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A facile synthesis of Alka-2/3-yn-1-yl 2-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6H)-yl)acetamido)-3-phenylpropanoate

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Abstract

2-((tert-butoxycarbonyl)amino)-3-phenylpropanoic acid **(1)** reacts with ethynol to form prop-2-yn-1-yl 2-((tert-butoxycarbonyl)amino)-3-phenylpropanoate **(3)**, which on deprotection gives prop-2-yn-1-yl 2-amino-3-phenylpropanoate **(4)**. Compound 3 reacts with bromoacetic acid to give prop-2-yn-1-yl 2-(2-bromoacetamido)-3-phenylpropanoate **(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 analyses.

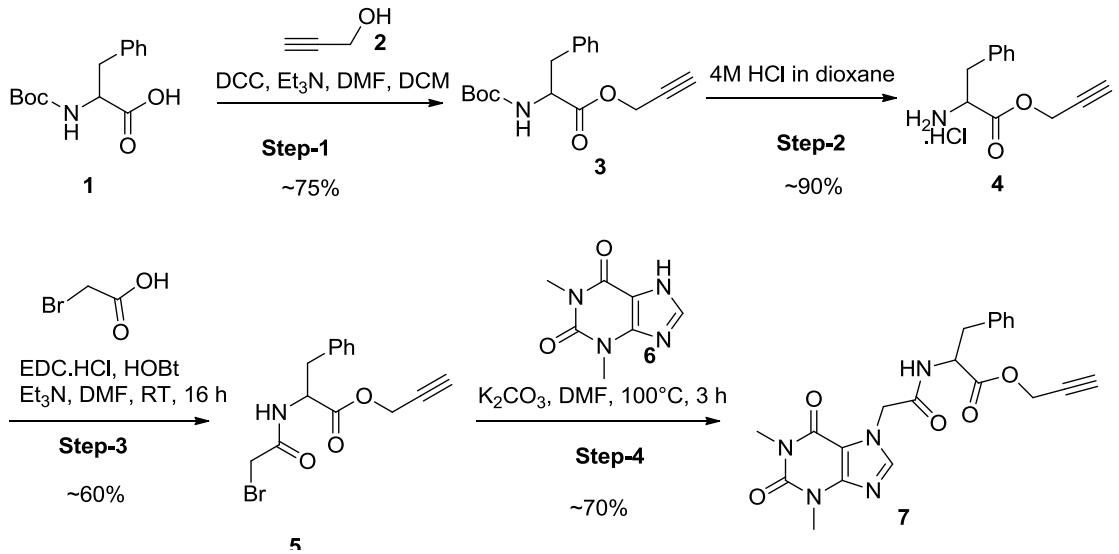
INTRODUCTION

Guanosine triphosphate cyclohydrolase I (GTPCH I) is the first enzyme in the biosynthetic pathway leading to dihydrofolate and the pathway leading to tetrahydrobiopterin, two essential metabolic cofactors.[1] Recent clarification of the crystal structure of GTPCH I[2] has demonstrated the presence of a zinc cation at the active site and assigned it a role in acid–base catalysis of the hydrolytic opening of the purine ring. This information has strengthened the information for the design of inhibitors of GTPCH I. Such inhibitors may have value in antibacterial therapy or in

agrochemistry.[3] It is notable that several antibiotics containing deazaguanines as aglycones have been discovered.[4]

Over the past decade, we have witnessed unparalleled advances in our understanding of the basic biological processes that contribute many human disorders, although a detailed understanding of the etiology of complex psychiatric disorders remains elusive. Psychiatric diseases are chronic and recurrent and have a complex etiology. Human genomics and biological studies have revealed an unprecedented number of promising molecular targets for neuropsychiatric disorders, including G-protein-coupled receptors and transporters, intracellular and synaptic proteins and microRNAs. Serotonin (5-HT) is one of the most attractive targets for medicinal chemists and the discovery of ligands with affinity for the family of 5-HT receptors (5-HTRs) is an area of intense research, because of the potential to find new therapeutic drugs, due to their involvement in numerous physiological and pathophysiological processes. Among the 14 5-HTRs identified, the 5-HT_{1A} and 5-HT_7 subtypes are the best studied due to effects of their full or partial agonists or antagonists on anxiety, depression and schizophrenia[5-10]

Scheme



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 shimazu 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), ABq (AB quartert); 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. All the reactions were performed under inert atmosphere.

Prop-2-yn-1-yl 2-((tert-butoxycarbonyl)amino)-3-phenylpropanoate (3)

DCC (1.1 eq.) fallowed by Et_3N (2 eq.) was added to a stirred solution of compd-**1** (1 eq.) and Compd-**2** (1 eq.) in 1 : 1 DCM : DMF (10 mL/ 1 g) at 0°C and stirred at RT for 16 h. Solid waste was filtered . Filtrate was diluted with DCM washed with water, dried over anhydrous Na2SO4 and concentrated. Crude material was purified by Silica gel (100-200 mesh) column chromatography using 0-20% EA in hexane.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.23 (m, 5H), 6.25 (d, 1H, *J*=4.8Hz), 5.01 (ABq, 2H), 4.48 (m, 1H), 3.58 (s, 1H), 2.99 (m, 2H), 1.49 (s, 9H); **Mass**: *(m/z)* = 304 $[M+H]^+$

Prop-2-yn-1-yl 2-amino-3-phenylpropanoate (4)

4M HCl in dioxane (10 mL/ 1 g) was added to the soution of compound **3** (1 eq.) in dioxane (10 mL/ 1 g) at 10° C and stirred at RT for 4 h. Solvent was evparated under reduced pressure to get compound **4**.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.24 (m, 5H), 6.20 (brs, 3H), 5.00 (ABq, 2H), 4.47 (m, 1H), 3.59 (s, 1H), 2.98 (m, 2H); **Mass**: *(m/z)* = 204 $[M+H]^+$

Prop-2-yn-1-yl 2-(2-bromoacetamido)-3-phenylpropanoate (5)

To the solution of 2-bromoacetic acid (1 eq.) in DMF (10 mL/ 1 g) were added EDC.HCl (1.5 eq.), Hobt (1 eq.) and Et3N (4 eq.) at 0 °C and stirred for 15 min, then compound **4** (1.05 eq.) was added and comtinued stirring at RT for 16 h. Reaction mixture was diluted with water, extracted with EtOAc. Organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated**.** Crude material was purified by Silica gel (100-200 mesh) column chromatography using 0-40% EA in hexane.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.80 (d, 1H, *J*=5.4 Hz), 7.22 (m, 5H), 5.01 (ABq, 2H), 4.71 (s, 2H), 4.46 (m, 1H), 3.58 (s, 1H), 2.99 (m, 2H); **Mass**: *(m/z)* = 324 $[M+H]^+$

Prop-2-yn-1-yl 2-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6H)-yl)acetamido)-3-arylpropanoate

potassium carbonate (1.5 eq.) was added to the mixture of compound **5** (1.05 eq.) & **6** (1 eq.) in dry DMF (10 mL/ 1 g) at RT and stirred at 100 ^{o}C for 3 h. Reaction mixture was diluted with water, extracted with EtOAc. Organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated**.** Crude material was purified by Silica gel (100-200 mesh) column chromatography using 0-10% MeOH in DCM

Prop-2-yn-1-yl 2-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6H)-yl)acetamido)-3-phenylpropanoate (7a)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.80 (d, 1H, *J*=6.4 Hz), 7.98(s, 1H), 7.22 (m, 5H), 5.01 (ABq, 2H), 4.71 (s, 2H), 4.51 (m, 1H), 3.59 (s, 1H), 3.41 (s, 3H), 3.20 (s, 3H), 2.99(m, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) : 170.76, 166.74, 154.75, 151.44, 148.27, 144.08, 137.00, 129.64, 128.72, 127.09, 106.76, 78.50, 78.40, 54.11, 52.84, 48.27, 37.10, 29.86, 27.89; **Mass**: *(m/z)* = 457 $[M+H]^+$

Prop-2-yn-1-yl-3-(4-chlorophenyl)-2-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamido)propanoate (7b)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81 (d, 1H, *J*=6.2 Hz), 7.99(s, 1H), 7.38 (d, 2H, *J*=7.8 Hz), 7.18 (d, 2H, *J*=7.8 Hz), 5.00 (ABq, 2H), 4.69 (s, 2H), 4.51 (m, 1H), 3.60 (s, 1H), 3.40 (s, 3H), 3.20 (s, 3H), 2.99(m, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) : 170.75, 166.74, 154.74, 151.44, 148.27, 144.08, 137.00, 129.63, 128.72, 125.87, 106.76, 78.50, 78.40, 54.11, 52.84, 48.27, 37.10, 29.86, 27.90; **Mass**: *(m/z)* = 457 $[M+H]^+$

Prop-2-yn-1-yl-3-(3-chlorophenyl)-2-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamido)propanoate (7c)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.80 (d, 1H, *J*=6.2 Hz), 8.00(s, 1H), 7.33 (m, 3H,), 7.18 (s, 1H,), 5.02 (ABq, 2H), 4.71 (s, 2H), 4.51 (m, 1H), 3.60 (s, 1H), 3.40 (s, 3H), 3.21 (s, 3H), 2.98(m, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) : 170.75,

166.74, 154.74, 151.44, 148.27, 144.08, 137.00, 129.63, 128.72, 125.88, 106.76, 78.50, 78.40, 54.11, 52.84, 48.27, 37.10, 29.86, 27.90; **Mass**: *(m/z)* = 457 $[M+H]^+$

Prop-2-yn-1-yl 3-(4-fluoroorophenyl)-2-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamido)propanoate (7d)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.85 (d, 1H, *J*=6.4 Hz), 7.99(s, 1H), 7.40 (m, 2H), 7.22 (m, 2H), 5.04 (ABq, 2H), 4.70 (s, 2H), 4.52 (m, 1H), 3.59 (s, 1H), 3.40 (s, 3H), 3.20 (s, 3H), 2.99(m, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) : 170.75, 166.74, 154.74, 151.44, 148.27, 144.08, 137.00, 129.68, 128.72, 126.88, 106.76, 78.50, 78.40, 54.11, 52.84, 48.27, 37.10, 29.86, 27.88; **Mass**: *(m/z)* = 442 $[M+H]^+$

Prop-2-yn-1-yl-3-(3-fluoroorophenyl)-2-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamido)propanoate (7e)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.86 (d, 1H, *J*=6.4 Hz), 7.99 (s, 1H), 7.43 (m, 3H,), 7.21 (s, 1H,), 5.01 (ABq, 2H), 4.70 (s, 2H), 4.51 (m, 1H), 3.60 (s, 1H), 3.40 (s, 3H), 3.21 (s, 3H), 2.98(m, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) : 170.75, 166.74, 154.74, 151.44, 148.27, 144.08, 137.00, 129.63, 128.72, 126.88, 106.76, 78.50, 78.40, 54.11, 52.84, 48.27, 37.10, 29.86, 27.88; **Mass**: *(m/z)* = 442 $[M+H]^+$

But-3-yn-1-yl 2-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamido)-3-phenylpropanoate (7f)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.79 (d, 1H, *J*=5.8 Hz), 7.97(s, 1H), 7.22 (m, 5H), 5.01 (ABq, 2H),4.42 (m, 1H), 4.03 (s, 2H), 3.40 (s, 3H), 3.21 (s, 3H), 3.01 (m, 2H), 2.79 (s, 1H), 2.10 (m, 2H), 1.63 (m, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) : 171.43, 166.67, 154.78, 151.45, 148.29, 144.13, 137.24, 129.58, 128.72, 127.05, 106.76, 83.87, 71.98, 63.72, 54.41, 48.26, 37.27, 29.86, 27.88, 27.45, 14.80; **Mass**: *(m/z)* = 438 $[M+H]^+$

But-3-yn-1-yl 2-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamido)-3-(4-chloroorophenyl)propanoate (7g)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.79 (d, 1H, *J*=5.8 Hz), 7.98 (s, 1H), 7.38 (d, 2H, *J*=8.2 Hz), 7.18 (d, 2H, *J*=8.2 Hz), 5.01 (ABq, 2H),4.42 (m, 1H), 4.04 (s, 2H), 3.40 (s, 3H), 3.20 (s, 3H), 3.01 (m, 2H), 2.79 (s, 1H), 2.10 (m, 2H), 1.63 (m, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) : 171.43, 166.67, 154.78, 151.45, 148.29, 144.13,

137.24, 129.58, 128.73, 126.06, 106.76, 83.87, 71.98, 63.72, 54.41, 48.26, 37.27, 29.86, 27.88, 27.45, 14.80; **Mass**: *(m/z)* = 472 $[M+H]^+$

But-3-yn-1-yl 2-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamido)-3-(3-chlorooropheny)propanoate (7h)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.79 (d, 1H, *J*=5.8 Hz), 7.98(s, 1H), 7.39 (m, 3H), 7.18 (s, 1H), 5.01 (ABq, 2H),4.42 (m, 1H), 4.04 (s, 2H), 3.41 (s, 3H), 3.20 (s, 3H), 3.02 (m, 2H), 2.79 (s, 1H), 2.11 (m, 2H), 1.63 (m, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) : 171.44, 166.67, 154.78, 151.45, 148.29, 144.13, 137.24, 129.58, 128.73, 126.06, 106.76, 83.87, 71.98, 63.72, 54.41, 48.26, 37.27, 29.86, 27.88, 27.46, 14.80; **Mass**: *(m/z)* = 472 $[M+H]^+$

But-3-yn-1-yl 2-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamido)-3-(4-fluorophenyl)propanoate (7i)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.80 (d, 1H, *J*=5.4 Hz), 7.98(s, 1H), 7.42 (m, 2H), 7.20 (m , 2H), 5.01 (ABq, 2H),4.42 (m, 1H), 4.04 (s, 2H), 3.40 (s, 3H), 3.20 (s, 3H), 3.01 (m, 2H), 2.79 (s, 1H), 2.10 (m, 2H), 1.63 (m, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) : 171.43, 166.67, 154.78, 151.45, 148.29, 144.13, 137.24, 129.58, 128.73, 125.05, 106.77, 83.87, 71.98, 63.72, 54.42, 48.26, 37.27, 29.86, 27.88, 27.45, 14.81; **Mass**: *(m/z)* = 456 $[M+H]^+$

But-3-yn-1-yl 2-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamido)-3-(3-fluorophenyl)propanoate (7j)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.80 (d, 1H, *J*=5.4 Hz), 7.98(s, 1H), 7.42 (m, 3H), 7.20 (m , 1H), 5.01 (ABq, 2H),4.41 (m, 1H), 4.04 (s, 2H), 3.40 (s, 3H), 3.20 (s, 3H), 3.01 (m, 2H), 2.79 (s, 1H), 2.10 (m, 2H), 1.63 (m, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) : 171.43, 166.67, 154.78, 151.45, 148.29, 144.13, 137.24, 129.58, 128.73, 125.05, 106.77, 83.87, 71.98, 63.72, 54.42, 48.26, 37.27, 29.86, 27.88, 27.45, 14.80; **Mass**: *(m/z)* = 456 $[M+H]^+$

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