International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.7, pp 440-445, 2017

Synthesis of 2-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1H-pyrrolo[3,2-d]pyrimidin-5(2H)-yl)acetamido)-3-phenyl-N-(Alka-2/4-yn-1- yl) propanamide

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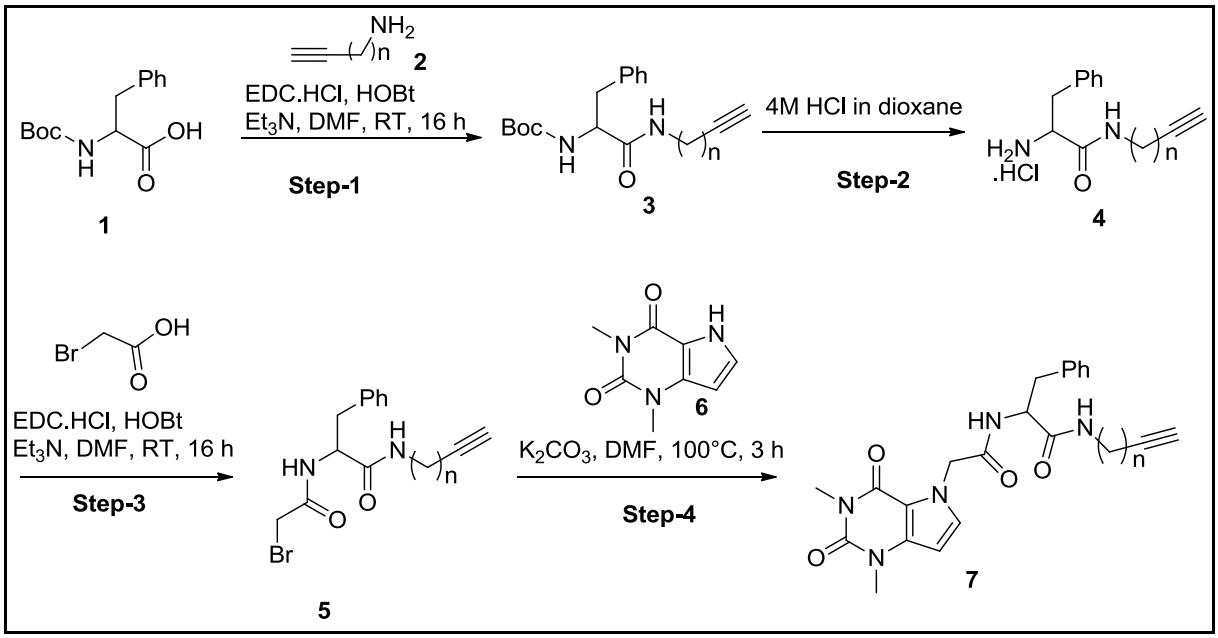
Abstract : 2-((tert-butoxycarbonyl)amino)-3-phenylpropanoic acid **(1)** reacts with proporgylamide to form tert-butyl (1-oxo-3-phenyl-1-(prop-2-yn-1-ylamino)propan-2-yl)carbamate **(3)**, which on deprotection gives 2-amino-3-phenyl-N-(prop-2-yn-1-yl)propanamide **(4)**. Compound 3 reacts with bromoacetic acid to give 2-(2-bromoacetamido)-3-phenyl-N-(prop-2-yn-1-yl) propanamide **(5)**, which is coupled with 1,3-dimethyl-1H-purine-2,6(3H,7H)-dione to form title compound. All the compounds were confirmed by spectral analysis. The said compound exhibit broad biological activity as antitumor, antifungal, antibacterial and anti-HIV agents.
Keywords : Pyrimidine, amide, carbamate and antifungal.

Introduction

Nitrogen heterocyclics have received a best deal of attention in the literature as a result of their role as pharmacophores of great historical significance. Among these heterocyclic systems, those containing pyrimidine in particular have been the subject of expanding research efforts in hetero aromatic and biological chemistry. The structural diversity and biological importance of pyrimidines have made them attractive synthesis targets for many years. The pyrimidine is a wide spread heterocyclic moiety, present in numerous natural products as well as synthetic pharmacophores with biological activities [1–4]. Substituted pyrimidines, particularly with amino groups at the 2 and 4 positions, are known pharmacophores in several structure-based drug design approaches in medicinal chemistry [5–7]. Pyrimidines and their fused derivatives have been studied continuously because they exhibit broad biological activity as antitumor [8–11], antifungal [12, 13], antibacterial [12, 14–16], anti-HIV agents [17–19]. In view of the importance of pyrrolopyrimidines it is undertaken to synthesize the title compounds.

Scheme



n = 1, 3

Experimental

All the Chemical and reagents used were purchased from Aldrich. All the solvents were of analytical grade. Thin-layer chromatography (TLC) was checked by Merck AL silica gel 60 F_{254} plates and visualized under UV light. IR spectra were recorded in KBr pellet with a shimadzu spectrum gx FTIR instrument and all the diagnostic, intense peaks are reported. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO- d_6 with a Varian Mercury plus 400 MHz and 100 MHz instruments respectively. 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 on a Shimadzu LCMS-QP 1000 mass spectrometer. Melting points were determined in open glass capillaries on a Stuart SMP30 apparatus and are uncorrected. Reagents and solvents, which are used in the preparation of given compounds are dimethyl formamide (DMF), ethylacetate (EtOAc), triethylamine(Et_3N), Hydoxybenzo triazole(HOBT), ethylene diamine hydrochloride (EDC. HCl),

tert-butyl (1-oxo-3-phenyl-1-(prop-2-yn-1-ylamino)propan-2-yl)carbamate (3) Step-1:

To the solution of compound **1** (1 eq.) in dimethyl formamide (10 mL/ 1 g) were added 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.5 eq.), Hydroxybenzotriazole (1 eq.) and triethyl amine (3 eq.) at 0 °C and stirred for 15 min at same temperature and then added propargylamine (2 eq.) and allowed to stirred at room temperature for 16 hours. After completion of reaction (checked by Thin Layer Chromatography), reaction mixture was diluted with water, extracted with EtOAc. The organic layer was washed with water, brine, dried at sodium sulphate and concentrated**.** The resultant crude material was purified by Silica gel (100-200 mesh) column chromatography by using Ethyl acetate in hexane (4:6)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62 (d, 1H, -NH-), 8.38 (d, 1H, -NH-), 7.21 (m, 5H, Ar-H), 4.98 (s, 2H, -CH2-Ar), 4.43 (m, 1H, -CH-CH2), 3.11 (s, 1H, CH-C-), 3.02 (m, 1H, -N-CH-C-), 2.78 (m, 1H, -N-CH-C-), 1.48 (s, 9H, -Boc); **Mass**: *(m/z)* = 303 $[M+H]^+$

2-amino-3-phenyl-N-(prop-2-yn-1-yl)propanamide (4) 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. After completion of reaction (checked by Thin Layer Chromatography). The resultant solvent was evaporated under reduced pressure to get compound **4**.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63 (d, 1H, -NH-), 7.22 (m, 5H, Ar-H), 4.97 (s, 2H, -CH2-Ar)), 4.42 (m, 1H, -CH-CH2), 3.84 (brs, 2H, -NH2Cl), 3.11 (s, 1H, CH-C-), 3.02 (m, 1H, -N-CH-C-), 2.78 (m, 1H, -N-CH-C-); **Mass**: *(m/z)* = 203 $[M+H]^+$

2-(2-bromoacetamido)-3-phenyl-N-(prop-2-yn-1-yl)propanamide (5) Step-3:

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

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63(d, 1H, -NH-CH2-Br), 8.39 (brs, 1H, -NH-CH2), 7.23 (m, 5H, Ar-H), 4.98 (s, 2H, -CH2-Ar), 4.43 (m, 1H, -CH-CH2), 3.78(m, 2H, -CH2-Br), 3.11 (s, 1H, CH-C-), 3.02 (m, 1H, -N-CH-C-), 2.78 (m, 1H, -N-CH-C-); **Mass**: *(m/z)* = 323 $[M+H]^+$

2-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1H-pyrrolo[3,2-d]pyrimidin-5(2H)-yl)acetamido)-3-phenyl-N-(Alka-2/4-yn-1- yl) propanamide Step-4:

Potassium carbonate (1.5 eq.) was added to the mixture of compound **5** (1.05 eq.) & **6** (1 eq.) in dry dimethyl formamide (10 mL/ 1 g) at room temperature and stirred at 100^o C for 3 hours. After completion of reaction (checked by Thin Layer Chromatography), reaction mixture was diluted with water and extracted with ethyl acetate. The obtain organic layer was washed with water, brine, dried sodium sulphate and concentrated**.** The resultant crude material was purified by Silica gel (100-200 mesh) column chromatography using methanol in dichloromethane (1:9)

The following are mentioned as examples of particularly preferred compounds

2-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1H-pyrrolo[3,2-d]pyrimidin-5(2H)-yl)acetamido)-3-phenyl-N-(prop-2-yn-1-yl)propanamide (7a)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62(d, 1H, -NH-CO), 8.40 (brs, 1H, NH-CH2), 7.94 (s, 1H, -N-CH-N-), 7.24 (m, 5H, Ar-H), 4.99 (s, 2H, CH2-Ar), 4.42 (m, 1H, CH-CH2), 3.78(m, 2H, -N-CH2-CO-), 3.41 (s, 3H, -N-CH3), 3.20 (s, 3H, -N-CH3), 3.10 (s, 1H, CH-C), 3.01 (m, 1H, N-CH-C-), 2.77 (m, 1H, N-CH-C-); **^{13}C NMR** (100 MHz, DMSO-d_6) : δ 170.66(-CO-), 166.48(-CO-), 154.97(-CO-), 151.39(-CO-), 148.43, 144.09, 137.96, 129.56, 128.55, 126.75, and 106.78(-ArC), 81.17(Acetylene-C), 73.59(Acetylene-CH), 54.58(-CH2-Ar), 48.61(N-CH-CO-), 37.96(-N-CH2-CO), 29.88(-N-CH2-CO), 28.46(-N-CH3), 27.93(-N-CH3); **Mass**: *(m/z)* = 423 $[M+H]^+$

2-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1H-pyrrolo[3,2-d]pyrimidin-5(2H)-yl)acetamido)-3-(4-chlorophenyl)-N-(prop-2-yn-1-yl)propanamide (7b)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63(d, 1H, -NH-CO), 8.38 (brs, 1H, NH-CH2), 7.93 (s, 1H, -N-CH-N-), 7.43 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.23 (d, 2H, *J* = 8.0 Hz, Ar-H), 4.98 (s, 2H, CH2-Ar), 4.40 (m, 1H, CH-CH2), 3.78(m, 2H, -N-CH2-CO-), 3.42 (s, 3H, -N-CH3), 3.20 (s, 3H, -N-CH3), 3.11 (s, 1H, CH-C), 3.02 (m, 1H, N-CH-C-), 2.78 (m, 1H, N-CH-C-); **^{13}C NMR** (100 MHz, DMSO-d_6) : δ 170.68(-CO-), 166.49(-CO-), 154.90(-CO-), 151.39(-CO-), 148.43, 144.10, 137.96, 129.58, 128.55, 126.76, and 106.79(-ArC), 81.18(Acetylene-C), 73.55(Acetylene-CH), 54.51(-CH2-Ar), 48.68(N-CH-CO-), 37.92(-N-CH2-CO), 29.86(-N-CH2-CO), 28.48(-N-CH3), 27.95(-N-CH3); **Mass**: *(m/z)* = 458 $[M+H]^+$

2-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1H-pyrrolo[3,2-d]pyrimidin-5(2H)-yl)acetamido)-3-(3-chlorophenyl)-N-(prop-2-yn-1-yl)propanamide (7c)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.64(d, 1H, -NH-CO), 8.39 (brs, 1H, NH-CH2), 7.94 (s, 1H, -N-CH-N-), 7.44 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.24 (d, 2H, *J* = 8.0 Hz, Ar-H), 4.99 (s, 2H, CH2-Ar), 4.38 (m, 1H, CH-CH2), 3.79(m, 2H, -N-CH2-CO-), 3.41 (s, 3H, -N-CH3), 3.21 (s, 3H, -N-CH3), 3.10 (s, 1H, CH-C), 3.01 (m, 1H, N-CH-C-), 2.79 (m, 1H, N-CH-C-); **^{13}C NMR** (100 MHz, DMSO-d_6) : δ 170.69(-CO-), 166.48(-CO-), 154.91(-CO-), 151.39(-CO-), 148.43, 144.11, 137.96, 129.54, 128.55, 126.78, and 106.78(-ArC), 81.19(Acetylene-C), 73.56(Acetylene-CH), 54.51(-CH2-Ar), 48.69(N-CH-CO-), 37.92(-N-CH2-CO), 29.85(-N-CH2-CO), 28.48(-N-CH3), 27.95(-N-CH3); **Mass**: *(m/z)* = 458 $[M+H]^+$

2-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1H-pyrrolo[3,2-d]pyrimidin-5(2H)-yl)acetamido)-3-(4-fluorophenyl)-N-(prop-2-yn-1-yl)propanamide (7d)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62(d, 1H, -NH-CO), 8.40 (brs, 1H, NH-CH2), 7.92 (s, 1H, -N-CH-N-), 7.44 (m, 2H, Ar-H), 7.24 (d, 2H, Ar-H), 4.97 (s, 2H, CH2-Ar), 4.41 (m, 1H, CH-CH2), 3.79 (m, 2H, -N-CH2-CO-), 3.43 (s, 3H, -N-CH3), 3.20 (s, 3H, -N-CH3), 3.10 (s, 1H, CH-C), 3.02 (m, 1H, N-CH-C-), 2.78 (m, 1H, N-CH-C-); **^{13}C NMR** (100 MHz, DMSO-d_6) : δ 171.68(-CO-), 166.49(-CO-), 154.90(-CO-), 151.38(-CO-), 148.44, 144.10, 137.93, 129.58, 128.55, 126.71, and 106.78(-ArC), 81.17(Acetylene-C), 73.55(Acetylene-CH), 54.53(-CH2-Ar), 48.68(N-CH-CO-), 37.92(-N-CH2-CO), 29.87(-N-CH2-CO), 28.49(-N-CH3), 27.94(-N-CH3); **Mass**: *(m/z)* = 441 $[M+H]^+$

2-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1H-pyrrolo[3,2-d]pyrimidin-5(2H)-yl)acetamido)-3-(3-fluorophenyl)-N-(prop-2-yn-1-yl)propanamide (7e)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63(d, 1H, -NH-CO), 8.41 (brs, 1H, NH-CH2), 7.92 (s, 1H, -N-CH-N-), 7.43 (m, 3H, Ar-H), 7.23 (d, 1H, Ar-H), 4.98 (s, 2H, CH2-Ar), 4.42 (m, 1H, CH-CH2), 3.78 (m, 2H, -N-CH2-CO-), 3.44 (s, 3H, -N-CH3), 3.21 (s, 3H, -N-CH3), 3.11 (s, 1H, CH-C), 3.01 (m, 1H, N-CH-C-), 2.78 (m, 1H, N-CH-C-); **^{13}C NMR** (100 MHz, DMSO-d_6) : δ 171.58(-CO-), 165.65(-CO-), 154.95(-CO-), 151.50(-CO-), 148.44, 144.10, 137.91, 129.60, 128.58, 126.70, and 106.80(-ArC), 81.18(Acetylene-C), 73.56(Acetylene-CH), 55.53(-CH2-Ar), 48.62(N-CH-CO-), 37.92(-N-CH2-CO), 29.88(-N-CH2-CO), 28.50(-N-CH3), 27.95(-N-CH3); **Mass**: *(m/z)* = 441 $[M+H]^+$

2-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1H-pyrrolo[3,2-d]pyrimidin-5(2H)-yl)acetamido)-N-(pent-4-yn-1-yl)-3-phenylpropanamide (7f)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.64(d, 1H, -NH-CO), 8.38 (brs, 1H, NH-CH2), 7.95 (s, 1H, -N-CH-N-), 7.21 (m, 5H, Ar-H), 4.96 (s, 2H, CH2-Ar), 4.44 (m, 1H, CH-CH2), 3.82(m, 2H, -N-CH2-CO-), 3.41 (s, 3H, -N-CH3), 3.21 (s, 3H, -N-CH3), 3.10 (s, 1H, CH-C), 3.02 (m, 1H, N-CH-C-), 2.79 (m, 1H, N-CH-C-), 2.20(t, 2H, -CH2-), 1.95 (m, 2H, -CH2-); **^{13}C NMR** (100 MHz, DMSO-d_6) : δ 171.43(-CO-), 166.67(-CO-), 154.78(-CO-), 151.45(-CO-), 148.29, 144.13, 137.24, 129.58, 128.72, 127.05, and 106.76(-ArC), 83.87(Acetylene-C), 71.98(Acetylene-CH), 63.72(-CH2-), 54.41(-CH2-Ar), 48.26(N-CH-CO-), 37.27(-N-CH2-CO), 29.86(-N-CH2-CO), 27.88(-N-CH3), 27.45(-N-CH3), 14.80 (-CH2-); **Mass**: *(m/z)* = 451 $[M+H]^+$

2-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1H-pyrrolo[3,2-d]pyrimidin-5(2H)-yl)acetamido)-N-(pent-4-yn-1-yl)-3-(4-chlorophenyl)propanamide (7g)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63(d, 1H, -NH-CO), 8.39 (brs, 1H, NH-CH2), 7.96 (s, 1H, -N-CH-N-), 7.42 (m, 2H, Ar-H), 7.22 (m, 2H, Ar-H), 4.97 (s, 2H, CH2-Ar), 4.43 (m, 1H, CH-CH2), 3.83(m, 2H, -N-CH2-CO-), 3.40 (s, 3H, -N-CH3), 3.22 (s, 3H, -N-CH3), 3.11 (s, 1H, CH-C), 3.02 (m, 1H, N-CH-C-), 2.78 (m, 1H, N-CH-C-), 2.21(t, 2H, -CH2-), 1.96 (m, 2H, -CH2-); **^{13}C NMR** (100 MHz, DMSO-d_6) : δ 171.44(-CO-), 166.68(-CO-), 154.78(-CO-), 151.45(-CO-), 148.29, 144.14, 137.24, 129.58, 128.73, 127.06, and 106.77(-ArC), 83.88(Acetylene-C), 71.98(Acetylene-CH), 63.72(-CH2-), 54.42(-CH2-Ar), 48.26(N-CH-CO-), 37.27(-N-CH2-CO), 29.86(-N-CH2-CO), 27.89(-N-CH3), 27.46(-N-CH3), 14.81 (-CH2-); **Mass**: *(m/z)* = 486 $[M+H]^+$

2-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1H-pyrrolo[3,2-d]pyrimidin-5(2H)-yl)acetamido)-N-(pent-4-yn-1-yl)-3-(3-chlorophenyl)propanamide (7g)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62(d, 1H, -NH-CO), 8.38 (brs, 1H, NH-CH2), 7.97 (s, 1H, -N-CH-N-), 7.43 (m, 2H, Ar-H), 7.23 (m, 2H, Ar-H), 4.96 (s, 2H, CH2-Ar), 4.42 (m, 1H, CH-CH2), 3.84 (m, 2H, -N-CH2-CO-), 3.41 (s, 3H, -N-CH3), 3.21 (s, 3H, -N-CH3), 3.10 (s, 1H, CH-C), 3.01 (m, 1H, N-CH-C-), 2.78 (m, 1H, N-CH-C-), 2.20(t, 2H, -CH2-), 1.95 (m, 2H, -CH2-); **^{13}C NMR** (100 MHz, DMSO-d_6) : δ 171.45 (-CO-), 166.66 (-CO-), 154.77 (-CO-), 151.44 (-CO-), 148.28, 144.14, 137.23, 129.58, 128.74, 127.06, and 106.79 (-ArC), 83.89 (Acetylene-C), 71.97 (Acetylene-CH), 63.71 (-CH2-), 54.41 (-CH2-Ar), 48.25 (N-CH-CO-), 37.26 (-N-CH2-CO), 29.85 (-N-CH2-CO), 27.88 (-N-CH3), 27.45 (-N-CH3), 14.82 (-CH2-); **Mass**: *(m/z)* = 486 $[M+H]^+$

2-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1H-pyrrolo[3,2-d]pyrimidin-5(2H)-yl)acetamido)-N-(pent-4-yn-1-yl)-3-(4-fluorophenyl)propanamide (7i)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.64 (d, 1H, -NH-CO), 8.39 (brs, 1H, NH-CH2), 7.98 (s, 1H, -N-CH-N-), 7.48 (m, 2H, Ar-H), 7.24 (m, 2H, Ar-H), 4.96 (s, 2H, CH2-Ar), 4.42 (m, 1H, CH-CH2), 3.85 (m, 2H, -N-CH2-CO-), 3.42 (s, 3H, -N-CH3), 3.22 (s, 3H, -N-CH3), 3.11 (s, 1H, CH-C), 3.02 (m, 1H, N-CH-C-), 2.79 (m, 1H, N-CH-C-), 2.21 (t, 2H, -CH2-), 1.96 (m, 2H, -CH2-); **^{13}C NMR** (100 MHz, DMSO-d_6) : δ 171.46 (-CO-), 166.67 (-CO-), 154.78 (-CO-), 151.45 (-CO-), 148.29, 144.13, 137.24, 129.59, 128.75, 127.05, and 106.78 (-ArC), 83.88 (Acetylene-C), 71.95 (Acetylene-CH), 63.72 (-CH2-), 54.42 (-CH2-Ar), 48.22 (N-CH-CO-), 37.25 (-N-CH2-CO), 29.83 (-N-CH2-CO), 27.87 (-N-CH3), 27.46 (-N-CH3), 14.83 (-CH2-); **Mass**: *(m/z)* = 469 $[M+H]^+$

2-(2-(1,3-dimethyl-2,4-dioxo-3,4-dihydro-1H-pyrrolo[3,2-d]pyrimidin-5(2H)-yl)acetamido)-N-(pent-4-yn-1-yl)-3-(3-fluorophenyl)propanamide (7j)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63 (d, 1H, -NH-CO), 8.40 (brs, 1H, NH-CH2), 7.99 (s, 1H, -N-CH-N-), 7.47 (m, 2H, Ar-H), 7.27 (m, 2H, Ar-H), 4.95 (s, 2H, CH2-Ar), 4.41 (m, 1H, CH-CH2), 3.86 (m, 2H, -N-CH2-CO-), 3.41 (s, 3H, -N-CH3), 3.21 (s, 3H, -N-CH3), 3.10 (s, 1H, CH-C), 3.01 (m, 1H, N-CH-C-), 2.78 (m, 1H, N-CH-C-), 2.20 (t, 2H, -CH2-), 1.95 (m, 2H, -CH2-); **^{13}C NMR** (100 MHz, DMSO-d_6) : δ 171.46 (-CO-), 166.67 (-CO-), 154.78 (-CO-), 151.45 (-CO-), 148.28, 144.13, 137.25, 129.59, 128.74, 127.04, and 106.78 (-ArC), 83.88 (Acetylene-C), 71.95 (Acetylene-CH), 63.72 (-CH2-), 54.42 (-CH2-Ar), 48.22 (N-CH-CO-), 37.26 (-N-CH2-CO), 29.84 (-N-CH2-CO), 27.84 (-N-CH3), 27.42 (-N-CH3), 14.85 (-CH2-); **Mass**: *(m/z)* = 469 $[M+H]^+$

Acknowledgement:

The authors are thank full to Optimus drugs Ltd for providing financial assistance. The authors are also grateful to Organic Chemistry department of Dravidian University, Kuppam and Andhra University, Vishakhapatnam.

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