozol-1-yl)-N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl)benzamide (50c)</td>
<td>06</td>
<td>07</td>
<td>06</td>
<td>07</td>
</tr>
<tr>
<td>4</td>
<td>4-(4-(2-(4-ethoxyphenyl)hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrrozol-1-yl)-N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl)benzamide (50d)</td>
<td>06</td>
<td>05</td>
<td>06</td>
<td>07</td>
</tr>
<tr>
<td>5</td>
<td>4-(4-(2-(4-chlorophenyl)hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrrozol-1-yl)-N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl)benzamide (50e)</td>
<td>09</td>
<td>09</td>
<td>07</td>
<td>09</td>
</tr>
<tr>
<td>6</td>
<td>4-(4-(2-(4-bromophenyl)hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrrozol-1-yl)-N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl)benzamide (50f)</td>
<td>08</td>
<td>07</td>
<td>06</td>
<td>08</td>
</tr>
<tr>
<td>7</td>
<td>4-(4-(2-(4-nitrophenyl)hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrrozol-1-yl)-N-(2-oxo-2-((R)-1-oxo-1-((Z)-2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl)benzamide (50g)</td>
<td>10</td>
<td>08</td>
<td>06</td>
<td>08</td>
</tr>
<tr>
<td>8</td>
<td>N-(2-(t-(t)-1((Z)-2-(1-(morpholinomethyl)-2-oxoindol-3-ylidene)hydrazinyl)-1-oxopropan-2-ylamino)-2-oxoethyl)-5-(2-oxo-4-(2-phenylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrrozol-1-yl)benzamide (50h)</td>
<td>08</td>
<td>07</td>
<td>06</td>
<td>07</td>
</tr>
<tr>
<td>9</td>
<td>N-(2-(t-(t)-1((Z)-2-(1-(4-methylpiperazin-1-yl)methyl)-2-oxoindol-3-ylidene)hydrazinyl)-1-oxopropan-2-ylamino)-2-oxoethyl)-5-(2-oxo-4-(2-phenylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrrozol-1-yl)benzamide (50i)</td>
<td>08</td>
<td>06</td>
<td>07</td>
<td>08</td>
</tr>
</tbody>
</table>

Table 2. Antibacterial Activity by the disc diffusion method

RESULTS AND DISCUSSION

The development of carbon – nitrogen bond formation was described in all the steps of our synthetic sequence. The advent of microwave synthesis also implemented with the improved yield of 90%. A further step involves simple reaction conditions and good yield procedure. Compound 49 was allowed to undergo the manich reaction with different secondary amines namely piperidine, morpholine and N-methyl piperazine and formaldehyde in absolute ethanol to give compounds 50a-h respectively. The IR spectrum of 50 revealed the appearance of bands corresponding to the characteristic of 3150(NH), 1618(C=N), 1633(Pyrazoline C=O), 1741(Indole C=O), 1710(CONH). The appearance of a signal at δ 4.38 due to (N-CH2) shown 1341,1618,1658,1740,1868; EI ms:m/z; Anal.Calcd.for C30H30F3N1O6 (759.74); C,56.2; H, 4.7; N, 20.28; found(%);C,56.0; H, 4.2; N, 20.23;
Anti-Bacterial Activity
The anti-bacterial activity of 50a-i was determined by the disc diffusion method with Amoxicillin and Cefaclor as the reference antibiotics [20]. The newly synthesised compounds were examined, respectively, against *Staphylococcus aureus*, *Bacillus Cereus*, *Escherichia Coli* and *Pseudomonas aeruginosa* bacteria. The test results...
presented in the table-2, suggest that –Nitro, -Chloro and –Bromo exhibit high activity against the tested bacteria, the rest of the compounds were found to be either slightly active or inactive against the tested microorganisms.

REFERENCES

[22] Regaila, H.A; El-Bayonk, A.K.;hammad, M. Egypt.j.chem.20,197, 1979