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Synthesis of novel mannich bases containing pyrazolones and indole systems

P.Nagarjuna Reddy[*],L.K.Ravindranath[**],K.B.Chandrasekhar[*], P.Rameshbabu[**],G.Madhu[*],K.S.Bhavani Aiswarya[**]

Department of Chemistry, S.K .University, Anantapur

ABSTRACT

Novel mannich bases N-(2- ((R) -1- ((Z) -2- (1-((4-methyl piperazin-1-yl) methyl) -2-oxoindolin-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–oxo–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/marpholine/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-oxoindolin-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 ^{1}H-NMR,Mass, IR&Elemental analysis.

INTRODUCTION

Heterocyclic compounds represents an important class of biologically active molecules specifially, those containing the pyrazolone nucleus have been shown to posses high biological actives such as tranquillizing, 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 genaral 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. ^{1}H 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-tri fluoro-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-l)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)-3-(trifluoromethyl)-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 distilled out under redused pressure and acetified with con.Hcl , separated solid was filtered , washed with Hcl and water to afforded 4-(5-oxo-4-(2-phenyl hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzoic acid (44) yield 68%, m.p:142^{0}c; ^{1}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_6H_5 and C_6H_4 of two phenyl group; IR (KBR); ῡ=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 $C_{17}H_{11}F_3N_2O_3$ (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) propionate hydrochloride 45

The compound of alanine methyl ester hydrochloride was dissolved in chloroform and cooled to o^{0}c and the solution was stirred for 15 min. in the presence of NMM. To this solution N-Boc glycine was dissolved in $CHCl_3$ and DCC mixture was added and the resulting solution was stirred for 24h,the reaction was monitored by TLC. After the completion of the reaction with $CHCl_3$ and with 5% sodium bicarbonate and saturated sodium chloride solution, further solvent was distilled under redused pressure to give N-BOC-Glycine alanine methyl ester as a crude product. It was recrystallised from a mixture of chloroform and hexane to give semi solid. The yield is 80%.

Then the deprotection of butyloxycoronyl-glycyl-alanine methyl ester was carried out by dissolving dichloromethane and treated with trifluoroacetic acid and stirred for 2 hours, The reaction was moniter ed by TLC. After completion of the reaction, it was basified with saturated sodium bicarbonate solution and extracted with dichloromethane and the solvent was distilled off and treated with isopropyl alcohol hydrochloride. The precipitate was filtered to give (2R)-2(2-amino acetamido) propanoate hydrochloride45. The yield was 60%.

The compound synthesized (2R)-2(2-amino acetamido) 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) propionate 45. Showed absorptions around 3445-3425 , (m , -NH_2str , Gly) , 3122(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^{o}amide) 1534 (m ,-NHbend , 2^{o}amide) , 1272 (s , C-Ostr , ester);

IH-NMR(200MHz , $CDCI_3$); 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 o^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 $CHCl_3$,DCC and stirred for 24h, the reaction was monitored by TLC . After completion of the reaction, washed with $CHCl_3$,the filtarate 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 stirred with hexane to give (R)-methyl 2-(2-(4-(5-oxo-4-(2-phenyl hydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamido)acetamido propanoate 46. The yield was 60%.^{1}H-NMR(400MHz,DMSO-d_6, δ ppm); 2.15(t, 3H, $CHCH_3$), 4.27(q,2H,$COCH_2$), 5.25(q,1H,CH-CH_3),8.03(s,2H,CONH), 10.56(s,H,Ar-NH), 6.82-8.94(m, 9H, for C_6H_5 and C_6H_4 of two phenyl groups; IR (KBr); ῡ=3164, 1615, 1652,1689,1695cm^{-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 $C_{23}H_{21}F_3N_6O_5$ (518.44); C,53.28; H, 4.05; N, 16.20; found(%);C,53.16; H, 3.97; N, 16.06

(R)-N-(2-(1-hydrazinyl-1-oxo propane-2-ylamino)-2-oxo ethyl)-4-(5-oxo-4-(4-phenyl hydrazono)-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 (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(47) yield 64%, m.p.132^{0}c;^{1}H-NMR(400MHz,DMSO-d_6, δ ppm); 2.10 (d,3H, $CHCH_3$), 4.32 (S, 2H, NH_2), 5.25(q,1H,CH-CH_3),8.03(s ,2H,CONH),8.0(s,H,NH), 7.0(s,H,Ar-NH-N=), 6.82-7.94(m, 9H, for C_6H_5 and C_6H_4 of two phenyl groups; IR (KBr); ῡ=3420,3380, 3232,3208,1620,1654,1615cm^{-1} and these are due to –NH_2,CONH,Ar-NH exo >C=N, cyclic carbonyl in five membered heterocyclic ring, respectively *Anal*.Calcd for $C_{22}H_{21}F_3N_8O_4$ (518.45); C,50.96; H, 4.05; N, 21.61; found(%);C,50.92; H, 4.01; N, 21.56

The required isatin(48) was prepared by the procedure described by marvel and heris[25]

Synthesis of 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 (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)

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 (49 obtained as yellow orange crystals; yield 62%,m.p.216^{0}c;^{1}H-NMR(400MHz,DMSO-d_6, δ ppm); 1.56 (d, 3H, CH_3), 5.30(q, H, CH_3CH), 10.58(s, H, Ar-NH-N=),8.03(s,2H,CONH),8.1(s,H,CONH),7.3(s,H,CONH),6.78-8.37(m, 13H, for three phenyl groups. ^{13}C-NMR(400MHz,DMSO-d_6, δ ppm); C_1-143.0,C_2-113.9,C_3&C_5-129.5,C_4-122.4,C_6-113.9,C_7-128.7,C_8-149.3,C_9-157.5,C_{10}-122.3,C_{11}-143.7,C_{12}&C_{16}.- 121.7,C_{13}&C_{15}-129.6,C_{14}-129.8,C_{17}-167.8,C_{18}-43.9,C_{19}-170.7,C_{20}-54.6,C_{21}-175.5,C_{22}-18.2,C_{23}-134.5,C_{24}-168.5,C_{25}-129.4,C_{26}-124.4,C_{27}-131.2,C_{28}-119.4,C_{29}-141.2,C_{30}-117.7; IR (KBr); ῡ=3226,3280,1610,16521752,1682.cm^{-1} , EI ms:m/z; ; *Anal*.Calcd for $C_{30}H_{24}F_3N_9O$ (647.5796); C,55.64; H, 3.70; N, 19.46; found(%);C,55.60; H, 3.65; N, 19.41

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-p-tolylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide (49b): yield 65%, m,p.230^{0}C;^{1}H-NMR(400MHz,DMSO-d_6, δ ppm); 1.58 (d, 3H, CH_3), 5.33(q, H, CH_3CH), 10.59(s, H, Ar-NH-N=), 8.03(s,2H,CONH),8.1(s,H,CONH),7.3(s,H,CONH), 6.78-8.37(m, 12H, for three phenyl groups, 3.15(s,3H,Ar-CH_3). ^{13}C-NMR(400MHz,DMSO-d_6, δ ppm);; C_1-143.1,C_2-113.8,C_3&C_5-129.7,C_4-122.6,C_6-114.1,C_7-128.9,C_8-149.5,C_9-157.6,C_{10}-122.5,C_{11}-143.9,C_{12}&C_{16}.- 121.6,C_{13}&C_{15}-129.8,C_{14}-129.9,C_{17}-167.9,C_{18}-43.6,C_{19}-170.6,C_{20}-54.8,C_{21}-175.6,C_{22}-18.3,C_{23}-134.6,C_{24}-168.6,C_{25}-129.5,C_{26}-124.6,C_{27}-131.5,C_{28}-119.5,C_{29}-141.3,C_{30}-117.4, C_{31}-20.42;IR(KBr); ῡ=3227,3282,1610,1648,1740,1686.cm^{-1} , EI ms:m/z; ; *Anal*.Calcd for $C_{31}H_{26}F_3N_9O_5$ (693.59); C,53.68; H, 3.70; N, 18.17; found(%);C,53.62; H, 3.65; N, 18.10

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: yield64%,m.p.233^{0}C;^{1}HNMR(400MHz,DMSOd$_6$,δppm);1.57(d,3H,CH_3),5.34(q,H,CH_3CH),10.62(s,H,ArNHN=),8.03(s,2H,CONH),8.1(s,H,CONH),7.3(s,H,CONH), 6.78-8.37(m, 12H, for three phenyl groups), 3.7(s,3H,Ar-OCH_3)^{13}C-NMR(400MHz,DMSO-d$_6$, δ ppm); C_1-143.3,C_2-114.1,C_3&C_5-129.6,C_4-122.7,C_6-114.3,C_7-128.6,C_8-149.8,C_9-157.5,C_{10}-122.7,C_{11}-143.8,C_{12}&C_{16}.- 121.8,C_{13}&C_{15}-129.9,C_{14}-129.8,C_{17}-168.1,C_{18}-43.7,C_{19}-170.8,C_{20}-54.7,C_{21}-175.7,C_{22}-18.5,C_{23}-134.7,C_{24}-168.7,C_{25}-129.6,C_{26}-124.5,C_{27}-131.7,C_{28}-119.6,C_{29}-141.4,C_{30}-117.6, C_{31}-55.68; IR (KBr); ʊ=3218,3286,1612,1646,1744,1682cm^{-1} , EI ms:m/z; ; *Anal*.Calcd for $C_{31}H_{26}F_3N_9O_6$ (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 49d: yield 64%, m.p.233^{0}C;^{1}H-NMR(400MHz,DMSO-d$_6$, δ ppm1.57 (d, 3H, CH_3), 5.35(q, H, CH_3CH), 10.63 (s, H, Ar-NH-N=), 8.03(s,2H,CONH),8.1(s,H,CONH),7.3(s,H,CONH), 6.78-8.37(m, 12H, for three phenyl groups, 1.80(t,3H,CH_3) 3.18(q,2H,-OCH_2). ^{13}C-NMR(400MHz,DMSO-d$_6$, δ ppm) C_1-143.2,C_2-114.3,C_3&C_5-129.7,C_4-122.5,C_6-114.2,C_7-128.9,C_8-149.5,C_9-157.7,C_{10}-122.6,C_{11}-143.6,C_{12}&C_{16}.- 121.9,C_{13}&C_{15}-129.5,C_{14}-129.7,C_{17}-168.2,C_{18}-43.8,C_{19}-170.5,C_{20}-54.4,C_{21}-175.8,C_{22}-18.4,C_{23}-134.8,C_{24}-168.4,C_{25}-129.5,C_{26}-124.3,C_{27}-131.6,C_{28}-119.8,C_{29}-141.1,C_{30}-117.8, C_{31}-63.97, C_{32}-14.95; IR (KBrdisc cm^{-1}); 3220,3289,1615,1649,1746,1605,1685cm^{-1} , EI ms:m/z; ; *Anal*.Calcd for $C_{32}H_{28}F_3N_9O_6$ (691.62); C,55.57; H, 4.08; N, 18.22; found(%);C,55.51; H, 4.02; N, 18.17;

4-(5-oxo-4-(2-(4-chlorophenyl) 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 63%, m.p.223^{0}C;^{1}H-NMR(400MHz,DMSO-d$_6$, δ ppm); 1.58 (d, 3H, CH_3), 5.35(q, H, CH_3CH), 10.63(s, H, Ar-NH-N=), 8.03(s,2H,CONH),8.1(s,H,CONH),7.3(s,H,CONH), 6.78-8.37(m, 12H, for three phenyl groups.^{13}C-NMR(400MHz,DMSO-d$_6$, δ ppm);; C_1-143.2,C_2-114.2,C_3&C_5-129.6,C_4-122.8,C_6-114.3,C_7-128.8,C_8-149.7,C_9-157.9,C_{10}-122.9,C_{11}-143.9,C_{12}&C_{16}.- 121.9,C_{13}&C_{15}-129.7,C_{14}-129.8,C_{17}-167.9,C_{18}-43.8,C_{19}-170.6,C_{20}-54.6,C_{21}-175.4,C_{22}-18.6,C_{23}-134.4,C_{24}-168.6,C_{25}-129.4,C_{26}-124.6,C_{27}-131.4,C_{28}-119.3,C_{29}-141.4,C_{30}-117.9;IR (KBrdisc cm^{-1});3224,3292,1618,1650,1746,1686 cm^{-1} , EI ms:m/z; ; *Anal*.Calcd for $C_{30}H_{23}F_3N_9O_5Cl$ (682.01); C,52.83; H, 3.41; N, 18.48; found(%);C,52.80; H, 3.36; N, 18.42

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 49f: yield 64%, m.p.233^{0}C;^{1}H-NMR(400MHz,DMSO-d$_6$, δ ppm); 1.59 (d, 3H, CH_3), 5.36(q, H, CH_3CH), 10.63(s, H, Ar-NH-N=), 8.03(s,2H,CONH),8.1(s,H,CONH),7.3(s,H,CONH), 6.78-8.37(m, 12H, for three phenyl groups. ^{13}C-NMR(400MHz,DMSO-d$_6$, δ ppm); C_1-143.3,C_2-114.3,C_3&C_5-129.7,C_4-122.6,C_6-114.3,C_7-128.7,C_8-149.6,C_9-157.8,C_{10}-122.8,C_{11}-143.8,C_{12}&C_{16}.- 121.8,C_{13}&C_{15}-129.8,C_{14}-129.9,C_{17}-168.0,C_{18}-43.8,C_{19}-170.8,C_{20}-54.8,C_{21}-175.8,C_{22}-18.5,C_{23}-134.6,C_{24}-168.7,C_{25}-129.7,C_{26}-124.5,C_{27}-131.6,C_{28}-119.5,C_{29}-141.5,C_{30}-117.5; IR (KBr); ʊ=3220,3293,1618,1651,1748,1654cm^{-1} , EI ms:m/z; ; *Anal*.Calcd $C_{30}H_{23}F_3N_9O_5Br$(726.46); C,49.6; H, 3.19; N, 17.3; found(%);C,49.2; H, 3.14; N, 17.0

4-(5-oxo-4-(2-(4-nitrophenyl)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 50g: yield 62%, m.p.236^{0}C;^{1}H-NMR(400MHz,DMSO-d$_6$, δ ppm); 1.56 (d, 3H, CH_3), 5.36(q, H, CH_3CH), 10.62(s, H, Ar-NH-N=), 8.03(s,2H,CONH),8.1(s,H,CONH),7.3(s,H,CONH), 6.78-8.37(m, 12H, for three phenyl groups. ^{13}C-NMR(400MHz,DMSO-d$_6$, δ ppm); C_1-143.4,C_2-114.2,C_3&C_5-129.8,C_4-122.9,C_6-114.4,C_7-128.9,C_8-149.9,C_9-157.9,C_{10}-122.9,C_{11}-143.9,C_{12}&C_{16}.- 121.9,C_{13}&C_{15}-129.9,C_{14}-129.8,C_{17}-168.1,C_{18}-43.9,C_{19}-170.8,C_{20}-54.6,C_{21}-175.6,C_{22}-18.6,C_{23}-134.8,C_{24}-168.4,C_{25}-129.5,C_{26}-124.4,C_{27}-131.4,C_{28}-119.6,C_{29}-141.4,C_{30}-117.7; IR (KBr); ʊ=3220,3293,1618,1651,1748,1654cm^{-1} , EI ms:m/z; ; *Anal*.Calcd $C_{30}H_{23}F_3N_{10}O_7$ (692.5699); C,52.02; H, 3.31; N, 20.22; found(%);C,51.95; H, 3.28; N, 20.19

Synthesis of N-(2-oxo-2-((R)-1 -oxo-1-((Z)-2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene) hydrazinyl)propan-2-ylamino)ethyl0)-4-(5-oxo-4-(4-phenylhydrazono)-3-(trifluoromethyl)- 4,5-dihydro-1H-pyrazol-1-yl)benzamide50

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

overnight at room temperature, the obtained white solid was isolated and crystallized from ethanol to give compound 50a. The reaction procedure leading to 50a was then extended to the synthesis of 50b-50h.

N-(2-oxo-2-((R)-1 -oxo-1-((Z)-2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl0)-4-(5-oxo-4-(4-phenylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide50a obtained as yellow orange crystals; yield 68%, m.p.158^{0}C; ^{1}H-NMR(400MHz,DMSO-d_6, δ ppm): 1.82(d, 3H, CH_3), 2.58(m, 6H$(CH_2)_3$ of piperidine ring), 2.19(t, 4H –CH_2-N-CH_2 of piperidinering), 4.38(s, 2H, -N-CH_2-N-), 5.05(q, IH, CH_3CH),8.03(s, 2H, CONH), 7.11(s,H,CONH),10.65(s, 1H, Ar-NH-N=), 6.67-9.40(m, 13H, for three phenyl groups. ^{13}C-NMR(400MHz,DMSO-d_6, δ ppm) C_1-143.0,C_2-113.9,C_3&C_5-129.5,C_4-122.4,C_6-113.9,C_7-128.7,C_8-149.3,C_9-157.5,C_{10}-122.3,C_{11}-143.7,C_{12}&C_{16}.- 121.7,C_{13}&C_{15}-129.6,C_{14}-129.8,C_{17}-167.8,C_{18}-43.9,C_{19}-170.7,C_{20}-54.6,C_{21}-175.5,C_{22}-18.2,C_{23}-134.5,C_{24}-168.5,C_{25}-129.4,C_{26}-124.4,C_{27}-131.2,C_{28}-119.4,C_{29}-141.2,C_{30}-117.7, C_{31}-75.4, $C_{32\&}C_{36}$-54.5,C_{33}&C_{35}-25.6, C_{34}-24.5,; IR (KBr disc cm^{-1})3150,1618,1653,1751,1682; EI ms:m/z;Anal.Calcd.for $C_{36}H_{35}F_3N_{10}O_5$ (744.73); C,58.06; H, 4.7; N, 18.8; found(%);C,58.02; H, 4.2; N, 18.1

N-(2-oxo-2-((R)-1 -oxo-1-((Z)-2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl0)-4-(5-oxo-4-(4-phenylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide50b obtained as yellow orange crystals; yield 71%, m.p.162^{0}C; ^{1}H-NMR(400MHz,DMSO-d_6, δ ppm); 1712.10(d, 3H, CH_3), 2.59(m, 6H$(CH_2)_3$ of piperidine ring), 2.24(t, 4H –CH_2-N-CH_2 of piperidinering), 4.39(s, 2H, -N-CH_2-N-), 4.90-5.01(q, IH, CH_3CH), 8.03(s, 1H, CONH), 7.10(s,H,CONH) 10.65(s, 1H, Ar-NH-N=), 6.69-8.02(m, 12H, for three phenyl groups, 3.15(s,3H,Ar-CH_3); ^{13}C-NMR(400MHz,DMSO-d_6, δ ppm) ;C_1-143.1,C_2-113.8,C_3&C_5-129.7,C_4-122.6,C_6-114.1,C_7-128.9,C_8-149.5,C_9-157.6,C_{10}-122.5,C_{11}-143.9,C_{12}&C_{16}.- 121.6,C_{13}&C_{15}-129.8,C_{14}-129.9,C_{17}-167.9,C_{18}-43.6,C_{19}-170.6,C_{20}-54.8,C_{21}-175.6,C_{22}-18.3,C_{23}-134.6,C_{24}-168.6,C_{25}-129.5,C_{26}-124.6,C_{27}-131.5,C_{28}-119.5,C_{29}-141.3,C_{30}-117.4, C_{31}-75.6,$C_{32\&}C_{36}$-54.5,C_{33}&C_{35}-25.6, C_{34}-24.7,C_{37}-20.42; IR (KBr disc cm^{-1})3140,1616,1650,1748,1686; EI ms:m/z;Anal.Calcd.for for $C_{37}H_{37}F_3N_{10}O_5$ (758.75); C,58.57; H, 4.9; N, 18.46; found(%);C,58.52; H, 4.3; N, 18.40;

4-(4-(2-(4-methoxyphenyl)hydrazono)-3-(trifluromethyl)-4,5-dihydro-1 H-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 68%, m.p.164^{0}C; ^{1}H-NMR(400MHz,DMSO-d_6, δ ppm): 2.04(d, 3H, CH_3), 2.59(m, 6H$(CH_2)_3$ of piperidine ring), 2.27(t, 4H –CH_2-N-CH_2 of piperidinering), 4.41(s, 2H, -N-CH_2-N-), 5.06(q, IH, CH_3CH), 8.03(s, 1H, CONH), 7.10(s,H,CONH) 10.66(s, 1H, Ar-NH-N=), 6.70-8.04(m, 12H, for three phenyl groups, 3.7(s,3H,Ar-OCH_3); ^{13}C-NMR(400MHz,DMSO-d_6, δ ppm); C_1-143.3,C_2-114.1,C_3&C_5-129.6,C_4-122.7,C_6-114.3,C_7-128.6,C_8-149.8,C_9-157.5,C_{10}-122.7,C_{11}-143.8,C_{12}&C_{16}.- 121.8,C_{13}&C_{15}-129.9,C_{14}-129.8,C_{17}-168.1,C_{18}-43.7,C_{19}-170.8,C_{20}-54.7,C_{21}-175.7,C_{22}-18.5,C_{23}-134.7,C_{24}-168.7,C_{25}-129.6,C_{26}-124.5,C_{27}-131.7,C_{28}-119.6,C_{29}-141.4,C_{30}-117.6, C_{31}-75.7,$C_{32\&}C_{36}$-54.8,C_{33}&C_{35}-25.9 C_{34}-24.8, C_{37}-55.68,; IR (KBr disc cm^{-1})3142,1614,1653,1742,1682; EI ms:m/z;Anal.Calcd.for $C_{37}H_{37}F_3N_{10}O_6$ (774.75); C,57.36; H, 4.8; N, 18.07; found(%);C,57.31; H, 4.2; N, 18.02;

4-(4-(2-(4-ethoxyphenyl)hydrazono)-3-(trifluromethyl)-4,5-dihydro-1 H-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(50d) obtained as yellow crystals; yield 68%, m.p.149^{0}C; ^{1}H-NMR(400MHz,DMSO-d_6, δ ppm): 2.07(d, 3H, CH_3), 2.58(m, 6H$(CH_2)_3$ of piperidine ring), 2.30(t, 4H –CH_2-N-CH_2 of piperidinering), 4.43(s, 2H, -N-CH_2-N-), 5.07(q, IH, CH_3CH), 8.03(s, 2H, CONH), 7.10(s,H,CONH) 10.65(s, 1H, Ar-NH-N=), 6.71-8.02(m, 12H, for three phenyl groups, 1.80(t,3H,CH_3) 3.18(q,2H,-OCH_2). ^{13}C-NMR(400MHz,DMSO-d_6, δ ppm); C_1-143.2,C_2-114.3,C_3&C_5-129.7,C_4-122.5,C_6-114.2,C_7-128.9,C_8-149.5,C_9-157.7,C_{10}-122.6,C_{11}-143.6,C_{12}&C_{16}.- 121.9,C_{13}&C_{15}-129.5,C_{14}-129.7,C_{17}-168.2,C_{18}-43.8,C_{19}-170.5,C_{20}-54.4,C_{21}-175.8,C_{22}-18.4,C_{23}-134.8,C_{24}-168.4,C_{25}-129.5,C_{26}-124.3,C_{27}-131.6,C_{28}-119.8,C_{29}-141.1,C_{30}-117.8, C_{31}-75.6,$C_{32\&}C_{36}$-54.7,C_{33}&C_{35}-25.7 C_{34}-24.4, C_{37}-63.97 C_{38}-14.95.; IR (KBr disc cm^{-1})3145,1614,1652,1746,1685; EI ms:m/z;Anal.Calcd.for $C_{37}H_{37}F_3N_{10}O_5$ (788.78); C,57.82; H, 4.9; N, 17.7; found(%);C,57.78; H, 4.2; N, 17.1;

4-(4-(2-(4-chlorophenyl)hydrazono)-3-(trifluromethyl)-4,5-dihydro-1 H-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
(50e):obtained as yellow crystals;yield 64%, m.p.172^{0}C; ^{1}H-NMR(400MHz,DMSO-d_6, δ ppm): 2.07(d, 3H, CH_3), 2.56(m, 6H$(CH_2)_3$ of piperidine ring), 2.21(t, 4H –CH_2-N-CH_2 of piperidinering), 4.46(s, 2H, -N-CH_2-N-), 5.08(q, IH, CH_3CH), 8.03(s, 2H, CONH) 7.10(s,H,CONH), 10.64(s, 1H, Ar-NH-N=), 6.69-8.04(m, 12H, for three phenyl groups. ^{13}C-NMR(400MHz,DMSO-d_6, δ ppm); C_1-143.2,C_2-114.2,C_3&C_5-129.6,C_4-122.8,C_6-114.3,C_7-128.8,C_8-

149.7,C_9-157.9,C_{10}-122.9,C_{11}-143.9,C_{12}&C_{16}.- 121.9,C_{13}&C_{15}-129.7,C_{14}-129.8,C_{17}-167.9,C_{18}-43.8,C_{19}-170.6,C_{20}-54.6,C_{21}-175.4,C_{22}-18.6,C_{23}-134.4,C_{24}-168.6,C_{25}-129.4,C_{26}-124.6,C_{27}-131.4,C_{28}-119.3,C_{29}-141.4,C_{30}-117.9 C_{31}-75.9,$C_{32\&}C_{36}$-54.6,C_{33}&C_{35}-25.7, C_{34}-24.7;; IR (KBr disc cm^{-1})3140,1614,1659,1736,1686; EI ms:m/z;Anal.Calcd.for $C_{36}H_{34}F_3N_{10}O_5$ Cl (699.18); C,61.84; H, 4.9; N, 20.03; found(%);C,61.80; H, 4.2; N, 20.01;

4-(4-(2-(4-bromophenyl)hydrazono)-3-(triflurомethyl)-4,5-dihydro-1 H-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 (50f):obtained as yellow crystals;yield 71%, m.p.168^{0}C; ^{1}H-NMR(400MHz,DMSO-d_6, δ ppm): 2.08(d, 3H, CH_3), 2.62(m, 6H$(CH_2)_3$ of piperidine ring), 2.25(t, 4H –CH_2-N-CH_2 of piperidinering), 4.41(s, 2H, -N-CH_2-N-), 5.09(q, IH, CH_3CH), 8.03(s, 2H, CONH), 7.10(s,H,CONH) 10.65(s, 1H, Ar-NH-N=), 6.66-8.12(m, 12H, for three phenyl groups); . ^{13}C-NMR(400MHz,DMSO-d_6, δ ppm); C_1-143.3,C_2-114.3,C_3&C_5-129.7,C_4-122.6,C_6-114.3,C_7-128.7,C_8-149.6,C_9-157.8,C_{10}-122.8,C_{11}-143.8,C_{12}&C_{16}.- 121.8,C_{13}&C_{15}-129.8,C_{14}-129.9,C_{17}-168.0,C_{18}-43.8,C_{19}-170.8,C_{20}-54.8,C_{21}-175.8,C_{22}-18.5,C_{23}-134.6,C_{24}-168.7,C_{25}-129.7,C_{26}-124.5,C_{27}-131.6,C_{28}-119.5,C_{29}-141.5,C_{30}-117.5 C_{31}-75.8,$C_{32\&}C_{36}$-54.7,C_{33}&C_{35}-25.6, C_{34}-24.8;IR (KBr disc cm^{-1})3142,1616,1657,1733,1684; EI ms:m/z;Anal.Calcd.for $C_{36}H_{34}F_3N_{10}O_5$ Br(743.63); C,58.14; H, 4.6; N, 18.83; found(%);C,58.10; H, 4.1; N, 18.79;

4-(4-(2-(4-nitrophenyl)hydrazono)-3-(triflurомethyl)-4,5-dihydro-1 H-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 (50g):obtained as yellow crystals;yield 70%, m.p.165^{0}C; ^{1}H-NMR(400MHz,DMSO-d_6, δ ppm): 2.08(d, 3H, CH_3), 2.62(m, 6H$(CH_2)_3$ of piperidine ring), 2.25(t, 4H –CH_2-N-CH_2 of piperidinering), 4.41(s, 2H, -N-CH_2-N-), 5.09(q, IH, CH_3CH), 8.03(s, 2H, CONH), 7.10(s,H,CONH) 10.65(s, 1H, Ar-NH-N=), 6.66-8.12(m, 12H, for three phenyl groups); . ^{13}C-NMR(400MHz,DMSO-d_6, δ ppm); C_1-143.4,C_2-114.2,C_3&C_5-129.8,C_4-122.9,C_6-114.4,C_7-128.9,C_8-149.9,C_9-157.9,C_{10}-122.9,C_{11}-143.9,C_{12}&C_{16}.- 121.9,C_{13}&C_{15}-129.9,C_{14}-129.8,C_{17}-168.1,C_{18}-43.9,C_{19}-170.8,C_{20}-54.6,C_{21}-175.6,C_{22}-18.6,C_{23}-134.8,C_{24}-168.4,C_{25}-129.5,C_{26}-124.4,C_{27}-131.4,C_{28}-119.6,C_{29}-141.4,C_{30}-117.7 C_{31}-75.9,$C_{32\&}C_{36}$-54.9,C_{33}&C_{35}-25.8, C_{34}-24.9;IR (KBr disc cm^{-1})3142,1616,1657,1733,1684; EI ms:m/z;Anal.Calcd.for $C_{36}H_{34}F_3N_{11}O_7$ (788.733); C,54.8; H, 4.4; N, 19.5; found(%);C,54.2; H, 4.1; N, 19.1;

N-(2-((R)-1-((Z)-2-(1-(morpholinomethyl)-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)benzamide50h: obtained as orange crystals; yield64%,m.p.159^{0}C; 3.52(t,4H,-CH_2 –O-CH_2 of morpholine ring),2.45(t,4H, ,-CH_2 –N-CH_2 of morpholine ring), 4.41(s, 2H, -N-CH_2-N-), 5.09(q, IH, CH_3CH), 8.03(s, 2H, CONH), 7.10(s,H,CONH) 10.65(s, 1H, Ar-NH-N=), 6.66-8.12(m, 12H, for three phenyl groups; . ^{13}C-NMR(400MHz,DMSO-d_6, δ ppm); C_1-143.0,C_2-113.9,C_3&C_5-129.5,C_4-122.4,C_6-113.9,C_7-128.7,C_8-149.3,C_9-157.5,C_{10}-122.3,C_{11}-143.7,C_{12}&C_{16}.- 121.7,C_{13}&C_{15}-129.6,C_{14}-129.8,C_{17}-167.8,C_{18}-43.9,C_{19}-170.7,C_{20}-54.6,C_{21}-175.5,C_{22}-18.2,C_{23}-134.5,C_{24}-168.5,C_{25}-129.4,C_{26}-124.4,C_{27}-131.2,C_{28}-119.4,C_{29}-141.2,C_{30}-117.7 C_{31}-75.4,$C_{32\&}C_{36}$-54.5,C_{33}&C_{35}-25.6, C_{34}-24.5; IR (KBr disc cm^{-1})3143,1610,1650,1738,1685; EI ms:m/z;Anal.Calcd.for $C_{35}H_{33}F_3N_{10}O_6$ (746.70); C,56.29; H, 4.45; N, 18.7; found(%);C,56.24; H, 4.40; N, 18.2;

Table 1. Analytical data of the compounds 50a-f

Compound	Moleular formula	Yield (%)	M.P. * (^{0}C)	% Analysis					
				C		H		N	
				Cald	Found	Cald	Found	Cald	Found
50a	$C_{36}H_{35}F_3N_{10}O_5$	68	158-4	58.06	58.02	4.7	4.2	18.80	18.10
50b	$C_{37}H_{37}F_3N_{10}O_5$	71	162-6	58.57	58.52	4.9	4.3	18.46	18.40
50c	$C_{37}H_{37}F_3N_{10}O_6$	68	164-9	57.36	57.31	4.8	4.2	18.07	18.02
50d	$C_{37}H_{37}F_3N_{10}O_5$	68	149-9	57.82	57.78	4.9	4.2	17.70	17.10
50e	$C_{36}H_{34}F_3N_{10}O_5Cl$	64	172-4	61.84	61.80	4.9	4.2	20.03	20.01
50f	$C_{36}H_{34}F_3N_{10}O_5$ Br	71	168-3	58.14	58.10	4.6	4.1	18.83	18.79
50g	$C_{36}H_{34}F_3N_{11}O_7$	70	171-6	54.80	54.70	4.4	4.1	19.50	19.10
50h	$C_{35}H_{33}F_3N_{10}O_6$	64	159-1	56.29	56.24	4.45	4.40	18.70	18.20
50i	$C_{36}H_{36}F_3N_{11}O_5$	64	159-2	56.20	56.0	4.7	4.2	20.28	20.23

N-(2-((R)-1-((Z)-2-(1-(4-methylpiperazin-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; yield64%,m.p.159^{0}C; 2.26(s,3H,N-CH_3) 2.45(t,4H, ,-CH_2–N-CH_2 of morpholine ring), 4.41(s, 2H, -N-CH_2-N-), 5.09(q, IH, CH_3CH), 8.03(s, 2H, CONH), 7.10(s,H,CONH) 10.65(s, 1H, Ar-NH-N=), 6.66-8.12(m, 12H, for three phenyl groups; s ^{13}C-NMR(400MHz,DMSO-d_6, δ ppm); C_1-143.0,C_2-113.9,C_3&C_5-

129.5,C_4-122.4,C_6-113.9,C_7-128.7,C_8-149.3,C_9-157.5,C_{10}-122.3,C_{11}-143.7,C_{12}&C_{16}.- 121.7,C_{13}&C_{15}-129.6,C_{14}-129.8,C_{17}-167.8,C_{18}-43.9,C_{19}-170.7,C_{20}-54.6,C_{21}-175.5,C_{22}-18.2,C_{23}-134.5,C_{24}-168.5,C_{25}-129.4,C_{26}-124.4,C_{27}-131.2,C_{28}-119.4,C_{29}-141.2,C_{30}-117.7 C_{31}-75.4,C_{32}&C_{36}-54.5,C_{33}&C_{35}-25.6, C_{34}-24.5; IR (KBr disc cm^{-1})3141,1618,1658,1740,1686,; EI ms:m/z;Anal.Calcd.for $C_{36}H_{36}F_3N_{11}O_5$ (759.74); C,56.2; H, 4.7; N, 20.28; found(%);C,56.0; H, 4.2; N, 20.23;

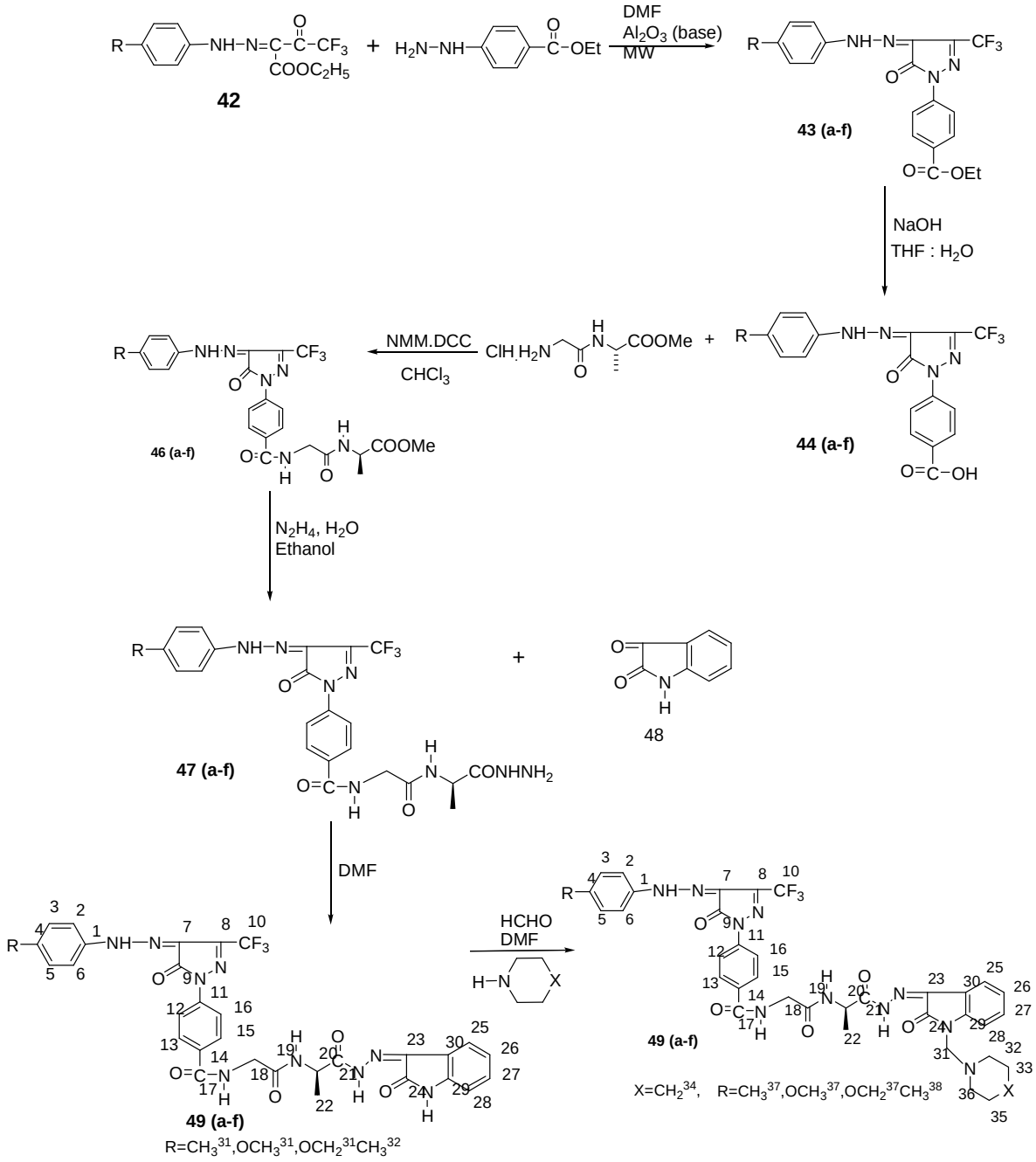
Table 2.Antibacterial Activity by the disc diffusion method

S.No	Compound	Zone of Inhibition			
		Staphylococcus aureus NCCS2079	*Bacillus Cereus* NCCS2106	*Escherichia Coli* NCCS2065	*Pseudomonas aeruginosa* NCCS2200
1	*N-(2-oxo-2-((R)-1 -oxo-1-((Z)-2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl0)-4-(5-oxo-4-(2-phenylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide50a*	07	06	06	08
2	*N-(2-oxo-2-((R)-1 -oxo-1-((Z)-2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-ylamino)ethyl0)-4-(5-oxo-4-(2-phenylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide50b*	05	06	05	07
3	4-(4-(2-(4-methoxyphenyl)hydrazono)-3-(trifluromethyl)-4,5-dihydro-1 H-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)	06	07	06	07
4	4-(4-(2-(4-ethoxyphenyl)hydrazono)-3-(trifluromethyl)-4,5-dihydro-1 H-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(50d)	06	05	06	07
5	4-(4-(2-(4-chlorophenyl)hydrazono)-3-(trifluromethyl)-4,5-dihydro-1 H-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 (50e)	09	09	07	09
6	4-(4-(2-(4-bromophenyl)hydrazono)-3-(trifluromethyl)-4,5-dihydro-1 H-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 (50f)	08	07	06	08
7	4-(4-(2-(4-nitrophenyl)hydrazono)-3-(trifluromethyl)-4,5-dihydro-1 H-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 (50g)	10	08	06	08
8	*N-(2-((R)-1-((Z)-2-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)hydrazinyl)-1-oxopropan-2-ylamino)-2-oxoethyl)-4-(5-oxo-4-(2-phenylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide50h*	08	07	06	07
9	*N-(2-((R)-1-((Z)-2-(1-(4-methylpiperazin-1-yl)methyl)-2-oxoindolin-3-ylidene)hydrazinyl)-1-oxopropan-2-ylamino)-2-oxoethyl)-4-(5-oxo-4-(2-phenylhydrazono)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)benzamide50i*	08	06	07	08
10	Amoxycillin	21	27	24	22

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 mannich reaction with different secondary amines namely piperidine, morpholine and N-methyl piparazine and formaldehyde in absolute ethanol to give compounds 50a-h respectively.The IR spectrum of 50 revealed the appearance of bands characteristics of 3150(NH), 1618(C=N), 1633(Pyrazoline C=O), 1741(Indole C=O), 1710(CONH).The appearence of a signal at **δ**4.38 due to (N-CH_2-N),3.52(t,4H, CH_2-O-CH_2),2.15-2.19 (t, 4H, CH_2-N-CH_2), 4.31(s, 2H,-N-CH_2-N-); The ^{13}C-NMR spectrum of ($CDCl_3$) shown δ: C_1-143.0,C_2-113.9,C_3&C_5-129.5,C_4-122.4,C_6-113.9,C_7-128.7,C_8-149.3,C_9-157.5,C_{10}-122.3,C_{11}-143.7,C_{12}&C_{16}.-121.7,C_{13}&C_{15}-129.6,C_{14}-129.8,C_{17}-167.8,C_{18}-43.9,C_{19}-170.7,C_{20}-54.6,C_{21}-175.5,C_{22}-18.2,C_{23}-134.5,C_{24}-168.5,C_{25}-129.4,C_{26}-124.4,C_{27}-131.2,C_{28}-119.4,C_{29}-141.2,C_{30}-117.7,C_{31}&C_{36}-54.5,C_{33}&C_{35}-25.6,C_{34}-24.5,C_{37}- 20.42,55.68,63.97,C_{38}-14.95 conformed the formation of mannich bases.

Scheme-1



SCHEME-1

R	H	$-CH_3$	$-OCH_3$	$-OC_2H_5$	Cl	Br	NO_2	H	H
X	$-CH_2$	$-CH_2$	$-CH_2$	$-CH_2$	$-CH_2$	$-CH_2$	$-CH_2$	-O-	-N-CH_3

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

[1] polevoi LG,*chem Abstr* 65,9147d,**1996**
[2] Batulin YM,*Framekol toksikol* 31,533 (1968) chem. Abstr 70,2236a, **1969**
[3] Parmar SS, pandey BR, Dwivedi C, Harbinson RD, *J. Pharm sci* 63, 1152, **1974**
[4] Soni N, pande K, Kalsi R, Gupta TK, parmar SS, barthwal JP, *Res commun chem pathol pharmacol*, 56,129 ,**1987**
[5] Turan-Zitouni G, chevallet P, kilic FS, Erol k: ,*Eur J Med Chem35*,635, **2000**
[6] Rajendra prasad Y, lakshmana Rao A, prasoona K, Rvi kumar P, *Bio.org. Med chem Lett* 15,5030, **2005**
[7] The merck index 10th ed., M.windholz, merck, rahway, **1983**
[8] Mrongovius, R.; Neugebauer, M.; Rucker, G.*eur.j. med.chem* 19, 161-166 ,**1984**
[9] Tomkins , P.T.; Cooper,K.L.; Titchmarsh, S.A.;Appleby, P.;Webber, D.G.J.*Immuno pharmacol* 17,357—366,**1995**
[10] Aonuma,s.;kohama,y.;komiyama, Y.;Fujimoto, S.*chem. pharm. Bull* 28, 1237-1244,**1980**
[11] Taylor , E.C.; patel, H.;kumar,H. *Tetrahyron* 48, 8089, **1992**
[12] Roelvan , S.G.; Arnold, C.; wellnga K.J. *Agric. Food chem*. 199, 84,406.
[13] Keats, G.H.*Brit.pat*. 1,209,631, **1970**
[14] Kedar , R,M.; Vidhale, N.N.; Chinkolkar,M.M. *Orient.j.chem*. 13,143,**1997**
[15] Singh,A.; Rathod,S.; Berad, B.N.; patil, S.D.; Dosh, A.G. *orient.J.CHEM*. 16,315, **2000**
[16] Katri, H.Z.; Vunni, S.A.J.Ind. chem. Soc. 58,168, **1981**
[17] Das , N.B.; Mitra, A.S.*Ind.J.chem*. 16B, 638,**1978**
[18] Azarifar,D.; Shaebanzadeh, M.*molecules* 7,885, **2002**
[19] Holla, B. Shivarama; akberali, P.M.; shivananda, M.K. *Farmaco* 55,256, **2000**
[20] Palaska , E.; Aytemir, M.; tayfun, I; Erol, K. Dilek, E. *Eur.j. Med. Chem. Chim. Ther.* 36,539,**2001**
[21] Garge, H.G.;chandraprakash, *J.pharm. sc*.14,649, **1971**
[22] Regaila, H.A; El-Bayonk, A.K.;hammad, M. *Egypt.j.chem*.20,197, **1979**
[23] Krishna, R.; pande, B.R.; Bharthwal, S.P.; Parmer, s,s.*eur.J.Med.chem*. 15,567, **1980**
[24] H.M.walborsky,M.E.BAUM, *J.Am.chem.soc*. 80(1) 187-192, **1958**
[25] Marvel CS and heris GS. Orgonic synthesis collective volume-1.2nd Ed.john wiley &sons, new york 423, **1941**
[26] *Turk J chem* 32(**2008**) ,205-215