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An efficient regioselective synthesis of *N*-alkylated purine-triazole analogues

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Nitrogen rich purine adduct **(2)** was prepared by reaction of 2,6-dichloro purine **(1)** with hydrazine hydrate was converted to hybrid purine-triazole ring **(4)** by a simple cyclisation process (con. HCl & methanol) on reaction with 3-phenoxy benzaldehyde. The regioselectivity of synthesized adducts was carried out by simple spectroscopic techniques *i.e.* IR, ^{1}H NMR & ^{13}C NMR spectra. These studies gave an idea regarding replacement of chlorine out of C-2 or C-6 position. Novelty was introduced by alkyl substation at *N*-9 position of imidazole ring and at –NH of triazole ring and a series of ***4-chloro-5a,6-dihydro-1,6-dialkylated-8-(3-phenoxyphenyl)-1H-[1,2,4]triazolo[3,4-e]purine*** **(5a-5g)** hybrids were synthesized.

Keywords: 2,6-Dichloropurine, triazoles, regioselectivity

Analogous having acyclic part in core nucleoside structures are currently used as antiviral agents, cancer therapy, for the treatment of human immunodeficiency virus (HIV), hepatitis B (HBV), and herpes diseases[1-3]. These types of modification can be introduced by attachment of heterocyclic moieties, ribose moieties and by specific functional groups to the natural nucleoside[4].

1,2,3-Triazoles have been a fruitful source of inspiration for medicinal chemists for many years due to their synthetic accessibility by click chemistry as well as their numerous biological activities[5]. 1,2,3-Triazole is a versatile moiety found in a large variety of bioactive molecules, such as anti-fungal[6], anti-bacterial[7], anti-allergic[8], anti-HIV[9], anti-tubercular[10] and anti-inflammatory agents[11].

In modern antiviral and antitumor therapy, an important role is played by modified nucleosides and their analogs, in which modified purine structures are frequently found[12]. Human cells have the capacity to salvage purines and pyrimidines for the synthesis of deoxyribonucleotides that are used for the DNA synthesis, and analogues of these nucleotide precursors have proven to be an important class of anticancer agents[13]. There are total of 14 types of purine antimetabolites that are approved by the FDA for the treatment of cancer, which account for nearly 20% of all drugs that are used to treat cancer. Some of the first compounds approved by the FDA for the treatment of cancer were in this class of compounds[14] (Figure 1). Several purine analogs have been evaluated for ATL. Among them, pentostatin has been most extensively evaluated as a single agent and in combination with other agents[15].

The traditional method for the synthesis of 2 or 6- substituted purine analogues is the amination of halo, oxo, mercapto or methylmercapto groups with various amines, which can be performed smoothly in organic solvents (Bu-OH, CH_3CN, dioxane, DMF, or DMSO) and in the presence of primary/ secondary/ tertiary amines using proper catalysts (P_2O_5, K_2CO_3 and Cu/K_3PO_4)[16].

Regioselectivity identification of any molecule is important in synthetic as well as pharmaceutical purpose. Regioselectivity in purine scaffolds were studied by many researchers at N-7 or N-9 substitution[17]. Special efforts have been directed toward the synthesis of C-6 branched representatives by amine substitution in purine. In general current scenario is to diversify purine molecules by chloroamine coupling at C-6 position and couple of work was put forwarded to make such coupling at

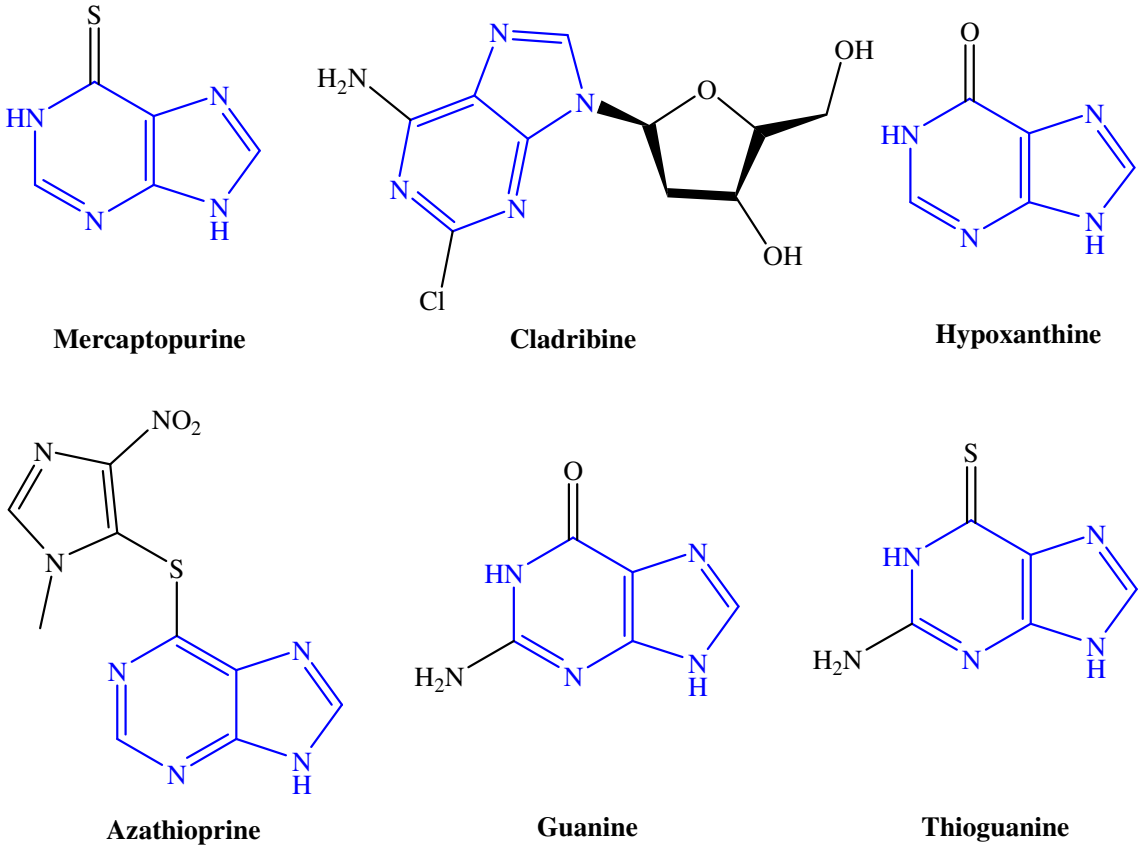


Figure 1 — FDA approved and marketed purine antimetabolites

C-2 position[18]. Commonly, the preparation of such branched derivatives by direct ring formation in purine encounters difficulties due to the low reactivity of the pyrimidine ring nitrogen which does not favors cyclisation in all cases[19].

In this paper, we extended our research on purine base to modify it and generate a novel compounds to improve its significance[17, 18]. In a previous paper we reported *N*-9 substitution in purine skeleton by click chemistry to generate hybrid of purine-triazole derivatives. Here, we are reports an original short-cut to novel *N*-9 alkylated analogues of modified purine base and identify its regioselectivity towards replacement of chloro group by hydrazine hydrate and finally formation of triazoles at 2nd position of purine based on the spectroscopic analysis *i.e.* IR, ^{1}H NMR and ^{13}C NMR spectra.

Experimental Section

Chemicals and solvents were purchased from the Sigma-Aldrich Chemical Co., Merck chemical, Finar and spectrochem Ltd. The entire chemicals were used without further purification. Thin-layer chromatography was accomplished on 0.2 mm precoated plates of Silica gel G60 F254 (Merck). Visualization was made under UV light (254 and 365nm). IR spectra were recorded on an "IR Affinity-1S spectrophotometer (Shimadzu)". ^{1}H (400 MHz) and ^{13}C (101.1 MHz) NMR spectra were recorded on a "Bruker AVANCE II spectrometer" in DMSO-d_6. Chemical shifts are expressed in δ ppms downfield from TMS. Mass spectra were determined by direct inlet probe on a "GC-MS-QP 2010 mass spectrometer (Shimadzu)". Solvents were evaporated with a "BUCHI rotary evaporator". Melting points were measured in open capillaries and are uncorrected.

Procedure for the synthesis of 1-(6-chloro-9*H*-purin-2-yl)hydrazine (2a). (Scheme I)

To an oven dried single neck flask, the suspension of purine (1 mmol) and hydrazine hydrate (3.20 mmol) was stirred at room temprature (RT) for 30 mints (yellow color was turned to cream white color with hazy suspension after completion of the reaction). Completion of the reaction was monitored by thin

layer chromatography using plain ethyl acetate as a mobile phase. After completion of the reaction, *n*-hexane was added to RBF and was filtered directly (photo sensitive material was isolated). The structure of product **(2a)** was confirmed by ^{1}H NMR & ^{13}C NMR spectroscopic techniques.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.44 (1H, Broad-s, -NH of Imidazole ring), 9.19 (1H, s, -NH proton of hydrazine), 8.12 (1H, s, Methine proton of imidazole ring), 5.00-3.34 (2H, Broad-m, - NH_2 of hydrazine group); ^{13}C NMR (DMSO-d_6, 101.1MHz): δ 154.84,152.27,151.79, 144.36 and 125.98.

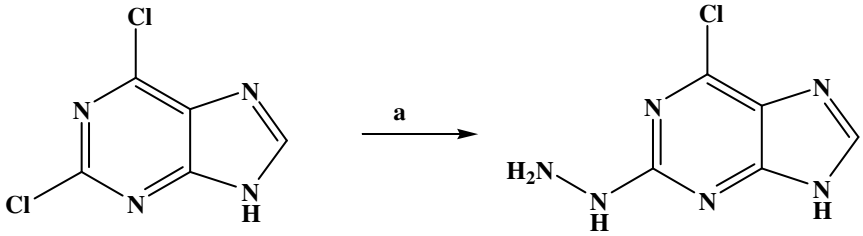
Procedure for the synthesis of 4-chloro-5*a*,6-dihydro-8-(3-phenoxyphenyl)-1*H*-[1,2,4]triazolo [3,4-*e*]purine (4b). (Scheme II)

To the previously prepared step I (Scheme I) **(2a)** product (2.0 mmol), 3-phenoxybenzaldehyde (2.0 mmol) **(3b)** and concentrated hydrochloric acid (0.02 mmol) were added in a methanol containing RBF.The reaction mixture was stirred at RT for 12.0 h. Completion of the reaction was monitored by TLC using three different mobile phase to identify product spot. After that reaction mixture was poured into ice crushed water and filtered using vaccum pump. To remove excess of acid, it was washed with cold water. Isolated dry product was used for the next step after crystallization in ethanol. Regioselectivity of compound **4b** was identified by NMR techniques *i.e.* IR, ^{1}H NMR and ^{13}C NMR.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.25-12.23 (1H, d, -NH of Imidazole ring), 8.46 (1H, s, Methine proton of imidazole ring), 8.29 (1H, s, Pyrimidine ring C-2 proton), 7.73-7.71 (2H,d, Phenoxy ring proton), 7.50-7.41 (5H, m, Merging of -NH and phenoxy ring proton), 7.19-7.03 (4H, m, Phenoxy ring proton); ^{13}C NMR (DMSO-d_6, 101.1 MHz): δ 162.03, 157.04, 156.87, 151.90, 150.00, 146.40, 136.62, 130.27, 123.52, 122.36, 199.97, 118.54, 117.65, 116.22, 115.95, 108.32.

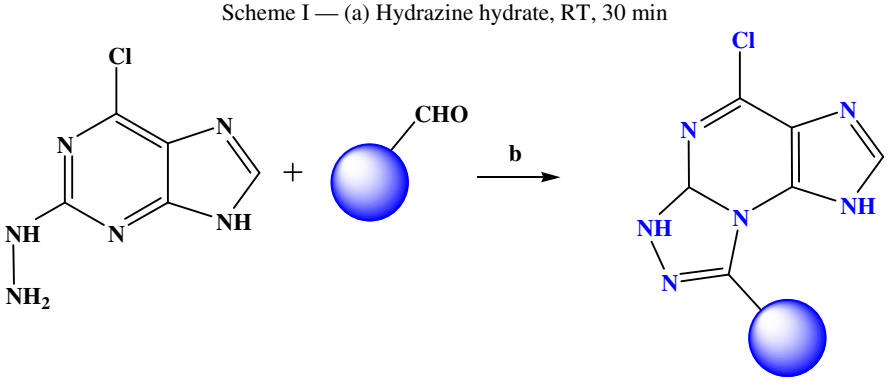
General procedure for the synthesis of 4-chloro-5a,6-dihydro-1,6-dialkylated-8-(3-phenoxyphenyl)-1*H*-[1,2,4]triazolo[3,4-*e*]purine (5a-5g). (Scheme III)

For the preparation of final adduct, step II (Scheme II) **(4b)** (1.0 mmol), dry K_2CO_3 powders (3.5 mmol) were mixed in DMF containing vessel. After 1.0 h heating at 70°C temperature, alkyl bromide (2.25 mmol) was added and it was further heated for 2.0 h. After completion of the reaction (monitored by TLC), reaction mixture was poured into ice cold water and filtered to dryness using vaccum filtration apparatus.



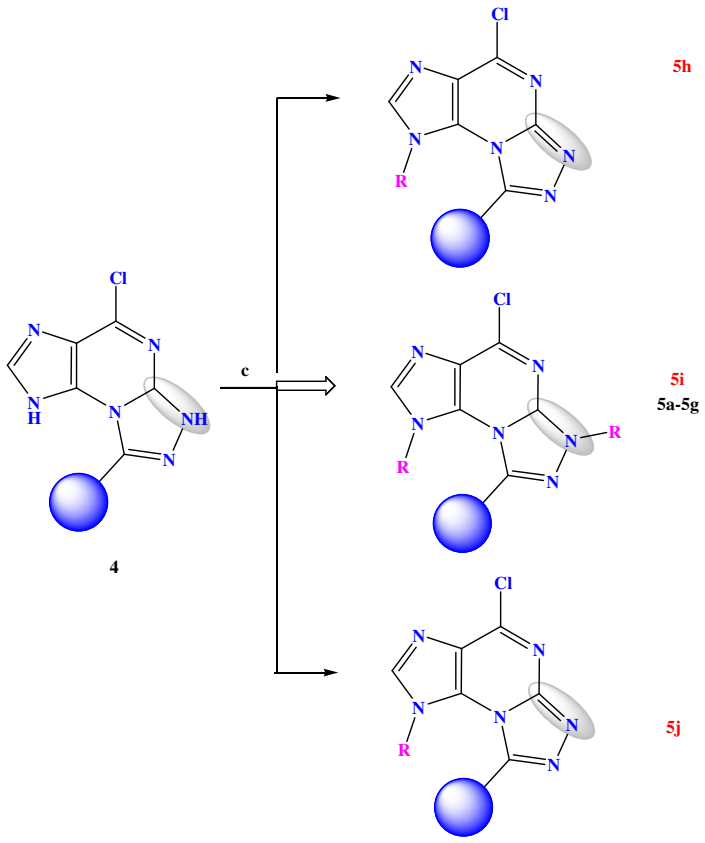
1 **2**

Scheme I — (a) Hydrazine hydrate, RT, 30 min



2 **3** **4**

Scheme II — (b) Methanol, Conc. HCl, 12.0 h



Scheme III — (c) R-Br, DMF, Dry K_2CO_3, 70°C Temp., 3.0 h

Purification of final molecules was carried out by column chromatography by using silica gel (60-120 mesh) in a Hexane: Ethyl acetate (8:2) as a mobile phase. Identification and characterization of derived scaffolds **(5a-5g)** were carried out by various spectroscopic techniques *i.e.* IR, NMR and MS (Scheme IV).

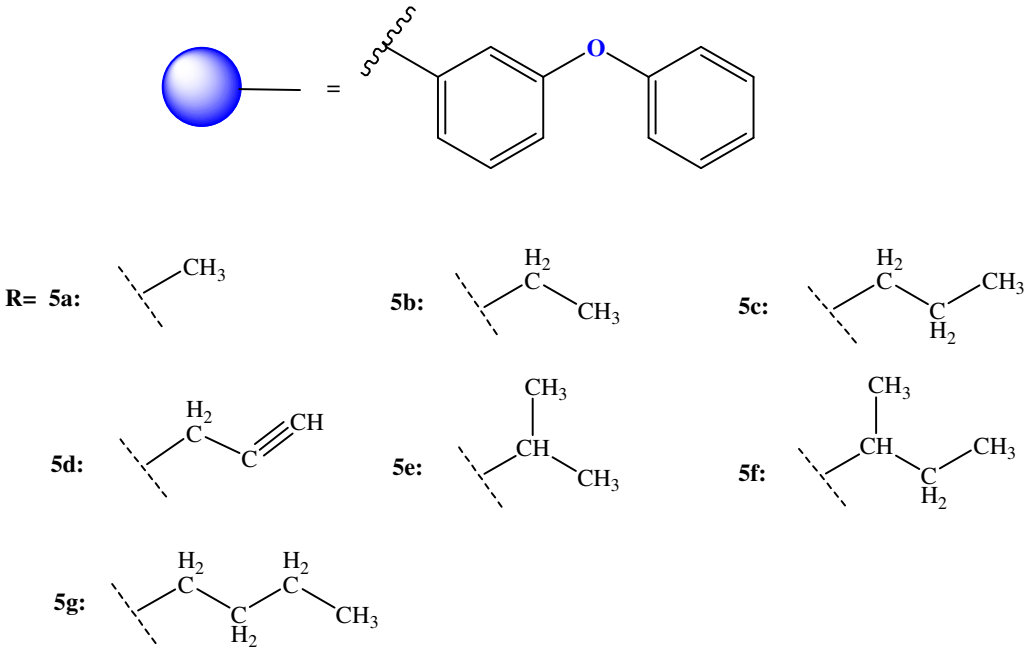
Spectral part

4-Chloro-5*a*,6-dihydro-1,6-dimethyl-8-(3-phenoxyphenyl)-1*H*-[1,2,4]triazolo[3,4-*e*]purine (5a)

This compound was obtained as off white colored powder; Yield: 92%; mp (melting point): 198°C; IR (cm^{-1}): 3107 (Aromatic C-H Stretch), 3030 (Alkane C-H stretch; Asym.), 2955 (Alkane C-H stretch; Sym.), 1699 (C=N Stretch), 1559, 1488, 1444 (Aromatic ring skeleton), 1321 (C-N Stretch of aromatic amines), 782 (C-Cl Stretch); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.56-8.54 (d, 2H, imidazole and triazole =CH proton), 7.80 (s, 1H), 7.80-7.78 (d, 1H), 7.51-7.45 (m, 3H), 7.22-7.20 (d, 1H), 7.19-7.16 (m, 2H), 7.09-7.06 (m, 1H), 3.60 (s, 3H, -Me attached to imidazole ring –NH), 2.99 (s,3H, -Me attached to triazole ring –NH); ^{13}C NMR (DMSO-d_6, 101.1 MHz): δ 160.04,157.29, 154.17, 153.13, 152.31, 144.24, 140.75, 138.99, 131.19, 124.73, 123.05, 120.88, 119.11, 117.40, 33.31, 36.30; Mass (*m/z*): 392.11 (M^+).

4-Chloro-1,6-diethyl-5*a*,6-dihydro-8-(3-phenoxyphenyl)-1*H*-[1,2,4]triazolo[3,4-*e*]purine (5b)

This compound was obtained as white colored powder; Yield: 94%; mp: 210°C; IR (cm^{-1}): 3104 (Aromatic C-H Stretch), 3020 (Alkane C-H stretch; Asym.), 2942 (Alkane C-H stretch; Sym.), 1681 (C=N Stretch), 1563, 1495, 1450 (Aromatic ring skeleton), 1324 (C-N Stretch of aromatic amines), 776 (C-Cl Stretch); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.19-8.18 (d, 2H, imidazole and triazole =CH proton), 7.76 (s, 1H), 7.79-7.77 (d, 1H), 7.48-7.42 (m, 3H), 7.25-7.23 (d, 1H), 7.00-6.99 (m, 2H), 6.80-6.74 (m, 1H), 3.86-3.84 (q, 2H, ethyl CH_2 attached to imidazole ring –NH), 3.40-3.36 (q, 2H, ethyl CH_2 attached to triazole ring –NH), 1.51-1.49 (t, 3H, terminal –Me attached to imidazole ring), 1.06-1.03 (t, 3H, terminal –Me to



Scheme IV

triazole ring); ^{13}C NMR (DMSO-d_6, 101.1 MHz): δ 157.98, 155.69, 153.58, 152.43, 151.50, 144.89, 140.42, 138.61, 132.68, 126.46, 123.28, 120.95, 119.01, 115.94, 44.09, 12.80 ;Mass (*m/z*): 420.14 (M^+).

4-Chloro-5*a*,6-dihydro-8-(3-phenoxyphenyl)-1, 6-dipropyl-1*H*-[1,2,4]triazolo[3,4-*e*]purine (5c)

This compound was obtained as dark red colored oily mass; Yield: 95%; IR (cm^{-1}): 3110 (Aromatic C-H Stretch), 3036 (Alkane C-H stretch; Asym.), 2942 (Alkane C-H stretch; Sym.), 1690 (C=N Stretch), 1561, 1483, 1441 (Aromatic ring skeleton), 1319 (C-N Stretch of aromatic amines), 771 (C-Cl Stretch); ^{1}H NMR (DMSO-d_6, 400 MHz):δ 8.22-8.21 (d, 2H, imidazole and triazole =CH proton), 7.85 (s, 1H), 7.77-7.75 (d, 1H), 7.51-7.45 (m, 3H), 7.29-7.27 (d, 1H), 7.12-7.09 (m, 2H), 7.09-7.06 (m, 1H), 4.40-4.37 (t, 2H, propyl first CH_2 attached to imidazole ring –NH), 3.02-2.99 (t, 2H, propyl first CH_2 attached to triazole ring –NH), 1.58 (m, 4H), 1.10 (m, 6H); ^{13}C NMR (DMSO-d_6, 101.1MHz): δ 159.23, 157.40, 154.57, 153.10, 152.00, 145.27, 144.23, 139.04, 132.04, 125.09,121.17, 120.27, 118.27, 117.08, 52.68, 48.40, 22.99, 20.58, 13.02; Mass (*m/z*): 448.17 (M^+).

4-Chloro-5a,6-dihydro-8-(3-phenoxyphenyl)-1,6-di(prop-2-ynyl)-1*H*-[1,2,4]triazolo[3,4-*e*]purine(5d)

This compound was obtained as dark red colored oily material; Yield: 97%; IR (cm^{-1}): 3100 (Aromatic C-H Stretch), 3029 (Alkane C-H stretch; Asym.), 2954 (Alkane C-H stretch; Sym.), 1666 (C=N Stretch), 1563, 1493, 1446 (Aromatic ring skeleton), 1310 (C-N Stretch of aromatic amines), 770 (C-Cl Stretch); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.16-8.15 (d, 2H, imidazole and triazole =CH proton), 7.76 (s, 1H), 7.71-7.69 (d, 1H), 7.43-7.38 (m, 3H), 7.16-7.14 (d, 1H), 7.07-7.04 (m, 2H), 7.03-7.00 (m, 1H), 5.84 (s, 1H, triazole ring side), 5.07 (s, 2H, -CH_2 attached to imidazole ring –NH), 4.43 (s, 2H, -CH_2 attached to triazole ring –NH), 2.34 (s, 1H, imidazole ring side); ^{13}C NMR (DMSO-d_6, 101.1MHz):δ 157.99, 155.91, 154.05, 153.13, 152.95, 144.19, 141.59, 138.66, 132.03, 125.88, 123.00, 120.30, 118. 8, 117.40,75.68, 73.56, 49.22, 31.00; Mass (*m/z*): 440.11 (M^+).

4-Chloro-5*a*,6-dihydro-1,6-diisopropyl-8-(3-phenoxyphenyl)-1*H*-[1,2,4]triazolo[3,4-*e*]purine (5e)

This compound was obtained as off white colored floppy powder; Yield: 87%; mp: 179°C; IR (cm^{-1}): 3101 (Aromatic C-H Stretch), 3040 (Alkane C-H stretch; Asym.), 2951 (Alkane C-H stretch; Sym.), 1682 (C=N Stretch), 1541, 1471, 1425 (Aromatic ring skeleton), 1330 (C-N Stretch of aromatic amines), 773 (C-Cl Stretch); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.21-8.20 (d, 2H, imidazole and triazole =CH proton), 7.90 (s, 1H), 7.82-7.80 (d, 1H), 7.54-7.48 (m, 3H), 7.31-7.29 (d, 1H), 7.16-7.13 (m, 2H), 7.11-7.08 (m, 1H), 4.44 (m, 1H), 3.58 (m, 1H), 1.76 (m, 6H), 1.21

(m, 6H); ^{13}C NMR (DMSO-d_6, 101.1MHz):δ 157.20, 156.99, 154.49, 154.01, 152.69, 145.06, 140.89, 139.55, 132.29, 124.58, 123.91, 120.86, 119.55, 117.63, 54.22, 49.58, 25.33, 31.29; Mass (*m/z*): 448.17 (M^+).

1,6-Di-sec-butyl-4-chloro-5*a*,6-dihydro-8-(3-phenoxyphenyl)-1*H*-[1,2,4]triazolo[3,4-*e*]purine (5f)

This compound was obtained as light yellow colored solid powder; Yield: 89%; mp: 196°C; IR (cm^{-1}): 3111 (Aromatic C-H Stretch), 3023 (Alkane C-H stretch; Asym.), 2949 (Alkane C-H stretch; Sym.), 1695 (C=N Stretch), 1561, 1485, 1442 (Aromatic ring skeleton), 1331 (C-N Stretch of aromatic amines), 775 (C-Cl Stretch); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.31-8.29 (d, 2H, imidazole and triazole =CH proton), 7.79 (s, 1H), 7.71-7.69 (d, 1H), 7.49-7.43 (m, 3H), 7.15-7.13 (d, 1H), 7.08-7.03 (m, 2H), 6.99-6.94 (m, 1H), 4.87 (m, 1H, -CH attached to imidazole ring –NH), 3.80 (m, 1H, -CH attached to triazole ring –NH), 1.70 (m, 2H, -CH_2 of imidazole ring side), 1.43 (m, 2H, - CH_2 of triazole ring side), 1.34 (d, 6H, branched -CH_3), 1.01 (m, 6H, terminal both –CH_3); ^{13}C NMR (DMSO-d_6, 101.1MHz):δ 159.59,157.36, 154.66, 153.56, 151.89, 143.22, 139.98, 137.65, 128.97, 122.78, 121.28, 118.99, 117.90, 111.29, 65.29, 58.66, 29.99, 23.12, 19.54, 13.06; Mass (*m/z*): 476.20 (M^+).

1,6-Dibutyl-4-chloro-5*a*,6-dihydro-8-(3-phenoxyphenyl)-1*H*-[1,2,4]triazolo[3,4-*e*]purine (5g)

This compound was obtained as cream white colored powder; Yield: 91%; mp: 204°C; IR (cm^{-1}): 3112 (Aromatic C-H Stretch), 3029 (Alkane C-H stretch; Asym.), 2954 (Alkane C-H stretch; Sym.), 1690 (C=N Stretch), 1558, 1480, 1446 (Aromatic ring skeleton), 1322 (C-N Stretch of aromatic amines), 779 (C-Cl Stretch); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.20-8.19 (d, 2H, imidazole and triazole =CH proton), 7.81 (s, 1H), 7.76-7.74 (d, 1H), 7.48-7.42 (m, 3H), 7.21-7.19 (d, 1H), 7.11-7.08 (m, 2H), 7.06-7.03 (m, 1H), 4.38 (s, 2H, butane first CH_2 attached to imidazole ring –NH), 4.17-4.13 (t, 2H, butane first CH_2 attached to triazole ring –NH), 1.79-1.75 (t, 2H), 1.62-1.60 (d, 2H), 1.40-1.36 (t, 2H), 1.28-1.22 (q, 2H), 0.96-0.88 (m, 6H: 3H+3H- two multiplet); ^{13}C NMR (DMSO-d_6, 101.1MHz):δ 157.24,156.41, 153.55, 153.13, 151.36, 143.07, 139.58, 137.64, 130.09, 123.64, 122.90,119.36, 119.09, 116.41, 42.80, 41.79, 31.11, 27.07, 19.48, 19.16, 13.64, 13.34; Mass (*m/z*): 476.20 (M^+).

Results and Discussions

Initially, on the basis of our previous work we concluded that the nucleophile attacks(-NH_2) preferred in purine at on C-6 position of pyrimidine ring[18] but we were surprised that the attack of hydrazine was at C-2 position and replaced the chloro group. The preparations of our targeted scaffolds (5a-5g) were achieved in three steps. Treatment of purine (1 mmol) with hydrazine hydrate (without any solvents) (3.20 mmol) under room temperature stirring gave step I product (2a) (Scheme I) which on reaction with 3-phenoxy benzaldehyde (2.0 mmol) in acidic condition followed by *N*-alkylation (R-X, 4.10 mmol) in purine imidazole ring –NH using traditional conditions [DMF, dry-powdered K_2CO_3 (3.5 mmol)] gave interesting novel molecules **(5a-5g)**. Purine-hydrazide **(2a)** was obtained in **98%** yield in 30 min by this reaction but the material isolated wasphoto sensitive. It is mandatory to mention over here is the need for more attention during the time of completion and during work up procedure as it would turned red in color by letting it stand in the reaction vessel with hydrazine or open in air for prolonged time. However, when **2a** was treated with 3-phenoxy benzaldehyde without acidic media at room temperature, the cyclisation reaction was comparatively slow and took a longer time (18 h) to afford **4b** in only **60%** yield (Scheme IV). Some selected results of the screening of the reaction with catalysts or without catalysts and optimized conditions for the reaction under this study are presented in Table I and Table II. Among them the following features draw attention: By observed in Table I, entry **10**, it is clear that hydrazine hydrate in 3.20 mmol ratio and also it acts as a solvent gave excellent yield in a short time.

Table I, entry **1-12** gave a conclusion that CuI is better catalyst than the proline for chloro-amine coupling but it's took longer time. And the amount of product was the same either we used CuI or without any catalyst. In short, it seemed better not to use any catalyst as there was no any effect in % of yield.

By the viewing entry **10** and entry **12** (Table I), it is evident that 3.20 mmol of hydrazine is the maximum amount required and increasing beyond it does not affect the time of the completion of the reaction.

Table II gave a general idea regarding types of catalysts and their effects on product yields. All the four entry shows that methanol gave higher yield as compared to other by using con. HCl as catalyst (Entry **1**).

Table I — Synthesis of adduct 2a [Purine, 1a (1 mmol), RT]

Entry	Hydrazine, mmol	Solvents	Catalysts, mol %; Time		Isolated, Yield[a](%)
1	1.0	Water, 2 ml	None[c]	Proline[b], 20	-
2	1.0	None	None[b]	CuI, 20; 5 h	-
3	1.5	Methanol, 2 ml	None[c]	Proline[c], 15	-
4	1.5	None	None[c]	CuI, 15; 5 h	-
5	2.0	Methanol, 2 ml	None*	Proline[b], 20	52
6	2.0	None	None; 2 h	CuI, 10; 3 h	89
7	2.5	Methanol, 2 ml	None*	Proline[b], 20	80
8	2.5	None	None; 1 h	CuI, 5; 3 h	91
9	3.2	Methanol, 2 ml	None*	Proline[c], 20	90
10	3.2	None	None; 30 Mints	CuI, 5; 2 h	98
11	5.0	Methanol, 2 ml	None*	Proline[c], 20	80
12	5.0	None	None; 30 Mints	CuI, 5; 2 h	98

[a]Yield expressed in reaction which performed without using any catalysts; [b]Not observed any progress in the reaction; [c]Yield of product is less than 10%; *Reaction not complies after stirring of 24 h.

Table II — Synthesis of adduct **4b** [Step II, 2a (2.0 mmol); 3-Phenoxybenzaldehyde (2.0 mmol), RT]

Entry	Solvents	Catalyst	Yield
1	Me-OH	Con. HCl	96%
2	Et-OH	Con. HCl	89%
3	H_2O	Con. HCl	58%
4	DMSO	Con. HCl	62%

The step II was also performed without using catalyst (con. HCl) and it could be concluded that the reaction has progressed but required more than 24 h to complete and the yield was in the range of 88-92%.

Reaction Scheme

Preparation of purine-triazole adducts **(5a-5g)**. Literature review reveals that, amine substitution would be preferably being at C-6 chlorine of the pyrimidine ring in purine[18]. Although shielding and deshielding effect in NMR spectra of the product (4b) direct us to infer the substitution of hydrazine at C2-Cl (Structure (a)) and triazole ring formation was take place. Ideally predicted C2-H (Structure (a)) PMR value should be ~8.2 δppm if substitution of hydrazine take place at C2-C1 and if substitution of hydrazine take place at C6-C1, so C6-H (Structure (b)) value should be ~5.0 δppm after triazole ring formation in purine. But in final adduct ^{1}H NMR (Supplementary Information) shows value at 8.2 δ ppm (for C2-H proton) which confirm that C2-Cl was substituted by hydrazine.

In addition, ^{13}C NMR also helps to define regioselectivity of intermediate product (4b) by studying ^{13}C chemical shift of following two structures [Figure. 2 (a) and Figure. 2 (b)] to confirm the orientation of ring formation. Predicted ^{13}C NMR value of C-4 and C-5 should be at ~156 and ~142 δ ppm respectively, if structure **(a)** was possible. In opposite case, if structure **(b)** was possible than the ^{13}C NMR value for C-4 and C-5 should be at ~142 and ~115 δ ppm respectively, due to the difference in electronegative nuclei attached to the C-6. On looking at thecompound **(4b)** ^{13}C NMR spectra (Supplementary Information) gave C-4 and C-5 peak at 156.36 and 146.40 δ ppm respectively. This value was near to the predicted ^{13}C NMR value of the structure **(a)**.

Chemically three possibilities for regioselective nature was put forwarded on the basic of IR and ^{1}H NMR spectroscopy. First possible adduct may be by the removal of two protons*i.e.* C2-H proton of purine ring and –NH[11] proton of triazole ring, and formation of double bond in the presence of basic media (Dry K_2CO_3) **(5h)**. Second possibility may be obtained by alkylation at only the imidazole ring –NH and triazole ring –NH remains unblocked by alkyl halides **(5j)**. And third possibility surprised us with the alkyl group being attached at both the –NH *i.e.* imidazole ring and triazole ring **(5j)** (Scheme IV, Step III). First and third possibilities was dated out on the basis of IR study (Supplementary Information) as it has been concluded that in final products **(5a-5g)** –NH frequency has disappeared and no frequency was found at ~3300 cm^{-1} and also presence of almost double proton peak corresponding to alkyl group in ^{1}H NMR. Now second criteria **(5i)** for possible adducts exactly fit on the basis of IR and ^{1}H NMR study and the reason behind this was above two conclusion about –NH frequency and NMR protons of the alkyl groups.

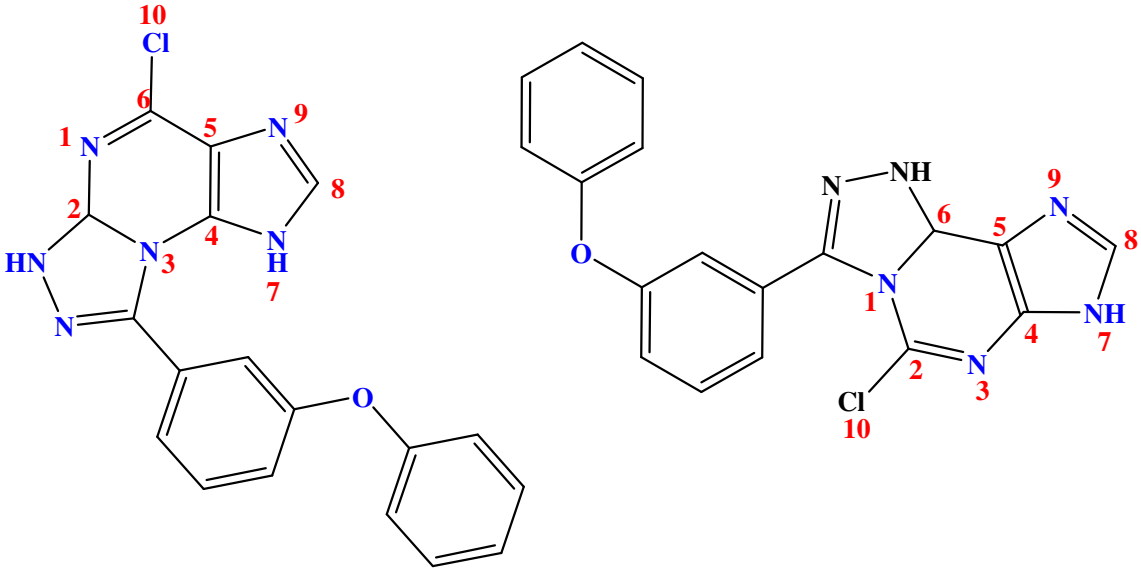


Figure 2 — Two possible orientations for the formation of triazole ring in purine

In conclusion

It was realize that purine gave a variant look if we substitute the chlorine by differentamine. Purine regioselectivity was identified on the basis of IR, ^{1}H NMR and ^{13}C NMR and concluded that triazole ring formation has taken place at C-2 carbon atom. Novelty of the product was introduced by alkyl substitution in imidazole ring –NH to make a better nucleotide to enhance pharmaceutical applications. Surprising results areobserved in the final step (alkylation in imidazole ring) that -NH group of triazole ring was alkylated by the removal of the proton and the same was confirmed by a simple IR spectroscopy.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60. For the confirmation of spectral discussion see the spectra of the representative compound in Supplementary information.

Conflict of interest

The authors confirm that this article content has no conflict of interest.

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References

1 Boris A, Anastasiya G, Valentina V, Olesya A, Angela P, Lyudmila I, Olga N, Grigorii G & Oleg A, *Tetrahedron*, 66 (2010) 1699.

2 Kotian P, Kumar V, Lin T, El-Kattan Y, Ghosh A, Wu M, Cheng X, Bantia S, Babu Y & Chand P, *Nucleosides Nucleotides Nucleic Acids*, 25 (2006) 121.

3 Canoa P, Gonzalez-Moa M, Teijeira M, Teran C, Uriarte E, Pannecouque C & De Clercq E, *Chem Pharm Bull*, 54 (2006) 1418.

4 Vladimir A, *Organic Diselenides*, *Ditellurides*, *Polyselenides and Polytellurides. Synthesis and Reactions* (Willey: Organic Selenium and Tellurium) (2013).

5 (a) Kolb H & Sharpless K, *Drug Discov Today*, 24 (2009) 1128. (b) Agalave S, Maujan S & Pore V, *Chem Asian J*, 8 (2011) 2696.

6 Aher N, Pore V, Mishra N, Kumar A, Shukla P, Sharma A & Bhat M, *Bioorg Med Chem Lett*, 19 (2009) 759.

7 (a) Demaray J, Thuener J, Dawson M & Sucheck S, *Bioorg Med Chem Lett*, 18 (2008) 4868. (b) Wang X, Wan K & Zhou C, *Eur J Med Chem*, 45 (2010) 4631.

8 Buckle D, Outred D, Rockell C & Smith B, *J Med Chem*, 26, (1983), 251.

9 Giffin M, Heaslet H, Brik A, Lin Y, Cauvi G, Wong C, Mc Ree D, Elder J, Stout C & Torbett B, *J Med Chem*, 51 (2008) 6263.

10 Patpi S, Pulipati L, Yogeeswari P, Sriram D, Jain N, Sridhar B, Murthy R, Anjana D, Kalivendi S & Kantevar S, *J Med Chem*, 55 (2012) 3911.

11 Simone R, Chini M, Bruno I, Riccio R, Mueller D, Werz O & Bifulco G, *J Med Chem*, 54 (2011) 1565.

12 Lukin K, John C, Bellettini R & Narayanan B, *Nucleosides, Nucleotides and Nucleic Acids*, 19 (2006) 815.
13 (a) Kapadiya K, Pandya M, Rathod C, Dhalani J & Dhaduk B, *Journal of Scientific & Industrial Research*, 77 (2018) 219. (b) John E, *Curr Drug Targets*, 8 (2007) 31.
14 William B, *Chem Rev*, 109 (2009) 2880.
15 Tsukasaki K, Watanabe T & Tobinai K, *Adult T-cell leukemia–lymphoma*, (Abeloff's clinical oncology); Niederhuber J, Armitage J, Doroshow J, (Eds.; Philadelphia: Elsevier Saunders) (2013) p. 2076.
16 (a) Hu Y, Liu X & Lu M, *J Mex Chem Soc*, 54 (2010) 74. (b) Qu G, Han S, Zhang Z, Geng M & Xue F, *J Braz Chem Soc*, 17 (2006) 915. (c) Hamann H, Spaziano V, Chou T, Price C & Lin H, *Canadian Journal of Chemistry*, 46 (1968) 419.
17 Kapadiya K, Jadeja Y & Khunt R, *Journal of Heterocyclic Chemistry*, 55 (2018) 199.
18 Jadeja Y, Kapadiya K, Shah A & Khunt R, *Magn Reson Chem*, 54 (2016) 75.
19 Somerville R, *Purines*, *Encyclopedia of Genetics (*Acedemic Press) (2001).