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RESEARCH ARTICLE

SYNTHESIS AND CHARACTERIZATION OF PROP-2-YN-1-YL 3-(2-(1,3-DIMETHYL-2,4-DIOXO-3,4-DIHYDRO-1H-PYRROLO[3,2-D]PYRIMIDIN-5(2H)-YL)ACETAMIDO)-2,2-DIMETHYLPROPANOATE AND PENT-4-YN-1-YL 3-(2-(1,3-DIMETHYL-2,4-DIOXO-3,4-DIHYDRO-1H-PYRROLO[3,2-D]PYRIMIDIN-5(2H)-YL)ACETAMIDO)-3-METHYLBUTANOATE.

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Abstract

The synthesis of some pyrrolo[3,2-d]pyrimidine compounds is described. They were prepared from 3-((tert-butoxycarbonyl)amino)-2,2-dimethylpropanoic acid in a series of steps by conventional method by using simple reagents and its exhibits biological activity

Introduction:-

Nucleosides of pyrrolopyrimidines represent structural mimics of the parent purine compounds, they are useful as structural probes in DNA diagnostics as well as in antisense technology. The 7-position of 7-deazapurine system is supposed to be a matching position to the 5-position of pyrimidines. Recently, the 7-fluoro derivative of tubercidin was prepared which exhibits reduced cytotoxicity compared to the parent tubercidin.[1] Some halogenated 7-deazapurine (pyrrolo[2,3-d]pyrimidine) nucleosides have gained attention since some of them, such as 7-iodotubercidin,[2–4] 2¢-deoxy-2¢-fluoroarabinotubercidin[5] and 2-amino-2¢-deoxy-2¢-fluoroarabinotubercidin,[6,7] exhibit a broad spectrum of biological activity (purine numbering is used throughout the general section). Furthermore, 7-halogenated 7-deazapurine nucleosides can stabilize the DNA duplex structures.[8–11]

We were interested in combining the properties of pyrrolopyrimidines nucleoside with the well documented biological behaviors of alkyl group substitutions. Thus, alkyl substituent's were introduced into nucleosides.

Experimental section:-

Chemical and solvents used were purchased either from Fluka or Merck. All the reagents were of analytical grade. Thin-layer chromatography (TLC) was performed on E.Merck AL silica gel 60 F254 plates and visualized under UV light. ^{1}H NMR spectra were recorded in DMSO- d_6 with a Varian Mercury plus 400 MHz instrument. Signals due to residual protonated solvent (^{1} H NMR) served as the internal standard. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of coupling constants (*J*) corresponds to the order of multiplicity assignment. Mass spectra were recorded with a PE Sciex model API 3000 instrument. All the reactions were carried out under argon atmosphere.

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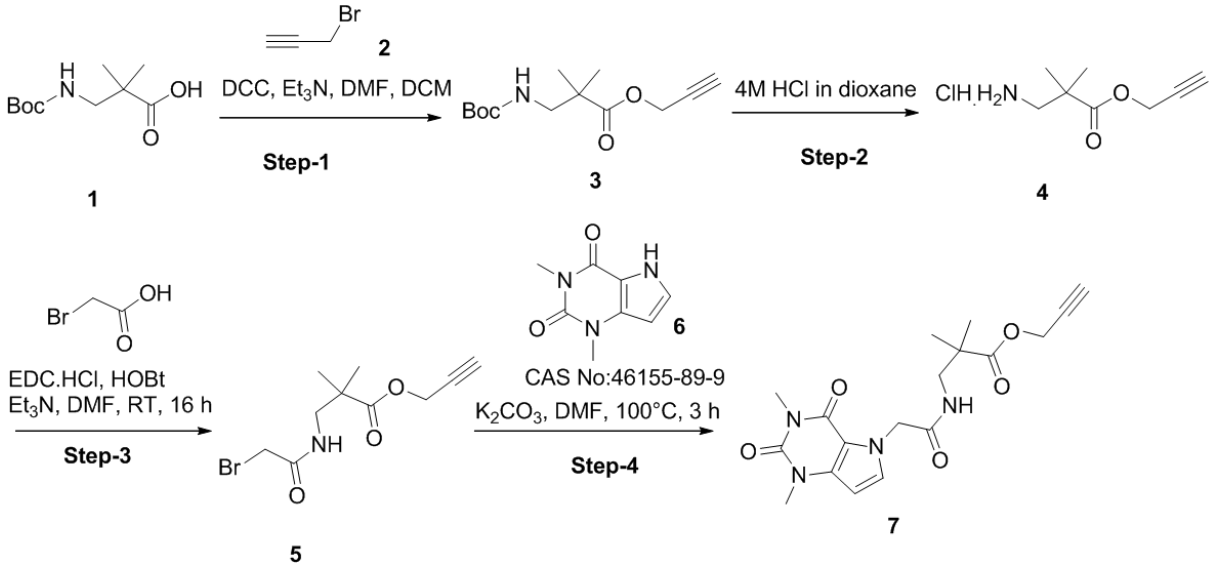
Scheme-1



Prop-2-yn-1-yl 3-((tert-butoxycarbonyl)amino)-2,2-dimethylpropanoate Step-1

Dicyclohexylcarbodiimide (1.1 eq.) and triethylamine (2 eq.) were added to a stirred solution of compd-1 (1 eq.) and Compd-2 (1 eq.) in 1 : 1 ratio of Dichloromethane (DCM) : Dimethylformamide (10 mL/ 1 g) at 0°C. The reaction mixture was stirred at room temperature for 16 hours. After completion of reaction (checked by TLC), solid waste was filtered. The resultant filtrate was diluted with DCM, followed by washing with water, dried over anhydrous sodium sulphate (Na2SO4) and concentrated. The obtain crude material was purified by Silica gel (100-200 mesh) column chromatography using (2:8) ethyl acetate in hexane.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21(brs, 1H, -NH-), 4.65 (s, 2H, Acetylene-CH2), 3.54 (s, 1H, Acetylene-CH), 3.08 (d, 2H, -N-CH2), 1.43 (s, 9H, -Boc), 1.09 (s, 6H, -2CH3); **Mass**: *(m/z)* =256 $[M+H]^+$

Prop-2-yn-1-yl 3-amino-2,2-dimethylpropanoate hydrochloride Step-2::-

4M HCl in dioxane (10 mL/ 1 g) was added to the solution of compound 3 (1 eq.) in dioxane (10 mL/ 1 g) at 10° C and stirred at room temperature for 4 hours till it complies the reaction. The resultant solvent in a reaction mixture was evaporated under reduced pressure to get a desired compound 4.

^{1}H NMR (400 MHz, DMSO-d_6): δ 5.03(brs, 2H, -NH2Cl), 4.65 (s, 2H, Acetylene-CH2), 3.53 (s, 1H, Acetylene-CH), 3.06 (d, 2H, -N-CH2), 1.08 (s, 6H, -2CH3); **Mass**: *(m/z)* =192 $[M+H]^+$

Prop-2-yn-1-yl 3-(2-bromoacetamido)-2,2-dimethylpropanoate Step-3:-

To the solution of 2-bromoacetic acid (1 eq.) in DMF (10 mL/ 1 g) were added 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.5 eq.), Hydroxybenzotriazole (1 eq.) and trimethyl amine (4 eq.) at 0 °C, stirred for 15 min, and then added compound 4 (1.05 eq.). The resultant mixture was stir at room temperature for 16 hours. After completion of reaction (checked by TLC), reaction mixture was diluted with water, extracted with ethyl acetate. The organic layer was washed with water, brine, dried with Na2SO4 and concentrated. The obtain crude material was purified by Silica gel (100-200 mesh) column chromatography using ethyl acetate in hexane (4:6).

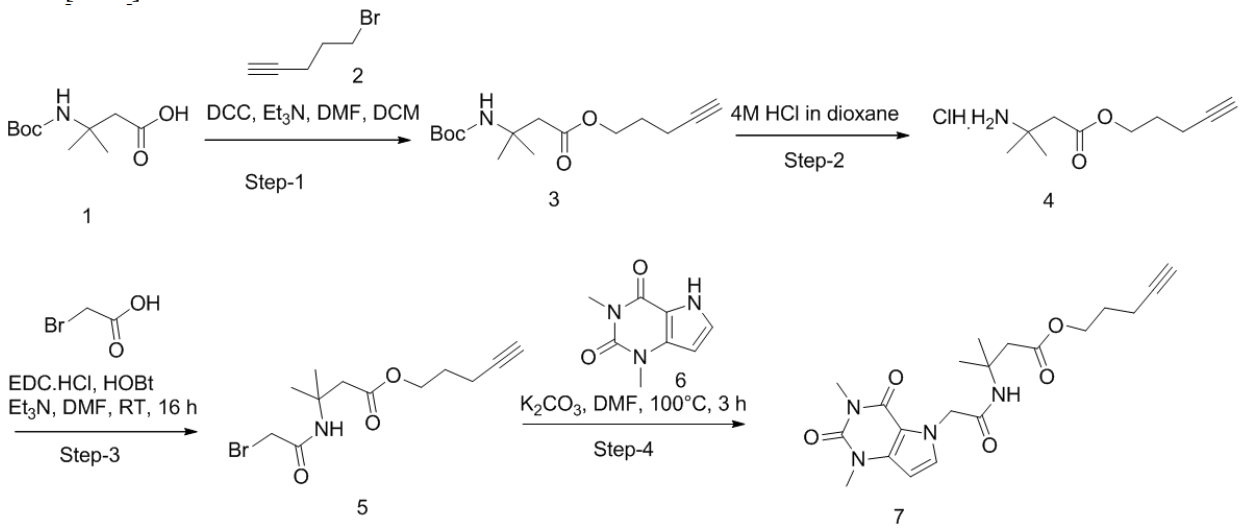
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20(brs, 1H, -NH-), 4.99 (s, 2H, -CH2Br), 4.64 (s, 2H, Acetylene-CH2), 3.55 (s, 1H, Acetylene-CH), 3.08 (d, 2H, -N-CH2), 1.08 (s, 6H, -2CH3); **Mass**: *(m/z)* =277 $[M+H]^+$

Prop-2-yn-1-yl 3-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1H-pyrrolo[3,2-d]pyrimidin-5(2H)-yl)acetamido)-2,2-dimethylpropanoate Step-4:-

Potassium carbonate (1.5 eq.) was added to the mixture of compound 5 (1.05 eq.) and compound 6 (1 eq.) in dry DMF (10 mL/ 1 g) at room temperature and stirred at 100oC for 3 hours. After completion of reaction (checked by TLC). The reaction mixture was diluted with water and extracted with ethyl acetate. The obtain organic layer was

washed with water, brine, dried at Na2SO4 and concentrated. The resultant crude material was purified by Silica gel (100-200 mesh) column chromatography using methanol in DCM (1:9)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (brs, 1H, -NH-), 7.99 (s, 1H, ArCH), 4.98 (s, 2H, -N-CH2CO), 4.65 (s, 2H, Acetylene-CH2), 3.55 (s, 1H, Acetylene-CH), 3.41 (s, 3H, N-CH3), 3.07 (d, 2H, -N-CH2), 3.18 (s, 3H, N-CH3), 1.09 (s, 6H, -2CH3); **^{13}C NMR** (100 MHz, DMSO-d_6) : δ 175.39(-CO-), 167.02(-CO-), 154.82(-CO-), 151.47(-CO-), 148.34, 144.11, and 106.88(Ar-C), 78.93(Acetylene-C), 78.09(Acetylene-CH), 52.57(-C-CO-), 48.50 (-O-CH2-), 46.65(-N-CH2-CO), 43.54(-N-CH2-C), 29.88(-N-CH3), 27.90(-N-CH3), 23.02 (2CH3); **Mass**: *(m/z)* =375 $[M+H]^+$



Pent-4-yn-1-yl 3-((tert-butoxycarbonyl)amino)-3-methylbutanoate Step-1:-
Dicyclohexylcarbodiimide (1.1 eq.) and trimethyl amine (2 eq.) were added to a stirred solution of compound-1 (1 eq.) and Compound-2 (1 eq.) in 1: 1 DCM: DMF (10 mL/ 1 g) at 0°C and stirred at room temperature for 16 hours. After completion of reaction (checked by TLC), the reaction mixture was filtered. The obtain filtrate was diluted with DCM, followed by washing with water, dried over anhydrous Na2SO4 and concentrated. The resultant crude material was purified by Silica gel (100-200 mesh) column chromatography using ethyl acetate in hexane (2:8)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.18(brs, 1H, -NH-), 4.05 (t, 2H, O-CH2), 2.80 (s, 1H, Acetylene-CH), 2.21 (m, 2H, -CH2-), 1.78(m, 2H, -CH2-), 1.48 (s, 9H, -Boc), 1.07 (s, 6H, -2CH3); **Mass**: *(m/z)* =284 $[M+H]^+$

Pent-4-yn-1-yl 3-amino-3-methylbutanoate hydrochloride Step-2:-
4M HCl in dioxane (10 mL/ 1 g) was added to the solution of compound 3 (1 eq.) in dioxane (10 mL/ 1 g) at 10° C and stirred at room temperature for 4 hours till complies the reaction. The resultant solvent in a reaction mixture was evaporated under reduced pressure to get a desired compound 4.

^{1}H NMR (400 MHz, DMSO-d_6): δ 5.05 (brs, 2H, NH2Cl), 4.03 (t, 2H, O-CH2), 2.81 (s, 1H, Acetylene-CH), 2.20 (m, 2H, -CH2-), 1.79(m, 2H, -CH2-), 1.08 (s, 6H, -2CH3); **Mass**: *(m/z)* =220 $[M+H]^+$

Pent-4-yn-1-yl 3-(2-bromoacetamido)-3-methylbutanoate Step-3:-
To the solution of 2-bromoacetic acid (1 eq.) in DMF (10 mL/ 1 g) were added 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.5 eq.), Hydroxybenzotriazole (1 eq.), trimethyl amine(4 eq.) at 0 °C, stirred for 15 min and then added compound 4 (1.05 eq.). The reaction mixture was stir at room temperature for 16 hours. After completion of reaction (checked by TLC), reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine, dried with Na2SO4 and concentrated. The resultant crude material was purified by Silica gel (100-200 mesh) column chromatography using ethyl acetate in hexane (4:6)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.18(brs, 1H, -NH-), 4.99 (s, 2H, -CH2Br), 4.06 (t, 2H, O-CH2), 3.15 (d, 2H, -CH2-CO), 2.81 (s, 1H, Acetylene-CH), 2.22 (m, 2H, -CH2-), 1.77(m, 2H, -CH2-), 1.08 (s, 6H, -2CH3); **Mass**: *(m/z)* =305 $[M+H]^+$

Pent-4-yn-1-yl 3-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1H-pyrrolo[3,2-d]pyrimidin-5(2H)-yl)acetamido)-3-methylbutanoate Step-4:-

Potassium carbonate (1.5 eq.) was added to the mixture of compound 5 (1.05 eq.) and compound 6 (1 eq.) in dry DMF (10 mL/ 1 g) at room temperature and stirred at 100 oC for 3 hours. After completion of reaction (checked by TLC). The reaction mixture was diluted with water and extracted with ethyl acetate. The obtain organic layer was washed with water, brine, dried at Na2SO4 and concentrated. The resultant crude material was purified by Silica gel (100-200 mesh) column chromatography using methanol in DCM (1:9)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (brs, 1H, -NH-), 7.99 (s, 1H, Ar-CH), 4.98 (s, 2H, -N-CH2-), 4.05 (t, 2H, O-CH2), 3.42 (s, 3H, -NCH3), 3.23 (d, 2H, -CH2-CO), 3.20 (s, 3H, -NCH3), 2.81 (s, 1H, Acetylene-CH), 2.21 (m, 2H, -CH2-), 1.78(m, 2H, -CH2-), 1.07 (s, 6H, -2CH3); **^{13}C NMR** (100 MHz, DMSO-d_6) : δ 176.10(-CO-), 166.96(-CO-), 154.80(-CO-), 151.45(-CO-), 148.31, 144.10, and 106.85(Ar-C), 83.92(Acetylene-C), 72.00(Acetylene-CH), 63.40(-N-C-CO), 48.51(-O-CH2-), 46.75(-N-CH2-CO), 43.54(-CH2-CO), 29.86(-N-CH3), 27.87(-N-CH3), 23.20 (2CH3), 14.94 (2CH2-); **Mass**: *(m/z)* =403 $[M+H]^+$

Conclusion:-

In conclusion, a convenient and highly efficient method for the synthesis of prop-2-yn-1-yl 3-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1h-pyrrolo[3,2-d]pyrimidin-5(2h)-yl)acetamido)-2,2-dimethylpropanoate and pent-4-yn-1-yl 3-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1h-pyrrolo[3,2-d]pyrimidin-5(2h)-yl)acetamido)-3-methylbutanoate.In some of these compounds showed low to moderate antibacterial activity and not cytotoxic to vero cells.

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