Novel triazolo pyridine derivatives and their anti cancer activity

Kumara Swamy M. and Bhaskar K.*
Department of Chemistry, University College of Science, Osmania University, Hyderabad, TS, 500007, INDIA
*kuthati18@gmail.com; kumar.mudam6@gmail.com

Abstract

A series of novel triazole functionalized trifluoromethyl pyridine derivatives was prepared starting from pyridine 1. Compound 1 on reaction with sulphuric acid gave compound 2 which on chlorination followed by hydrazine hydrate and obtained compound 3 and 4. Compound 4 on reaction with diverse substituted aliphatic and aromatic acid chlorides produced amide derivatives 4a-h and 5a-h.

All the final compounds were evaluated for anti cancer activity against four human cancer cell lines such as HeLa - Cervical cancer (CCL-2); COLO 205- Colon cancer (CCL-222); HepG2- Liver cancer (HB-8065); MCF7 - Breast cancer (HTB-22). Promising compounds 4f and 4g were identified.

Keywords: Pyridine, Chloropyridine, Hydrazide pyridine, Anticancer activity.

Introduction

Among all types of heterocyclic compounds, pyridine moiety occupies a crucial place to promote biological activity due to wide range of biological applications. Pyridine itself can possess bioactivities like anticancer, antiviral, antimicrobial and many more. Pyridine as a core moiety with trifluoromethyl group at strategic position can alter the properties like lipophilicity, oral bio availability.[6,9-14,16,19]

Heterocyclic compounds have wide range of applications in medicinal chemistry. Many synthetic heterocyclic drugs are used as anticonvulsants, antiseptics, antineoplastics, antiviral, antihistaminics, anti-tumor etc. Heterocycles have enormous potential as the most promising molecules as lead structures for the design of new drugs.[5,17,18,20] Triazole fused heterocycles were paid great attention due to their unique chemical and structural properties and they have found wide applications in medicinal chemistry[1-3,15,21] especially as anticancer agents.[4,7,8,22] Some of pyridine fused heterocyclic containing drugs illustrated in figure 1.

Trifluoromethyl group also plays an important role in compounds activity. Trifluoromethyl groups at particular/ strategic position on molecule can alter the properties like lipophilicity and oral bio-availability. Considering all these literature reports, we designed and synthesized novel 1,2,4-triazolo pyridine derivatives 4a-h and 5a-h, all the final compounds (cyclized and uncyclized) were evaluated for anti cancer activity against four human cancer cell lines such as HeLa - Cervical cancer (CCL-2); COLO 205- Colon cancer (CCL-222); HepG2- Liver cancer (HB-8065); MCF7 - Breast cancer (HTB-22). Promising compounds 4f and 4g were identified.

Material and Methods

IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Bruker AV 300 MHz in $CDCl_3$ and DMSO-d_6 using TMS as internal standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. All high-resolution spectra were recorded on QSTARXL hybrid MS/MS system (Applied Biosystems, USA) under electro spray ionization. All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F_{254}; spots were visualized with UV light. Merck silica gel (60-120 mesh) was used for column chromatography.

2-Oxo-4,6-bis(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (1)2-Chloro-4,6-bis(trifluoromethyl) nicotinonitrile (2): 10 -12ml of $POCl_3$ was slowly added to 2-oxo-4,6-bis(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile 2 and this reaction mixture was allowed to reflux for about 12 hours. After completion of the reaction, $POCl_3$ was completely removed under vacuum. Ethyl acetate and water were added to that reaction mixture, organic layer was separated and dried with sodium sulphate. Concentrate to get 2-chloro-4,6-bis(trifluoromethyl)pyridine 2.

Yellow solid; Yield 86%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.98 (s, 1H, Ar-H); MS (ESI): m/z [$(M+H)^+$]: 275; Anal. calc. for $C_8HClF_6N_2$: C 35.00, H 0.37, N 10.20 %. Found: C 35.02, H 0.34, N 10.23%.

2-Hydrazinyl-4,6-bis(trifluoromethyl)nicotinonitrile (3): 0.5 mg of 2-Chloro-4,6-bis(trifluoromethyl) nicotinonitrile 3 was taken in 15-20 ml of hydrazine hydrate and heated at 100 ° C for about 17 hours. After product confirmation by TLC, reaction mixture was dissolved in water and solid was separated and dried.

White solid; Yield 70%; IR (KBr, cm^{-1}):): 3319, 3295 (-NH_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.69 (br s, 2H, NH_2), 8.01(s, 1H, Ar-H), 8.68 (br, 1H, -NH-); MS (ESI): m/z [$(M+H)^+$]: 271; Anal. calc. for $C_8H_4F_6N_4$: C 35.57, H 1.49, N 20.74 %. Found: C 35.58, H 1.50, N 20.75%.

N'-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)formohydrazide (4a): 2-Hydrazinyl-4,6-bis(trifluoromethyl)

nicotinonitrile 3 on reaction with aromatic /aliphatic acid chloride under refluxing condition for about 6 hours and collected by filtration and dried to get solid product 4.

IR (KBr, cm^{-1}): 3422 (-CONH-), 1661 (-CONH-), 1162, 1121 (C-F); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.16(s, 1H, Ar-H), 8.64 (br. s., 1H, -NH-) 10.21(br. s., 1H,-NH-); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 118.4, 120.1, 122.6, 124.5, 128.7, 132.4, 136.4, 142.7, 160.1; MS (ESI): m/z [$(M+H)^+$]: 299 [$(M+Na)^+$]: 304; Anal. Calcd for $C_9H_4F_6N_4O$: C 36.26, H 1.35, N 18.79%. Found: C 36.27, H 1.36, N 18.80%.

N'-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)aceto hydrazide (4b): IR (KBr, cm^{-1}): 3423 (-CONH-), 1662 (-CONH-), 1161, 1123 (C-F); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.05 (s, 3H, $-CH_3$), 8.14 (s, 1H, Ar-H), 8.61 (br. s., 1H,-NH-) 10.13(br. s., 1H,-NH-); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 21.4, 119.6, 120.2, 121.9, 124.6, 127.8, 132.6, 136.4, 141.6, 160.2; MS (ESI): m/z [$(M+H)^+$]: 313; Anal. Calcd for $C_{10}H_6F_6N_4O$: C 38.47, H 1.94, N 17.95%. Found: C 38.48, H 1.95, N 17.96%.

N'-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)propio nohydrazide (4c): IR (KBr, cm^{-1}): 3421 (-CONH-), 1645 (-CONH-), 1162, 1125 (C-F); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.05 (t, 3H, $-CH_3$), 2.28 (q, 2H, $-CH_2$), 7.94 (s, 1H, Ar-H), 8.63 (br. s., 1H,-NH-) 10.15 (br. s., 1H,-NH-); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 10.8, 29.6, 118.5, 119.7, 121.2, 123.8, 126.7, 132.8, 135.3, 142.8, 160.3; MS (ESI): m/z [$(M+H)^+$]: 327; Anal. Calcd for $C_{11}H_8F_6N_4O$: C 40.50, H 2.47, N 17.18%. Found: C 40.51, H 2.48, N 17.20%.

N'-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)benzo hydrazide (4d): IR (KBr, cm^{-1}): 3418 (-CONH-), 1639 (-CONH-), 1158, 1125 (C-F); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32-7.41 (m, 3H, Ar-H), 7.53-7.58 (m, 2H, Ar-H), 7.91 (s, 1H, Ar-H), 8.59 (br. s., 1H,-NH-) 10.11 (br. s., 1H,-NH-); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 119.8, 120.3, 121.8, 123.2, 125.7, 126.7, 128.6, 132.8, 136.3, 140.5, 142.8, 147.5, 160.3; MS (ESI): m/z [$(M+H)^+$]: 375; Anal. Calcd for $C_{15}H_8F_6N_4O$: C 48.14, H 2.15, N 14.97%. Found: C 48.15, H 2.18, N 14.99%.

N'-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-4-met hylbenzohydrazide (4e): IR (KBr, cm^{-1}): 3421 (-CONH-), 1635 (-CONH-), 1152, 1121 (C-F); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.35 (s, 3H, $-CH_3$), 7.38 (d, 2H, Ar-H), 7.52 (d, 2H, Ar-H), 7.89 (s, 1H, Ar-H), 8.65 (br. s., 1H,-NH-) 10.10 (br. s., 1H,-NH-); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 21.5, 118.4, 120.7, 121.9, 123.3, 125.4, 126.8, 128.9, 131.9, 135.2, 140.3, 142.6, 147.3, 160.1; MS (ESI): m/z [$(M+H)^+$]: 375; Anal. Calcd for $C_{16}H_{10}F_6N_4O$: C 49.49, H 2.60, N 14.43%. Found: C 49.50, H 2.59, N 14.42%.

N'-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-3-met hoxybenzohydrazide (4f): IR (KBr, cm^{-1}): 3419 (-CONH-), 1628 (-CONH-), 1149, 1129 (C-F); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.81 (s, 3H, $-OCH_3$), 7.10 (s, 1H, Ar-H), 7.28-7.34 (m, 3H, Ar-H), 7.88 (s, 1H, Ar-H), 8.62 (br. s., 1H,-NH-) 10.12 (br. s., 1H,-NH-); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 55.8, 119.3, 120.8, 121.3, 121.8, 123.2, 124.7, 126.7, 128.4, 129.4, 131.8, 136.3, 140.1, 142.5, 148.2, 160.3; MS (ESI): m/z [$(M+H)^+$]: 405; Anal. Calcd for $C_{16}H_{10}F_6N_4O_2$: C 47.54, H 2.49, N 13.86%. Found: C 47.53, H 2.50, N 13.87%.

N'-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-4-(trif luoromethyl)benzohydrazide (4g): IR (KBr, cm^{-1}): 3418 (-CONH-), 1626 (-CONH-), 1148, 1129 (C-F); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38 (d, 2H, Ar-H), 7.53 (d, 2H, Ar-H), 7.84 (s, 1H, Ar-H), 8.63 (br. s., 1H,-NH-) 10.13 (br. s., 1H,-NH-); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 118.2, 120.4, 121.4, 122.9, 123.1, 125.5, 126.8, 128.3, 130.5, 131.7, 136.2, 140.4, 142.7, 148.3, 160.2; MS (ESI): m/z [$(M+H)^+$]: 443; Anal. Calcd for $C_{16}H_7F_9N_4O$: C 43.45, H 1.60, N 12.67%. Found: C 43.46, H 1.62, N 12.68%.

N'-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)nicotin ohydrazide (4h): M. P. 184-186; IR (KBr, cm^{-1}): 3421 (-CONH-), 1625 (-CONH-), 1142, 1121 (C-F); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.33-7.38 (m, 3H, Ar-H), 7.48 (s, 1H, Ar-H), 7.81 (s, 1H, Ar-H), 8.62 (br. s., 1H,-NH-) 10.15 (br. s., 1H,-NH-); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 119.3, 120.5, 121.3, 122.7, 123.2, 125.2, 126.7, 128.2, 130.1, 136.3, 140.5, 142.6, 148.1, 160.1; MS (ESI): m/z [$(M+H)^+$]: 376; Anal. Calcd for $C_{14}H_7F_6N_5O$: C 44.81, H 1.88, N 18.66%. Found: C 44.82, H 1.89, N 18.69%.

5,7-bis(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-8-carbonitrile (5a): The N'-(3-cyano-4,6-bis (trifluoromethyl)pyridin-2-yl)formohydrazide 4 (0.2 g, 0.7 mmol) and $POCl_3$ (6–8mL) and PCl_5 0.05 g were taken in a clean and dry round bottom flask. 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 (30mL 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.

M. P. 184-186; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.92 (s, 1H, Ar-H), 8.71 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 117.4, 119.5, 120.2, 123.4, 126.8, 128.7, 134.4, 140.2, 142.8; MS (ESI): m/z [$(M+H)^+$]: 281; Anal. Calcd for $C_9H_2F_6N_4$: C 38.59, H 0.72, N 20.00%. Found: C 38.58, H 0.75, N 20.02%.

3-Methyl-5,7-bis(trifluoromethyl)-[1,2,4]triazolo[4,3-a] pyridine-8-carbonitrile (5b): M. P. 165-167; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.41 (s, 3H, $-CH_3$), 8.72 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ14.2, 118.3, 120.2, 122.7, 124.8, 125.4, 127.8, 132.7, 139.7, 142.2,; MS (ESI): m/z

[(M+H)$^+$]: 295; Anal. Calcd for $C_{10}H_4F_6N_4$: C 40.83, H 1.35, N 19.05%. Found: C 40.83, H 1.36, N 19.06%.

3-ethyl-5,7-bis(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-8-carbonitrile (5c): M. P. 182-184; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24(t, 3H, -CH_3), 3.28 (q, 2H, -CH_2), 8.47 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 12.8, 23.4, 119.4, 120.8, 123.7, 125.7, 128.4, 130.5, 133.5, 140.6, 142.3; MS (ESI): m/z [(M+H)$^+$]: 309; Anal. Calcd for $C_{11}H_6F_6N_4$: C 42.87, H 1.96, N 18.18%. Found: C 42.88, H 1.97, N 18.20%.

3-Phenyl-5,7-bis(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-8-carbonitrile (5d): M. P. 205-207; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36-7.44 (m, 3H, Ar-H), 7.56-7.60 (m, 2H, Ar-H), 8.41 (br. s., 1H,-NH-); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 120.1, 123.6, 125.5, 126.7, 128.1, 129.0, 130.7, 133.3, 134.3, 135.1, 139.7, 141.9, 148.4,; MS (ESI): m/z [(M+H)$^+$]: 357; Anal. Calcd for $C_{15}H_6F_6N_4$: C 50.57, H 1.70, N 15.73%. Found: C 50.58, H 1.71, N 15.75%.

3-(p-tolyl)-5,7-bis(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-8-carbonitrile (5e): M. P. 221-223; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.36 (s, 3H, -CH_3), 7.34 (d, 2H, Ar-H), 7.50 (d, 2H, Ar-H), 8.41 (s, 1H, Ar-H), ^{13}C NMR ($CDCl_3$, 300 MHz): δ 21.6, 119.5, 120.6, 122.6, 123.4, 125.7, 126.7, 127.5, 129.7, 132.8, 135.6, 140.2, 142.8, 147.2; MS (ESI): m/z [(M+H)$^+$]: 371; Anal. Calcd for $C_{16}H_8F_6N_4$: C 51.90, H 2.18, N 15.13%. Found: C 51.92, H 2.20, N 15.14%.

3-(3-Methoxyphenyl)-5,7-bis(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-8-carbonitrile (5f): M. P. 221-223; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.82 (s, 3H, -OCH_3), 7.32 (s, 1H, Ar-H), 7.48-7.52 (m, 3H, Ar-H), 8.45 (s, 1H, Ar-H), ^{13}C NMR ($CDCl_3$, 300 MHz): δ 54.8, 118.6, 120.4, 121.3, 122.7, 123.6, 125.8, 126.4, 127.5, 129.8, 132.5, 132.8, 135.4, 140.3, 142.5, 147.7; MS (ESI): m/z [(M+H)$^+$]: 387; Anal. Calcd for $C_{16}H_8F_6N_4O$: C 49.75, H 2.09, N 14.51%. Found: C 49.76, H 2.10, N 14.53%.

5,7-Bis(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridine-8-carbonitrile (5g): M. P. 231-233; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38 (d, 2H, Ar-H), 7.52 (d, 2H, Ar-H), 8.43 (s, 1H, Ar-H), ^{13}C NMR ($CDCl_3$, 300 MHz): δ 117.8, 119.2, 121.7, 122.3, 123.5, 125.8, 126.7, 127.4, 129.8, 132.5, 136.3, 140.4, 142.3, 146.7; MS (ESI): m/z [(M+H)$^+$]: 425; Anal. Calcd for $C_{16}H_5F_9N_4$: C 45.30, H 1.19, N 13.21%. Found: C 45.32, H 1.20, N 13.22%.

3-(Pyridin-3-yl)-5,7-bis(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine-8-carbonitrile (5h): M. P. 218-220; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48-7.50 (m, 3H, Ar-H), 7.81(s, 1H, Ar-H), 8.45 (s, 1H, Ar-H), ^{13}C NMR ($CDCl_3$, 300 MHz): δ 118.2, 120.5, 121.4, 123.2, 125.4, 126.6, 127.5, 128.1, 129.4, 132.6, 136.2, 140.3, 142.4, 146.3; MS (ESI): m/z [(M+H)$^+$]: 358; Anal. Calcd for $C_{14}H_5F_6N_4$: C 47.07, H 1.41, N 19.61%. Found: C 47.08, H 1.42, N 19.63%.

Results and Discussion

Structure activity relation studies reveal that triazolo pyridine derivatives were tested for anticancer activity among four human cancer cell lines such as HeLa - Cervical cancer (CCL-2); COLO 205- Colon cancer (CCL-222); HepG2- Liver cancer (HB-8065); MCF7 - Breast cancer (HTB-22). HEK-293 – Human Embryonic Kidney cells (CRL-1573). 5-Fluorouracil was used as standard control.

Table 1
Preparation of substituted 4,6-bistrifluoromethyl-pyridine-2-yl hydrazide derivatives 4a-h and 5,7-bistrifluorormethyl-1,2,4-triazolo[4,3-*a*]pyridine derivatives 4a-h and 5a-h.

R	Compound No.	Yield %	Compound No.	Yield %
H	**4a**	48	**5a**	60
CH_3	**4b**	50	**5b**	47
CH_2CH_3	**4c**	56	**5c**	41
C_6H_5	**4d**	68	**5d**	63
4-CH_3-C_6H_4	**4e**	72	**5e**	52
3-OCH_3-C_6H_4	**4f**	66	**5f**	69
4-CF_3-C_6H_4	**4g**	73	**5g**	54
3-Pyridyl	**4h**	71	**5h**	49

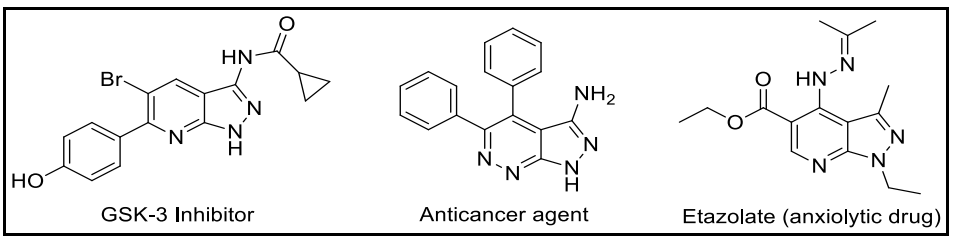
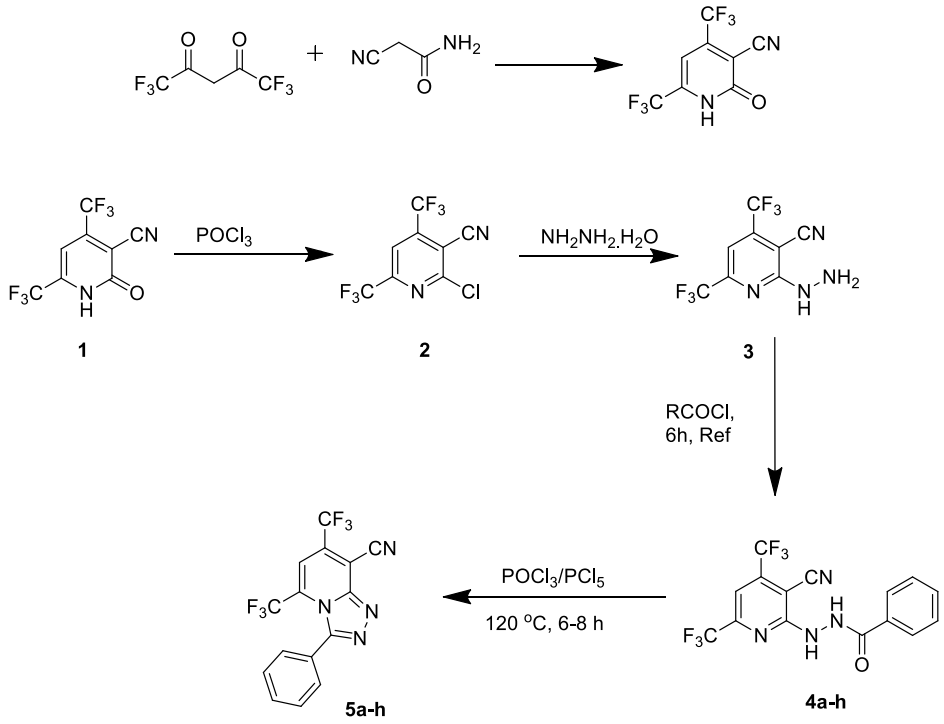


Fig. 1: Some biological active compounds based on fused pyridine



Scheme 1: Sequence of reactions

Table 2
***In vitro* cytotoxicity of compounds 4a-h and 5a-h.**

Compd.	IC_{50} values (in µM)				
	HeLa	**COLO205**	**HepG2**	**MCF7**	**HEK93**
4a	---	---	---	---	120 ± 0.52
4b	---	---	---	---	90 ± 0.62
4c	---	---	---	---	82 ± 0.54
4d	65.2 ± 0.62	28.7± 0.16	---	45.3± 0.36	98 ± 0.85
4e	42.5± 0.32	31.4± 0.26	---	---	59 ± 0.45
4f	48.5 ± 0.32	35.5 ± 0.32	41.2± 0.45	28.7± 0.28	48 ± 0.34
4g	18.4 ± 0.15	23.4 ± 0.21	34.4 ± 0.65	19.7± 0.32	111 ± 0.82
4h	28.4 ± 0.25	21.7± 0.21	---	39.2± 0.41	48 ± 0.31
5a	---	---	---	---	31 ± 0.22
5b	---	---	---	---	28 ± 0.43
5c	121.2± 0.62	---	---	---	44 ± 0.21
5d	---	61.5 ± 0.36	89.8 ± 0.23	59.7± 0.22	59 ± 0.48
5e	78.4 ± 0.62	---	94.3 ± 0.82	---	62 ± 0.71
5f	---	---	80.4 ± 0.62	---	54 ± 0.71
5g	73.4 ± 0.65	61.5 ± 0.36	89.8 ± 0.23	59.7± 0.22	25 ± 0.29
5h	---	---	54.2 ± 0.41	---	36 ± 0.41
5-FU (Std control)	1.8 ± 0.09	1.9 ± 0.11	1.7 ± 0.08	1.8± 0.07	19.6 ± 0.18

---indicates IC_{50} value > 121.2 µM; Cell lines used: HeLa - Cervical cancer (CCL-2); COLO 205- Colon cancer (CCL-222); HepG2- Liver cancer (HB-8065); MCF7 - Breast cancer (HTB-22); HEK-293 – Human Embryonic Kidney cells (CRL-1573). 5-FU-5-Fluorouracil (Standard Control);

Among all compounds, some showed activity up to the IC_{50} values of 121.2 µM. Compounds 4a, 4b, 4c, 5a and 5b did not show any activity on four cancer cell lines. All compounds showed good IC_{50} values on human healthy cell lines that is HEK93 when compared to standard 5-fluorouracil (19.6 µM). Among all compounds tested, 4f and 4g compounds showed promising activity on four cell lines. When compared to cyclized compounds 5a-5h, uncyclized

4a-4h compounds were found to have more activity due to availability of N-H protons.

N-attached hydrogen in Schiff's base link and amide functional group participated in H-bonding (H-attached with electronegative atom like N), almost all the compounds showed activity against four cancer cell lines at micro molar concentration. Among all the compounds, 4f and 4g showed promising activity. The activity data is shown in table 2.

Conclusion

In conclusion, a series of novel triazolo pyridine derivatives 4a-h and 5a-h were prepared and evaluated for anticancer activity against four human cancer cell lines such as 'HeLa - Cervical cancer (CCL-2); COLO 205- Colon cancer (CCL-222); HepG2- Liver cancer (HB-8065); MCF7 - Breast cancer (HTB-22); HEK-293 – Human Embryonic Kidney cells (CRL-1573) using MTT assay. Among all the compounds screened, the compounds 4f and 4g showed significant activity against all cell lines at micro molar concentration.

References

1. Alvarez R., Velazques S., San F., Aquaro S., De C., Perno M.C.F., Karlesson A., Balzarini J. and Camarasa M.J., 1,2,3-Triazole-[2,5-Bis-O-(tertbutyldimethylsilyl)-.beta.-D-ribofuranosyl]-3'-spiro-5"-(4"-amino-1",2"-oxathiole 2",2"-dioxide) (TSAO) Analogs: Synthesis and Anti-HIV-1 Activity, *Journal of Med. Chem*., **37**, 4185-94 **(1994)**

2. Borne Y., Kolb H.C., Radiac Z., Sharpless K.B., Taylor K. and Marchot P., Proceedings of the National Academy of Sciences of the United States of America, 1449 **(2004)**

3. Chanin Nantasenamat, Apilak Worachartcheewan, Supaluk Prachayasittikul, Chartchalerm Isarankura-Na-Ayudhya and Virapong Prachayasittikul, QSAR modeling of aromatase inhibitory activity of 1-substituted 1,2,3-triazole analogs of letrozole, *Eur. J. Med. Chem*., **69**, 99-114 **(2013)**

4. Cozzi P., Mongelli N. and Suarato A., Recent anticancer cytotoxic agents, *Curr. Med. Chem. Anticancer Agents*, **4**, 93–121 **(2004)**

5. Dubey Sushma, Singh Jaya, Sinha Chandrashekhar and Gupta Saurabh, Diversity of Myco-flora associated with plants of Dumna Nature Park and their antimicrobial potential, *Res. J. Biotech*, **17(1)**, 60-63 **(2022)**

6. Eftekhari-Sis B., Zirak M. and Akbari A., Arylglyoxals in synthesis of heterocyclic compounds, *Chem. Rev*., **113**, 2958–3043 **(2013)**

7. Glowacka I.E., Jan Balzarini and Wróblewski A., The synthesis, antiviral, cytostatic and cytotoxic evaluation of a new series of acyclonucleotide analogues with a 1,2,3-triazole linker, *Eur. J. Med. Chem*., **70**, 703-722 **(2013)**

8. Isanbor C. and O'Hagan D., Synthesis of Fluorinated Heterobicyclic Nitrogen Systems Containing 1,2,4-Triazine Moiety as CDK2 Inhibition Agents, *J. Fluorine Chem*., **12**, 303–319 **(2006)**

9. Ju Y. and Varma R.S., Aqueous N-heterocyclization of primary amines and hydrazines with dihalides: microwave-assisted syntheses of N-azacycloalkanes, isoindole, pyrazole, pyrazolidine and phthalazine derivatives, *J. Org. Chem.,* **71**, 135–141 **(2006)**

10. Kalaria P.N., Karad S.C., Raval D.K., A review on diverse heterocyclic compounds as the privileged sca_olds in antimalarial drug discovery, *Eur. J. Med. Chem*., **158**, 917–936 **(2018)**

11. Kerru N., Bhaskaruni S.V.H.S., Gummidi L., Maddila S.N., Maddila S. and Jonnalagadda S.B., Recent advances in heterogeneous catalysts for the synthesis of imidazole derivatives, *Synth. Commun*., **49**, 2437–2459 **(2019)**

12. Kerru N., Maddila S. and Jonnalagadda S.B., Design of carbon–carbon and carbon–heteroatom bond formation reactions under green conditions, *Curr. Org. Chem.*, **23**, 3156–3192 **(2019)**

13. Kerru N., Singh P., Koorbanally N., Raj R. and Kumar V., Recent advances (2015–2016) in anticancer hybrids, *Eur. J. Med. Chem*., **142**, 179–212 **(2017)**

14. Leeson P.D. and Springthorpe B., The influence of drug-like concepts on decision-making in medicinal chemistry, *Nat. Rev. Drug Discov*., **6**, 881–890 **(2007)**

15. Lewis W.G., Green L.G., Grynszpan F., Radic Z., Carlier P.R., Taylor P., Finn M.G. and Sharpless K.B., Click chemistry in situ: acetylcholinesterase as a reaction vessel for the selective assembly of a femtomolar inhibitor from an array of building blocks, *Ang. Chem. Int. Ed*., **41**, 1053-1057 **(2002)**

16. Li X., He L., Chen H., Wu W. and Jiang H., Copper-catalyzed aerobic C(sp^2)–H functionalization for C–N bond formation: Synthesis of pyrazoles and indazoles, *J. Org. Chem*., **78**, 3636–3646 **(2013)**

17. Paget C.J. Jr., Wikl J.H. and Often G., s-triazolo [3,4-b] benzothiazles, Ger Offen 2, 509,843, 1975, *Chem Abstr*, **84**, 44070 **(1976)**

18. Prasad A.R., Ramalingam T., Rao A.B., Diwan P.V. and Sattur P.B., *Indian J. Chem.*, **25B**, 566-668 **(1986)**

19. Santos C.M.M., Freitas M. and Fernandes E., A comprehensive review on xanthone derivatives as glucosidase inhibitors, *Eur. J. Med. Chem*., **157**, 1460–1479 **(2018)**

20. Shaban M.A.E. and Nasr A.Z., The synthesis of condensed 1,2,4-triazolo (3,4-z) heterocycles, *Advances in Heterocyclic Chemistry*, **49**, 277-383 **(1990)**

21. Yakaiah C., Domatti A.K., Sarfaraz A., Singh S.P., Arigari N.K., Gupta Namita, Satya K.V.N., Kumar J.K., Feroz Khan Tiwari A.K. and Paramjit G., Synthesis, biological evaluation and molecular modeling studies of some novel thiazolidinediones with triazole ring, *Eur. J. Med. Chem.*, **70**, 308-314 **(2013)**

22. Ying-Chao Duan, Yi-Chao Zheng, Xiao-Chen Li, Meng-Meng Wang, Xian- Wei Ye, Yuan-Yuan Guan, Gai-Zhi Liu, Jia-XinZheng and Hong-Min Liu, Design, synthesis and antiproliferative activity studies of novel 1,2,3-triazole–dithiocarbamate–urea hybrids, *Eur. J. Med. Chem*., **64**, 99-110 **(2013)**

23. Zarate D.Z., Aguilar R., Hernandez-Benitez R.I., Labarrios E.M., Delgado F. and Tamariz J., Synthesis of-ketols by functionalization of captodative alkenes and divergent preparation of heterocycles and natural products, *Tetrahedron*, **71**, 6961–6978 **(2015)**.

(Received 20th April 2023, accepted 28th June 2023)