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Synthesis of some newN- heterocyclic substituted derivatives of barbituric acid

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ABSTRACT

A series of N-substituted barbital have been synthesized. The nitrogen atoms have been alkylated first to form N-carboxymethyl followed by cyclization reaction to form heterocyclic/substituted aryl groups. All the synthesized compounds have been identified using I.R, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

Keywords: 5,5-substituted Barbituric acid; Hiburic acid, 1,3-Oxazole, Imidazole, 1,2,4-Triazole, 1,3,4-oxadiazole.

INTRODUCTION

Barbituric acids [1] have concerned the interest of the pharmaceutical population for over 100 years due to their therapeutic value. The broad spectra of biological activities shown by barbiturate and thiobarbiturate derivatives are well known [2-4]. Structure activity relationship shows that heterocyclic/substituted aryl moieties at the 5th position of barbituric acid nucleus remarkably increase the anticonvulsant activity [5]. The antiinfammatory drugs in use today [6] are characterized by presence of both hydrophilic and lypophilic groups. To increase the solubility in wate5-alkyl and 5,5-dialkyl barbituric acids were prepared having different substituent on nitrogen atom. Previously synthesized N-carboxyalkylbarbituric acids include 1-carboxymethylphenobarbiton, [7,8] 1- carboxymethylallobarbitone, [9] 1-butyl, 1-cyclohexyl, 1-octyl and 1-phenyl-3-carboxymethylbarbituric acids [10] and 1,3-dicarboxymethylallobarbiton. All the compounds tested are very weak inhibitors of prostaglandin synthetase. On the other hand N-carboxyalkyl barbital derivatives have been synthesized by the reaction of haloacetal with barbital and methylphenobarbital in polar aprotic solvents in the presence of K_2CO_3. All the prepared compounds lack anticonvulsant slight sedative and analgesic action [11]. The antibacterial and antifungal activity of the N-isoxazolyl barbitals have been studied recently [12]. Taken these observations into our consideration it was considered useful to synthesize some newer potent derivatives of barbituric acid in which both nitrogen atoms bonded to one or two heterocyclic/substituted aryl groups.

MATERIALS AND METHODS

Instruments: Melting point determinations were performed by the open capillary method using a Gallenkamp melting point apparatus and are reported uncorrected. The IR spectra (KBr-discs) were recorded with a pye-Unicam Sp-300 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker

AV500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C measurements. Chemical shifts are reported relative to TMS and coupling constants *J* are in Hz and have been rounded to the nearest whole number. Assignments of signals are based on coupling patterns and expected chemical shift values and have not been rigorously confirmed. Signals with similar characteristics might be interchanged.

Materials: Chemicals were obtained from Aldrich Chemical Company and used without further purification.

Methods:

Synthesis of 2,2'-((2,2'-(5,5-diethyl-2,4,6-trioxodihydropyrimidine-1,3(2H,4H)-diyl) bis(acetyl)) bis(azanediyl))diacetic acid(S2): Compound 1 (0.01mol) in (5ml) dioxane was added to a stirring solution of glycine (1.4g, 0.02mol) and sodium hydroxide (20ml, 10%solution). Then, the reaction mixture was stirring over night and a few grams of crushed ice were added with stirring. After that, the solution was acidified with conc. HCl and the combined solution was concentrated in vacuo and the residual precipitate dissolved in ethanol .The inorganic salts were filtered .the remaining solution concentrated in vacuo. The remained crude oily. Yield: 71%; m.p. Oily; IR (v, cm^{-1}): 2,974- 3,392 brod ($OH_{carboxyl}$), 1,735 ($C=O_{carboxyl}$), 1,687 ($C=O_{amid}$), 3,392 (NH); ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 1.05 (t ,6H,-CH_3), 1.90 (q, 4H,-CH_2-), 4.48 (S, 4H, N-CH_2-CO), 8.58 (t, 2H, -CO-NH), 3.45 (d, 4H, -CH_2-CO); ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm): 10.00 (-CH_3), 20.00 (-CH_2-), 55.00 (NH-*C*H_2-CO), 57.40 (N-*C*H_2-CO), 60.00 (*C*(CH_2CH_3)$_2$), 150.00 (-N-CO-N-), 167.00 (-CH_2-*C*O-NH-), 169.00 (-CH_2-*C*O-OH), 173.00 (-C-*C*O-N-), ($C_{16}H_{22}N_4O_9$ (Mol.Wt. 414).

Synthesis of 1,3-bis(((E)-4-(4-arylidene)-5-oxo-4,5-dihydrooxazol-2-yl)methyl)-5,5-diethyl pyrimidine -2,4,6(1H,3H,5H)-trione (S3-5): Aromatic aldehyde (0.02 mol) was added to a stirring mixture of compound4 (0.01 mol) acetic acid (10 ml) and acetic anhydride (40 ml) and the refluxing was continued for (7h),then the mixture was poured into crushed ice and stirred (30 min) the product was collected.

1,3-bis(((E)-4-(4-bromobenzylidene)-5-oxo-4,5-dihydrooxazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6 (1H,3H,5H)-trione (S3): Yield: 61%; m.p 78-80 °C; IR (v, cm^{-1}): 3,086 (C-H_{ar}), 2,972 – 2,879 (C-H_{aliph}), 1,799 ($C=O_{oxazole}$), 1,654 (C=N), 1,234 (C-O),1,589-1,485 ($C=C_{ar}$); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.88 (t ,6H,-CH_3) , 2.00 (q, 4H,-CH_2-) ,4.59 (S, 4H, N-CH_2-) ,7.53 (S, 2H, =CH-) ,7.59 (d, 4H, CH=C-CH)ar ,7.78 (d, 4H, CH=CBr-CH)ar; ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm): 10.00 (-CH_3), 21.10 (-CH_2-), 21.26 (N-*C*H_2-C=N), 51. 19 (*C* (CH_2CH_3)$_2$), 77.46 (CH-ph-Br), 77.66 (-C-Br)ar, 77.77 (-C-*C*H=CH-C-Br)ar, 89.53 (-C-CH=*C*H-C-Br)ar, 169.00 (-CH_2-*C*O-OH), 124.40 (-*C*-CH=CH-C-Br)ar,.128.84 (C=CH-ph-Br), 132.22 (-N-CO-N-), 134.83 (-N-CH_2-*C*=N-) 169.17 (-O-C=O-), 176.50 (-C-*C*O-N-), $C_{30}H_{24}Br_2N_4O_7$(Mol.Wt. 712).

1,3-bis(((E)-4-(4-chlorobenzylidene)-5-oxo-4,5-dihydrooxazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione (S4): Yield: 80%; m.p 132-135 °C; IR (v, cm^{-1}): 3,028 (C-H_{ar}), 2,974 – 2,883 (C-H_{aliph}), 1,751 ($C=O_{oxazole}$), 1,697 (C=N), 1,238 (C-O), 1,653-1,541 ($C=C_{ar}$); ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.89 (t , 6H,-CH_3) , 2.10 (q, 4H,-CH_2-) ,4.72 (S, 4H,N-CH_2-) ,7.29 (S, 2H, =CH-) ,7.41 (d, 4H, CH=C-CH)ar ,7.53 (d, 4H, CH=CCl-CH)ar , $C_{30}H_{24}Cl_2N_4O_7$ (Mol.Wt. 623) .

1,3-bis(((E)-4-(4-benzylidene)-5-oxo-4,5-dihydrooxazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6 (1H,3H,5H)-trione (S5): Yield: 85%; m.p oily; IR (v, cm^{-1}):3,009 (C-H_{ar}), 2,937 – 2,823 (C-H_{aliph}), 1.743 ($C=O_{oxazole}$), 1.693 (C=N), 1,232 (C-O), 1,664-1,599 ($C=C_{ar}$); ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.88 (t , 6H, -CH_3) , 2.10 (q, 4H, -CH_2-) ,4.66 (S, 4H, N-CH_2-) ,7.42 (S, 2H, =CH-) ,7.49 (d, 4H, CH=C-CH)ar ,7.53 (d, 6H, CH=C-CH)ar .$C_{30}H_{26}N_4O_7$ (Mol.Wt. 555).

Synthesis of 1,3-bis(((E)-1-amino-4-(argiomethylene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione(S6-8): Hydrazine hydrate (20 ml) was added to a mixture of compound (3-5) (0.01 mole) in dry benzene (10 ml), The reaction mixture was refluxed for (25 h).Then, the mixture was allowed to cool to room temperature and benzene was removed.

1,3-bis(((E)-1-amino-4-(4-bromobenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione(S6): Yield: 90%; m.p 250 °C; IR (v, cm^{-1}): 3,360 – 3,275 (NH_2), 3,049 (C-H_{ar}), 2,918-2,852 (C-$H_{aliph.}$), 1,654 (C=O), 1,597-1,487 (C=C_{ar}); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 0.79 (t , 6H, -CH_3) , 1.61(q, 4H, -CH_2-), 4.40 (S, 4H, N-CH_2-), 7.15 (S, 2H, =CH-), 7.20-7.60 (dd, 8H, CHar), 8.20 (S, 4H, N-NH_2); ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm): 10.00 (-CH_3), 20.85 (-CH_2-), 20.93 (N-*C*H_2-C=N), 52.20 (*C*(CH_2CH_3)$_2$), 77.05 (CH-ph-Br), 77.26 (-C-Br)ar, 77.37 (-C-*C*H=CH-C-Br)ar, 122.55 (-C-CH=*C*H-C-Br)ar, 127.59 (-CH_2-*C*O-OH), 131.62 (-*C*-CH=CH-C-Br)ar,.134.09 (*C*=CH-ph-Br), 141.66 (-N-CO-N-), 161.24 (-N-CH_2-*C*=N-) 171.03 (-O-C=O-), 174.85 (-C-*C*O-N-), $C_{30}H_{28}Br_2N_8O_5$ (Mol.Wt. 740).

1,3-bis(((E)-1-amino-4-(4-chlorobenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione(S7): Yield**:** 85%; m.p oily; IR (v, cm^{-1}): 3,331 – 3,201 (NH_2), 3,049 (C-H_{ar}), 2,970-2,879 (C-$H_{aliph.}$), 1,674 (C=O), 1,541-1,491 (C=C_{ar}); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 0.75 (t , 6H,-CH_3), 1.76 (q, 4H, -CH_2-), 4.33 (S, 4H, N-CH_2-), 7.70 (S, 2H, =CH-), 7.00-7.60 (dd, 8H, CHar), 7.90 (S, 4H, N-NH_2). $C_{30}H_{28}Cl_2N_8O_5$ (Mol.Wt. 651).

1,3-bis(((E)-1-amino-4-benzylidene-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)-5,5-diethyl pyrimidine -2,4,6(1H,3H,5H)-trione(S8): Yield: 83%; m.p oily; IR (v, cm^{-1}): 3,331 – 3,227 (NH_2), 3,063 (C-H_{ar}), 2,968-2,879 (C-$H_{aliph.}$), 1,668 (C=O), 1,558-1,456 (C=C_{ar}); ^{1}H NMR (500 MHz, DMSO-d_6). δ (ppm): 0.72 (t , 6H, -CH_3), 1.76 (q, 4H, -CH_2-), 3.43 (S, 4H, N-CH_2-), 7.75 (S, 2H, =CH-), 7.00-7.50 (dd, 8H, CHar), 7.95 (S, 4H, N-NH_2). $C_{30}H_{30}N_8O_5$ (Mol.Wt. 583).

Synthesis of diethyl 2,2'-(((4E,4'E)-2,2'-((5,5-diethyl-2,4,6-trioxodihydropyrimidine-1,3(2H,4H)-diyl)bis(methylene))bis(4-(argiomethylene)-5-oxo-4,5-dihydro-1H-imidazole-2,1-diyl)) bis azanediyl)) diacetate(S9-11): The corresponding compound (6-8) (0.01 mol) was refluxed with (0.02 mol) of sodium in absolute ethanol for (2h). Then, ethyl bromoacetate (3.62g, 0.02mol) was added and refluxed for an additional (5h).After evaporating the solvent under reduced pressure.

Diethyl 2,2'-(((4E,4'E)-2,2'-((5,5-diethyl-2,4,6-trioxodihydropyrimidine-1,3(2H,4H)-diyl) bis (methylene))bis(4-(4-bromobenzylidene)-5-oxo-4,5-dihydro-1H-imidazole-2,1-diyl)) bis (azanediyl)) diacetate (S9): Yield:85% ; m.p. oily; IR: (v, cm^{-1}) 3,462 (NH), 3,043 (C-$H_{ar.}$), 2,941- 2881 (C-H_{aliph}), 1,734 (C=O_{ester}), 1,624 (C=$O_{imidazole}$), 1,585-1,483 (C=C_{ar}); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 0.82 (t , 6H, -CH_3) , 2.00 (q, 4H, -CH_2-) ,8.11 (S, 2H, =CH-) ,7.60-7.90 (dd, 8H, CHar) ,1.10 (t, 6H, -CH_3) ,3.53 (d, 4H, -CH_2-CO) ,3.35 (t, 2H, N-NH); ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm): 8.69 (-CH_3), 14.06 (*C*H_3-CH_2-O-), 20.21 (-CH_2-), 21.60 (N-*C*H_2-C=N), 51.55 (*C* (CH_2CH_3)$_2$), 54.92(-N-NH-*C*H_2-CO-Et) 60.44 (CH_3-*C*H_2-O-), 120.19 (CH-ph-Br), 123.95 (-C-Br), 127.24 (-C-*C*H=CH-C-Br)ar, 130.19 (-C-CH=*C*H-C-Br)ar, 130.86 (-*C*-CH=CH-C-Br)ar,.131.36 (*C*=CH-ph-Br), 135.41 (-N-CO-N-), 141.30 (-N-CH_2-*C*=N-) 168.52 (HN-N-C=O-), 168.78 (-C-*C*O-N-), $C_{38}H_{40}Cl_2N_8O_9$ (Mol.Wt. 913).

Diethyl 2,2'-(((4E,4'E)-2,2'-((5,5-diethyl-2,4,6-trioxodihydropyrimidine-1,3(2H,4H)-diyl) bis (methylene))bis(4-(4-chlorobenzylidene)-5-oxo-4,5-dihydro-1H-imidazole-2,1-diyl)) bis (azanediyl)) diacetate (S10): Yield: 78%; m.p. gamy; IR: (v, cm^{-1}) 3,298 (NH), 3,032 (C-$H_{ar.}$), 2,972-2883 (C-H_{aliph}), 1,735 (C=O_{ester}), 1,678 (C=$O_{imidazole}$), 1,539-1,514 (C=C_{ar}); ^{1}H NMR (500 MHz, DMSO-d_6). δ (ppm) 0.79 (t , 6H, -CH_3) , 1.75 (q, 4H, -CH_2-) ,4.33 (S, 4H, N-CH_2-) ,7.91 (S, 2H, =CH-) ,7.05-7.60 (dd, 8H, CHar) ,1.06-1.10 (t, 6H, -CH_3) ,3.46 (d, 4H, -CH_2-CO) ,4.10 (q, 4H, O-CH_2-),2.25 (t, 2H, N-NH). $C_{38}H_{40}N_{10}O_{13}$ (Mol.Wt. 824).

Diethyl 2,2'-(((4E,4'E)-2,2'-((5,5-diethyl-2,4,6-trioxodihydropyrimidine-1,3(2H,4H)-diyl) bis (methy lene)) bis (4-benzylidene-5-oxo-4,5-dihydro-1H-imidazole-2,1-diyl))bis(azanediyl)) diacetate (S11): Yield: 73%; m.p. oily; IR: (v, cm^{-1}) 3,396 (NH), 3,051(C-$H_{ar.}$), 2,978-2,883 (C-H_{aliph}), 1,735 (C=O_{ester}),

1,645 ($C=O_{imidazole}$), 1,587-1,560 ($C=C_{ar}$); ^{1}H NMR (500 MHz, DMSO-d_6). δ (ppm) 0.77 (t , 6H, $-CH_3$), 1.75 (q, 4H, $-CH_2$-), 4.49-4.33 (S, 4H, N-CH_2-), 7.90 (S, 2H, =CH-), 7.05-7.55 (dd, 8H, CHar), 1.02 (t, 6H, $-CH_3$), 3.40 (d, 4H, $-CH_2$-CO), 4.05 (q, 4H, O-CH_2-), 2.25 (t, 2H, N-NH). $C_{38}H_{42}N_8O_9$ (Mol.Wt. 755).

Synthesis of 2,2'-(((4E,4'E)-2,2'-((5,5-diethyl-2,4,6-trioxodihydropyrimidine-1,3(2H,4H)-diyl) bis (methylene))bis(4-(argiomethylene)-5-oxo-4,5-dihydro-1H-imidazole-2,1-diyl)) bis (azanediyl)) di (acetohydrazide) (S12-14): A mixture of compound 9-11 (0.01, mole) and hydrazine hydrate (80% 0.64 g, 0.02 mole) in ethanol (25 mL) was refluxed for 8 hrs. Upon cooling the solution a solid appeared. This was recrystallized from ethanol to afford the desired compound.

2,2'-(((4E,4'E)-2,2'-((5,5-diethyl-2,4,6-trioxodihydropyrimidine-1,3(2H,4H)-diyl) bis (methylene)) bis (4-(4-bromobenzylidene)-5-oxo-4,5-dihydro-1H-imidazole-2,1-diyl)) bis (azanediyl)) di (acetohydrazide) (S12): Yield: 87%; m.p. oily; IR: (v, cm^{-1}) 3,311-3221 (NH_2), 3,130 (NH), 3,045 ($C-H_{ar.}$), 2,968-2,856 ($C-H_{aliph}$), 1,672 ($C=O_{imidazole}$), 1,620 ($C=O_{amide}$), 1,525-1,458 ($C=C_{ar}$); ^{1}H NMR (400 MHz, DMSO-d_6). δ (ppm): 0.86 (t , 6H, $-CH_3$), 1.90 (q, 4H, $-CH_2$-), 4.53 (S, 4H, N-CH_2), 7.95 (S, 2H, =CH-), 6.80-7.50 (dd, 8H, CHar), 2.58 (d, 4H, $-CH_2$-CO), 3.35 (d, 4H, $-NH_2$), 2.85 (t, 2H, N-NH-), 9.00 (t, 2H, CO-NH), $C_{34}H_{36}Br_2N_{12}O_7$(Mol.Wt. 885).

2,2'-(((4E,4'E)-2,2'-((5,5-diethyl-2,4,6-trioxodihydropyrimidine-1,3(2H,4H)-diyl) bis (methylene)) bis(4-(4-chlorobenzylidene)-5-oxo-4,5-dihydro-1H-imidazoles-2,1-diyl)) bis (azanediyl)) di (acetohydrazide) (S13): Yield: 77%; m.p. oily; IR: (v, cm^{-1}) 3,317-3,201 (NH_2), 3,111 (NH), 3,037 ($C-H_{ar.}$), 2,908-2,831 ($C-H_{aliph}$), 1,654 ($C=O_{imidazole}$), 1,606 ($C=O_{amide}$), 1,519-1,454 ($C=C_{ar}$); ^{1}H NMR (500 MHz, DMSO-d_6). δ (ppm): 0.75 (t , 6H, $-CH_3$), 1.80 (q, 4H, $-CH_2$-), 7.70 (S, 2H, =CH-), 7.10-7.40 (dd, 8H, CHar), 3.10 (d, 4H, $-CH_2$-CO), 3.80 (d, 4H, $-NH_2$), 3.23 (t, 2H, N-NH-), 9.00 (t, 2H, CO-NH); $C_{34}H_{36}Cl_2N_{12}O_7$ (Mol.Wt. 796).

2,2'-(((4E,4'E)-2,2'-((5,5-diethyl-2,4,6-trioxodihydropyrimidine-1,3(2H,4H)-diyl) bis (methylene)) bis(4-benzylidene-5-oxo-4,5-dihydro-1H-imidazole-2,1-diyl))bis(azanediyl))di(acetohydrazide) (S14): Yield**:** 88%; m.p oily; IR: (v, cm^{-1}) 3,402-3,329(NH_2), 3,215 (NH), 3,061 ($C-H_{ar.}$), 2,922-2,818 ($C-H_{aliph}$), 1,676 ($C=O_{imidazole}$), 1,620 ($C=O_{amide}$), 1,539-1,456 ($C=C_{ar}$); ^{1}H NMR (500 MHz, DMSO-d_6). δ (ppm): 0.70 (t , 6H, $-CH_3$), 1.75 (q, 4H, $-CH_2$-), 7.43 (S, 2H, =CH-), 6.95-7.55 (dd, 8H, CHar), 3.11 (d, 4H, $-CH_2$-CO), 3.70 (d, 4H, $-NH_2$), 3.23 (t, 2H, N-NH-), 7.90 (t, 2H, CO-NH); $C_{34}H_{38}N_{12}O_7$ (Mol.Wt. 727).

Synthesis of 1,3-bis(((E)-4-(4-substitutedbenzylidene)-1-(((5-mercapto-1,3,4-oxadiazol-2-yl)methyl) amino)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione (S15-17): The corresponding compounds (15-17) (0.01 mole) and CS_2 (1.2 ml, 0.02mole) were added to a solution of KOH (1.12 g, 0.02 mole) in ethanol (30 ml). The reaction mixture was refluxed for (3 h). After evaporation under reduced pressure to dryness, a solid was obtained. This was dissolved in water (200 ml) and acidified with conc. HCl. The precipitate was filtered off, washed with water.

1,3-bis(((E)-4-(4-bromobenzylidene)-1-(((5-mercapto-1,3,4-oxadiazol-2-yl)methyl)amino)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione (S15): Yield: 50%; m.p. 93-95 °C; IR: (v, cm^{-1}) 3,174 (NH), 3,047 ($C-H_{ar.}$), 2,933 – 2,856 ($C-H_{aliph.}$), 2,407 (SH), 1,654 ($C=O_{imidazole}$), 1,626 (C=N), 1,508-1,487 ($C=C_{ar}$); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 0.77 (t , 6H,-CH_3), 1.84 (q, 4H, $-CH_2$-), 3.88 (S, 4H, N-CH_2), 8.00 (S, 2H, =CH-), 7.05-7.70 (dd, 8H, CHar), 3.55 (d, 4H, $-CH_2$-), 9.72 (S, 2H, -SH), $C_{36}H_{32}Br_2N_{12}O_7S_2$;(Mol.Wt. 969).

1,3-bis(((E)-4-(4-chlorobenzylidene)-1-(((5-mercapto-1,3,4-oxadiazol-2-yl)methyl)amino)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione(S16): Yield: 57%; m.p 148-150 °C; IR: (v, cm^{-1}) 3,221 (NH), 3,070 ($C-H_{ar.}$), 2,968 – 2,837 ($C-H_{aliph.}$), 2,569 (SH), 1,683 ($C=O_{imidazole}$), 1,624 (C=N), 1,593-1,491 ($C=C_{ar}$); ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 0.93 (t ,

6H,-CH_3), 1.90 (q, 4H, -CH_2-), 4.68 (S, 4H, N-CH_2), 8.03 (S, 2H, =CH-), 7.00-7.40 (dd, 8H, CHar), 2.09 (t, 2H, N-NH), 3.75 (d, 4H, -CH_2-), 10.00 (S, 2H, -SH), $C_{36}H_{32}Cl_2N_{12}O_7S_2$;(Mol.Wt. 880).

1,3-bis(((E)-4-benzylidene-1-(((5-mercapto-1,3,4-oxadiazol-2-yl)methyl)amino)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione(17): Yield: 63%; m.p. 157-160 $^{\circ}$C; IR: (v, cm^{-1}) 3,188 (NH), 3,070 (C-$H_{ar.}$), 2,910 – 2,812 (C-$H_{aliph.}$), 2,584 (SH), 1,662 (C=$O_{imidazole}$), 1,616 (C=N), 1,508-1,400 (C=C_{ar}); $C_{36}H_{34}N_{12}O_7S_2$ (Mol.Wt. 811).

Synthesis of 1,3-bis(((E)-1-(((4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)methyl)amino)-4-(4-substitutedbenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6 (1 H, 3H, 5H)-trione (S18-20): The corresponding compounds (15-17) (0.01 mole) and CS_2 (1,2 ml, 0.02 mole) were added to a solution of KOH (1.12g, 0.02 mole) in ethanol (20 ml) were stirred for(12 hrs). Then, diethyl ether (18 ml) was added. The precipitated solid thus obtained was filtered, washed with cold diethyl ether, and without isolation and purification dissolved in water (10 ml) and hydrazine hydrate (0.02 mole) was added. The reaction mixture was refluxed for (1 h). Cooled, diluted with water and acidified with acetic acid. The precipitate was filtered off, washed with water.

1,3-bis(((E)-1-(((4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)methyl)amino)-4-(4-bromobenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione (S18): Yield: 75%; m.p. oily; IR: (v, cm^{-1}) 3,421-3,325 (NH_2), 3,227 (NH), 3047 (C-$H_{ar.}$), 2,982-2,864 (C-$H_{aliph.}$), 2,360 (SH), 1,668 (C=O_{amid}), 1,635 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 0.86 (t , 6H,-CH_3), 1.92 (q, 4H, -CH_2-), 4.00 (S, 4H, N-CH_2), 8.20 (S, 2H, =CH-), 7.65-7.90 (dd, 8H, CHar), 2.30 (t, 2H,N -NH), 8.66 (S, 2H, -SH), 5.45 (S,4H,N-NH_2); $C_{36}H_{36}Br_2N_{16}O_5S_2$ (Mol.Wt. 997).

1,3-bis(((E)-1-(((4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)methyl)amino)-4-(4-chlorobenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione (S19): Yield: 80%; m.p. oily; IR: (v, cm^{-1}) 3,414-3,290 (NH_2), 3,190 (NH), 3043 (C-$H_{ar.}$), 2,935-2,854 (C-$H_{aliph.}$), 2,500 (SH), 1,666 (C=O_{amid}), 1,626 (C=N); $C_{36}H_{36}Cl_2N_{16}O_5S_2$ (Mol.Wt. 908).

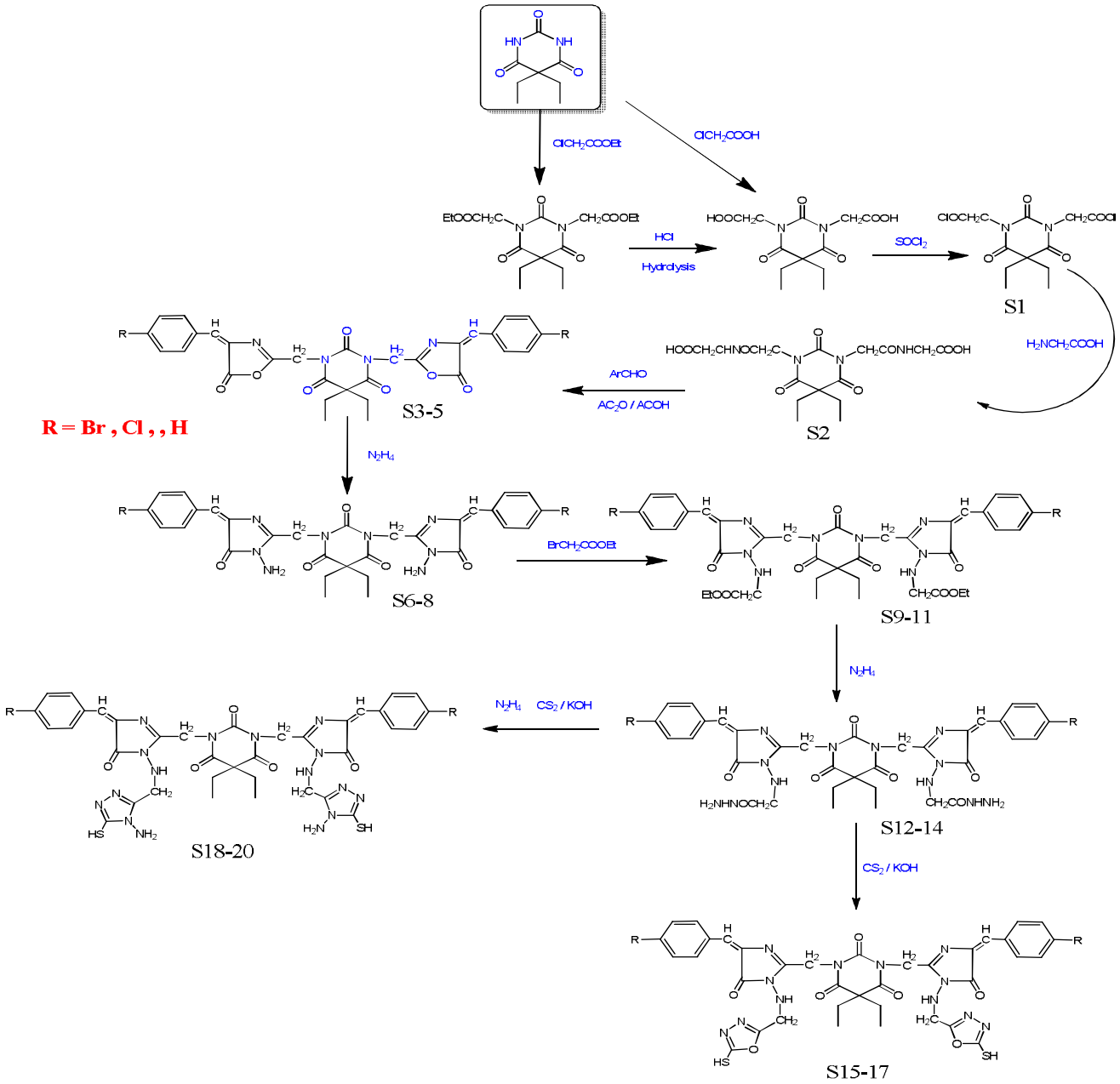
1,3-bis(((E)-1-(((4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)methyl)amino)-4-benzylidene-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione (S20): Yield: 78%; m.p. oily; IR: (v, cm^{-1}) 3,400-3,302 (NH_2), 3,213 (NH), 3086 (C-$H_{ar.}$), 2,976-2,879 (C-$H_{aliph.}$), 2,430 (SH), 1,662 (C=O_{amid}), 1,627 (C=N); $C_{36}H_{38}N_{16}O_5S_2$ (Mol.Wt. 839).

RESULTS AND DISCUSSION

The designated compounds were synthesized according to Scheme 1. Compound S2 (2,2'-((2,2'-(5,5-diethyl-2,4,6-trioxodihydropyrimidine-1,3(2H,4H)-diyl)bis(acetyl))bis(azanediyl))diacetic acid have been prepared by reaction of acid chloride of substituted barbituric acid with an amino acid (Glycine) [13]. The IR spectrum has shown the disappearance of absorption band due to Carbonyl group at 1,805 cm^{-1} and presence of OH absorption at 3,270-2,650 cm^{-1}. The ^{1}H-NMR has shown triplet peaks resonated at 8.58 ppm due to (-CH_2-NH).

The reaction of compound S2 with different substituted Benzaldehyde in the presence of acetic anhydride (scheme 1) afforded 1,3-bis(((E)-4-(4-substitutedbenzylidene)-5-oxo-4,5-dihydrooxazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione S3-5 [14]. The structures of compounds S3-5 were characterized via IR and ^{1}H-NMR. The IR spectrum has shown the disappearance of OH absorption at 3,298-2,650 cm^{-1} and NH signal at 3,170 cm^{-1}, also an increase in the absorption band for the carbonyl group have been made to be 1,799 cm^{-1} due to the cyclization reaction. The ^{1}H-NMR spectra of compounds S3-5 showed new double doublet signals at 7.61-7.49 ppm integrated for four protons assigned to aryl group, also a single peak at 7.41 ppm appeared suitable to (C=CH) group. Compound 1,3-bis(((E)-

1-amino-4-(4-substitutedbenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)-5,5-diethylpyrimidin e-2,4,6(1H,3H,5H)-trione S6-8 have been prepared by the reaction of S3-5 compound with hydrazine 80% [15]. A significant decrease in the absorption band of the carbonyl group to be 1,668 cm^{-1} and the appearance of asymmetrical absorption band at 3,360-3,201 cm^{-1} for the NH_2 group was a clear indication for the formation of S6-8 compounds. The appearance of single peak at 8.00 ppm in the ^{1}H-NMR spectra of compound S6-S8 could be a good prove for the substitution of oxygen atom by N-NH_2 group. Alkylation of compound S6-8 with ethyl bromoacetate (Scheme 1) produced diethyl 2,2'-(((4E,4'E)-2,2'-((5,5-diethyl-2,4,6-trioxodihydropyrimidine-1,3(2H,4H)-diyl)bis(methylene))bis(4-(4-substituted benzylid ene)-5-oxo-4,5-dihydro-1H-imidazole-2,1-diyl))bis(azanediyl))diacetate S9-11 [16]. All the prepared compounds (S9-11) have been characterized using IR and ^{1}H-NMR. The IR spectra has shown the appearance of a sharp absorption band at 1,735 cm^{-1} related to carbonyl of ester group and the disappearance of asymmetrical absorption band at 3,360-3,201 cm^{-1} for the NH_2 group. The ^{1}H-NMR spectra of compounds S9-11 has shown the disappearance of singlet peak of NH_2 group at 8.00 ppm and the appearance of triplet peak at 2.64 ppm due to NH group, also the appearance of multiplet peak at 4.07 ppm and the triplet peak at 1.06 ppm due to ethyl CH_2 and CH_3 groups respectively could be a good indication for the formation of S9-11 compounds. Compounds 2,2'-(((4E,4'E)-2,2'-((5,5-diethyl-2,4,6-trioxodihydropyrimidine-1,3(2H,4H)-diyl)bis(methylene))bis(4-(4-substitutedbenzylidene)-5-oxo-4,5-di hydro-1H-imidazole-2,1-diyl))bis(azanediyl))di(acetohydrazide S12-14 have been prepared by the reaction of S9-11 with Hydrazine 80% [17]. The IR spectra of the prepared compounds has shown the appearance of asymmetrical absorption band at 3,402-3,201 cm^{-1} related to NH_2 group and the stretching band at 3,215 cm^{-1} related to NH group. A significant decrease in the absorption band of the carbonyl group appeared to become 1,620 cm^{-1} was a good indication for the formation of imides carbonyl group. In the ^{1}H-NMR spectra, the proton signals due to ethyl group of ester O-CH_2-CH_3 near 4.07 ppm and 1.06 ppm were disappeared. The proton signals due to NH_2 group recorded at 3.61 ppm. Acid hydrazides are useful intermediates leading to the formation of some heterocyclic rings such as 1,3,4-oxadiazoles and 1,2,4-triazoles. The condensation of S12-14 with carbon disulfide in the presence of potassium hydroxide (Scheme1)produced1,3-bis(((E)-4-(4-substitutedbenzylidene)-1-(((5-mercapto-1,3,4-oxadiazol-2-yl) meth yl)amino)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione S 15-17[16]. In contrast to those of S15-17, the IR spectra of compounds S15-17 displayed the SH absorption at 2,584-2,407 cm^{-1} in addition to the absorption at 1,210-1,280 cm^{-1}.The NH and SH protons resonated between 9.72 – 10.00 ppm as a broad singlet integrated for two protons**.** Moreover, $NHNH_2$ signals disappeared from the ^{1}H-NMR and IR spectra. The condensation of compounds S12-14 with Carbon disulfide in the presence of potassium hydroxide produced a potassium salt, that without isolation and purification was treated with hydrazine hydrate to give 1,3-bis(((E)-1-(((4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)methyl)amino)-4-(4-substitutedbenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl) methyl)-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione S18-20 (Scheme 1) [18]. The IR spectra of compounds S18-20 displayed the SH absorption at 2,500-2,430 cm^{-1} in addition to the absorption at 1,292-1,249 cm^{-1}.The NH and SH protons resonated between 8.66-9.90 ppm as a broad singlet integrated for two proton. Moreover, the disappearance of $NHNH_2$ signals and the appearance of N-NH_2 instead (5.45 ppm) would be a good indication for the formation of S18-20 compounds.



Scheme.1

APPLICATIONS

In the present study new derivatives of barbituric acid were synthesized. In future we will study their pharmaceutical activity.

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