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Design and Synthesis, Characterization of series of different 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1,8-naphthyridine scaffolds

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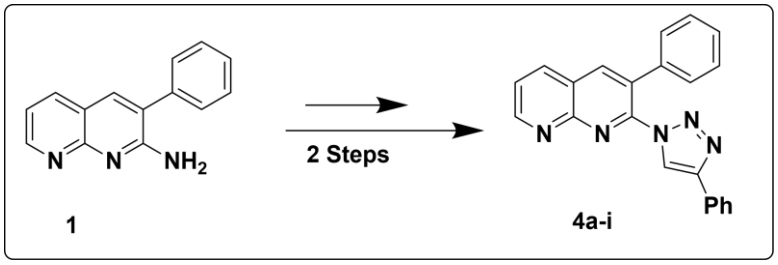
ABSTRACT

Herein, we have depicted the two step synthesis of series of different 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1,8-naphthyridine scaffolds through azide formation followed [3+2] click protocol cyclo addition by means of $CuSO_4.5H_2O$ and sodium ascorbate namely Sharpless catalyst to give promising yields of triazoles 4a-i shown in Scheme I and further confirmed by spectral and elemental analysis from Table 1 to 4.



Graphical Abstract

KEYWORDS 1,2,3-triazole,1,8-naphthyridine, $CuSO_4.5H_2O$ and sodium ascorbate, $TMSN_3$

INTRODUCTION

N-heterocycles are employed for medicines, dyes, elastic chemicals and adhesives.[1] Searching for the new agent is the most difficult tasks for the medicinal chemist. Due to their usefulness in a variety of applications, the synthesis of high *N*-containing heterocyclic structures has fascinated budding interest in the last era, applications like explosives, propellants, pyrotechnics and particularly chemotherapy.

Due to its wide range of actions,[2] low toxicity, strong pharmacokinetic and pharmacodynamic profiles, 1,2,3 & 1,2,4-triazole has drawn considerable interest from the 1,2,3-triazole to medicinal chemists of 20 years. The triazoles manufactured from aminoguanidine set-up on large scale, useful as herbicides.[3] *N*-substituted triazole and 1,8-naphthyridine with another substituent and it exhibited biological activity such as anti-inflammatory,[4] anti-convulsant,[5] anti-cancer,[6] anti-mycobacterial,[7] anti-oxidant [8] and anti-malarials.[9] Herein, we design, synthesis and characterization of target is shown below.

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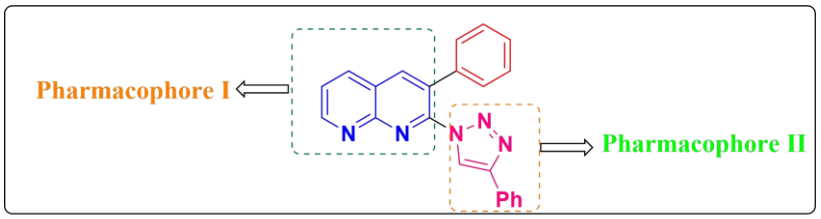
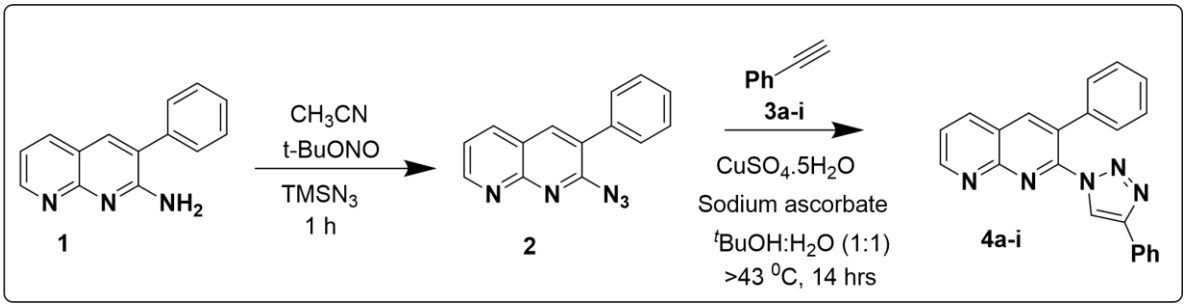


Designed Target 4a-i

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. Elemental analyses were performed on Carlo Ebra 106 and Perkin Elmer Model 240 analyzers. Two step synthesis of 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1,8-naphthyridines designed targets 4a-i are depicted below in Schem I.



Scheme I Synthesis of 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1,8-naphthyridine 4a-i

RESULTS AND DISCUSSIONS

Step I: 3-phenyl-1,8-naphthyridin-2-amine (1) (200 mg, 2.14 mmol) was dissolved in CH_3CN (4 mL) in a 25 mL round-bottomed flask and cooled to 0°C in an ice bath. To this stirred mixture was added t-BuONO (331 mg, 380 µL, 3.21 mmol) followed by $TMSN_3$ (300 mg, 340 µL, 2.56 mmol) drop-wise. The resulting solution was stirred at room temperature for 1 h. [10-11] The reaction mixture was concentrated under vacuum and the crude product was purified by silica gel chromatography (hexane) to give 2-azido-3-phenyl-1,8-naphthyridine (2) from step one.

General procedure for the synthesis of series of -2-(4-phenyl-1H-1,2,3-triazol-1-yl)-1,8-naphthyridine (4a-4i):

3-phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-1,8-naphthyridine (4a):

Step II: In a 100 ml RB flask, the phenylacetylene(3a) 0.102 gm (1 mmol), 2-azido-3-phenyl-1,8-naphthyridine (2) 0.48 gm (1.2 mmol), $CuSO_4.5H_2O$ 0.025 gm (10 mol%) and

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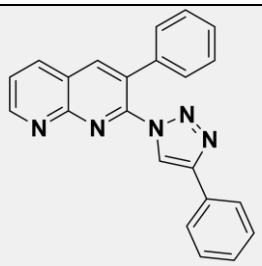
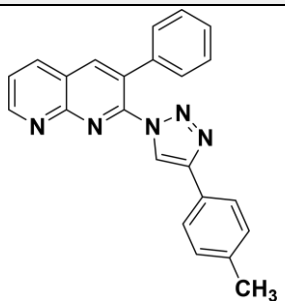
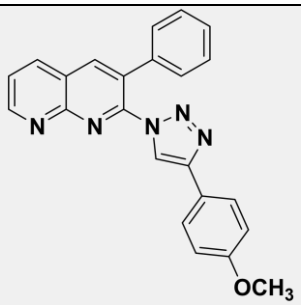
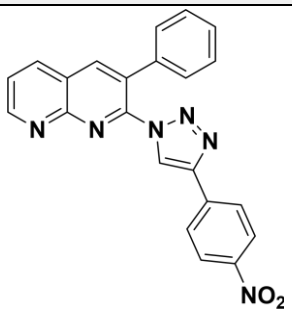
sodium ascorbate 0.0396 gm (0.2 mmol) {Sharpless catalyst, [3+2] click protocol cyclo addition} in 5 mL of tBuOH/H_2O (1:1) solution, were added. The resulting reaction mixture was heated at 43°Cfor 14 hours. The progress of the reaction as analyzed by TLC, then the reaction mixture was extracted twice with 10 ml of water-ethyl acetate and the organic layer was dried using Na_2SO_4, filtered and the excess of organic layer was concentrated under rotary evaporator. Finally, the crude product was purified by column chromatography using (1:1) ethyl acetate/hexane as eluent to afford the pure product 4a in 71% yield. Similar procedure was applied to synthesize the rest of the compounds by taking various substituted phenyl acetylenes. [12-15].

Table 1: Structures and Yield % of Compounds 4a-4i

Entry	Name	Structure	Yield %
4a	3-phenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1,8-naphthyridine		71
4b	3-phenyl-2-(4-(p-tolyl)-1*H*-1,2,3-triazol-1-yl)-1,8-naphthyridine		82
4c	2-(4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)-3-phenyl-1,8-naphthyridine		75
4d	2-(4-(4-nitrophenyl)-1*H*-1,2,3-triazol-1-yl)-3-phenyl-1,8-naphthyridine		78

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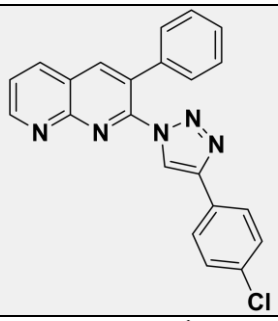
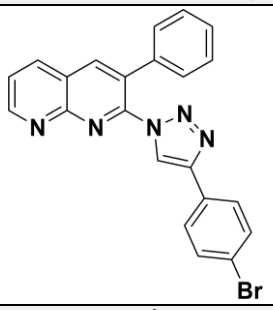
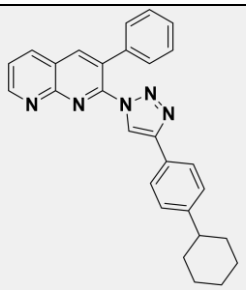
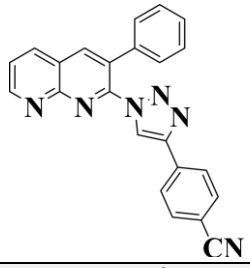
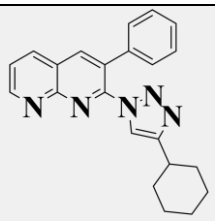
4e	2-(4-(4-chlorophenyl)-1*H*-1,2,3-triazol-1-yl)-3-phenyl-1,8-naphthyridine		79
4f	2-(4-(4-bromophenyl)-1*H*-1,2,3-triazol-1-yl)-3-phenyl-1,8-naphthyridine		81
4g	2-(4-(4-cyclohexylphenyl)-1*H*-1,2,3-triazol-1-yl)-3-phenyl-1,8-naphthyridine		63
4h	4-(1-(3-phenyl-1,8-naphthyridin-2-yl)-1*H*-1,2,3-triazol-4-yl) benzonitrile		67
4i	2-(4-cyclohexyl-1*H*-1,2,3-triazol-1-yl)-3-phenyl-1,8-naphthyridine		70

Table 2: Physical data and analytical data of compounds 4a-4i

Entry	m.p.°C	MF	Found (%) (Calcd)		
			C	H	N
4a	177-179	$C_{22}H_{15}N_5$	75.75 (75.63	4.34 4.33	20.06 20.04)
4b	180-182	$C_{23}H_{17}N_5$	76.13 (76.01	4.73 4.72	19.29 19.27)

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4c	184-186	$C_{23}H_{17}N_5O$	72.93 (72.81	4.53 4.52	18.48 18.46)
4d	210-212	$C_{22}H_{14}N_6O_2$	67.12 (67.00	3.59 3.58	21.33 21.31)
4e	176-178	$C_{22}H_{14}ClN_5$	68.96 (68.84	3.69 3.68	18.27 18.25)
4f	214-216	$C_{22}H_{14}BrN_5$	61.82 (61.70	3.30 3.29	16.37 16.35)
4g	202-204	$C_{28}H_{25}N_5$	78.05 (77.93	5.85 5.84	16.25 16.23)
4h	196-198	$C_{23}H_{14}N_6$	73.90 (73.78	3.78 3.77	22.47 22.45)
4i	186-188	$C_{22}H_{21}N_5$	74.46 (74.34	5.97 5.96	19.72 19.70)

Table 3: ^{1}H & ^{13}CNMR data of titled compounds 4a-4i

Entry	**^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm)**	**^{13}CNMR (100 MHz, $CDCl_3$) (δ, ppm)**
4a	9.07 (s, 1H), 8.66 (s, 1H), 8.30 (s, 1H), 8.08 (s, 1H), 7.57 – 7.49 (m, 3H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.41 – 7.33 (m, 5H), 7.27 (t, *J* = 8.1 Hz, 1H)	157.38, 155.22, 153.45, 141.98, 136.14, 130.41, 129.24 (2C), 128.86 (2C), 128.47 (2C), 127.63 (2C), 126.28 (2C), 125.77 (2C), 121.03, 118.81, 116.24.
4b	9.05 (s, 1H), 8.66 (s, 1H), 8.32 (s, 1H), 8.08 (s, 1H), 7.48 (dd, *J* = 25.9, 6.2 Hz, 5H), 7.37 – 7.25 (m, 5H), 2.35 (s, 3H).	157.38 (2C), 155.22 (2C), 153.45 (2C), 141.98 (2C), 136.14, 130.31, 129.24 (2C), 128.90 (2C), 128.47, 127.61 (2C), 126.37 (2C), 121.03, 118.81, 116.24, 21.12.
4c	9.07 (s, 1H), 8.66 (s, 1H), 8.30 (s, 1H), 8.08 (s, 1H), 7.48 (d, *J* = 37.3 Hz, 5H), 7.31 (d, *J* = 37.6 Hz, 3H), 7.00 (d, *J* = 7.5 Hz, 2H), 3.81 (s, 3H).	159.63, 157.38, 155.22, 153.45, 141.98 (2C), 136.14, 135.90, 129.24 (2C), 128.47, 127.61 (3C), 125.92 (2C), 124.61, 121.03, 118.81, 116.24, 114.40 (2C), 56.03.
4d	9.05 (s, 1H), 8.67 (s, 1H), 8.30 (d, *J* = 16.9 Hz, 3H), 8.08 (s, 1H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.51 (s, 1H), 7.45 (s, 2H), 7.35 (s, 2H), 7.27 (s, 1H).	157.38,155.22, 153.54 (2C), 146.40, 141.98, 136.14, 137.16, 135.90, 134.60, 129.24(2C),128.47,127.61(2C),124.82(2C) ,124.45 (2C), 121.03, 118.81, 116.24.
4e	9.05 (s, 1H), 8.67 (s, 1H), 8.30 (d, *J* = 16.9 Hz, 3H), 8.08 (s, 1H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.51 (s, 1H), 7.45 (s, 2H), 7.34 (s, 2H), 7.27 (s, 1H).	157.38,155.22,153.54(2C),141.98,136.14, 134.14, 129.56 (2C), 129.22 (2C), 128.28 (2C),128.28(2C),127.63(2C),127.59, 121.25, 121.03, 118.81, 116.24.
4f	9.05 (s, 1H), 8.67 (s, 1H), 8.30 (d, *J* = 16.9 Hz, 3H), 8.08 (s, 1H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.51 (s, 1H), 7.45 (s, 2H), 7.35 (s, 2H), 7.26 (s, 1H).	157.38,155.22, 153.54 (2C), 141.98,136.14, 135.91, 129.44 (2C), 129.04 (2C), 128.28 (2C),128.28(2C),127.63(2C),127.59, 121.35, 121.03, 118.81, 116.25.
4g	8.89 (s, 1H), 8.58 (s, 1H), 8.26 (s, 1H), 8.08 (s, 1H), 7.58 (d, *J* = 10.7 Hz, 4H), 7.49 – 7.33 (m, 6H), 3.11 (s, 1H), 2.11 (s, 2H), 1.72 (s, 3H), 1.59 (s, 2H), 1.40 (s, 3H).	157.38,155.22, 153.50, 146.52, 141.98, 136.14,135.91, 131.58, 129.44 (2C), 129.04 (2C),128.47 (2C), 127.62 (2C), 127.14 (2C), 124.57 (2C), 121.03, 118.81, 116.25, 42.16, 32.72, 32.41, 25.92, 24.95,24.73.

4h	9.07 (s, 1H), 8.67 (s, 1H), 8.32 (s, 1H), 8.08 (s, 1H), 7.75 (s, 4H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.37 – 7.27 (m, 3H).	157.38,155.22,153.45(2C),141.98,136.14, 132.48,130.14(2C)129.24(2C),128.47(2C), 127.61(2C),127.59,125.27(2C),121.03,119 .12,118.12, 116.24, 113.07.
4i	9.05 (s, 1H), 8.65 (s, 1H), 8.32 (s, 1H), 8.08 (s, 1H), 7.49 (d, *J* = 34.5 Hz, 3H), 7.33 (d, *J* = 43.0 Hz, 3H), 3.39 (s, 1H), 2.16 (s, 2H), 1.90 (s, 2H), 1.57 (s, 6H).	166.05, 155.22, 153.45, 141.98, 136.14, 135.90,132.15(2C), 129.24 (2C), 128.81 (2C), 127.61 (2C), 121.15 (2C), 118.81, 116.24, 37.20, 32.14, 25.91, 25.14.

Table 4: Mass Spectral data of compounds 4a-4i

Entry	ESI [m+H]
4a	350
4b	364
4c	380
4d	394
4e	384
4f	428
4g	432
4h	374
4i	356

CONCLUSION

Two-Step synthesis of 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1,8-naphthyridine scaffolds were developed with promising yields, and further confirmed by spectral and elemental analysis.

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