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REGULAR ARTICLE

Design, synthesis and biological evaluation of novel 1,2,3-triazole-based xanthine derivatives as DPP-4 inhibitors

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Abstract. Inhibitors of dipeptidyl peptidase-4 (DPP4) have been shown to be effective treatments for type 2 diabetes. A series of novel 1,2,3-triazole based xanthine derivatives were designed and evaluated for *in vitro* dipeptidyl peptidase-4 (DPP-4) activity. Among them, the representative compounds 7b, 7e, 7g and 6e showed excellent inhibitory activity of DPP-4 with IC_{50} values ranging from 87.41 to 16.34 nM, respectively. The SAR of these xanthine derivatives have been discussed, which would be useful for developing novel DPP-4 inhibitors as treating type 2 diabetes.

Keywords. 1, 2, 3-triazole; Cycloaddition; Xanthine; DPP-4 inhibitory activity.

1. Introduction

Diabetes is becoming a serious epidemic in the 21st century. Currently, it affects almost 425 million people worldwide in 2017, and this number will increase to 700 million in 2045.[1] Type 2 diabetes (T2D), previously non-insulin dependent diabetes, accounts for at least 90% of all cases of the disease.[2] The inhibition of dipeptidyl peptidase-4 (DPP-4) has been shown to be an effective treatment to improve glycemic control in patients with type 2 diabetes.[3] Some oral antidiabetic drugs show low tolerability during chronic treatment and are associated with unwanted side effects, such as hypoglycemia and weight gain.[4] Further understanding of the biological mechanism of dipeptidyl peptidase-4 (DPP-4) has contributed to the development of DPP-IV inhibitors as a new class of oral antidiabetic drugs.[5,6] To date, some inhibitors of DPP4 (Sitagliptin-1, Vildagliptin-2, Saxagliptin-3, Alogliptin-4 and Linagliptin-5) have been approved for the treatment of T2DM (Figure 1).[7–14] Efforts are being made in the development of new inhibitors of DPP-4, since there are some undesirable side effects in current drugs. Linagliptin-5, with xanthine scaffold, has been shown to be a highly potent and selective DPP-4 inhibitor.[15,16]

1,2,3-triazoles are five-member N-heterocyclic compounds and occur in a variety of bioactive molecules in medicinal chemistry research.[17–22] 1,2,3-triazoles derivatives have a broad spectrum of applications in various fields, such as pharmaceuticals, polymers, supramolecular chemistry, pesticides, bioconjugations, and surface science.[23–26] Bibliographic research has shown that 1,2,3-triazole derivatives are endowed with numerous therapeutic activities, such as antifungal,[27] antibacterial,[28] antitubercular,[29] antidiabetic,[30] anticancer,[31–33] anti-HIV,[34] antileishmanial,[35] and antiviral activities.[36] Compound **A** in Figure 2, a novel 1,2,3-triazole analogue of sitagliptin derivatives were reported by Haeil Park and his group in 2016. While evaluating its DPP4 inhibitory activity using sitagliptin as a reference drug, most compounds have shown good DPP4 inhibitory activity.[37] In addition, Compound **B** in Figure 3, the new 1,2,3-triazole analogues of the alogliptin derivatives were described by Qing and his coworkers in 2016, and some of the derivatives showed good DPP4 inhibitory activity.[38]

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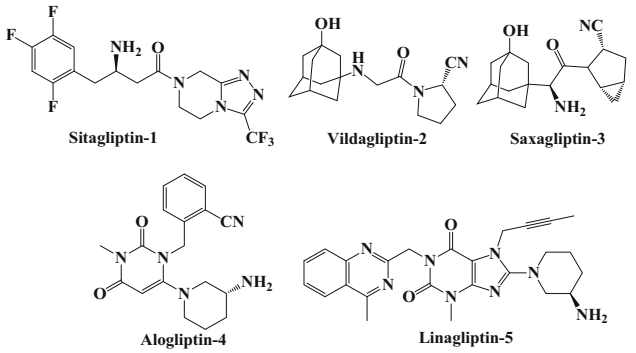


Figure 1. DPP4 inhibitors on the market and under development.

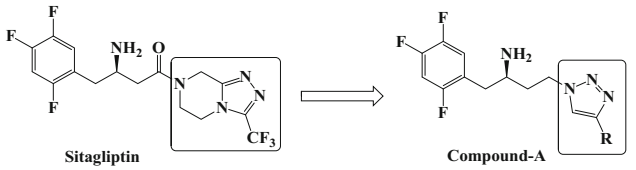


Figure 2. Sitagliptin analogues with a 1,2,3-triazole.

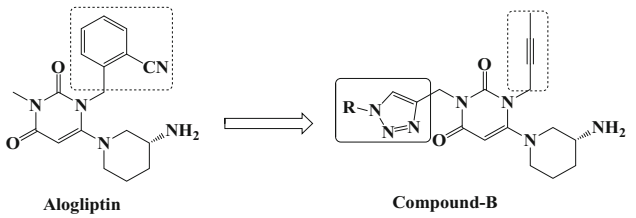


Figure 3. Alogliptin analogues with a 1,2,3-triazole.

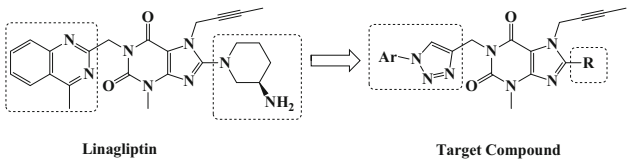


Figure 4. Linagliptin analogues with a 1,2,3-triazole.

The literature shows that compounds containing 1,2,3-triazole skeletons have remarkable biological activities. It has also been disclosed that triazoles having a linagliptin residue have not been reported. In light of this and in search of better new therapies for the DPP-4 inhibitor, it has been suggested that it would be worthwhile to design and synthesize the title compounds 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((1-aryl-1H-1,2,3-triazol-4-yl)methyl)-1H-purine-2,6 (3H,7H)-dione (6a-6j) and 7-(but-2-yn-1-yl)-3-methyl-8-morpholino-1-((1-aryl-1H-1,2,3-triazol-4-yl)methyl)-1H-purine-2,6(3H,7H)-dione (7a-7j) through readily available starting materials (Figure 4).

2. Experimental

All the reagents were of analytical grade or chemically pure. Analytical TLC was performed on silica gel 60 F_{254} plates. ^{1}H NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker 100 MHz spectrometer. Chemical shift values are given in ppm (δ) with tetramethylsilane as an internal standard. Mass spectral measurements were carried out by the EI method. Elemental analyses were performed on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers.

Synthesis of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-(prop-2-yn-1-yl)-1H-purine-2,6 (3H,7H)-dione (4): To a mixture of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1H-purine-2,6(3H,7H)-dione (**3**) (0.017 mol) and Cs_2CO_3 (0.052 mol) in DMF (50 mL) was added propargyl bromide (0.023 mol) at room temperature and stirred for 1 h. After completion of the reaction by TLC analysis, the resulting mixture was concentrated under vacuum to afford crude product. The crude was diluted with cold water (50 mL) and stirred for 1 h. The resulting precipitate was collected and crude product was purified by silica gel chromatography using an eluent (15% ethyl acetate in hexane). Yellow solid (71%), M.p. 75–77 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.11 (s, 2H, N-CH_2), 4.78 (s, 2H, N-CH_2), 3.57 (s, 3H, N-CH_3), 2.18 (s, 1H, -CH), 1.80 (s, 3H, -CH_3). ESI-MS: 336 $[M+2H]^+$; Anal. Calcd for $C_{13}H_{11}BrN_4O_2$: C, 46.59; H, 3.31; N, 16.72. Found: C, 46.51; H, 3.27; N, 16.68.

Synthesis of 7-(but-2-yn-1-yl)-3-methyl-8-morpholino-1-(prop-2-yn-1-yl)-1H-purine-2,6 (3H,7H)-dione (5): To a mixture of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-(prop-2-yn-1-yl)-1H-purine-2,6 (3H,7H)-dione (4) (0.006 mol) and K_2CO_3 (0.018 mol) in DMF (50 mL) was added morpholine (0.007 mol) at 75 °C temperature and stirred for 4 h. After completion of the reaction by TLC analysis, the resulting mixture was concentrated under vacuum to afford crude product. The crude was diluted with cold water (50 mL) and stirred for 1 h. The resulting precipitate was collected and crude product was purified by silica gel chromatography using an eluent (15% ethyl acetate in hexane). White solid (68%), M.p. 84–86 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.89 (d, J = 2.3 Hz, 2H, N-CH_2), 4.79 (d, J = 2.4 Hz, 2H, N-CH_2), 3.87–3.84 (m, 4H, 2-OCH_2), 3.54 (s, 3H,N-CH_3), 3.43–3.39 (m, 4H, 2-NCH_2), 2.16 (s, 1H, -CH), 1.82 (t, J = 2.2 Hz, 3H,-CH_3). ESI-MS: 342 $[M+H]^+$; Anal. Calcd for $C_{17}H_{19}N_5O_3$: C, 59.81; H, 5.61; N, 20.52. Found: C, 59.73; H, 5.57; N, 20.44.

General procedure for the synthesis of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((1-aryl-1H-1,2,3-triazol-4-yl)methyl)-1H-purine-2,6 (3H,7H)-dione (6a-6j) and 7-(but-2-yn-1-yl)-3-methyl-8-morpholino-1-((1-aryl-1H-1,2,3-triazol-4-yl)methyl)-1H-purine-2,6 (3H,7H)-dione (7a-7j)

To a stirred solution of alkyne (**4** or **5**) (1.0 mmol) and aryl azide (1.2 mmol) in THF (15 mL) was added CuI (10 mol%) and the reaction mixture was stirred at room temperature for 6–8 h. After completion of the reaction, the

reaction mixture was diluted with water (15 mL) and the product was extracted with ethylacetate (2×15 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated under vacuum and the crude product obtained was purified by column chromatography (hexane/ethyl acetate gradient) to afford the title compounds in good yields.

8-bromo-7-(but-2-yn-1-yl)-1-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (6a): Pale yellow solid (77%), M.p. 138–140 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H, triazole-H), 7.61–7.57 (m, 2H, Ar), 7.01–6.97 (m, 2H, Ar), 5.39 (s, 2H, N-CH_2), 5.13 (s, 2H,N-CH_2), 3.85 (s, 3H, O-CH_3), 3.56 (s, 3H, N-CH_3), 1.80 (s, 3H,-CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 159.76, 153.26, 150.96, 148.36, 143.81, 130.57, 127.85, 122.26, 121.84, 114.69, 108.60, 82.57, 71.24, 55.63, 37.20, 36.21, 29.93, 3.64; ESI-MS: 485 $[M+2H]^+$; Anal. Calcd for $C_{20}H_{18}BrN_7O_3$: C, 49.60; H, 3.75; N, 20.24. Found: C, 49.55; H, 3.69; N, 20.16.

8-bromo-7-(but-2-yn-1-yl)-1-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-methyl-1H-purine-2,6 (3H,7H)-dione (6b): Pale yellow solid (66%), M.p. 129–131 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H, triazole-H), 7.66 (d, J = 8.8 Hz, 2H, Ar), 7.47 (d, J = 8.8 Hz, 2H, Ar), 5.40 (s, 2H, N-CH_2), 5.12 (d, J = 2.4 Hz, 2H, N-CH_2), 3.56 (s, 3H, N-CH_3), 1.80 (t, J = 2.3 Hz, 3H,-CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 153.58, 150.95, 148.39, 144.33, 136.03, 132.84, 127.95, 122.32, 121.96, 121.52, 108.57, 82.60, 71.21, 37.22, 36.12, 29.94, 3.64; ESI-MS: 489 $[M+2H]^+$; Anal. Calcd for $C_{19}H_{15}BrClN_7O_2$: C, 46.69; H, 3.09; N, 20.06. Found: C, 46.63; H, 3.11; N, 20.01.

8-bromo-7-(but-2-yn-1-yl)-1-((1-(4-butylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (6c): Pale yellow solid (69%), M.p. 132–134 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H, triazole-H), 7.59 (d, J = 8.3 Hz, 2H, Ar), 7.30–7.26 (m, 2H, Ar), 5.40 (s, 2H, N-CH_2), 5.13 (d, J = 2.0 Hz, 2H, N-CH_2), 3.56 (s, 3H, N-CH_3), 2.65 (t, J = 2.3 Hz, 2H, Ar-CH_2-*CH_2*-*CH_2*-CH_3), 1.80 (s, 3H, -CH_3), 1.61–1.58 (m, 2H, Ar-*CH_2*-CH_2-CH_2-CH_3), 1.40–1.32 (m, 2H, Ar-CH_2-*CH_2*-*CH_2*-CH_3), 0.93 (t, J = 7.3 Hz, 3H, Ar-CH_2-CH_2-CH_2-*CH_3*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 153.61, 150.95, 148.37, 143.81, 129.56, 127.86, 120.63, 108.61, 82.58, 71.25, 37.21, 36.21, 35.20, 33.46, 29.94, 22.27, 13.93, 3.65; ESI-MS: 511 $[M+2H]^+$; Anal. Calcd for $C_{23}H_{24}BrN_7O_2$: C, 54.12; H, 4.74; N, 19.21. Found: C, 54.19; H, 4.82; N, 19.14.

8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-purine-2,6 (3H,7H)-dione (6d): Yellow solid (60%), M.p. 159–161 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H, triazole-H), 8.29 (ddd, J = 8.3, 2.2, 1.0 Hz, 1H, Ar), 8.22–8.15 (m, 2H, Ar), 7.73 (s, 1H, Ar), 5.43 (s, 2H, N-CH_2), 5.13 (q, J = 2.3 Hz, 2H, N-CH_2), 3.57 (s, 3H, N-CH_3), 1.81 (s, 3H, -CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 153.61, 150.97, 148.40, 144.18, 133.38, 127.95, 125.51, 122.65, 122.56, 120. 52, 116.55, 108.59, 82.61, 71.22, 37.22, 36.14, 29.95, 3.65; ESI-MS: 498 $[M+2H]^+$; Anal. Calcd for $C_{19}H_{15}BrN_8O_4$: C, 45.71; H, 3.03; N, 22.44. Found: C, 45.66; H, 2.95; N, 22.36.

8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-purine-2,6(3H,7H)-dione (6e): Pale red solid (61%), M.p. 165–167 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H, triazole-H), 7.96 (d, J = 7.0 Hz, 2H, Ar), 7.70–7.63 (m, 2H, Ar), 5.42 (s, 2H, N-CH_2), 5.13 (s, 2H, N-CH_2), 3.57 (s, 3H, N-CH_3), 1.80 (s, 3H, -CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 153.67, 150.31, 148.10, 143.90, 137.22, 131.25, 130.63 130.31, 127.90, 125.27–125.18 (m), 123.90 (s), 122.13 (d, J = 6.4 Hz), 108.52, 82.73, 71.23, 37.25, 36.19, 29.92, 3.66; ESI-MS: 523 $[M+2H]^+$; Anal. Calcd for $C_{20}H_{15}BrF_3N_7O_2$: C, 45.99; H, 2.89; N, 18.77. Found: C, 45.93; H, 2.83; N, 18.71.

8-bromo-7-(but-2-yn-1-yl)-1-((1-(3,4-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (6f): Pale yellow solid (70 %), M.p. 133–135 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H, triazole-H), 7.28 (d, J = 7.4 Hz, 1H, Ar), 7.17 (d, J = 7.6 Hz, 1H, Ar), 7.13 (s, 1H, Ar), 5.42 (s, 2H, N-CH_2), 5.13 (d, J = 2.3 Hz, 2H, N-CH_2), 3.56 (s, 3H, N-CH_3), 2.34 (s, 3H, Ar-CH_3), 2.01 (s, 3H, Ar-CH_3), 1.80 (s, 3H, -CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 153.88, 150.93, 148.30, 148.38, 130.87, 127.24, 125.22, 121.65, 121.37, 119.28, 117.44, 114.69, 108.30, 82.21, 71.60, 37.23, 36.13, 29.72, 22.26, 20.12, 3.66; ESI-MS: 483 $[M+2H]^+$; Anal. Calcd for $C_{21}H_{20}BrN_7O_2$: C, 52.29; H, 4.18; N, 20.33. Found: C, 52.21; H, 4.12; N, 20.25.

8-bromo-7-(but-2-yn-1-yl)-1-((1-(3,5-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (6g): Pale red solid (60%), M.p. 166–168 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H, triazole-H), 7.67 (d, J = 1.7 Hz, 2H, Ar), 7.41 (s, 1H, Ar), 5.40 (s, 2H, N-CH_2), 5.13 (d, J = 2.4 Hz, 2H, N-CH_2), 3.57 (s, 3H, N-CH_3), 1.81 (s, 3H, -CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 153.65, 150.80, 148.39, 144.33, 134.42, 127.65, 124.80, 123.02, 122.07, 120.23, 120.13, 108.42, 82.65, 71.23, 37.26, 36.12, 29.93, 3.64; ESI-MS: 522 $[M+2H]^+$; Anal. Calcd for $C_{19}H_{14}BrCl_2N_7O_2$: C, 43.62; H, 2.70; N, 18.74. Found: C, 43.54; H, 2.68; N, 18.66.

8-bromo-7-(but-2-yn-1-yl)-1-((1-(3,5-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (6h): Pale yellow solid (65%), M.p. 139–141 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H, triazole-H), 7.31 (s, 2H, Ar), 7.04 (s, 1H, Ar), 5.40 (s, 2H, N-CH_2), 5.13 (dd, J = 4.6, 2.2 Hz, 2H, N-CH_2), 3.56 (s, 3H, N-CH_3), 2.37 (s, 6H, 2A-CH_3), 1.80 (t, J = 2.3 Hz, 3H, -CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 153.57, 150.81, 148.62, 143.96, 130.62, 127.81, 119.36, 117.55 114.59, 108.62, 82.55, 71.37, 37.20, 36.21, 29.93, 21.63, 3.64; ESI-MS: 483 $[M+2H]^+$; Anal. Calcd for $C_{21}H_{20}BrN_7O_2$: C, 52.29; H, 4.18; N, 20.33. Found: C, 52.20; H, 4.12; N, 20.27.

8-bromo-1-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methyl)-7-(but-2-yn-1-yl)-3-methyl-1H-purine-2,6(3H,7H)-dione (6i): Yellow solid (65%), M.p. 157–159 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H, triazole-H), 7.65–7.58 (m, 4H, Ar), 5.40 (s, 2H, N-CH_2), 5.12 (d, J = 2.4 Hz, 2H, N-CH_2), 3.56 (s, 3H, N-CH_3), 1.80 (s, 3H, -CH_3). ESI-MS: 532 $[M+2H]^+$; Anal. Calcd for $C_{19}H_{15}Br_2N_7O_2$: C, 42.80; H, 2.84; N, 18.39. Found: C, 42.71; H, 2.74; N, 18.31.

8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-purine-2,6(3H,7H)-dione (6j): Yellow solid (61%), M.p. 163–165 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H, triazole-H), 8.16–8.11 (m, 2H, Ar), 7.96–7.92 (m, 2H, Ar), 5.45 (s, 2H, N-CH_2), 5.16–5.12 (m, 2H, N-CH_2), 3.58 (s, 3H, N-CH_3), 1.80 (s, 3H, -CH_3). ESI-MS: 500 $[M+2H]^+$; Anal. Calcd for $C_{19}H_{15}BrN_8O_4$: C, 45.71; H, 3.03; N, 22.44. Found: C, 45.68; H, 3.07; N, 22.36.

7-(but-2-yn-1-yl)-1-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-methyl-8-morpholino-1H-purine-2,6(3H,7H)-dione (7a): White solid (78%), M.p. 147–149 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H, triazole-H), 7.58 (d, J = 8.0 Hz, 2H, Ar), 6.99 (d, J = 8.0 Hz, 2H, Ar), 5.40 (s, 2H, N-CH_2), 4.90 (d, J = 4.0 Hz, 2H, N-CH_2), 3.87 (t, J = 4.0 Hz, 4H, 2-OCH_2), 3.84 (s, 3H, O-CH_3), 3.52 (s, 3H, N-CH_3), 3.40 (t, J = 4.0 Hz, 4H, 2-NCH_2), 1.81 (d, J = 4.0 Hz, 3H, -CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 159.76, 155.12, 153.66, 151.36, 147.81, 130.57, 127.85, 123.21, 118.41, 114.89, 104.89, 81.24, 72.57, 66.35, 55.74, 50.12, 36.21, 35.61, 29.76, 3.74; ESI-MS: 491 $[M+H]^+$; Anal. Calcd for $C_{24}H_{26}N_8O_4$: C, 58.77; H, 5.34; N, 22.84. Found: C, 58.77; H, 5.34; N, 22.84.

7-(but-2-yn-1-yl)-1-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-methyl-8-morpholino-1H-purine-2,6(3H,7H)-dione (7b): White solid (63%), M.p. 168–170 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H, triazole-H), 7.71–7.64 (m, 2H, Ar), 7.18 (dd, J = 8.8, 8.2 Hz, 2H, Ar), 5.40 (s, 2H, N-CH_2), 4.90 (d, J = 2.4 Hz, 2H, N-CH_2), 3.87–3.83 (m, 4H, 2-OCH_2), 3.53 (s, 3H, N-CH_3), 3.42–3.37 (m, 4H, 2-NCH_2), 1.82 (t, J = 2.3 Hz, 3H, -CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 155.57, 153.68, 151.53, 147.89, 136.33, 132.82, 129.95, 125.32, 123.52, 121.89, 104.53, 81.35, 72.53, 66.24, 50.13, 36.26, 35.67, 29.79, 3.73; ESI-MS: 495 $[M+H]^+$; Anal. Calcd for $C_{23}H_{23}ClN_8O_3$: C, 55.81; H, 4.68; N, 22.64. Found: C, 55.74; H, 4.63; N, 22.57.

7-(but-2-yn-1-yl)-1-((1-(4-butylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-methyl-8-morpholino-1H-purine-2,6(3H,7H)-dione (7c): White solid (69%), M.p. 150–152 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H, triazole-H), 7.58 (d, J = 8.4 Hz, 2H, Ar), 7.28 (s, 2H, Ar), 5.40 (s, 2H, N-CH_2), 4.90 (d, J = 2.3 Hz, 2H, N-CH_2), 3.87–3.83 (m, 4H, 2-OCH_2), 3.52 (s, 3H, N-CH_3), 3.41–3.36 (m, 4H, 2-NCH_2), 2.68–2.61 (m, 2H,, Ar-CH_2-CH_2-CH_2-CH_3), 1.81 (t, J = 2.2 Hz, 3H, -CH_3), 1.63–1.54 (m, 2H, Ar-CH_2-CH_2-CH_2-CH_3), 1.35 (d, J = 7.6 Hz, 2H, Ar-CH_2-CH_2-CH_2-CH_3), 0.93 (t, J = 7.3 Hz, 3H, Ar-CH_2-CH_2-CH_2-CH_3). ESI-MS: 517 $[M+H]^+$; Anal. Calcd for $C_{27}H_{32}N_8O_3$: C, 62.77; H, 6.24; N, 21.69. Found: C, 62.70; H, 6.21; N, 21.63.

7-(but-2-yn-1-yl)-3-methyl-8-morpholino-1-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-purine-2,6(3H,7H)-dione (7d): Yellow solid (68%), M.p. 155–157 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H, triazole-H), 7.72 (d, J = 7.5 Hz, 1H, Ar), 7.54–7.48 (m, 1H, Ar), 7.44 (t, J = 7.1 Hz, 1H, Ar), 7.36 (dd, J = 10.9, 4.5 Hz, 1H, Ar), 5.43 (s, 2H, N-CH_2), 4.90 (d, J = 2.1 Hz, 2H, N-CH_2), 3.89–3.82 (m, 4H, 2-OCH_2), 3.53 (s, 3H, N-CH_3), 3.43–3.36 (m, 4H, 2-NCH_2), 1.81 (s, 3H, -CH_3). ESI-MS: 506$[M+H]^+$; Anal. Calcd for $C_{23}H_{23}N_9O_5$: C, 54.65; H, 4.59; N, 24.94. Found: C, 54.61; H, 4.53; N, 24.88.

7-(but-2-yn-1-yl)-3-methyl-8-morpholino-1-((1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-purine-2,6(3H,7H)-dione (7e): Pale yellow solid (63%), M.p. 171–173 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H, triazole-H), 8.01 (d, J = 8.0 Hz, 2H, Ar), 7.78–7.68 (m, 2H, Ar), 5.45 (s, 2H, N-CH_2), 5.17 (s, 2H, N-CH_2), 3.86 (t, J = 4.0 Hz, 4H, 2-OCH_2), 3.58 (s, 3H, N-CH_3), 3.40 (t, J = 4.0 Hz, 4H, 2-NCH_2), 1.80 (s, 3H, -CH_3). ESI-MS: 529 $[M+H]^+$; Anal. Calcd for $C_{24}H_{23}F_3N_8O_3$: C, 54.54; H, 4.39; N, 21.20. Found: C, 54.50; H, 4.31; N, 21.15.

7-(but-2-yn-1-yl)-1-((1-(3,4-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-methyl-8-morpholino-1H-purine-2,6(3H,7H)-dione (7f): White solid (69%), M.p. 143–145 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H, triazole-H), 7.28 (s, 1H, Ar), 7.20–7.10 (m, 2H, Ar), 5.41 (s, 2H, N-CH_2), 4.90 (s, 2H, N-CH_2), 3.85 (d, J = 4.2 Hz, 4H, 2-OCH_2), 3.53 (s, 3H, N-CH_3), 3.40 (d, J = 4.1 Hz, 4H, 2-NCH_2), 2.34 (s, 3H, Ar-CH_3), 2.01 (s, 3H, Ar-CH_3), 1.81 (s, 3H, -CH_3). ESI-MS: 489 $[M+H]^+$; Anal. Calcd for $C_{25}H_{28}N_8O_3$: C, 61.46; H, 5.78; N, 22.94. Found: C, 61.41; H, 5.72; N, 22.86.

7-(but-2-yn-1-yl)-1-((1-(3,5-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-methyl-8-morpholino-1H-purine-2,6(3H,7H)-dione (7g): Pale yellow solid (60%), M.p. 181–183 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H, triazole-H), 7.66 (d, J = 1.6 Hz, 2H, Ar), 7.39 (d, J = 1.7 Hz, 1H, Ar), 5.39 (s, 2H, N-CH_2), 4.90 (d, J = 2.1 Hz, 2H, N-CH_2), 3.87–3.84 (m, 4H, 2-OCH_2), 3.53 (s, 3H, N-CH_3), 3.42–3.39 (m, 4H, 2-NCH_2), 1.82 (s, 3H, -CH_3). ESI-MS: 529 $[M+H]^+$; Anal. Calcd for $C_{23}H_{22}Cl_2N_8O_3$: C, 52.18; H, 4.19; N, 21.17. Found: C, 52.12; H, 4.11; N, 21.23.

7-(but-2-yn-1-yl)-1-((1-(3,5-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-methyl-8-morpholino-1H-purine-2,6(3H,7H)-dione (7h): White solid (69%), M.p. 150–152 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H, triazole-H), 7.31 (s, 2H, Ar), 7.02 (s, 1H, Ar), 5.39 (s, 2H, N-CH_2), 4.90 (d, J = 1.9 Hz, 2H, N-CH_2), 3.87–3.82 (m, 4H, 2-OCH_2), 3.53 (s, 3H, N-CH_3), 3.41–3.36 (m, 4H, 2-OCH_2), 2.37 (s, 6H,,2Ar-CH_3), 1.82 (s, 3H, -CH_3). ^{13}C-NMR (100 MHz,

$CDCl_3$): δ_C 155.53, 153.96, 151.42, 147.74, 139.55, 130.18, 121.72, 118.14, 104.67, 81.81, 72.96, 66.45, 50.19, 36.01, 35.62, 29.77, 21.31, 3.75; ESI-MS: 489 $[M+H]^+$; Anal. Calcd for $C_{25}H_{28}N_8O_3$: C, 61.46; H, 5.78; N, 22.94. Found: C, 61.41; H, 5.72; N, 22.88.

1-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methyl)-7-(but-2-yn-1-yl)-3-methyl-8-morpholino-1H-purine-2,6(3H,7H)-dione (7i): Pale yellow solid (65%), M.p. 170–172 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H, triazole-H), 7.68–7.53 (m, 4H, Ar), 5.39 (s, 2H, N-CH_2), 4.89 (d, J = 2.2 Hz, 2H, N-CH_2), 3.91–3.80 (m, 4H, 2-OCH_2), 3.52 (s, 3H, N-CH_3), 3.45–3.33 (m, 4H, 2-NCH_2), 1.81 (s, 3H, -CH_3). ESI-MS: 540 $[M+2H]^+$; Anal. Calcd for $C_{23}H_{23}BrN_8O_3$: C, 51.22; H, 4.30; N, 20.77. Found: C, 51.16; H, 4.33; N, 20.71.

7-(but-2-yn-1-yl)-3-methyl-8-morpholino-1-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-purine-2,6(3H,7H)-dione (7j): Yellow solid (60%), M.p. 182–184 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H, triazole-H), 7.66 (d, J = 8.8 Hz, 2H, Ar), 7.46 (d, J = 8.8 Hz, 2H, Ar), 5.40 (s, 2H, N-CH_2), 4.89 (d, J = 2.3 Hz, 2H, N-CH_2), 3.87–3.82 (m, 4H, 2-OCH_2), 3.53 (s, 3H, N-CH_3), 3.42–3.37 (m, 4H, 2-OCH_2), 1.82 (s, 3H, -CH_3). ESI-MS: 506 $[M+H]^+$; Anal. Calcd for $C_{23}H_{23}N_9O_5$: C, 54.65; H, 4.59; N, 24.94. Found: C, 54.57; H, 4.51; N, 24.86.

In vitro assay for inhibition of DPP-4: DPP-4 was extracted from confluent Sf9 cells. The activity was measured as described, using the Gly-Pro-p-nitroanilide substrate, which can be decomposed by DPP-4 into Gly-Pro and p-nitroaniline. Compounds **6a** to **7j** were dissolved in an aqueous solution of 1% DMSO and incubated at a fixed value of 50 to 250 nM/mL tested. Compounds with an inhibition rate of more than 50% entered the second round of selection in which the inhibitory concentration of 50% (IC_{50}) was determined and the result was listed in Table 1. The inhibitory rate relative to the control without inhibitor was calculated and IC50 value was determined by nonlinear regression fitted by GraphPad Prism 5.

3. Results and Discussion

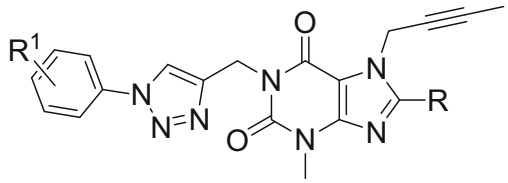
The desired compounds are the new 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((1-aryl-1H-1,2,3-triazol-4-yl)Methyl)-1H-purine-2,6(3H,7H)-dione (**6a-6j**) and 7-(but-2-yn-1-yl) -3-methyl-8-morpholino-1-((1-aryl-1H-1,2,3-triazol-4-yl) methyl)-1H-purine-2,6(3H, 7H)-dione (**7a-7j**) were synthesized from 3-methyl-1H-purine 2,6 (3H,7H)-dione (**1**). 3-Methyl-1H-purine-2,6(3H,7H)-dione (**1**) was allowed to react with bromine in acetic acid in the presence of sodium acetate at room temperature for 2 h to give an intermediate of 8-bromio-3-methyl-1H-purin-2,6(3H,7H)-dione (**2**). Subsequent treatment of 2 with 1-bromo-2-butyne in the presence of DIEA gave 8-bromo-7-(but2)-yn-1-yl)-3-methyl-1H-purine-2,6(3H,7H)-dione(**3**).[16] Intermediate **3** interacted with propargyl bromide in the presence of Cs_2CO_3 in DMF at room temperature for 1 h to give a key intermediate, 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-(prop-2-yn-1-yl)-1H-purine-2,6(3H, 7H)-dione (**4**). Subsequent nucleophilic substitution of bromine by morpholine gave another key intermediate, 7-(but-2-yn-1-yl)-3-methyl-8-morpholino-1-(prop-2-yn-1-yl)-1H-Purine-2,6(3H, 7H)-dione (**5**). The key step in the synthesis, that is, additicon of the 1,3-dipolar cycle of the terminal alkyne (**4** or **5**) with various aryl azides using a catalytic amount of copper iodide at room temperature, gave the corresponding 1,4-disubstituted 1,2,3-triazoles (**6a-6j** and **7a-7j**) in good to excellent yields (Scheme 1).[39]

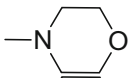
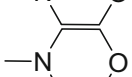
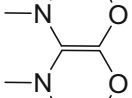
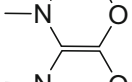
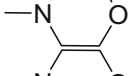
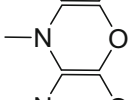
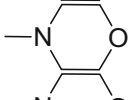
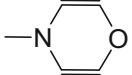
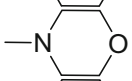
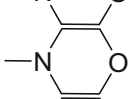
The structures of the newly synthesized compounds (**6a–7j**) were confirmed by ^{1}H-NMR, ^{13}C-NMR, ESI-MS and elemental (CHN) analysis data. All the spectral and analytical data of the synthesized compounds were in full agreement with the proposed structures and also discussed for a representative compound **6a**. From the ^{1}H NMR spectrum, the presence of the signals that appeared at δ 7.98 (s, 1H, CH, triazole), δ 7.61–6.97 (m, 4H, Ar-H), 5.39 (s, 2H, N-CH_2), 5.13 (s, 2H,N-CH_2), 3.85 (s, 3H, O-CH_3), 3.56 (s, 3H, N-CH_3), and δ 1.80 (s, 3H,-CH_3) confirmed the presence of required protons. From the ^{13}C NMR, the presence of carbon signals at 159.76 ppm (***C***-OCH_3), 82.57, 71.24 ppm (2C, alkyne), 55.63 ppm (-O***C***H_3), 37.20, 36.21 ppm (2N-***C***H_2), 29.93 ppm (N-***C***H_3), and 3.64 (C-***C***H_3) confirmed the presence of characteristic carbon signals. The presence of [M+2H] ion peak at m/z 485 in ESI-Mass spectra and the elemental analysis (CHN) data (C, 49.55; H, 3.69; N, 20.16) confirmed molecular formula ($C_{20}H_{18}BrN_7O_3$) of compound **6a**.

3.1 *DPP-4 Activity and SAR analysis of target compounds*

DPP-4 was extracted from confluent Sf9 cells. The activity was measured as described,[40,41] using the Gly-Pro-p-nitroanilide substrate, which can be decomposed by DPP-4 into Gly-Pro and p-nitroaniline. The compounds with good inhibition rates at 100 nM were further selected to determine their IC_{50} values. The inhibitory activities were depicted in Table 1. As far as the structure-activity relationship (Figure 5) was concerned, variations at 8-morpholino-1,2,3-triazolo-1H-purine (**7a-7j**) exhibited better inhibitory effect for DPP-4 than 8-bromo-1,2,3-triazolo-1H-purine (**6a-6j**). A wide variety of substituents were introduced to benzene ring. As shown in Table 1, some of the compounds confirmed

Table 1. *In vitro* DPP-4 inhibitory activities of compounds **6a-7j**.



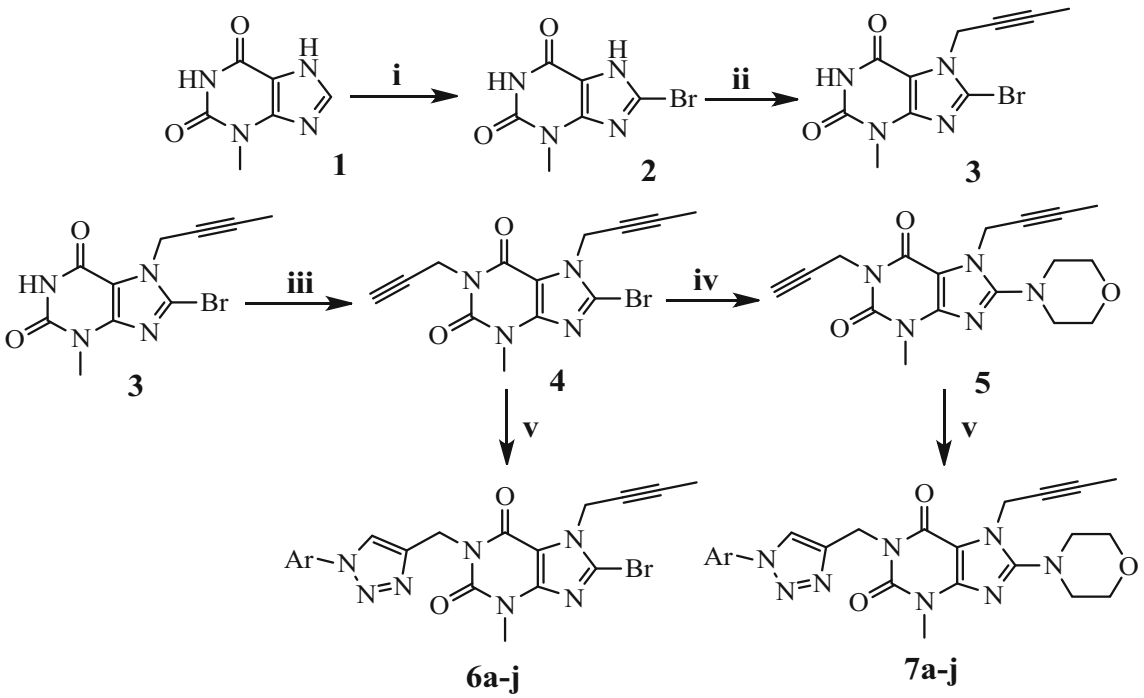
Compound	R	R1	% Inhibition at 100 nM	IC_{50} (nM) [a,b]
6a	Br	4-OCH_3	14.31±1.34	NT
6b	Br	4-Cl	24.29±1.28	NT
6c	Br	4-C_4H_9	28.82±1.69	NT
6d	Br	3-NO_2	19.62±1.33	NT
6e	Br	3-CF_3	**57.72±1.86**	**87.41**
6f	Br	3, 4-diMe	8.18±2.44	NT
6g	Br	3,5-diCl	34.24±1.65	NT
6h	Br	3, 5-diMe	17.88±1.31	NT
6i	Br	4-Br	28.15±1.29	NT
6j	Br	4-NO_2	20.98±1.03	NT
7a		4-OCH_3	21.83±1.33	NT
7b		4-Cl	**72.53±1.76**	**67.98**
7c		4-C_4H_9	34.52±1.29	NT
7d		3-NO_2	31.30±1.41	NT
7e		3-CF_3	**78.53±1.24**	**16.34**
7f		3, 4-diMe	16.32±1.30	NT
7g		3,5-diCl	**76.48±1.64**	**29.87**
7h		3, 5-diMe	28.98±1.36	NT
7i		4-Br	33.43±2.61	NT
7j		4-NO_2	31.44±1.71	NT
Alogliptin	–	–	**88.16±3.21**	**6.28**
Linagliptin	–	–	**98.26±3.12**	**1.32**

Biologically potent molecules are shown in bold

[a]Measured in three independent experiments.

[b]NT: not tested.

significant *in vitro* DPP-4 inhibitory activity. Among all of the compounds tested, compound **7e**, having a morpholine at 8th position of xanthine and 3-(trifluoromethyl) group benzene ring, exhibited potent activity with IC_{50} values of **16.34** *n*M. Similarly, compound **7g** having a morpholine at 8th position of xanthine and 3,5-dichloro group benzene ring exhibited good activity with IC_{50} values of **29.87***n*M. However, the addition of monochloro atom at para position of benzene ring somewhat reduced the DPP-4 inhibitory potency (**7b**) as compared to the meta-dichloro derivative (with the IC_{50} of **67.98** nM). Similarly, compound **6e** having bromine at 8th



Scheme 1. Reagents and conditions**:** (i) Br_2, AcONa, AcOH, r.t.–60 °C, 2 h; (ii) 1-Bromo-2-butyne, DIEA, DMF, 80 °C, 6 h; (iii) Propargyl bromide, Cs_2CO_3, DMF, rt, 1h; (iv) Morpholine, K_2CO_3, DMF, 75 °C, 4h; (v) ArN_3, CuI, THF, rt, 6–8 h.

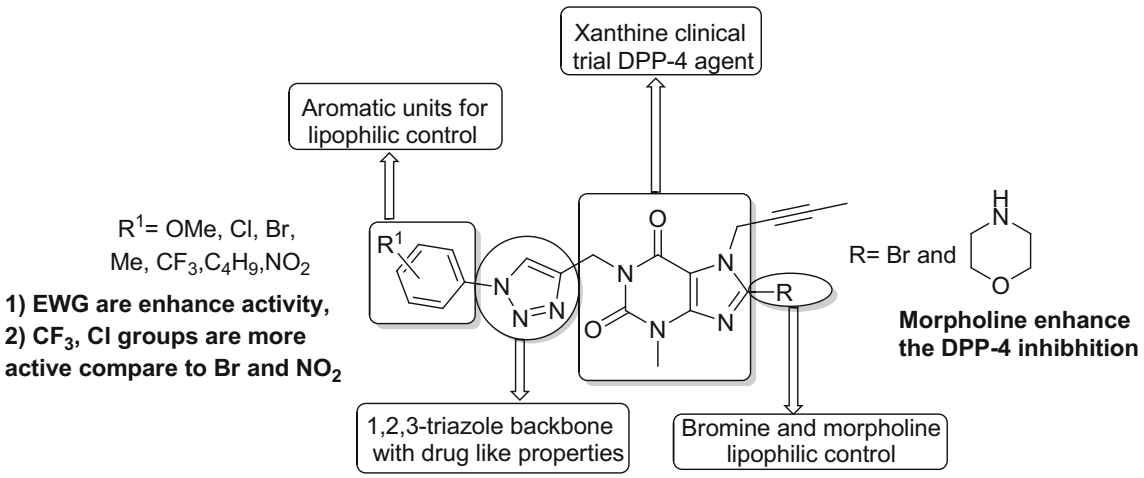


Figure 5. SAR of target 1,2,3-triazole based Xanthine derivatives.

position of xanthine and 3-(trifluoromethyl) group benzene ring has shown good activity with IC_{50} values of **87.41** nM. In addition, the presence of electron-donating groups like methyl, methoxy, and *n*-butyl present at benzene ring reduced inhibitory activity (compounds **6a**, **6c**, **6f**, **6h**, **7a**, **7c**, **7f** and **7h**). Among all electron-withdrawing groups, nitro and bromo groups present at benzene ring (compounds **6d**, **6i**, **6j**, **7d**, **7i** and 7j) displayed slightly reduced inhibitory potency compared to chloro and 3-(trifluoromethyl) (6b, 6e, 6g, 7b, 7e, and 7g). Compound **7e** exhibited 5.3-fold, **7g** exhibited 3.0-fold, and **7b** exhibited 1.2-fold more potent inhibitory activity compared to compound **6e**. Finally, a search for the inhibitory activities of these triazole-based xanthine derivatives showed that compound **7e**, **7g** and **7b** display attractive inhibitory, but their activities were still less potent than standard drugs alogliptin (IC_{50} = 6.28 nM) and linagliptin (IC_{50} = 1.32 nM).

4. Conclusions

In conclusion, we have synthesized a series of new twenty 1,2,3-triazole based Xanthine derivatives in good to excellent yields *via* copper-catalyzed [3+2] cycloaddition reaction and well-characterized by

^{1}HNMR, ^{13}CNMR, mass and elemental analysis. The newly synthesized compounds were evaluated for their dipeptidyl peptidase-4 activity using the Gly-Pro-p-nitroanilide substrate, which can be decomposed by DPP-4 into Gly-Pro and p-nitroaniline. The substituents were introduced to substituted phenyl group at N-1 position of 1,2,3-triazole, and the resulting compounds were apparent weak to moderate DPP-4 inhibitory activities. Among all compound **7e** is proved to possess significant DPP-4 inhibitory activity. These results are suggesting that a simple modification of compound **7e** can be better candidates for future investigations to produce new drugs.

Supplementary Information (SI)

Copies of ^{1}H-NMR and ^{13}C-NMR of **3, 4, 5a-j** and **6a-j** are available at www.ias.ac.in/chemsci.

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