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SYNTHESIS OF NOVELTHIAZOLES CONTAINING PYRAZOLONE SYSTEMS AND ANTIMICROBIAL ACIVITY

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ABSTRACT

Several thiazoles and pyrazolone carrying heterocyclic nucleus were synthesized and tested as antimicrobial agents. All compounds and some of the nitro substituted derivatives have effective antibacterial properties against Gram positive bacteria (*Staphylococcus aureus* NCCS 2079 and *Bacillus cereus* NCCS 2106), Gram negative bacteria (*Escherichia coli* NCCS 265 and *Pseudomonas aeruginosa* NCCS2200). The antifungal activity of synthesized compounds were studied by disc diffusion method against the organisms of *Aspergillus niger* NCCS 1196 and *Candida albicans* NCCS 3471. The chemical structures of these newly synthesized compounds were characterized by ^{1}H-NMR, Mass, and IR spectral data.

KEYWORDS : Thiazole derivatives, Pyrazolones derivatives, microwave irradiation, antimicrobial activity

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INTRODUCTION

Thiazole and isothiazole derivatives have received and continue to considerable attention[1-2].The chemistry of thiazoles dates back to 1879 when benzo thiazole came into light. The interest in the preparation of compounds containing the thiazole moiety has been increasing steadily in view of their utility in the field of medicine, dyes, fungicides, insecticides, wetting agents, photo sensitizers and rubber vulcanization[3-5]. Recently, the thiazole ring has been identified as a central feature of a number of biologically active natural products[6]

In view of these, we report here the synthesis of aryl hydrazone pyrazoline-5-one containing different substituted thiazole moieties.

MATERIALS AND METHODS

All the chemicals were used as received without further purification. Melting points were determined in open capillary tubes in Buchi 530 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.

^{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.

Biological Screening Antimicrobial activity test:

The test was performed according to the disk diffusion method[7] adopted with some modifications for the prepared compounds using amoxicillin, and cefaclor as references. The prepared compounds were tested against one strain of Gram positive bacteria (*Staphylococcus aureus* NCCS 2079 and *Bacillus cereus* NCCS 2106), Gram negative bacteria (*Escherichia coli* NCCS 265 and *Pseudomonas aeruginosa* NCCS2200). Nutrient agar was used as a culture media and DMSO was used as a solvent control for antibacterial activity.

The antifungal activity of synthesized compounds were studied by disc diffusion method against the organisms of *Aspergillus Niger* NCCS 1196 and *Candida albicans* NCCS 3471. Nutrient agar was used as a culture media and DMSO was used as a solvent control for antibacterial activity. The minimum inhibitory concentrations (MIC) for all test compounds were noted.

The synthesized compounds were used at the concentration of 250 µg/mL and 500 µg/mL using DMSO as a solvent. The amoxicillin 10 µg/disc, cefaclor 30 µg/disc and ketaconazole 50 µg/mL were used as standards.

Similar procedure was adopted for studying the antibacterial activity against the other organisms. The results of the preliminary screening test are listed in Table 1 & 2.

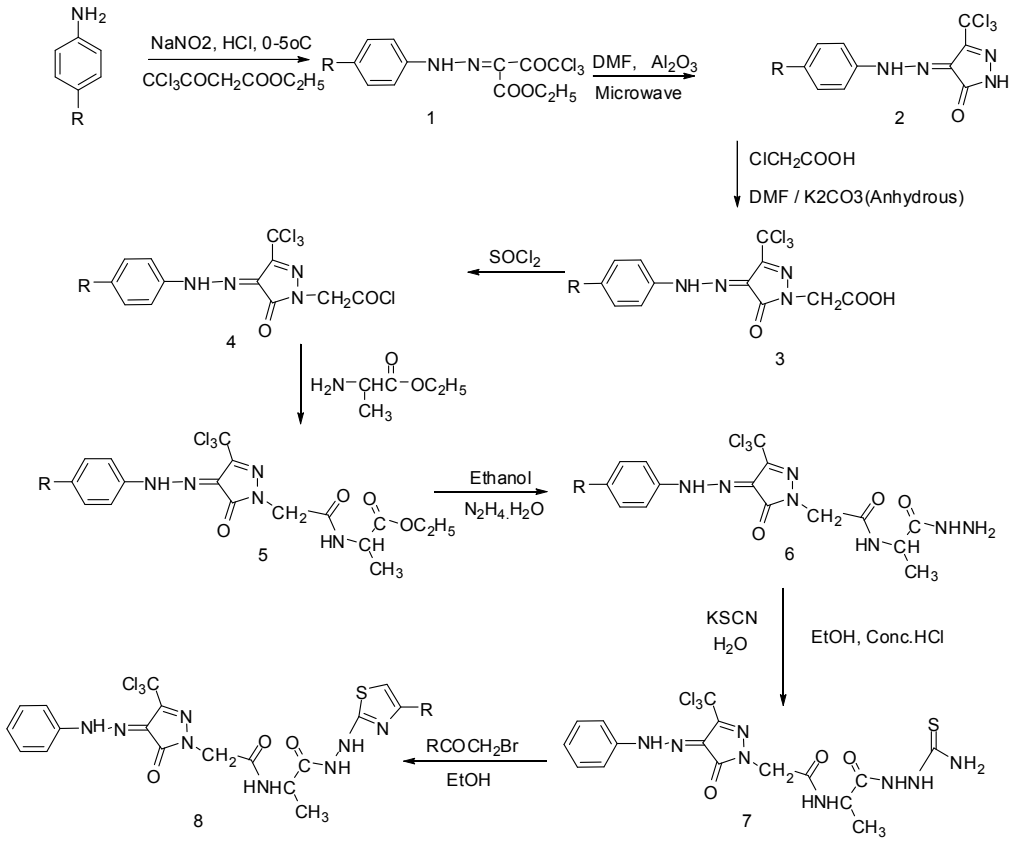
Table 1
***Antibacterial activity by disc diffusion method for thiazoles*.**

Comp	R	Zone of inhibition (mm)			
		***Staphylococcus aureus* NCCS 2079**	***Bacillus cereus* NCCS 2106**	***Escherichia coli* NCCS 2065**	***Pseudo-manas aeruginos* NCCS 2200**
8a	phenyl	6	7	7	6
8b	*p*-tolyl	5	6	6	7
8c	*p*-anisyl	6	6	7	6
8d	*p*-Hydroxy phenyl	7	6	6	5
8e	*p*-nitro phenyl	12	14	15	12
8f	*p*-chloro phenyl	12	15	15	12
8g	*p*-bromo phenyl	12	13	15	13
	Amoxcycillin	21	27	24	22
	Cefaclor	19	22	19	20

Table 2
Antifungal activity by disc diffusion method for thiazoles

Comp	R	Zone of inhibition (mm)	
		Aspergillus niger NCCS 1196	***Candida albicans* NCCS 2106**
8a	phenyl	10	10
8b	*p*-tolyl	11	11
8c	*p*-anisyl	12	15
8d	*p*-hydroxy phenyl	12	12
8e	*p*-nitro phenyl	14	14
8f	*p*-chloro phenyl	16	16
8g	*p*-bromo phenyl	14	15
	Ketoconazole	22	25

Scheme –I



R = Phenyl(8a), *p*-Tolyl(8b), p-anisyl(8c), p-Hydroxyphenyl(8d)

p-Nitrophenyl(8e), p-Chlorophenyl(8f), p-Bromophenyl(8g)

General procedure:

Ethyl 4,4,4-trichloro-3-oxo-2-(2-phenyl hydrazono) butanoate (1) was prepared by the procedure described by H.M.W.Alborsky, M.E.Baum[29]

4-(2-subtituted aryl hydrazono)-5-trichloromethyl-2, 4-dihydro-pyrazol-3-one (2)

Mixtures of (1) and hydrazine hydrate and DMF (10 drops) were 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 treated with cold water. The precipitate 3-methyl 4-(4'-substituted aryl hydrazono) pyrazoline-5-one (2) was filtered and recrystallized from ethanol. m.p. 180^{0}C, yield 87%.

2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetic acid (3)

A mixture of (2), 2-chloroacetic acid, anhydrous K_2CO_3 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 2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetic acid (3). Yield 71%, m.p.: 181^{0}C; ^{1}H-NMR (400 MHz,DMSO-d_6 ppm): 3.65(s,2H,N CH_2CO), 10.56 (s, H, Ar-NH), 12.68 (s,1H,COOH) 6.81 -7.88 (m, 5H, for C_6H_5 phenyl group);; ^{13}C-NMR (400 MHz,DMSO-d_6 ppm): 51.7 (CH_2), 116-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 168.4 (Acid C=O); IR (KBr): $\bar{\nu}$ = 1600, 3120,2967,1682,1617 cm^{-1} and these are due to C = N, NH, acid

carbonyl and cyclic carbonyl in five membered hetero cyclic ring respectively *Anal*. Calcd. for $C_{12}H_9Cl_3N_4O_3$ (363.58); C, 39.64; H, 2.50; N, 15.41; found (%); C: 38.23, H: 3.13, N: 22.31.

2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetyl chloride (4)

To a solution of 2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetic acid (3). (900 mg) in toluene (30 mL) was added thionyl chloride (0.90 mL) at room temperatures. The resulting solution was heated to reflux for 2 h. Then, it was cooled to room temperature and the excess thionyl chloride and toluene was removed under vacuum. The residue was dissolved one time in toluene and removed again under vacuum to afford 2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetyl chloride **(4)**. Yield 58%, m.p.: 173^0C; ^{1}H-NMR (400 MHz,DMSO-d_6 ppm): 3.81(s,2H,N CH_2CO), 10.70 (s, H, Ar-NH), 6.78 -7.88 (m, 5H, for C_6H_5 phenyl group) ; ^{13}C-NMR (400 MHz,DMSO-d_6 ppm): 64.5 (CH_2), 116-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 173.5 (Acid Chloride C=O) IR (KBr): $\bar{\nu}$ = 3180,1696,1617,1651 cm^{-1} and these are due to NH, cyclic carbonyl in five membered hetero cyclic ring exo > C = N, acid chloride respectively *Anal*. Calcd. for $C_{12}H_8Cl_4N_4O_2$ (382.03); C, 37.73; H, 2.11; N, 14.67; found (%); C: 38.23, H: 3.13, N: 22.31.

Ethyl 2-(2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamido) propanoate (5)

A solution of acid chloride **(4a-f)** (2.47 mmol) in dichloromethane (30 mL) were added L-Alanine ethyl ester hydrochloride (735 mg, 2.5 mmol) and diisopropylethylamine (1.3 mL, 7.5 mmol) at 0°C. Then, the solution warmed to room temperature and it was stirred overnight. Then, it was diluted with water (50 mL) and dichloromethane (50 mL). The two layers were separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layer was washed with brine solution and dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration of the solvent gave the crude residue which was purified by using column chromatography to give ethyl 2-(2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl) acetamido) propionate (5a-f) (1.5 g) as a colorless oil. Yield 65%, m.p.: 184^0C; ^{1}H-NMR (400 MHz,DMSO-d_6 ppm) : 1.25-1.28 (d,3H, CH_2CH_3), 2.12-2.15(t,3H,$CHCH_3$), 3.51(s,2H, NCH_2),4.22-4.27(q,2H OCH_2) 5.18-5.25(q,1H,CH CH_3), 10.72 (s, H, CONH), 12.58 (s, H, Ar-NH), 6.82 -7.94 (m, 5H, for C_6H_5 of phenyl group); ^{13}C-NMR (400 MHz,DMSO-d_6 ppm): 64.5 (CH_2), 116-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHNH_2), 168 (C=ONH), 49(CHC=O), 17.3(CH_3CH), 65(CH_2C=O) 14(CH_2CH_3); IR (KBr): $\bar{\nu}$ = 3164, 3120, 1592, 1617, 1689, 1732 cm^{-1} and these are due to >NH, CO-NH exo > C = N, cyclic carbonyl in five membered heterocyclic ring, carbonyl group, ester carbonyl group respectively. *Anal*. Calcd. for $C_{17}H_{18}Cl_3N_5O_4$ (462.71); C, 44.13; H, 3.92; N, 15.14; found (%); C: 44.20, H: 4.21, N: 22.31.

(N-(1-hydrazinyl-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl) -4,5-dihydro-1H-pyrazol-1-yl)acetamide (6)

A solution of **(5)** (0.01M) and hydrazine hydrate (0.015M) in ethanol 20 mL 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 afford **(6)** Yield 64%, m.p. 132^0C; ^{1}H-NMR (400 MHz,DMSO-d_6 ppm): 2.08-2.10 (d,3H, $CHCH_3$), 3.78(s,2H, NCH_2CO), 4.31(s, 2H, NH_2),4.77-4.82(q, H CH_3 CH), 9.72 (s, H, CONH), 11.16 (s, H, NH), 10.75(s, H, Ar-NH), 6.82 -7.98 (m, 5H, for C_6H_5 of phenyl group); ^{13}C-NMR (400 MHz,DMSO-d_6 ppm): 64.5 (CH_2), 116-144 (Ar-C), 132 (NH-N=C), 153 (pyrazole C=O), 91 (CCl_3), 145 (CCl_3 - C), 171 (C=ONHNH2) 168 (C=ONH) 49(CHC=O); IR (KBr): $\bar{\nu}$ = 3420, 3380, 3198, 3132, 3108, 1720, 1680, 1615 and these are due to – NH_2, CO–NH, >NH, Ar-NH exo > C = N, cyclic

carbonyl in five membered hetero cyclic ring respectively, *Anal*. Calcd. for $C_{15}H_{16}Cl_3N_7O_3$ (448.69); C: 40.15, H: 3.59, N: 21.85 found (%); C: 40.17, H: 3.62, N: 21.88.

N-(1-(2-carbamothioylhydrazinyl)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide (7)

A mixture of 2(N-(1-hydrazinyl-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl) -4,5-dihydro-1H-pyrazol-1-yl)acetamide **(6)** (0.01 M), potassium thiocyanate (0.02 M), concentrated hydrochloric acid (1mL), ethanol (10mL) and water (20 mL) were refluxed for 3 h. The solid obtained after cooling was collected by filtration, washed with water, dried and recrystallized from ethanol-DMF mixture to yield N-(1-(2-carbamothioylhydrazinyl)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide **7a.** Yield 60%, m.p. 220^{0}C; ^{1}H-NMR (400 MHz,DMSO-d_6 ppm): 1.78-1.80 (d,3H, CH_3), 2.23 (s,2H, NCH_2CO), 4.65 (s,2H, N-CH_2),4.22-4.27 (q,1H CH_3CH) 9.12 (s, 2H, NH_2), 9.81 (s, H, CONH), 10.80 (s, H, N -NH), 12.65 (s, H, Ar-NH);. IR: 3420, 3380, 3210, 3108, 1798,1688,1610,2947 and 3180 cm^{-1} due Ar-NH, NH_2,CO-NH,NH-N,C = N, C = O, C = S, and NH str functional groups respectively; ms: m/z: 506.02; *Anal*. Calcd. for $C_{16}H_{17}Cl_3N_8O_3S$(507.78) C, 35.75 (37.85) ; H, 2.77 (3.37); N, 22.45 (22.07).

N-(1-oxo-1-(2-(4-phenylthiazol-2-yl)hydrazinyl)propan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide (8a-g)

A mixture of N-(1-(2-carbamothioylhydrazinyl)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide **7** (0.01M) in DMF (10mL) and various bromo acetyl derivatives (0.01 M) in ethanol (10mL) was stirred at room temperature for 1-2 h. The solid separated was filtered, dried and recrystallized from ethanol-DMF mixture.

N-(1-(2-carbamothioylhydrazinyl)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenyl hydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide8a: yield 74%, mp 176-178^{0}C; ^{1}H NMR (DMSO-d_6): 1.82-1.84 (d,3H, CH_3), 3.60(s,2H, NCH_2CO), 4.35 (s, H, NH N), 4.79-4.84(q,1H CH_3CH) 10.02 (s, H, CONH), 11.01 (s, H, N -NH), 13.25 (s, H, Ar-NH), 6.37 -8.16 (m, 10H, for C_6H_5 and C_6H_4 of two phenyl groups and thiazole H); IR: 3398,3260,3140,3002,1748,1601,1688,1610 cm^{-1} ; ms: m/z: 606.05; *Anal*. Calcd. for $C_{24}H_{21}Cl_3N_8O_3S$ (607.90): C: 47.42, H: 3.48, N: 18.43. Found(%): C: 47.46, H: 3.52, N: 18.48.

N-(1-oxo-1-(2-(4-p-tolylthiazol-2-yl)hydrazinyl)propan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide 8b**:** yield 67%, mp 192-193^{0}C; ^{1}H NMR (DMSO-d_6): 3.10 (s, 3H, Ar- CH_3), 1.81-1.83 (d,3H, CH_3), 3.62(s,2H, NCH_2CO), 4.34 (s, H, NH N), 4.80-4.85(q,1H CH_3CH) 10.03 (s, H, CONH), 11.02 (s, H, N -NH), 13.26 (s, H, Ar-NH), 6.38 -8.17 (m, 10H, for C_6H_5 and C_6H_4 of two phenyl groups and thiazole H); IR: 3397,3262,3143,3001,1749,1605,1686,1613 cm^{-1}; EI ms: m/z: 620.07; *Anal*. Calcd. for $C_{25}H_{23}Cl_3N_8O_3S$ (621.93): C: 48.28, H: 3.73, N: 18.02 Found (%): C: 48.32, H: 3.75, N: 18.22.

N-(1-(2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazinyl)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide 8c : yield 72%, mp 187-189^{0}C; ^{1}H NMR (DMSO-d_6): 3.83 (s, 3H, O-CH_3), 1.80-1.82 (d,3H, CH_3), 3.63(s,2H, NCH_2CO), 4.33 (s, H, NH N), 4.78-4.83(q,1H CH_3CH) 10.04 (s, H, CONH), 11.03 (s, H, N -NH), 13.27 (s, H, Ar-NH), 6.39 -8.18 (m, 10H, for C_6H_5 and C_6H_4 of two phenyl groups and thiazole H). 3396,3266,3145,3006,1743,1602,1685,1611 cm^{-1}; EI ms: m/z: 636.06 *Anal*. Calcd. for $C_{25}H_{23}Cl_3N_8O_4S$ (637.93) : C: 47.07, H: 3.63, N: 17.57. Found (%): C: 47.09, H: 3.64, N: 17.62

N-(1-(2-(4-(4-hydroxyphenyl)thiazol-2-yl)hydrazinyl)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide 8d **:** yield 68%, mp 175-177^{0}C; ^{1}H NMR (DMSO-d_6): □ 5.48 (s, 1H, Ar-OH), 1.83-1.85 (d,3H, CH_3), 3.64(s,2H, NCH_2CO), 4.32 (s, H, NH N), 4.77-4.82(q,1H CH_3CH) 10.04 (s, H, CONH), 11.04 (s, H, N -NH), 13.28 (s, H, Ar-NH), 6.36 -8.15 (m, 10H, for C_6H_5 and C_6H_4 of two phenyl groups and thiazole H).; IR: 3392,3261,3146,3007,1742,1606,1682,1614 cm^{-1}; EI ms: m/z: 622.05 *Anal*. Calcd. for $C_{24}H_{21}Cl_3N_8O_4S$ (623.90): C: 46.20, H: 3.39, N: 17.96. Found (%): C: 46.22, H: 3.41 N: 18.01.

N-(1-(2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazinyl)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide 8e : yield 63%, mp 198-200^{0}C; ^{1}H NMR (DMSO-d_6): □ 1.84-1.86 (d,3H, CH_3), 3.65(s,2H, NCH_2CO), 4.31(s, H, NH N), 4.76-4.81(q,1H CH_3CH) 10.02 (s, H, CONH), 11.05 (s, H, N -NH), 13.24(s, H, Ar-NH), 6.35 -8.14 (m, 10H, for C_6H_5 and C_6H_4 of two phenyl groups and thiazole H); IR: 3394,3264,3142,3008,1744,1604,1683,1618 cm^{-1}; EI ms: m/z: 651.04 *Anal*. Calcd. for $C_{24}H_{20}Cl_3N_9O_5S$ (652.90): C: 44.15, H: 3.09, N: 19.31. Found (%): C: 44.17, H: 3.11 N: 19.33.

N-(1-(2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazinyl)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide 8f **:** yield 71%, mp 179-181^{0}C; ^{1}H NMR (DMSO-d_6): □ 1.85-1.87 (d,3H, CH_3), 3.66(s,2H, NCH_2CO), 4.36 (s, H, NH N), 4.75-4.80(q,1H CH_3CH) 10.02 (s, H, CONH), 11.06 (s, H, N -NH), 13.23 (s, H, Ar-NH), 6.34 -8.13 (m, 10H, for C_6H_5 and C_6H_4 of two phenyl groups and thiazole H); IR: 3391,3263,3148,3004,1746,1603,1681,1616 cm^{-1}; EI ms: m/z: 640.01 *Anal*. Calcd. for $C_{24}H_{20}Cl_4N_8O_3S$ (642.34): C: 44.88, H: 3.14, N: 17.44. Found (%): C: 44.90, H: 3.16, N: 17.46

N-(1-(2-(4-(4-bromophenyl)thiazol-2-yl)hydrazinyl)-1-oxopropan-2-yl)-2-(5-oxo-4-(2-phenylhydrazono)-3-(trichloromethyl)-4,5-dihydro-1H-pyrazol-1-yl)acetamide 8g: yield 70%, mp 170-172^{0}C; ^{1}H NMR (DMSO-d_6): □1.86-1.88 (d,3H, CH_3), 3.67(s,2H, NCH_2CO), 4.37 (s, H, NH N), 4.82-4.87(q,1H CH_3CH) 10.06 (s, H, CONH), 11.07 (s, H, N -NH), 13.22 (s, H, Ar-NH), 6.33 -8.12 (m, 10H, for C_6H_5 and C_6H_4 of two phenyl groups and thiazole H).; IR: 3395,3268,3147,3003,1745,1607,1684,1613 cm^{-1}; EI ms: m/z: 683..96 *Anal*. Calcd. for $C_{24}H_{20}BrCl_3N_8O_3S$ (686.80): C: 41.97, H: 2.94, N: 16.34. Found (%): C: 42.02, H: 3.01, N: 16.34.

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