A Facile Approach for the Synthesis of Novel 1,2,4-Triazolo[4,3-a] Pyridine Derivatives in Single Step

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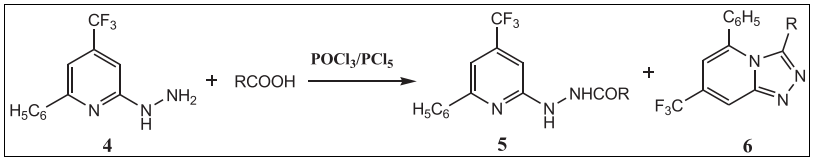

4 5 6

A series of novel substituted 4-trifluoromethyl-pyridin-2-yl hydrazide derivatives **5** and 7-trifluoromethyl-1,2,4-triazolo[4,3-a]pyridine derivatives **6** were synthesized through a facile method in single step from 2-hydrazino-pyridine derivatives **4** and their reaction with aliphatic/aromatic acids in the presence of $POCl_3$ and PCl_5. In each reaction, an intermediate **5** and product **6** were formed in definite proportion except in **5a**, **5d**, and **6e** and were independent of reaction time and temperature.

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INTRODUCTION

The 1,2,4-triazolo[4,3-a]pyridine ring system is known since 1903 [1]; however, extensive studies have not been initiated even though they have interesting pharmacological properties [2–5] such as use in cancer chemotherapy [6]. The 1,2,4-triazole-fused heterocycles were reviewed more recently [7], some of them found to show anti-inflammatory [8], bactericidal [9], fungicidal [10], analgesic [11–13], and anxiolytic [14] activity. The method of synthesis of 1,2,4-triazolo[4,3-a]pyridines is mainly from 2-pyridyl hydrazine by cyclodehydration agents [15–22]. On the basis of the importance and continuation of our efforts [23–25] to synthesize potential molecules, we have developed a convenient method for the synthesis of novel 1,2,4-triazolo[4,3-a]pyridine derivatives, and are reporting here for the first time.

RESULTS AND DISCUSSION

The 2-hydrazino-4-trifluoromethyl-6-phenyl pyridine **4** was prepared from 1,1,1-trifluoro-4-phenyl-butane-2,4-dione on reaction with cyanoacetamide to form exclusively 3-cyano-4-trifluoromethyl-6-phenyl 2(1H)pyridone **1** [26]. Compound **1** on hydrolysis followed by decarboxylation resulted in 4-trifluoro-methyl-6-phenyl 2(1H)pyridone **2** [27]. Compound **2** on reaction with $POCl_3$ formed 2-chloro-4-trifluoromethyl-6-phenyl pyridine **3** [27] followed by reaction with hydrazine hydrate, which resulted in the formation of compound **4** [27]. The 2-hydrazino-4-trifluoromethyl-6-phenyl pyridine **4** was further reacted with acetic acid under different set of conditions by using H_2SO_4, $ZnCl_2$, PTSA, $POCl_3$, high temperature, and under-microwave-irradiation conditions. In all the cases, the acylation product was found to be formed. To have cyclized product, we reacted compound **4** with aliphatic/aromatic acids in $POCl_3/PCl_5$, and obtained N-acylated product **5** and cyclized product **6** in definite proportions. The sequence of reaction is mainly acylation, then chlorination followed by cyclization. Specifically, with compound **4** on reaction with formic acid or trifluoroacetic acid, exclusively *N*-formyl or *N*-trifluoroacetyl products **5** are formed, irrespective of long reaction time at reflux temperature, and it is attributed to no-enol form as a result of the abscence of chlorination. Thereby, there was no cyclization. The infrared spectrum of compound **5** shows the presence of amide peak for NH at 3420 Cm^{-1} and amide carbonyl peak at 1660 Cm^{-1}. In all other cases, the acyl product is in keto–enol equilibrium form, and enol form promoted chlorination and formed product **6**, whereas keto form retained to have product **5** only. On the other hand, compound **4** on reaction with benzoic acid gave exclusively product **6e**, which is assumed to be the formation of benzoyl derivative in enol form followed by chlorination and cyclization. The sequence of reactions outlined in Schemes 1 and 2, mechanism in Scheme 3, and products are presented in Table 1.

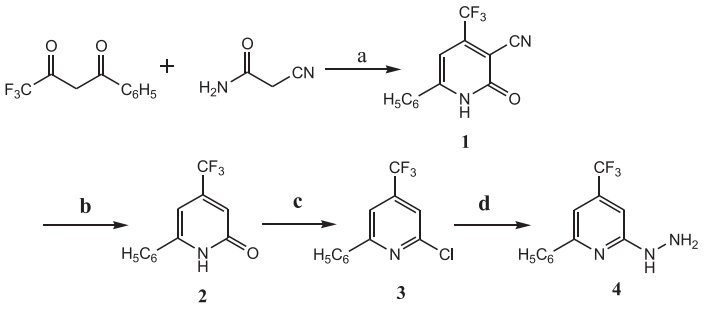
CONCLUSION

A series of novel substituted 4-trifluoromethyl-pyridin-2-yl hydrazides **5** and 7-trifluoromethyl-1,2,4-triazolo [4,3-a]pyridine derivatives **6** were prepared in a single step by facile method and is applicable to the synthesis of diverse functionalized pyridine derivatives.

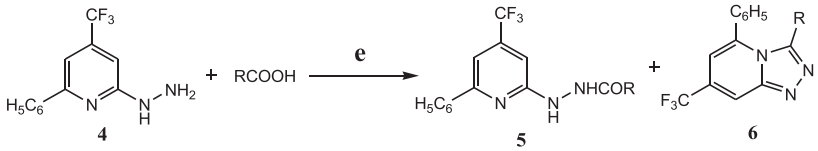
EXPERIMENTAL

Melting points were recorded using open glass capillaries on Casia-siamia (VMP-AM) melting point apparatus and were uncorrected. Infrared spectra were recorded on a Perkin-Elmer

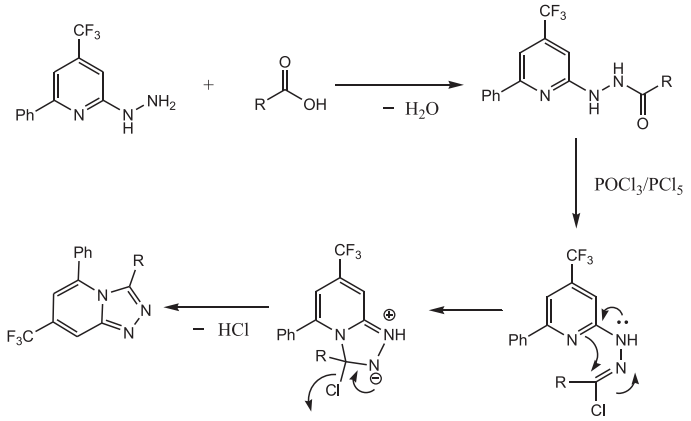
Scheme 1



Scheme 2



Scheme 3



FT-IR 240-C spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Avance (Bruker, Switzerland) 300-MHz spectrometer in $CDCl_3$ and DMSO-d_6 using TMS as an internal standard. EI and chemical ionization mass spectra were recorded on VG-7070 H instrument at 70 eV. All reactions were monitored by TLC on pre-coated silica gel 60 F_{254} (mesh). Spots were visualized with UV light. Merck silica gel (100–200 mesh) was used for column chromatography. CHN analyses were recorded on a Vario EL analyzer.

Preparation of 3-cyano-4-trifluoromethyl-2(1H)pyridone (1) [26]

Preparation of 4-trifluoromethyl-2(1H)pyridone (2) [27]

Preparation of 2-chloro-6-phenyl-4-(trifluoromethyl)pyridine (3) [27]

Preparation of 1-(6-phenyl-4-(trifluoromethyl)pyridin-2-yl)hydrazine (4) [27]

Preparation of 4-trifluoromethyl-6-phenyl-pyridine-2-yl hydrazide (5)/substituted 7-trifluoromethyl-1,2,4-triazolo [4,3-a]pyridine derivatives (6): General procedure.

The 2-hydrazino-4-trifluoromethyl-6-phenyl pyridine **4** (0.2 g, 0.7 mmol) and aliphatic/aromatic acid (1.1 mmol) were taken in a clean and dry round bottom flask having $POCl_3$ (6–8 mL), and PCl_5 (0.05 g) was added. The reaction mixture was refluxed for 6–8 h, at 120°C and cooled to room temperature. The excess $POCl_3$ was distilled under vacuum, and the residue was treated with crushed ice. The aqueous solution was extracted with ethyl acetate twice (30 mL each), and combined extract was washed with saturated sodium bicarbonate solution followed by distilled water till washings were neutral in pH. The organic layer was separated, dried over sodium sulfate, and concentrated. The crude product was purified by passing it through a column packed with silica gel and ethyl acetate–*n*-hexane used as eluents.

Spectral data

N′-(6-Phenyl-4-(trifluoromethyl)pyridin-2-yl)formohydrazide (5a). IR (KBr, cm^{-1}): 3420 (-CONH-), 1660 (-CONH-), 1168, 1125 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42-7.58(m, 4H, Ar-H), 7.99-8.03(m, 2H, Ar-H), 8.18(s, 1H, Ar-H), 8.68 (br, 1H,-NH-) 8.99 (s, 1H, Ar-H), 10.21(br, 1H,-NH-); MS (ESI): m/z [$(M+H)^+$]: 382, [$(M+Na)^+$]: 304; *Anal*. Calcd for $C_{13}H_{10}F_3N_4O$: C 55.52, H 3.58, N 14.94%. Found: C 55.21, H 3.47, N 14.82%.

N′-(6-Phenyl-4-(trifluoromethyl)pyridin-2-yl)acetohydrazide (5b). IR (KBr, cm^{-1}): 3421 (-CONH-), 1658 (-CONH-), 1172,

Table 1

Preparation of substituted 4-trifluoromethyl-pyridine-2-yl hydrazide derivatives **5** and 7-trifluorormethyl-1,2,4-triazolo[4,3-a]pyridine derivatives **6**.

R	Compound No.	mp °C	Yield %	Compound No.	mp °C	Yield %
H	**5a**	255–257	78	—	—	—
CH_3	**5b**	262–264	61	**6b**	171–173	31
CH_2CH_3	**5c**	260–262	68	**6c**	178–180	27
CF_3	**5d**	256–257	82	—	—	—
C_6H_5	—	—	—	**6e**	194–196	69
4-CH_3-C_6H_4	**5f**	268–270	32	**6f**	201–204	56
4-OCH_3-C_6H_4	**5g**	250–252	28	**6g**	207–209	50
3-OCH_3-C_6H_4	**5h**	245–247	31	**6h**	201–203	48
4-F-C_6H_4	**5i**	240–242	38	**6i**	198–200	42
3-F-C_6H_4	**5j**	252–254	35	**6j**	191–193	45
4-Cl-C_6H_4	**5k**	268–270	28	**6k**	220–221	41
3-Cl-C_6H_4	**5l**	261–262	29	**6l**	211–213	40
3-Br-C_6H_4	**5m**	278–280	31	**6m**	232–234	48
3-CN-C_6H_4	**5n**	258–261	28	**6n**	228–232	45
3-pyridyl	**5o**	251–252	45	**6o**	200–202	38
2-furyl	**5p**	238–242	30	**6p**	209–212	39

1128 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.21(s, 1H,-CH_3), 6.82(s, 1H, Ar-H), 7.00(br, 1H,-NH-), 7.42(s, 1H, Ar-H), 7.48–7.52(m, 3H, Ar-H), 7.60(br, 1H,-NH-), 7.90–7.96(m, 2H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 296, [(M + Na)$^+$]: 318; *Anal*. Calcd for $C_{14}H_{12}F_3N_4O$: C 56.95, H 4.10, N 14.23%. Found: C 56.72, H 4.05, N 14.10%.

3-Methyl-5-phenyl-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a] pyridine (6b). IR (KBr, cm^{-1}): 1648 (C=N), 1172, 1139 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.12(s, 3H,-CH_3), 6.78(s, 1H, Ar-H), 7.42–7.48(m, 2H, Ar-H), 7.52–7.60(m, 3H, Ar-H), 8.05 (s, 1H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 278, [(M + Na)$^+$]: 300; *Anal*. Calcd for $C_{13}H_{10}F_3N_3$: C 60.65, H 3.64, N 15.16%. Found: C 60.42, H 3.69, N 15.08%.

N'-(6-Phenyl-4-(trifluoromethyl)pyridin-2-yl)propionohydrazide (5c). IR (KBr, cm^{-1}): 3422 (-CONH-), 1660 (-CONH-), 1174, 1138 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38(t, 3H,-CH_3), 2.41 (q, 2H,-CH_2-), 6.80(s, 1H, Ar-H), 7.02(br, 1H,-NH-), 7.42(s, 1H, Ar-H), 7.48–7.51(m, 3H, Ar-H), 7.61(br, 1H,-NH-), 7.89–7.96 (m, 2H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 310, [(M + Na)$^+$]: 332; *Anal*. Calcd for $C_{15}H_{14}F_3N_3O$: C 58.25, H 4.56, N 13.59%. Found: C 57.95, H 4.49, N 13.09%.

3-Ethyl-5-phenyl-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (6c). IR (KBr, cm^{-1}): 1649 (C=N) 1169, 1135 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.40(t, 3H,-CH_3), 2.32(q, 2H,-CH_2-), 6.79 (s, 1H, Ar-H), 7.42–7.48(m, 2H, Ar-H), 7.53–7.60(m, 3H, Ar-H), 8.04 (s, 1H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 292; *Anal*. Calcd for $C_{15}H_{12}F_3N_3$: C 61.85, H 4.15, N 14.43%. Found: C 61.56, H 4.21, N 14.39%.

2,2,2-Trifluoro-N'-(6-phenyl-4-(trifluoromethyl)pyridin-2-yl)acetohydrazide (5d). IR (KBr, cm^{-1}): 3422 (-CONH-), 1660 (-CONH-), 1170, 1123 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.80(s, 1H, Ar-H), 7.02(br, 1H,-NH-), 7.42 (s, 1H, Ar-H), 7.48–7.51(m, 3H, Ar-H), 7.61(br, 1H,-NH-), 7.89–7.96(m, 2H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 350, [(M + Na)$^+$]: 372; *Anal*. Calcd for $C_{14}H_9F_6N_3O$: C 48.15, H 2.60, N 12.03%. Found: C 47.88, H 2.53, N 12.01%.

3,5-Diphenyl-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (6e). IR (KBr, cm^{-1}): 1618 (C=N) 1159, 1123 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.97(s, 1H, Ar-H), 7.05–7.11(m, 8H, Ar-H), 7.19–7.24(m, 2H, Ar-H), 8.26(s, 1H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 340, [(M + Na)$^+$]: 362; *Anal*. Calcd for $C_{19}H_{12}F_3N_3$: C 67.25, H 3.56, N 12.38%. Found: C 67.02, H 3.49, N 12.23%.

4-Methyl-N'-(6-phenyl-4-(trifluoromethyl)pyridin-2-yl) benzohydrazide (5f). IR (KBr, cm^{-1}): 3420 (-CONH-), 1656 (-CONH-), 1168, 1130 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.30(s, 3H,-CH_3), 7.02(s, 1H, Ar-H), 7.12 (br, 1H,-NH-), 7.31–7.49(m, 7H, Ar-H), 7.51–7.52(m, 3H, Ar-H), 8.41(br, 1H,-NH-); MS (ESI): m/z [(M + H)$^+$]: 372; *Anal*. Calcd for $C_{20}H_{16}F_3N_3O$: C 64.69, H 4.34, N 11.32%. Found: C 64.32, H 4.39, N 11.41%.

5-Phenyl-3-p-tolyl-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a] pyridine (6f). IR (KBr, cm^{-1}): 1659 (C=N) 1172, 1128 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.27(s, 3H,-CH_3), 6.84–6.96 (m, 5H, Ar-H), 7.06–7.12(m, 4H, Ar-H), 7.23(s, 1H, Ar-H), 8.18 (s, 1H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 354, [(M + Na)$^+$]: 376; *Anal*. Calcd for $C_{20}H_{14}F_3N_3$: C 67.98, H 3.99, N 11.89%. Found: C 67.77, H 3.89, N 11.80%.

4-Methoxy-N'-(6-phenyl-4-(trifluoromethyl)pyridin-2-yl) benzohydrazide (5g). IR (KBr, cm^{-1}): 3423 (-CONH-), 1660 (-CONH-),1171, 1125 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.91 (s, 3H,-OCH_3), 6.90(s, 1H, Ar-H), 7.12(br, 1H,-NH-), 7.31–7.49 (m, 7H, Ar-H), 7.51–7.52(m, 3H, Ar-H), 8.41(br, 1H,-NH-); MS (ESI): m/z [(M + H)$^+$]: 388, [(M + Na)$^+$]: 410; *Anal*. Calcd for $C_{20}H_{16}F_3N_4O_2$: C 62.01, H 4.16, N 10.85%. Found: C 61.88, H 4.19, N 10.89%.

3-(4-Methoxyphenyl)-5-phenyl-7-(trifluoromethyl)-[1,2,4] triazolo[4,3-a]pyridine (6g). IR (KBr, cm^{-1}): 1647 (C=N) 1164, 1139 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.89(s, 3H,-OCH_3), 7.12–7.21(m, 2H, Ar-H), 7.35–7.55(m, 4H, Ar-H), 7.65–7.78(m, 4H, Ar-H), 7.99(s, 1H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 370, [(M + Na)$^+$]: 392; *Anal*. Calcd for $C_{20}H_{14}F_3N_3O$: C 65.04, H 3.82, N 11.38%. Found: C 64.85, H 3.78, N 11.28%.

3-Methoxy-N'-(6-phenyl-4-(trifluoromethyl)pyridin-2-yl) benzohydrazide (5h). IR (KBr, cm^{-1}): 3422 (-CONH-), 1668 (-CONH-), 1174, 1138 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.90(s, 3H,-OCH_3), 6.90(s, 1H, Ar-H), 7.12 (br, 1H,-NH-), 7.31–7.49(m, 7H, Ar-H), 7.51–7.52(m, 3H,

Ar-H), 8.41(br, 1H,-NH-); MS (ESI): m/z [(M + H)$^+$]: 388, [(M + Na)$^+$]: 410; *Anal*. Calcd for $C_{20}H_{16}F_3N_4O_2$: C 62.01, H 4.16, N 10.85%. Found: C 62.32, H 4.09, N 10.98%.

3-(3-Methoxyphenyl)-5-phenyl-7-(trifluoromethyl)-[1,2,4] triazolo[4,3-a]pyridine (6h). IR (KBr, cm^{-1}): 1653 (C=N) 1169, 1122 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.90(s, 3H,-OCH_3), 7.11–7.21(m, 2H, Ar-H), 7.35–7.76(m, 8H, Ar-H), 8.01 (s, 1H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 370, [(M + Na)$^+$]: 392; *Anal*. Calcd for $C_{20}H_{14}F_3N_3O$: C 65.04, H 3.82, N 11.38%. Found: C 64.73, H 3.79, N 11.46%.

4-Fluoro-N'-(6-phenyl-4-(trifluoromethyl)pyridin-2-yl) benzohydrazide (5i). IR (KBr, cm^{-1}): 3413 (-CONH-), 1662 (-CONH-), 1170, 1138 (C-F); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.92(s, 1H, Ar-H), 7.36–7.50(m, 5H, Ar-H), 7.72(s, 1H, Ar-H), 7.94–8.06(m, 4H, Ar-H), 8.51(br, 1H,-NH-), 10.58(br, 1H,-NH-); MS (ESI): m/z [(M + H)$^+$]: 376, [(M + Na)$^+$]: 398; *Anal*. Calcd for $C_{19}H_{13}F_4N_3O$: C 60.80, H 3.49, N 11.20%. Found: C 60.62, H 3.52, N 11.15%.

3-(4-Fluorophenyl)-5-phenyl-7-(trifluoromethyl)-[1,2,4] triazolo[4,3-a]pyridine (6i). IR (KBr, cm^{-1}): 1638 (C=N) 1172, 1138 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.72–6.79 (m, 2H, Ar-H), 6.93(s, 1H, Ar-H), 7.05–7.19(m, 6H, Ar-H), 7.31(m, 1H, Ar-H) 8.19(s, 1H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 358, [(M + Na)$^+$]: 380; *Anal*. Calcd for $C_{19}H_{11}F_4N_3$: C 63.87, H 3.10, N 11.76%. Found: C 63.99, H 3.19, N 11.80%.

3-Fluoro-N'-(6-phenyl-4-(trifluoromethyl)pyridin-2-yl) benzohydrazide (5j). IR (KBr, cm^{-1}): 3413 (-CONH-), 1661 (-CONH-), 1168, 1128 (C-F); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.92(s, 1H, Ar-H), 7.36–7.50(m, 5H, Ar-H), 7.72(s, 1H, Ar-H), 7.94–8.06(m, 4H, Ar-H), 8.51(br, 1H,-NH-), 10.58(br, 1H,-NH-); MS (ESI): m/z [(M + H)$^+$]: 376, [(M + Na)$^+$]: 398; *Anal*. Calcd for $C_{19}H_{13}F_4N_3O$: C 60.80, H 3.49, N 11.20%. Found: C 60.92, H 3.38, N 11.32%.

3-(3-Fluorophenyl)-5-phenyl-7-(trifluoromethyl)-[1,2,4] triazolo[4,3-a]pyridine (6j). IR (KBr, cm^{-1}): 1649 (C=N) 1165, 1125 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.73–6.79 (m, 2H, Ar-H), 6.96(s, 1H, Ar-H), 7.05–7.20(m, 6H, Ar-H), 7.35 (m, 1H, Ar-H) 8.20(s, 1H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 358, [(M + Na)$^+$]: 380; *Anal*. Calcd for $C_{19}H_{11}F_4N_3$: C 63.87, H 3.10, N 11.76%. Found: C 63.66, H 3.06, N 11.89%.

4-Chloro-N'-(6-phenyl-4-(trifluoromethyl)pyridin-2-yl) benzohydrazide (5k). IR (KBr, cm^{-1}): 3422 (-CONH-), 1662 (-CONH-), 1169, 1133 (C-F); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.82(s, 1H, Ar-H), 7.36–7.50(m, 5H, Ar-H), 7.72(s, 1H, Ar-H), 7.94–8.06(m, 4H, Ar-H), 8.78(br, 1H,-NH-), 10.49(br, 1H,-NH-); MS (ESI): m/z [(M + H)$^+$]: 392, [(M + Na)$^+$]: 414; *Anal*. Calcd for $C_{19}H_{13}ClF_3N_3O$: C 58.25, H 3.34, N 10.73%. Found: C 58.56, H 3.41, N 10.68%.

3-(4-Chlorophenyl)-5-phenyl-7-(trifluoromethyl)-[1,2,4] triazolo[4,3-a]pyridine (6k). IR (KBr, cm^{-1}): 1656 (C=N) 1172, 1128 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.96(s, 1H, Ar-H), 7.00–7.10(m, 6H, Ar-H), 7.12–7.18(m, 2H, Ar-H), 7.32 (m, 1H, Ar-H) 8.20(s, 1H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 374, [(M + Na)$^+$]: 396; *Anal*. Calcd for $C_{19}H_{11}ClF_3N_3$: C 61.06, H 2.97, N 11.24%. Found: C 61.23, H 2.88, N 11.35%.

3-Chloro-N'-(6-phenyl-4-(trifluoromethyl)pyridin-2-yl) benzohydrazide (5l). IR (KBr, cm^{-1}): 3423 (-CONH-), 1660 (-CONH-), 1169, 1139 (C-F); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.92 (s, 1H, Ar-H), 7.36–7.50(m, 5H, Ar-H), 7.72(s, 1H, Ar-H), 7.94–8.06 (m, 4H, Ar-H), 8.51(br, 1H,-NH-), 10.58(br, 1H,-NH-); MS (ESI): m/z [(M + H)$^+$]: 392, [(M + Na)$^+$]: 414; *Anal*. Calcd for $C_{19}H_{13}ClF_3N_3O$: C 58.25, H 3.34, N 10.73%. Found: C 58.42, H 3.48, N 10.82%.

3-(3-Chlorophenyl)-5-phenyl-7-(trifluoromethyl)-[1,2,4] triazolo[4,3-a]pyridine (6l). IR (KBr, cm^{-1}): 1649 (C=N) 1170, 1138 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.96(s, 1H, Ar-H), 7.01–7.12(m, 6H, Ar-H), 7.12–7.18(m, 2H, Ar-H), 7.33 (m, 1H, Ar-H) 8.21(s, 1H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 374, [(M + Na)$^+$]: 396; *Anal*. Calcd for $C_{19}H_{11}ClF_3N_3$: C 61.06, H 2.97, N 11.24%. Found: C 61.23, H 2.89, N 11.36%.

3-Bromo-N'-(6-phenyl-4-(trifluoromethyl)pyridin-2-yl) benzohydrazide (5m). IR (KBr, cm^{-1}): 3400 (-CONH-), 1659 (-CONH-), 1171, 1135 (C-F); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.90(s, 1H, Ar-H), 7.35–7.25(m, 5H, Ar-H), 7.70 (s, 1H, Ar-H), 7.94–8.07(m, 4H, Ar-H), 8.58(br, 1H,-NH-), 10.60 (br, 1H,-NH-); MS (ESI): m/z [(M + H)$^+$]: 436; *Anal*. Calcd for $C_{19}H_{13}BrF_3N_3O$: C 52.31, H 3.00, N 9.63%. Found: C 52.19, H 3.12, N 9.49%.

3-(3-Bromophenyl)-5-phenyl-7-(trifluoromethyl)-[1,2,4] triazolo[4,3-a]pyridine (6m). IR (KBr, cm^{-1}): 1637 (C=N) 1169, 1128 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.98–7.00 (m, 2H, Ar-H), 7.05–7.22(m, 6H, Ar-H), 7.30–7.39(m, 2H, Ar-H), 8.21(s, 1H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 418; *Anal*. Calcd for $C_{19}H_{11}BrF_3N_3$: C 54.57, H 2.65, N 10.05%. Found: C 54.31, H 2.58, N 10.09%.

3-Cyano-N'-(6-phenyl-4-(trifluoromethyl)pyridin-2-yl) benzohydrazide (5n). IR (KBr, cm^{-1}): 3338 (-CONH-), 1663 (-CONH-), 1170, 1136 (C-F); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.91(s, 1H, Ar-H), 7.35–7.26(m, 5H, Ar-H), 7.70(s, 1H, Ar-H), 7.95–8.06(m, 4H, Ar-H), 8.59(br, 1H,-NH-), 10.61 (br, 1H,-NH-); MS (ESI): m/z [(M + H)$^+$]: 383; *Anal*. Calcd for $C_{20}H_{13}F_3N_4O$: C 62.83, H 3.43, N 14.65%. Found: C 62.72, H 3.35, N 14.76%.

3-(3-Cyanophenyl)-5-phenyl-7-(trifluoromethyl)-[1,2,4]triazolo [4,3-a]pyridine (6n). IR (KBr, cm^{-1}): 1649 (C=N) 1172, 1123 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.95(s, 1H, Ar-H), 7.00–7.10(m, 6H, Ar-H), 7.12–7.18(m, 2H, Ar-H), 7.32(m, 1H, Ar-H) 8.20(s, 1H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 365; *Anal*. Calcd for $C_{20}H_{11}F_3N_4$: C 65.93, H 3.04, N 15.38%. Found: C 65.71, H 3.12, N 15.49%.

N'-(6-Phenyl-4-(trifluoromethyl)pyridin-2-yl)nicotinohydrazide (5o). IR (KBr, cm^{-1}): 3382 (-CONH-), 1660 (-CONH-), 1172, 1136 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.58(m, 7H, Ar-H), 7.99–8.03(m, 2H, Ar-H), 8.20–8.25(d, 1H, Ar-H), 8.68(br, 1H,-NH-) 8.99 (s, 1H, Ar-H), 9.22(br, 1H,-NH-); MS (ESI): m/z [(M + H)$^+$]: 359, [(M + Na)$^+$]: 381; *Anal*. Calcd for $C_{18}H_{13}F_3N_4O$: C 60.34, H 3.66, N 15.64%. Found: C 60.10, H 3.52, N 15.75%.

5-Phenyl-3-(pyridin-3-yl)-7-(trifluoromethyl)-[1,2,4]triazolo [4,3-a]pyridine (6o). IR (KBr, cm^{-1}): 1653 (C=N) 1172, 1135 (C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.98(s, 1H, Ar-H), 7.36–7.55(m, 4H, Ar-H), 7.66–7.76(m, 5H, Ar-H), 8.19(s, 1H, Ar-H); MS (ESI): m/z [(M + H)$^+$]: 341; *Anal*. Calcd for $C_{18}H_{11}F_3N_4$: C 63.53, H 3.26, N 16.46 %. Found: C 63.31, H 3.31, N 16.38 %.

N'-(6-Phenyl-4-(trifluoromethyl)pyridin-2-yl)furan-2-carbohydrazide (5p). IR (KBr, cm^{-1}): 3183(-CONH-), 1659 (-CONH-), 1170, 1136 (C-F); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.82(s, 1H, Ar-H), 7.12–7.21(m, 3H, Ar-H), 7.38–7.45(m, 2H, Ar-H), 7.99–8.03(m, 2H, Ar-H), 8.20–8.25 (d, 1H, Ar-H), 8.88(br, 1H,-NH-) 8.99 (s, 1H, Ar-H), 10.21(br, 1H,-NH-); MS (ESI): m/z [(M + H)$^+$]: 348; *Anal*. Calcd for $C_{17}H_{12}F_3N_3O_2$: C 58.79, H 3.48, N 12.10%. Found: C 58.61, H 3.29, N 12.08%.

3-(Furan-2-yl)-5-phenyl-7-(trifluoromethyl)-[1,2,4]triazolo [4,3-a]pyridine (6p). IR (KBr, cm^{-1}): 1651 (C=N) 1170, 1138

(C-F); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.96(s, 1H, Ar-H), 7.36–7.55 (m, 4H, Ar-H), 7.66–7.78(m, 4H, Ar-H), 8.19(s, 1H, Ar-H); MS (ESI): m/z [$(M+H)^+$]: 330; *Anal*. Calcd for $C_{17}H_{10}F_3N_4O$: C 62.01, H 3.06, N 12.76%. Found: C 62.28, H 3.11, N 12.89%.

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