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Synthesis and Characterization of different (1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-1-methyl-1*H*-1,2,4-triazoloamines

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ABSTRACT

To a stirred suspended solution of 1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidine-4-carboxylic acid **(1)** were added oxalyl chloride (0.47 mL, 5.481 mmol) and dry DMF catalytic at 0°C and reaction mixture was stirred at rt for 3h to obtain 1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidine-4-carbonyl chloride **(2)** to obtain 5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-4H-1,2,4-triazol-3-amine **(3X).**Compound **(3X)** and phthalic anhydride was stirred at 170°C for 40 min to give 2-(5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl)piperidin-4-yl)-4H-1,2,4-triazol-3-yl)isoindoline-1,3-dione**(4).**This is further treated with ammonia solution and stirred for 3 h to obtain 3-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-1-methyl-1*H*-1,2,4-triazol-5-amine **(3B) &** 5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-1-methyl-1*H*-1,2,4-triazol-3-amine **(3C)**

KEYWORDS 1,2,4-triazoles, piperidine, TBAB.

INTRODUCTION

Triazole exists in two isomeric forms such as 1,2,4-triazole and 1,2,3-triazole [1]. The SAR studies of triazole derivative reveals that substitution on positions 3, 4 and 5 of triazole ring can be varied but the greatest changed in physicochemical properties and biological profile is exerted by the groups attached to the nitrogen atom at the 4th position [2]. It favours the hydrogen bonding and is also constant for metabolic degradation, which could be favourable in increasing solubility as well as in binding bimolecular targets [3]. Novel triazole drugs naked and developed by smearing bio isosteric replacement system with encompassing biological activities also captured a special attention in medicinal field. [4].

1,2,4-Triazoles are key scaffold in a large number of molecular architectures that display antibacterial, anti-fungal, anti-tubercular, anti-oxidant, anti-tumour, analgesic, anti-inflammatory or pesticidals. [5-12]

Heterocycles are a very imperative compounds and make up more than half of all known organic chemicals [13]. Among them, heterocyclic amines, particularly pyrrolidine and piperidine derivatives, have attracted considerable attention because these are important

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structural motifs in a wide variety of applications including pharmaceuticals, natural products, and biologically active compounds such as pergolide, scopolamine, morphine, nicotine, hygrine, and procyclidine [14-16]. Herein, we report the synthesis and characterization of different (1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-1-methyl-1*H*-1,2,4-triazoloamines are depicted in Scheme I.

EXPERIMENTAL SECTION

Material and Methods

All the commercially available chemicals and reagents were further used without purification. The purity of the compounds was analyzed by TLC using Merck 60F254 silica gel plates. The ^{1}H & ^{13}CNMR spectra recorded with a Mercury Plus spectrometer had chemical shifts that were referenced to TMS. ESI mass spectra were obtained using a Shimadzu QP5050A quadrupole-based mass spectrometer.

RESULTS AND DISCUSSIONS

Synthetic scheme of Target-3A, 3B and 3C:

Synthesis of 2-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidine-4-carbonyl) hydrazine-1-carboximidamide: (2)

To a stirred suspended solution of 1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidine-4-carboxylic acid **(1)** (550 mg, 1.827 mmol) in dry DCM (20 mL) were added oxalyl chloride (0.47 mL, 5.481 mmol) and dry DMF catalytic at 0°C and reaction mixture was stirred at rt for 3h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated under inert atmosphere to obtain 1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidine-4-carbonyl chloride **(2)** as brown solid (660 mg, crude). Crude compound was used as such in next step.

Synthesis of 5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-4*H*-1,2,4-triazol-3-amine: (3X)

The above crude compound was dissolved in 4N NaOH (8 mL) and stirred at 110°C for 40 minutes. Progress of reaction was monitored by TLC. The reaction was diluted with cold water (20 mL) and extracted with EtOAc (3x50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography (silica gel 100-200 mesh, eluted with 5-10 % of MeOH in DCM) to obtain 5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-4H-1,2,4-triazol-3-amine **(3X)** (125 mg, 20.12 % yield) as off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.52 (br-s, 1H), 8.46 (d, J = 1.6 Hz, 1H), 8.31-8.18 (m, 2H), 7.62 (d, J = 7.6 Hz, 1H), 7.27 (dd, J = 2.4, 8.4 Hz, 1H), 7.1-6.98 (m, 1H), 5.75 (br-s, 2H), 3.43-3.31 (m, 2H), 2.7 (t, J = 12 Hz, 2H), 1.8-1.66 (m, 2H), 1.64-1.45 (m, 2H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 165.79, 163.69, 161.45 (2C), 155.79, 152.13, 147.78, 146.20, 133.29, 132.59, 130.77(2C), 129.60, 116.20, 108.94, 47.46, 27.04.
Chemical Formula: $C_{17}H_{18}FN_7$, Mass: (m/z) 339.16.

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Synthesis of 2-(5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl)piperidin-4-yl)-N-methyl-4*H*-1,2,4-triazol-3-yl)isoindoline-1,3-dione: (4 &5)

Step-3: In a sealed tube containing 5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-4*H*-1,2,4-triazol-3-amine **(3X)** (250 mg, 0.735 mmol) and pthalic anhydride (120.51 mg, 0.808 mmol) was stirred at 170°C for 40 min. Progress of reaction was monitored by TLC. The crude compound was washed with pentane and dried to obtain 2-(5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl)piperidin-4-yl)-4H-1,2,4-triazol-3-yl)isoindoline-1,3-dione**(4)** (330 mg, crude) as brown colour solid and used as such in next step without purification.

Step-4: To a stirred solution of 2-(5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl)piperidin-4-yl)-4H-1,2,4-triazol-3-yl)isoindoline-1,3-dione (330 mg, 0.705 mmol) in dry DMF (10 mL) was added sodium hydride (60%, 42.28 mg, 1.057 mmol) at 0°C and stirred for 90 minutes. Then methyl iodide (0.065 mL, 1.057 mmol) was added and stirred at 0-5°C for 5 h. The progress of the reaction was monitored by TLC. The reaction was quenched with water, then extracted with EtOAc (3x50 mL), organic layer was dried over Na_2SO_4 and concentrated under reducer pressure. The crude compound was purified by column chromatography (silica gel 100-200 mesh, eluted with 0-5% of MeOH in DCM) to obtain 2-(5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl)piperidin-4-yl)-N-methyl-4H-1,2,4-triazol-3-yl)isoindoline-1,3-dione as a off-white solid (120 mg, 33.78 % yield). Exact position of methyl was confirmed in next step.

1H NMR (400 MHz, DMSO-d_6): δ 8.47 (d, J = 2.4 Hz, 1H), 8.33-8.2 (m, 2H), 8.05-7.9 (m, 4H), 7.63 (dd, J = 2, 7.6 Hz, 1H), 7.28 (dd, J = 2.8, 8.4 Hz, 1H), 7.06 (dd, J = 4.8, 7.2 Hz, 1H), 3.88 (s, 3H), 3.45 (d, J = 12.8 Hz, 2H), 3.1 (t, J = 4 hz, 1H), 2.78 (t, J = 12 Hz, 2H), 1.82 (d, J = 11.2 Hz, 2H), 1.72-1.54 (m, 2H).

Step 5: Synthesis of 3-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-1-methyl-1*H*-1,2,4-triazol-5-amine & 5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-1-methyl-1*H*-1,2,4-triazol-3-amine: (3B, 3C)

The RBF containing 2-(5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-N-methyl-4*H*-1,2,4-triazol-3-yl) isoindoline-1,3-dione (120 mg, 0.248 mmol) was added ammonia solution (25%, 6 mL) and stirred for 3 h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated, crude was diluted with water, solid was filtered and dried. The crude compound was purified by preparative TLC to obtain 3-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-1-methyl-1*H*-1,2,4-triazol-5-amine **(3B)**

(12 mg, 13.68 % yield) as an off-white solid **&** 5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-1-methyl-1*H*-1,2,4-triazol-3-amine **(3C)** as an off-white solid (58 mg, 66.13 % yield). Both compounds were confirmed by 1H NMR& ^{13}CNMR

3-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-1-methyl-1*H*-1,2,4-triazol-5-amine: (3B)

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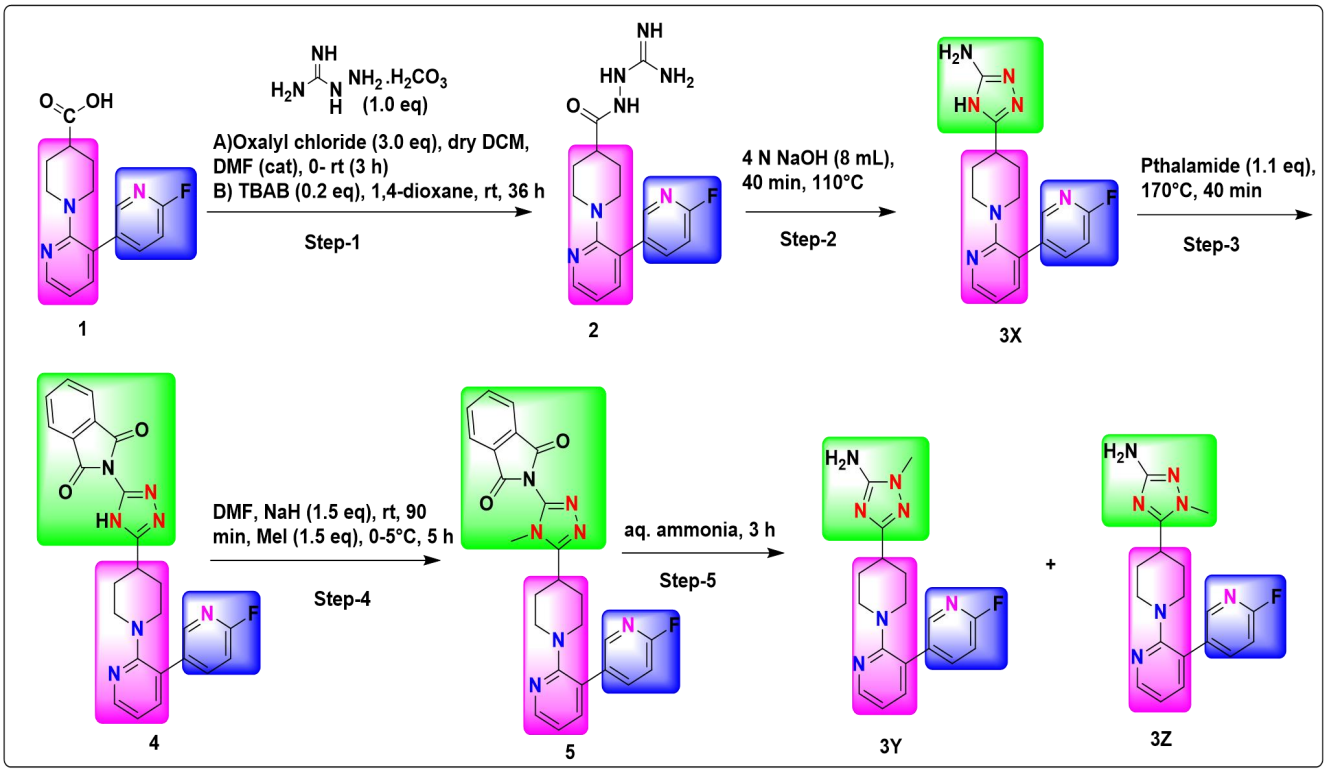
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (d, J = 2 Hz, 1H), 8.28-8.2 (m, 2H), 7.61 (dd, J = 1.6, 7.6 Hz, 1H), 7.27 (dd, J = 2.8, 8.8 Hz, 1H), 7.03 (dd, J = 4.8, 7.6 Hz, 1H), 5.99 (s, 2H, D_2O exchange), 3.41 (s, 3H), 3.38-3.32 (m, 1H), 2.75-2.63 (m, 2H), 2.48-2.38 (m, 2H), 1.77-1.66 (m, 2H), 1.6-1.46 (m, 2H).^{13}C NMR (100 MHz, DMSO-d_6) δ 165.79, 163.69, 161.45, 159.15, 152.49, 147.78, 146.20, 133.29, 132.59, 130.77, 129.60, 116.20, 109.16, 47.46, 35.49, 29.99, 26.56.

Chemical Formula: $C_{18}H_{20}FN_7$, Exact Mass: 353.18.

5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl)piperidin-4-yl)-1-methyl-1*H*-1,2,4-triazol-3-amine: (3C)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (d, J = 2 Hz, 1H), 8.3-8.18 (m, 2H), 7.63 (dd, J = 1.6, 7.6 Hz, 1H), 7.29 (dd, J = 2.8, 8.4 Hz, 1H), 7.05 (dd, J = 5.2, 7.2 Hz, 1H), 5.06 (s, 2H, D_2O exchange), 3.51 (s, 3H), 3.4 (d, J = 12.4 Hz, 2H), 2.86-2.62 (m, 3H), 1.71-1.5 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.79, 163.69, 161.45, 161.07, 156.13, 147.78, 146.20, 133.29, 132.65, 130.77, 129.60, 116.20, 108.94, 47.46, 35.28, 29.70, 27.54.

Chemical Formula: $C_{18}H_{20}FN_7$ Exact Mass: 353.18



Scheme I Synthesis of different (1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-1-methyl-1*H*-1,2,4-triazoloamines

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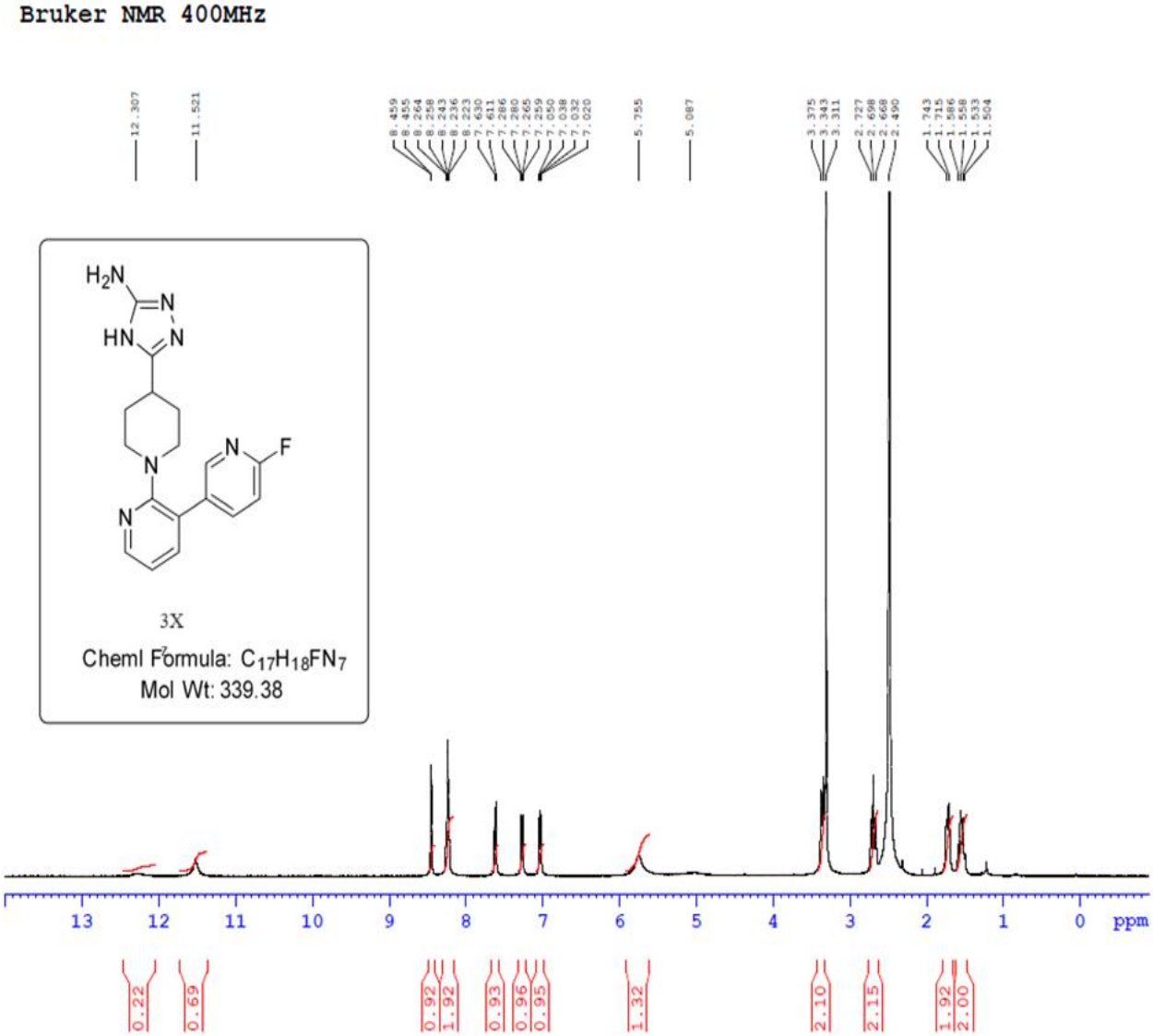

[1]HNMR (400 MHz, DMSO-d6) of 5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-4*H*-1,2,4-triazol-3-amine: (3X)

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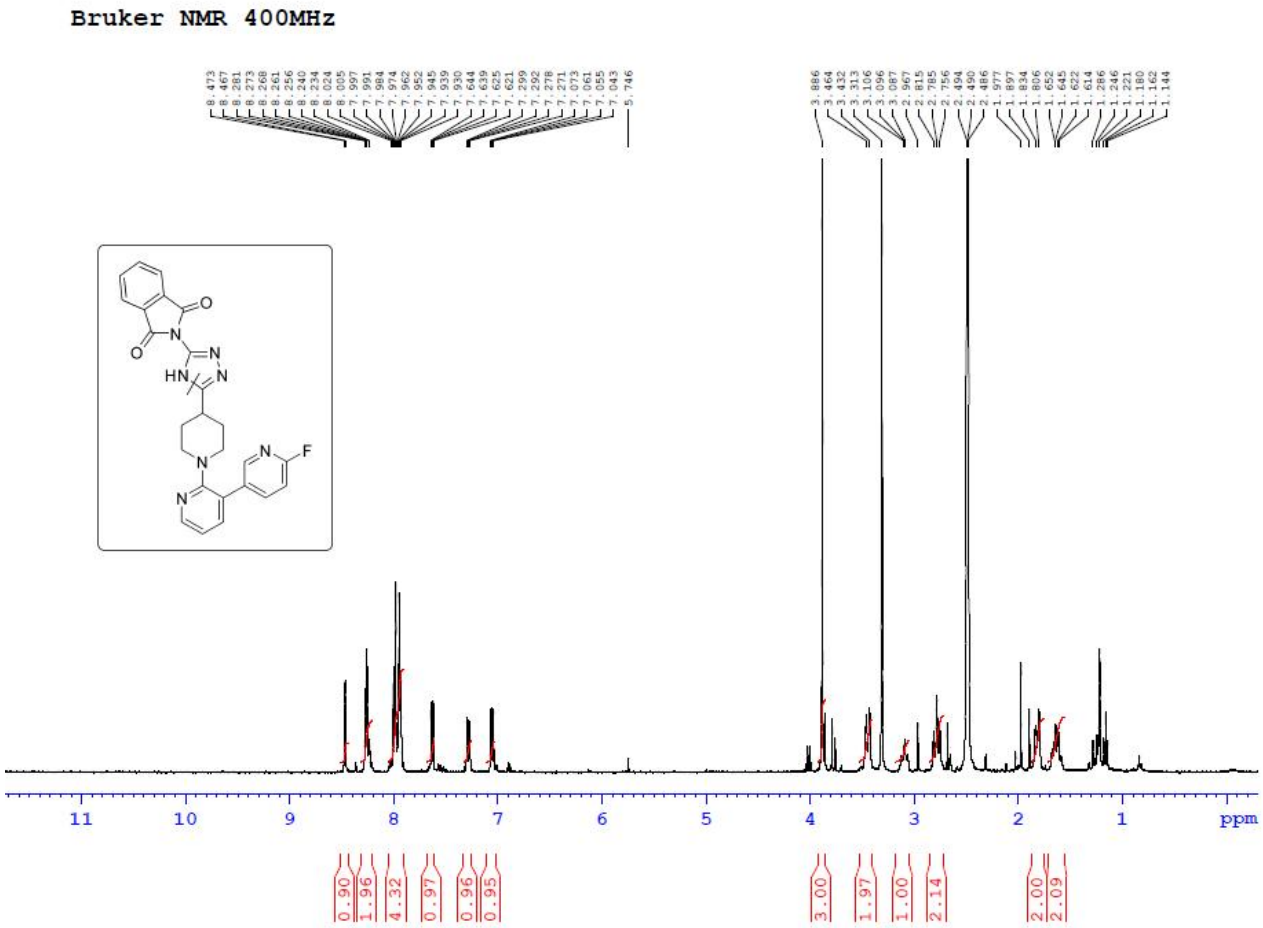

[1]HNMR (400 MHz, DMSO-d6) of compound (4)

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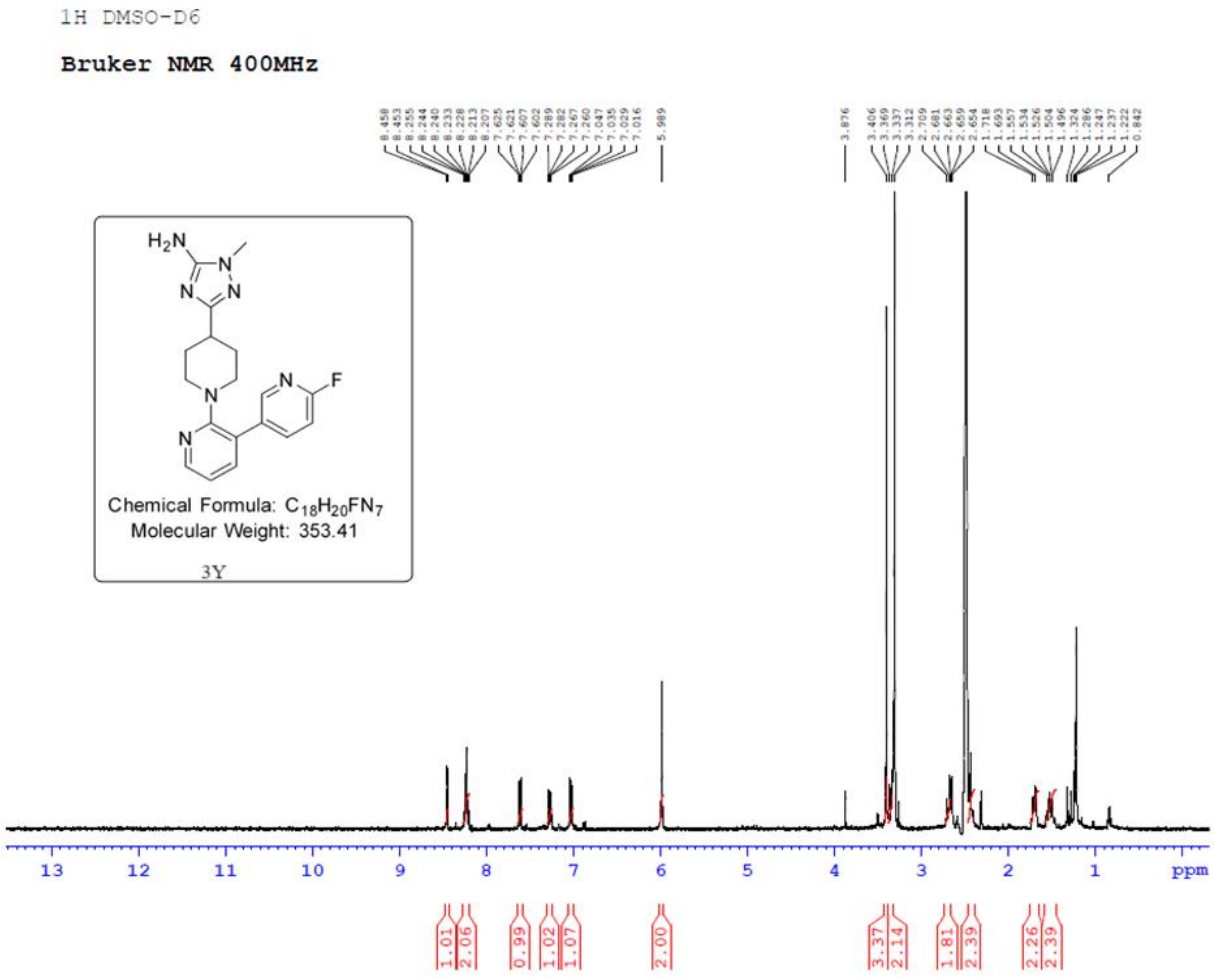

[1]HNMR (400 MHz, DMSO-d6) of 3-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-1-methyl-1*H*-1,2,4-triazol-5-amine: (3Y)

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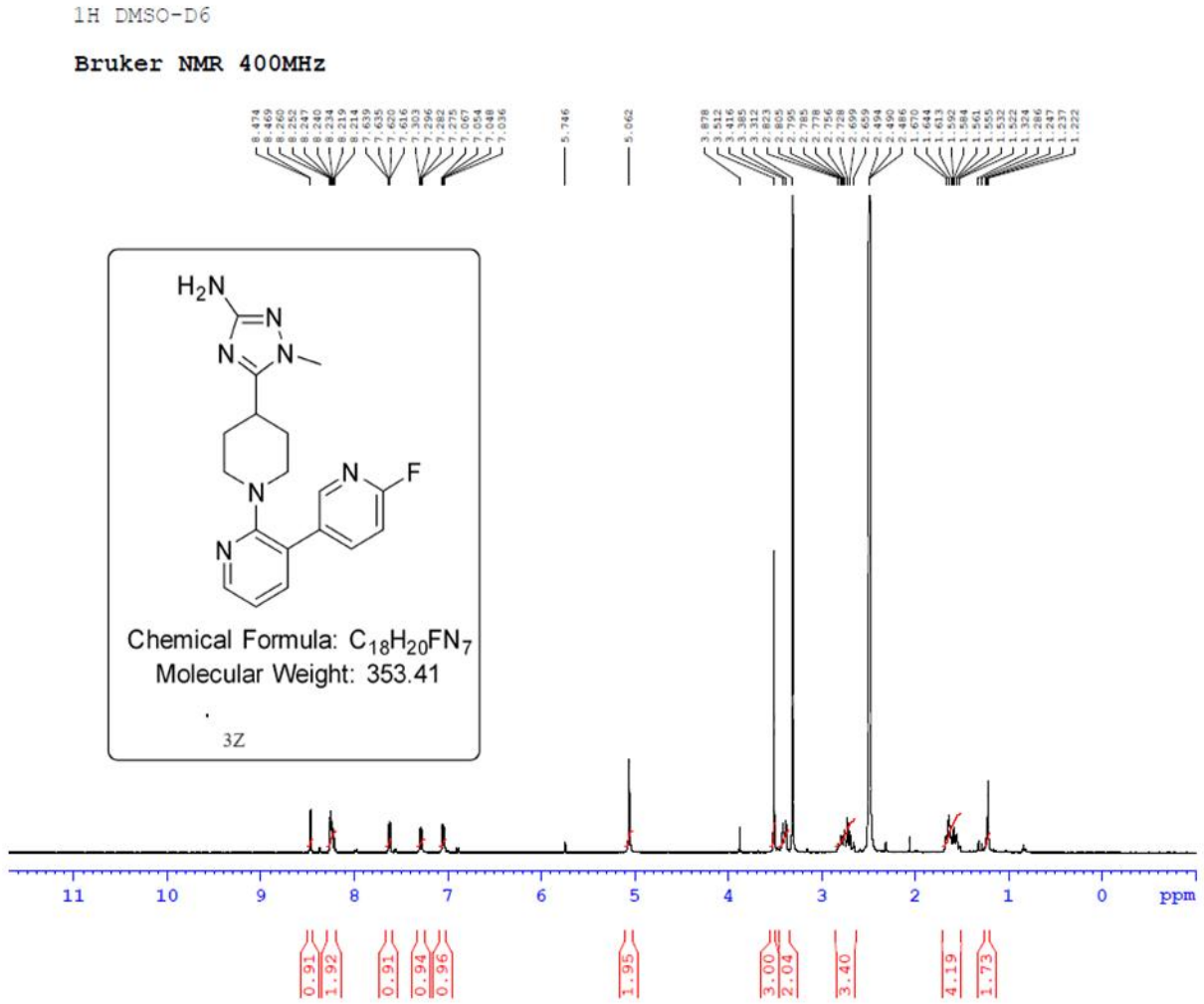

[1]HNMR (400 MHz, DMSO-d6) of 5-(1-(6'-fluoro-[3,3'-bipyridin]-2-yl)piperidin-4-yl)-1-methyl-1*H*-1,2,4-triazol-3-amine: (3C)

CONCLUSION

Herein, we have described the synthesis of different (1-(6'-fluoro-[3,3'-bipyridin]-2-yl) piperidin-4-yl)-1-methyl-1*H*-1,2,4-triazoloamines are depicted.

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