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Synthesis of Novel (S)-Imidazolo[1,2c][1,2,3]triazolo-[4,5e]pyrimidine Derivatives

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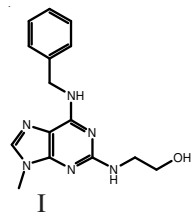
Isopropyl azide (**1**) was reacted with cyanoacetamide (**2**) in the presence of sodium ethoxide to obtain 4-amino-3-isopropyl-3*H*-[1,2,3]triazolo-5-carboxamide (**3**) which on treatment with excess of diethyl carbonate and sodium ethoxide gave 3-isopropyl-3*H*-[1,2,3]triazolo[4,5-d]pyrimidine-5,7-diol (**4**). The latter on treatment with $POCl_3$ and 2,6-lutidine in the presence of catalytic amount of PCl_5 resulted in 5,7-dichloro-3-isopropyl-3*H*-[1,2,3]triazolo[4,5-d] pyrimidine (**5**) in good yields. Compound **5** on condensation with L-prolinol (**6**) in ethanol yielded (S)- [1-(5-chloro-3-isopropyl-3*H*-[1,2,3]triazolo[4,5-d]pyrimidine-7-yl)pyrrolidine-2-yl-meth anol (**7**). Compound **7** on treatment with anilines (**8a-8j**) gave (S)-(1-(3-isopropyl-5-(arylamino)-3*H*-[1,2,3]triazolo[4,5-d]pyrimidine-7-yl)pyrrolidine-2-yl) methanol (**9a-j**) by the nucleophilic displacement of the chlorine at 5th -position. **9a-j** on treatment with $POCl_3$ afforded a series of novel chiral derivatives of (S)-N-(3-isopropyl-7a,8,9,10[1'2':3,4]imidazolo[1,2c] [1,2,3]triazolo[4,5e]pyrimidine5(7H)yl-idine) aniline hydrochloride (**10a-j**) by dehydrative cyclization. This cyclization also takes place with $SOCl_2$ under refluxing conditions, but yields are low compared to the $POCl_3$ conditions.

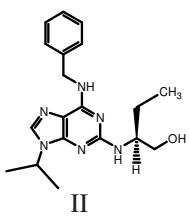
Keywords: Isopropylazide, Cyanoacetamide, L-Prolinol, Triazole, Triazolopyrimidine.

INTRODUCTION

Among the nitrogen containing heterocyclic compounds, purines and azapurines are important class of compounds[1-3]. Azapurines are theoretically obtained[2] by replacing the 2nd -carbon atom with nitrogen atom in the purine ring system. Purines and their derivatives are biologically active[4,5]. Examples are olomocine (I), (R)-roscovitine (II) and purvalanol-B (III), which are known to posses anticancer activity[4]. Based on this presumption, it was thought that azapurine derivatives and imidazo[1,2-c]pyrimidine derivatives may also have similar type of biological activity.



I



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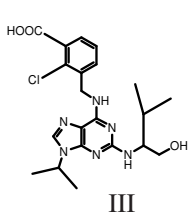


III

Apart from anticancer properties[3,6], [1,2,3]triazoles and azapurines are known to exhibit antiviral[1], antifungal[3], anti-tuberculosis[7] and anti-HIV[8,9] activity. Azapurines are also used as purine nucleosides[8]. Similarly, imidazo[1,2c]-pyrimidines show biological activity in the treatment of various allergic disorders and auto immune diseases[9].

Herein we wish to report the synthesis of some fused azapurines as potentially biologically active compounds and also as new chemical entities.

EXPERIMENTAL

Unless stated otherwise, reactions were performed under nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel 100-200 and 230-400 mesh using hexane, ethyl acetate, dichloromethane. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$, DMSO-d_6 and CD_3OD solution by using Bruker AC-300 and 400 MHz spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Infrared spectra were recorded on a perkin-Elmer1720 FT-IR spectrometer (KBr Pellets). Melting points were determined in a polmon m.p. apparatus and are uncorrected. Mass spectra were recorded on Agilent 6120 LCMS instrument giving M^+ values either on (M^+ + 1) or (M^+-1) modes.

Preparation of 4-Amino-3-isopropyl-1*H*-[1,2,3]triazolo-5-carboxamide (3): Cyanoacetamide (96 g, 0.96 mol) and isopropyl azide (163.2 g, 1.92 mol) were added to a solution of sodium ethoxide (195.84 g, 2.88 mol) in absolute ethanol (2 L). The mixture was stirred for 1 h at room temperature and

slowly the temperature was raised to reflux, maintained at reflux for 36 h, while the reaction was monitored by TLC. Ethanol was then distilled out under reduced pressure and the residue was cooled to RT. Water (100 mL) was added to the residue and the mixture cooled to 10 °C, adjusted the pH to 7.0-7.5 using 6N HCl with stirring for 1 h at 10 °C. The mixture was filtered, the insoluble solid was washed with cold water (50 mL) and dried. Yield = 110.32 g, (68 %), m.r: 211-216 °C. (Lit[2]. m.p: 209-215 °C).

Preparation of 3-isopropyl-3*H*-[1,2,3]triazolo[4,5-d]pyrimidine-5,7-diol (4): To a solution of sodium ethoxide (96.56 g, 1.42 mol) in absolute ethanol (1.5 L), **3** (48 g, 0.284 mol) was added and the temperature raised to 80 °C. The mixture was stirred for 2 h, then diethyl carbonate (301.6 g, 2.58 mol) was added dropwise over 2.5 h at the same temperature and the reaction mixture stirred for 24 h at 85-90 °C while the reaction was monitored by TLC. Ethanol was then distilled out under reduced pressure and the residue cooled to RT. Water (500 mL) was added to the residue and the mixture cooled to 0 °C, adjusted the pH to 6.0-6.5 using 6N HCl with stirring for 0.5 h at 10 °C. The insoluble solid was filtered and washed with cold methanol (100 mL) and then dried to get pale brown coloured solid. Yield = 47.8 g, (88 %), m.r: > 300 °C. (Lit[2]. m.p: 303-306 °C).

Preparation of 5,7-dichloro-3-isopropyl-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidine (5): To a suspension of **4** (30 g, 0.153 mol) in phosphorus oxychloride (450 mL), containing PCl_5 (5 g) was added and the mixture cooled to (-) 20 °C. 2,6-Lutidine (90.5 g, 0.846 mol) was then added drop-wise over a period of 45 min. After this, the temperature was slowly raised to RT, then the reaction mixture was slowly heated to 120 °C with stirring for 12 h, while the reaction was monitored by TLC. At the end of this period, $POCl_3$ was distilled out under reduced pressure at 60 °C and the mixture cooled to RT, the residue was poured into crushed ice (500 g) and the aqueous layer extracted with MTBE (4 × 200 mL). The MTBE layer was dried over anh. Na_2SO_4 and concentrated under reduced pressure to obtain a solid residue that was recrystallized using hexane to get an off-white solid. Yield = 27.36 g, (77 %), m.r: 73-75 °C.

Preparation of (S)-[1-(5-chloro-3-isopropyl-3*H*[1,2,3]-triazolo[4,5,d]pyrimidine-7-ly)-pyrrolidin-2-yl-methanol (7): A solution of **5** (12 g, 0.051 mol) in absolute ethanol (100 mL) was cooled to 0 °C. L-prolinol (10.34 g, 0.103 mol) was added to it drop-wise over 0.5 h. After this, the mixture was stirred for 0.5 h, while the reaction was monitored by TLC. Then, the reaction mixture was poured into water (200 mL) and extracted with DCM (3 × 100 mL). The organic layer was washed with 2N HCl (100 mL) followed by water (2 ×100 mL) and then dried over anhyd. Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residual solid was stirred with hexane (75 mL) and filtered to obtain pale yellow insoluble solid that was dried. Yield = 13.5 g, (94.6 %), m.r.: 95-97 °C; Standard optical rotation value $[\alpha]^{25}_{D}$ = (-)103.68 °C = 0.25 % w/v in methanol. H NMR (400 MHz, DMSO-d_6) δ: 5-4.85 (m, 2H), 4.1(m, 1H), 4.4 (bs, 1H), 3.67-3.61(m, 3H), 2.06-1.98 (m, 3H), 1.58-1.56 (d, 6H); ^{13}C NMR (100 MHz, CD_3OD): 159.0, 158.8, 154.2, 154.0, 151.4, 151.3, 126.2, 125.6, 63.1, 62.49, 62.41, 62.0, 51.9, 51.7, 49.5, 29.0, 28.2, 24.9, 22.7, 22.18, 22.16, 22.12; LC-MS: *m/z* = 297 [M^+ + 1].

Preparation of (S)-(1-(3-isopropyl-5-(arylamino)-3*H*[1,2,3]triazolo-[4,5-d]pyrimidine-7-yl)pyrrolidine-2-yl)methanol (9a-j). (General procedure): A mixture of **7** (0.8 g, 2.7 mmol, 1eq) and appropriate aniline **8a-j** (10 mmol, 4 eq) was heated to 140 °C, as neat reactants with stirring for 45 min, while the reaction was monitored by TLC. At the end of this period, the mixture was cooled to RT and diluted with ethyl acetate. The mixture was washed with 3N HCl followed by water. The organic layer was dried over anhyd. Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure, to get a residual solid. This solid was stirred with hexane and filtered to obtain **9** (**a-j**). The aq acidic layer was basified with commercial caustic lye and extracted with DCM (2 × 100 mL). The organic layer was dried over anh Na_2SO_4 and concentrated under reduced pressure to get unreacted anilines (**8a-j**).

9a: light brown solid; 0.90 g, (95 %), m.r.: 139-142 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.81-7.79 (2H, d), 7.34-7.28 (2H, m), 6.99-6.96 (1H, m), 4.98-4.97 (2H, dd), 4.14 (1H, m), 3.83-3.58 (3H, m), 2.19-2.01 (4H, m), 1.6 (6H, d); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.9, 150.6, 140.6, 129.1, 121.8, 121.4, 118.6, 115.9, 67.1, 65.1, 61.8, 60.9, 50.9, 47.8, 28.8, 28.2, 24.5, 21.9, 21.6; LC-MS: *m/z* = 354 [M^+ + 1].

9b: Off-white solid; 0.92 g, (92%), m.r.: 122-127 °C; IR (KBr, ν_{max}, cm^{-1}): 3400 (-OH, str), 3300 (N-H, str), 1596 (N=N, str), 1324 (C-N, str); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.95 (1H,S), 7.87-7.85 (1H, m), 7.44-7.41 (1H, S), 7.22-7.19 (1H, t), 6.62 (1H, t), 4.99 (2H, m), 4.22 (1H, m), 3.80-3.2 (4H, m), 2.5-2.0 (5H, m), 1.9-1.6 (6H, d); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 129.2, 114.0, 108.1, 106.1, 105.8, 66.05, 61.3, 60.5, 50.2, 27.7, 24.0, 21.3; LC-MS: *m/z* = 372 [M^+ + 1].

9c: Off -white solid; 1.1 g, (95 %), m.r.: 143-146 °C; IR (KBr, ν_{max}, cm^{-1}): 3393 (-OH, str), 3309 (N-H, str), 1577 (N=N, str), 1322 (C-N, str); ^{1}H NMR (300 MHz, DMSOd_6) δ: 8.95 (1H, S), 8.3-8.2 (1H, m), 7.647.41 (1H, S), 7.12 (1H, t), 4.94.95 (1H, m), 4.22 (1H, m), 3.7 (3H, m), 3.1 (2H, m), 2.0 (3H, m), 1.66 (6H, d); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.8, 154.0, 140.9, 129.8, 124.9, 121.7,117.4, 66.8, 65.1, 61.6, 60.8, 50.6, 47.7, 50.3, 50.1, 28.1, 28.8, 24.4, 21.6, 21.9; LC-MS: *m/z* = 432 [M^+ + 1].

9d: Off-white coloured solid; 0.97 g, (93 %), m.r.: 134-137 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.7 (1H, bs), 8.14-8.01 (1H, dd), 7.6-7.7 (1H, dd), 7.4-7.37 (1H, d d), 6.9 (1H, m), 4.97-4.94 (2H, m), 3.7 (3H, m), 3.1 (2H, m), 2.0 (3H, m) 1.66 (6H, d); LC-MS: *m/z* = 388 [M^+ + 1].

9e: Off-white solid; 0.95 g, (96 %), m.r.: 142146 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ: 9.4 (1H, NH), 7.7 (1H, d), 7.5 (1H, dd), 7.15 (1H, d), 6.75 (1H, d), 5 (1H, m), 4.2 (1H, m), 3.5 (3H, m), 2.2 (3H, s), 2.1 (5H, m), 1.6 (6H, d). Its LC-MS: *m/z* = 368 [M^+ +1].

9f: Off -white solid; 1 g, (95 %), m.r.: 136-140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.6 (1H, dd), 8.4 (1H, s), 7.8-7.7 (1H, dd), 7.5 (1H, d), 7.4 (1H, m), 5 (1H, m), 4.8 (1H, S), 4.2 (2H, m), 3.7-3.8 (3H, m), 2.1-2.4 (4H, m), 1.6 (6H, d); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.9, 150.6, 140.6, 129.1, 121.8, 121.4, 118.6, 115.9, 67.1, 65.1, 61.8, 60.9, 50.9, 47.8, 28.8, 28.2, 24.5, 21.9, 21.6; LC-MS: *m/z* = 422 [M^+ +1].

9g: Pale yellow solid; 1 g, (93 %), m.r.: 139-145 °C; IR (KBr, ν_{max}, cm^{-1}): 3392 (-OH, str), 3310 (N-H str), 1601(N=N,

str), 1335 (C-N, str); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.6 (1H, bs), 9.1 (1H, dd), 7.9 (1H, dd), 7.7 (1H, m), 7.4 (1H, m), 5.1 (2H, m), 4.2 (1H, m), 3.7-3.8 (4H, m), 2.0-2.2 (4H, m), 1.6 (6H, d); LC-MS : *m/z* = 399 [M$^+$+1].

9h: Off-white solid; 0.96 g, (93 %), m.r.: 156-159 °C; IR (KBr, ν_{max}, cm^{-1}): 3392 (-OH, str), 3311, (N-H, str), 1600, (N=N, str), 1326 (C-N, str); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.6 (1H, bs), 7.6 (1H, dd), 7.2 (2H, m), 6.5 (1H, m), 5.1 (2H, m), 4.2 (1H, m), 3.7-3.8 (4H, m), 2.0-2.2 (4H, m), 1.6 (6H, d); LC-MS: *m/z* = 384 [M$^+$+1].

9i: Off-white solid; 0.96 g, (96 %), m.r.: 161-165 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.4 (1H, bs), 7.6 (1H, m), 7.2 (2H, m), 7.05 (1H, d), 6.75 (1H, d), 5 (1H, m), 4.2 (1H, m), 3.5 (3H, m), 2.2 (3H, s), 2.1 (5H, m), 1.6 (6H, d). LC-MS: *m/z* = 368 [M$^+$+1].

9j: Off-white solid; 1.09 g, (93 %), m.r.:164-169 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.8 (1H, bs), 7.8 (2H, dd), 7.2 (2H, dd), 5.1 (2H, m), 4.2 (1H, m), 3.7-3.8 (4H, m), 2.0-2.2 (4H, m), 1.6 (6H, d). Its LC-MS: *m/z* = 438 [M$^+$ + 1].

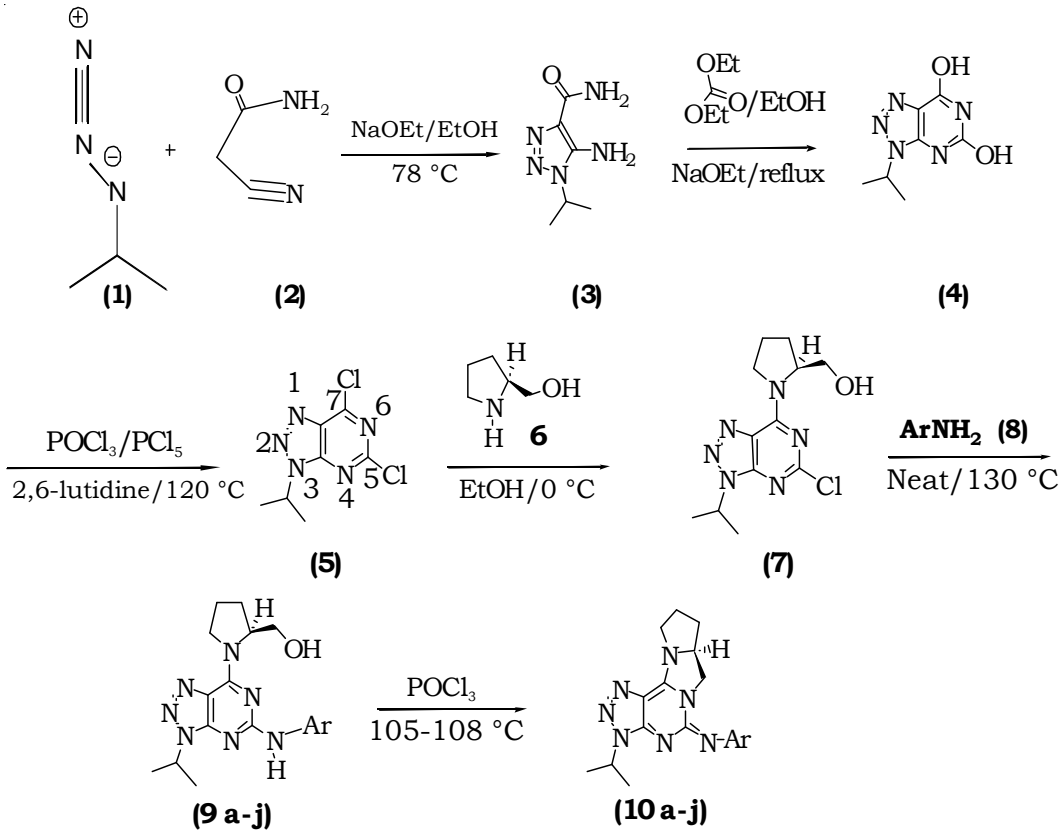
General procedure for preparation of (S)-N-(3-isopropyl-7a,8,9,10[1'2':3,4] imidazolo[1,2c][1,2,3]triazolo[4,5e]-pyrimidine-5(7*H*)-ylidine)aniline hydrochloride (10 a-j): A mixture of **9a-j** in $POCl_3$ (5 volumes) was heated to 105-108 °C with stirring for 1.5 h, while the reaction was monitored by TLC. At the end of this period, the mixture was cooled to RT and poured into crushed ice (5 times to $POCl_3$). The mixture was extracted with chloroform (3 × 50 mL) and the chloroform layer washed with water and then dried over anhyd. Na_2SO_4. The dried chloroform extract was concentrated under reduced pressure to obtain a crude solid as residue which was recrystallized from MTBE, as the clean hydrochloride salt of the product **10(a-j)** (**Scheme-I** and Table-1).

10a: Ash solid; 0.5 g, (97 %), m.r.: 131-133 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.5 (1H, bs, HCl), 7.74-7.72 (2H, d), 7.42-7.40 (2H m), 7.39-7.23 (1H, m), 5 (2H, m), 4.85 (1H, m), 4.5 (1H, m), 4.2 (1H, m), 4.05 (1H, m), 2.48 (3H, m), 2 (1H, m), 1.6 (6H, d); LC-MS: *m/z* = 336 [M + 1].

10b: Off-white solid; 0.49 g, (95 %), m.r.: 158-161 °C; IR (KBr, ν_{max}, cm^{-1}): 1702 (C=N, str), 1545, 1244, 1057; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.4 (1H, bs, HCl), 7.3-6.9 (3H, m), 7.0 (1H, m), 4.97-4.95 (1H, septet), 4.85 (2H, m), 4.5 (1H, m), 4.1(1H, m), 3.95 (1H, m), 2.21 (3H, m), 1.95 (1H, m), 1.56 (6H, d); ^{13}C (100 MHz, $CDCl_3$) δ: 150.8, 148.6, 138.4, 129.4, 118.9, 118.2, 111.8, 111.6, 110.4, 110.1, 64.2, 54.2, 51.3, 41.2, 30.5, 25.7, 21.5; LC-MS: *m/z* = 354 [M$^+$+1].

10c: Off-white solid; 0.49 g, (96 %), m.r.: 162-164 °C; IR (KBr, ν_{max}, cm^{-1}): 1685 (C=N, str), 1538, 1427, 1337; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.75 (1H, bs, HCl), 8 (1H, S), 7.7 (1H, dd), 7.4 (2H, dd), 5.0 (1H, septet), 4.75-7.56 (2H, m), 4.05-3.95 (2H, m), 3.95 (1H, m), 2.21 (3H, m), 1.95 (1H, m), 1.56 (6H, d); ^{13}C (100 MHz, $CDCl_3$) δ: 150.6, 148.4, 137.9, 129.7, 126.6, 122.6, 121.2, 118.8, 65.1, 51.5, 48.5, 26.4, 22.1, 21.8; LC-MS: *m/z* = 415 [M$^+$ + 2].

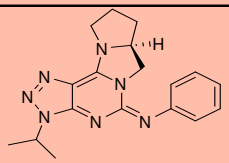
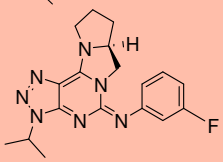
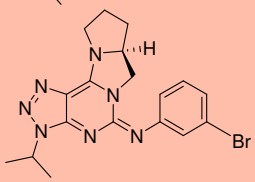
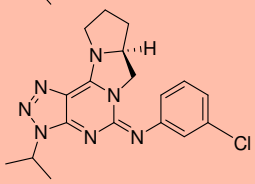
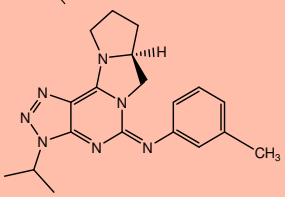
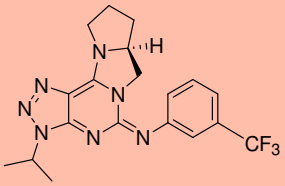
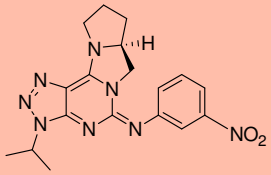
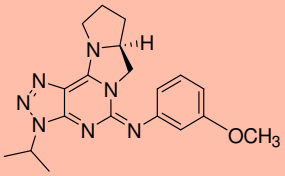
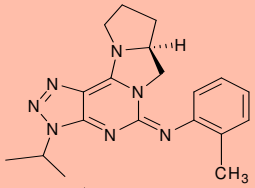
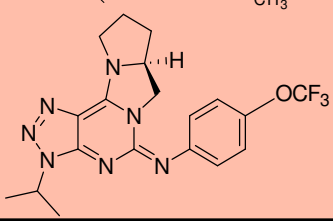
10d: Off-white solid; 0.49 g, (95 %), m.r.: 159-160 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11 (1H, bs, HCl), 8 (1H,



Ar = (a) -C_6H_5; (b) *m*-F-C_6H_4; (c) *m*-Br-C_6H_4; (d) *m*-Cl-C_6H_4; (e) *m*-CH_3-C_6H_4-CH_3; (f) *m*-CF_3-C_6H_4; (g) *m*-NO_2-C_6H_4-NO_2; (h) *m*-OCH_3-C_6H_4; (i) *o*-CH_3-C_6H_4; (j) *p*-OCF_3-C_6H_4

Scheme-I: General systhetic route-1

TABLE-1

S.No	Entry	Structure of compound	yield (%)		m.p. (°C)
			$POCl_3$	$SOCl_2$	
1	10a		97	45	131-133
2	10b		95	47	158-161
3	10c		96	44	162-164
4	10d		95	40	159-160
5	10e		97	42	141-144
6	10f		97	45	148-151
7	10g		95	41	185-188
8	10h		97	45	146-148
9	10i		95	41	140-142
10	10j		98	44	153-155

S), 7.8 (1H, dd), 7.35 (1H, t), 7.1 (1H, dd), 5.0 (1H, septet), 4.85 (2H, m), 4.2 (2H, m), 3.9 (1H, m), 2.21 (3H, m), 1.95 (1H, m),1.56 (6H, d). LC-MS: *m/z* = 370 [M^+ + 1].

10e: Pale brown solid; 0.5 g, (97 %), m.r.: 141-144 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ:10.35 (1H, bs, HCl), 7.5 (2H, m), 7.2 (1H, dd), 7.0 (1H, dd), 5 (1H, septet), 4.9-4.6 (2H, m), 4.2 (2H, m), 4 (1H, m), 2.4 (6H, m), 1.95 (1H, m), 1.6 (6H, d); ^{13}C (100 MHz, $CDCl_3$) δ: 151.0, 149.0, 138.1, 136.5, 128.0, 126.0, 124.0, 120.0, 118.1, 64.1, 54.0, 51.2, 47.3, 30.5, 25.7, 21.4, 21.3; LC-MS: *m/z* = 350 [M^+ + 1].

10f: Off-white solid; 0.5 g, (97 %), m.r.: 148-151 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.2 (1H, bs, HCl), 8.2 (1H, m), 8 (1H, m), 7.47 (2H, m), 5 (1H, septet), 4.9-4.6 (2H, m), 4.2 (2H, m), 4 (1H, m), 2.3 (3H, m), 1.8 (1H, m), 1.6 (6H, d); ^{13}C (100 MHz, $CDCl_3$) δ:151.8,150.6, 148. 5, 137.3, 129.2, 126.8, 121.6, 120.2, 118.6, 64.5, 51.8, 47.4, 47.0, 30.7, 21.3, 21.2; LC-MS: *m/z* = 404 [M^+ +1].

10g: Pale yellow solid; 0.49 g, (95 %), m.r.: 185-188 °C; IR (KBr, ν_{max}, cm^{-1}): 1689 (C=N, str), 1529, 1347, 1058; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.9 (1H, bs, HCl), 8.8 (1H, S), 8 (2H, m), 7.8 (1H, dd), 5 (1H, septet), 4.9-4.6 (2H, m), 4.2 (2H, m), 4 (1H, m), 2.2 (3H, m), 1.9 (1H, m), 1.6 (6H, d); LC-MS: *m/z* = 381 [M^+ +1].

10h: Off-white solid; 0.5 g, (97 %), m.r.: 146-148 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.9 (1H, bs, HCl), 7.3 (3H, m), 6.8 (1H, dd), 4.9 (1H, septet), 4.8-4.6 (2H, m), 4.1-3.9 (3H, m), 2.2 (3H, m), 1.8 (1H, m), 1.6 (6H, d); ^{13}C (100 MHz: $CDCl_3$) δ: 159.6, 151.1, 148.9, 129.0, 1′15.5, 111.7, 108.8, 64.2, 55.4, 51.3, 47.4, 30.8, 25.8, 21.6; LC-MS: *m/z* = 366 [M^+ +1].

10i: Pale coloured solid; 0.49 g, (95 %), m.r.: 140-142 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.1 (1H, bs, HCl), 7.3-7.2 (4H, m), 4.9 (1H, septet), 4.7 (2H, m), 4.5 (1H, m), 4.1-3.9 (2H, m), 2.2 (3H, m), 1.9 (1H, m),1.4 (6H, d); LC-MS: *m/z* = 350 [M^+ +1].

10j: Off-white solid; 0.51 g, (98 %), m.r.: 153-155 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.2 (1H, bs, HCl), 7.9 (2H, dd), 7.5 (2H, dd), 4.97 (2H, m), 4.8 (1H, m), 4.1(1H, m) 3.9 (2H, m), 2.2 (3H, m), 1.9 (1H, m),1.6 (6H, d); ^{13}C (100 MHz: $CDCl_3$) δ: 150.9, 148.8, 146.6, 135.3, 125.1, 120.9, 118.4, 64.3, 53.5, 51.3, 47.4, 30.6, 25.7, 21.5; LC-MS: *m/z* = 420 [M^+ +1].

RESULTS AND DISCUSSION

The reaction sequence leading to the formation of title compounds is outlined in **Scheme-I**.

Commercially available isopropyl azide (**1**) was reacted with cyanoacetamide (**2**) in the presence of sodium ethoxide yielding the previously known 4-amino-3-isopropyl-1*H*-[1,2,3]triazolo-5-carboxamide[2] (**3**). Treatment of **3** with diethyl carbonate and sodium ethoxide in ethanol gave 3-isopropyl-3*H*-[1,2,3]triazolo-[4,5-d]pyrimidine-5,7-diol (**4**) which is also known in literature[2]. **4** was reacted with $POCl_3$ in the presence of 2,6-lutidine containing a catalytic amount of PCl_5 to obtain 5,7-dichloro-3-isopropyl-3*H*-[1,2,3]triazolo-[4,5-d]pyrimidine (**5**) which is also reported in literature[2].

Reaction of **5** with L-prolinol (**6**) at 0 °C, yielded (S)-[1-(5-chloro-3-isopropyl-3*H*-[1,2,3]triazolo-[4,5-d]pyrimidine-7-yl)pyrrolidine-2-yl-methanol (**7**) which has been characterized on the basis of its spectral data. Thus, its IR-spectra showed characteristic -OH group at ν_{max} of 3500 Cm^{-1} (broad peak). ^{1}H NMR (DMSO-d_6/TMS) spectrum showed signals at δ 5.1 (septet, 1H, isopropyl-H), 5.0 (m, 2H,-CH_2-OH), δ 4.4 (bs, 1H, -OH, D_2O exchangeable), 4.1 (m, 1H), 3.7 (m, 3H, -CH_2-N-CH-), 2.2 (m, 4H, 2 × CH_2), 1.6 (d, *J* = 13, 6H, 2 × CH_3), LC-MS showed the (M^+ +1) ion peak at *m/z* = 297 corresponding to a molecular mass of 296, Optical rotation value was found to be $[\alpha]_{25}^{D}$ = (-) 103.68 (C = 0.25 % w/v in methanol).

Treatment of **7** individually with anilines (**8a-j**) as neat reactants at 140 °C gave (S)-(1-(3-isopropyl-5-(arylamino)-3*H*-[1,2,3]triazolo-[4,5-d]pyrimidine-7-ly)pyrrolidine-2-yl)-methanol (**9a-j**), respectively which have been characterized on the basis of their IR, ^{1}H-NMR and LC-MS data.

Treatment of **9(a-j)** individually with $POCl_3$ resulted in the formation of (S)-N-(3-isopropyl-7a,8,9,10[1'2':3,4]imidazolo[1,2c][1,2,3]triazolo[4,5e]pyrimidine-5(7H)-ylidine)aniline (**10a-j**), respectively isolated as clean hydrochloride salts, which have been characterized on the basis of their IR, ^{1}H-NMR, ^{13}C NMR spectra and LC-MS data. The process of cyclisation takes place in two steps. In the first step, OH group is converted into Cl. In the second step, cyclization occurs with the nitrogen of pyrimidine ring. This is a temperature dependant reaction, which is proved by the cyclization of **9a-j** at different temperatures. It is found that cyclization with $POCl_3$ as a neat reaction occurs at vigorous reflux at 105-108 °C affording high yields (> 95 %).

Furthermore, it has been found that thionyl chloride cannot be used in place of $POCl_3$, for the cyclization of **9a-j** to form **10a-j**, as the reaction cannot be raised to high temperatures and also the yields of products are poor (< 50 %), even after refluxing with $SOCl_2$ using prolonged reaction times.

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