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# SYNTHESIS OF TRISUBSTITUTED PURINE COUPLED WITH CARBOXAMIDE DERIVATIVES OF AMINO ACIDS

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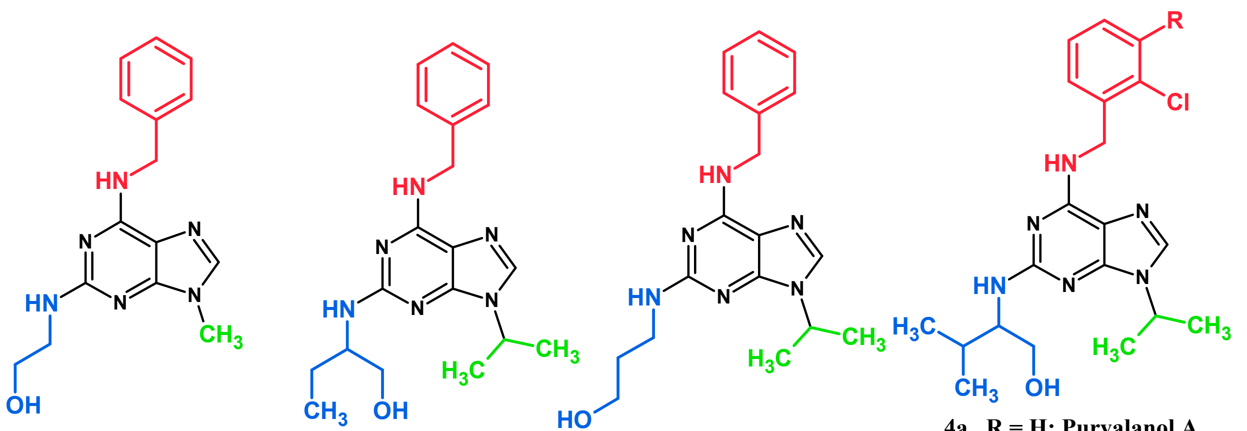
**ABSTRACT:**
A series of some trisubstituted purine coupled with carboxamide derivative of amino acids at the C2 position were synthesized. The targeted compounds were synthesized from coupling of 9-methyl-6-(piperidin-1-yl)-9*H*-purin-2-amine with carboxamide derivatives of amino acids. The newly synthesized compounds were characterized using IR, Mass, $^{1}$H-NMR, and $^{13}$C-NMR analysis.

**Keywords:** Trisubstituted purine, carboxamide, antimicrobial activity.

## INTRODUCTION

For biological studies, the synthesis of trisubstituted purine derivatives was an interesting objective. Particularly modified purine bearing substituent at the 2, 6 and 9 positions has been associated with a wide variety of interesting biological properties. It has broad biomedical value as therapeutics. Several types of 2, 6, 9-trisubstituted purine derivatives act as inhibitor of cell cycle dependent kinase (CDK) [ii] e.g. Olomoucine, Roscovitine, Bohemine, Purvalanol, (**Fig. 1**) microtubule assembly[ii] e.g. Myoseverin (**Fig. 2**) and Src tyrosine kinase[iii]. It also acts as antiviral[iv], anti cytostatic[v], sulfotransferases[vi], phosphodiesterase[vii], adenosine receptor antagonists[viii] and modulators of multidrug resistance.

Amino acids play very important role in nutrition, metabolic processes and translation of information so they have been an important target in the design of antimeatabolites. Currently there is a tendency to use amino acid/peptidyl residues during the prodrug design process. The literature reports that bioactive compounds show enhanced activity when linked to amino acids [x-xii]. The presence of an unusual amino acid has stimulated interest in new synthetic methodology and strategies to obtain a target structure. Again carboxamide derivatives showed very good antibacterial and antiviral activities[xiii, xiv], anti tuberculosis[xiv], anti-inflammatory/analgesic, anti-HIV-1 [xvi], anticancer[xvii], respiratory analeptic[xviii] and anti-anoxic activity[xix.]



1.Olomoucine 2. Roscovitine 3. Bohemine

4a. R = H; Purvalanol A

4b. R = COOH; Purvalanol B

**Figure 1. Chemical Structure of several types of potent CDK inhibitors**

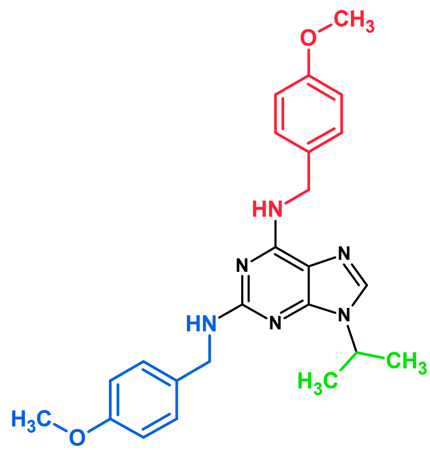
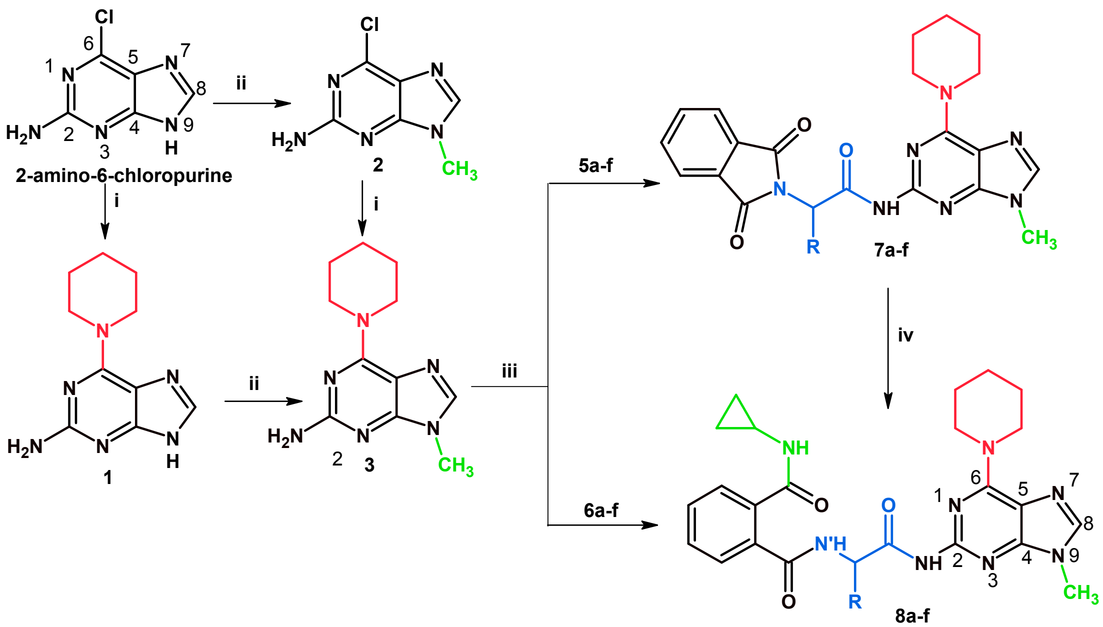


**Figure 2: Chemical Structure of Myoseverin**

These encouraging results led us to design other 2, 6, 9-trisubstituted purine as biologically relevant molecules with broad biomedical value as therapeutics. We have synthesized trisubstituted purine coupled with benzene 1, 2-dicarboxamide derivative of amino acids **8a-f ( Scheme 1).**

**RESULTS AND DISCUSSION:**

The purine ring system is susceptible to substitution through both nucleophilic $SN^{Ar}$ and alkylation with electrophilic reagents. The general synthesis of the trisubstituted purine using 2-amino-6-chloropurine is carried out by both the ways i.e. first reaction of piperidine at position C6 and then methylation using methyl iodide (MeI) at 9N-position or methylation at 9N-position and then reaction of piperidine at position C6. But we have observed that methylation of 2-amino-6-chloropurine gave 9N-methyl and 7N-methyl isomer in 80:20 but it dramatically reduced during methylation of 6-(piperidin-1-yl)-9*H*-purin-2-amine **(1)**. Finally coupling at most difficult and unreactive site C2 position was carried out.

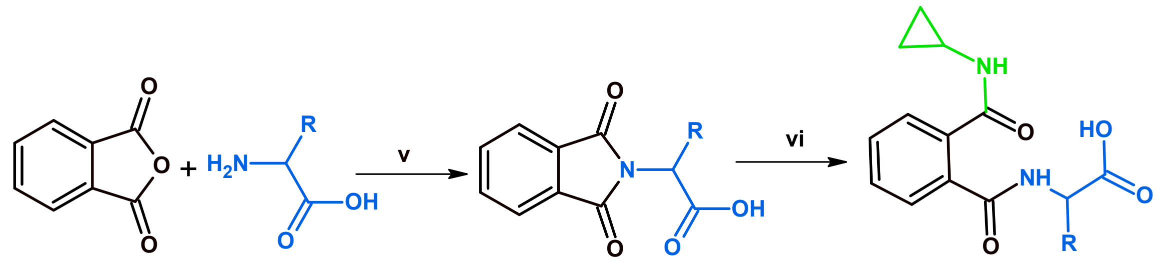



**R** = -H, $-CH_3$, -CH $(CH_3)_2$, $-CH_2CH$ $(CH_3)_2$, $-CH_2Ph$, $-CH_2Ph$ (pOBn).
**Reaction condition and reagents:** (i) Piperidine, $K_2CO_3$, Reflux, 5-6 h, 63-73 %; (ii) MeI, 40% TBAOH, MDC,RT, 1 h, 53-68%; (iii) $POCl_3$, pyridine, -15 °C to RT, 10-12 h, 40-65% ; (iv) cyclopropylamine, DMF, RT, 10-12h, 55-65 %.

**Scheme 1: Synthesis of trisubstituted purine (8a-f).**

The amination of 2-amino-6-chloropurine can be achieved by various synthetic technique reported in the literature using solvent like ethanol[xx,], n-butanol (n-BuOH)[xx,] acetonirtile [xxi], 1,4-dioxane[xxii], dimethylformamide (DMF)[xxii] or dimethyl sulphoxide (DMSO)[xxiii] and base like triethylamine (TEA)[xxiv], *N,N*-dimethyl cyclohexylamine[xxiv] or diisopropylethylamine[xxiv] at higher temperature. We used secondary amine i.e. piperidine, potassium carbonate ($K_2CO_3$) as base and n-BuOH as solvent reaction was carried out at reflux temperature. N9 alkylation is carried out using strong base like sodium hydride[xxv], $K_2CO_3$[xx], cesium carbonate[xx], sodium hydroxide[xxii], sodium ethoxide[xxii] , and tetrabutylammonium fluoride[xxi] in solvent like DMF[xx,xxii], 1,4-dioxane[xx,xxii] , ACN[xxi], N-methyl pyrolidine[xxii] , DMSO[xxii]. N9 alkylation is also carried out using Mitsunobu reaction[xxvi]. However, because of the presence of an additional amine function at C2, milder conditions were evaluated to avoid regioselectivity problems. We have tried N9 alkylation using 40% aq. solution of tetrabutylammonium hydroxide (TBAOH) [xxvii] as base in dichloromethane (DCM). As reaction is proceed faster and workup is also easy to carry out.
It is observed that coupling of carboxamide derivative of amino acid with C2-amino of purine is not working using standard coupling reagents. The use of well-known conventional coupling methods and reagents[xxviii] such as mixed carboxylic carbonic anhydrides[xxix], carbonyldiimidazole reagent, and DCC/HOBt[xxx] method were investigated but almost completely ineffective. The best results were obtained with the non-classical coupling system $POCl_3$ in pyridine**[xxxi, xxxii].**

The synthesis of carboxamide derivative of amino acids **(6a-f)** was carried out using readily available amino acids **(4a-f)**, phthalic anhydride in toluene at reflux temperature and further reaction with cyclopropylamine in DCM, methanol (MeOH) mixture as solvent[xxxiii]. **(Scheme 2).**




**Reaction condition and reagents:** (v) TEA, toluene, reflux, 3 h, 80-95%; (vi) Cyclopropylamine, MDC: MeOH, RT, 10-12h, 60-79%.

**Scheme 2: Synthesis of carboxamide derivatives of amino acid (5a-f and 6a-f)**

The aim of this work was to synthesize 2, 6, 9-trisubstituted purine derivatives. In the best of our knowledge and literature for coupling of amino acid at C2 position of purine is not available in public domain. An efficient methodology has been established for the synthesis of trisubstituted purine by using $POCl_3$ in pyridine for the coupling of phthalimido **(5a-f)** or carboxamide **(6a-f)** derivative with disubstituted purine 9-methyl-6-(piperidin-1-yl)-9*H*-purin-2-amine **(3)** at normal reaction temperature and condition to get corresponding **7a-f** and **8a-f** product. Further reaction of **7a-f** with cyclopropylamine in DMF also gave target molecule **8a-f.** The reactions were completed in 10-12 h and products were obtained in good yield after simple work up and purification using column chromatophy. The method was very simple and found to be very efficient compared to other conventional peptide coupling methods.

Moreover, the structures of the products were elucidated by MS, $^{1}$H-NMR, $^{13}$C-NMR and IR. $^{1}$H-NMR spectra of all the compounds was quite simple and proton at C8 position of purine of the entire synthesized compound found in the region of 8.08 - 8.2 ppm depending on the substituent. The aromatic protons of carboxamide ring appear as a multiplet in the region of 7.42 -7.88 ppm. The $C_2$ carbon of purine ring appears in the region 153.76-153.83, $C_4$ & $C_6$ at 151.61-153.7 $C_8$ at 136.26-138.81 and $C_5$ at 116.90-117.08. In IR spectrum C=O stretch appears in the region of 1722-1629 cm$^{-1}$.

## EXPERIMENTAL

All chemicals were purchased from commercial suppliers and used without further purification. Melting points were determined using a Veego VMP-PM melting point apparatus and are uncorrected. MS spectra were recorded on Waters Q-TOF instrument in only positive ion detection mode. $^{1}$H and $^{13}$C-NMR spectra were recorded on a Bruker Avance II 500 (500MHz) NMR instrument, using either in $CDCl_3$ or DMSO-$d_6$ as solvent and TMS as internal reference and chemical shifts were expressed in δ values (ppm). IR spectra were recorded on Perkin Elmer spectrum 100 FT-IR spectrometer. The course of the reactions was monitored and the purity of synthesized compounds was checked by TLC using silica gel 60 $F_{254}$ Al-plates (Merck, Germany) in Dichloromethane-Methanol (9:1) solvent system and the spots were visualized under UV illumination.

**General procedure for the synthesis of carboxamide derivatives of amino acid (5a-f):-**

In RBF fitted with Dean-stark apparatus and a reflux condenser, Phthalic acid anhydride (1.48 g, 10 mmol) and appropriate amino acids **(4a-f)** (10 mmol) were refluxed in toluene in the presence of 0.1 ml triethylamine for 3 h. The organic solvents were removed under reduced pressure to get sticky oily mass. Water was added to oily mass, acidified with hydrochloric acid and stirred for

30 minutes to get solid. Solid was filtered off, washed with water and dried to get compound **5a-f**. Further it dissolved in MeOH: MDC (1:2) mixture and cyclopropylamine (20 mmol) was added. Reaction Mixture was stirred at room temperature for 10-12 h. The organic solvent was removed under reduced pressure; an oily residue was obtained which was triturated with hexane and then stirred in ethyl acetate: hexane mixture to get respective carboxamide **5a-f** (**Scheme 2).** Physical characteristic data of the synthesized compounds are summarized in **Table-1**

***Synthesis of 6-(piperidin-1-yl)-9H-purin-2-amine*** **(1):-**
2-Amino-6-chloropurine (1.7 g, 10 mmol), piperidine (1.3 g, 15 mmol) and $K_2CO_3$ (2.7 g, 20 mmol) were heated in 30 ml n-BuOH at reflux temperature for 5-6 h. Reaction mass was filtered off and solvent was removed under reduced pressure. Sticky solid obtained was dissolved in ethyl acetate and wash with water. Solvent was removed under reduced pressure to get crude product. Product was recrystallized in ethanol. (**Scheme 1)**
Yield: 73%; white solid; mp: 234–236 $^oC$; molecular formula: $C_{10}H_{14}N_6$; molecular weight: 218.25 ; Yield: 73%; white solid; mp: 260–262 $^oC$; molecular formula: $C_{10}H_{14}N_6$; molecular weight: 218.25 ; IR (KBr, $cm^{-1}$): 3456 ($-NH_2$), 3107(-NH), 3070, 2966 (C-H), 1625 (C=N), 1339 (C–N) ; MS (*m*/*z*): $[MH]^+$ 219.53; $^1H$ NMR ($CDCl_3$, 500MHz) δ = 10.85 (br, 1H, 9-NH), 7.61 s, 1H, 8-CH), 4.58 (s, 2H,$-NH_2$), 4.19 (m, 4H, $-NCH_2$), 1.69-1.68 (m, 6H,$-CH_2$).
***Synthesis of 6-chloro-9-methyl-9H-purin-2-amine*** **(2):-**2-Amino-6-chloropurine (1.7 g, 10 mmol) dissolved in 50 ml dichloromethane. 40% aqueous tetrabutylammonium hydroxide (10 ml) and methyl iodide (3.6 g, 20 mmol) was added and stirred for 1 h. Organic layer was separated out, washed with water solvent and was removed under reduced pressure to get crude product. Further purified by crystallization in ethanol. (**Scheme 1)**
Yield: 53%; yellow solid; mp: 205-206 $^oC$; molecular formula: $C_6H_{16}ClN_5$; molecular weight: 183.59 ; IR (KBr, $cm^{-1}$): 3442 ($-NH_2$), 3077, 2964 (C-H), 1628 (C=N), 1336 (C–N); MS (*m*/*z*): $[MH]^+$ 184.073; $^1H$ NMR (DMSO $d_6$, 500MHz) δ = 7.99 (s, 1H, 8-CH), 3.74 (s, 3H, $9-NCH_3$),
***9-methyl-6-(piperidin-1-yl)-9H-purin-2-amine*** **(3):-**
Synthesis is carried out using procedure **1 & 2**
Yield: 63-68 %; off white solid; mp: 205-206 $^oC$; molecular formula: $C_{11}H_{16}N_6$; molecular Yield: 63-68 % ; off white solid; mp: 136-139 $^oC$; molecular formula: $C_{11}H_{16}N_6$; molecular weight: 232.28 ; IR (KBr, $cm^{-1}$): 3378 ($-NH_2$), 3072, 2969 (C-H), 1635 (N-H), 1626 (C=N), 1335 (C–N); MS (*m*/*z*): $[MH]^+$ 233.23; $^1H$ NMR ($CDCl_3$, 500MHz) δ = 7.45 (s, 1H, 8-CH), 4.62(s, 2H,$-NH_2$), 4.16(m, 4H, $-NCH_2$), 3.65 (s, 3H, $9-NCH_3$), 1.71-1.65 (m, 6H,$-CH_2$); $^{13}C$ NMR (DMSO d6, 125MHz): δ = 160.06 (s, $C_2$), 153.98-153.77 (d, $C_4$ & $C_6$), 137.35(s, $C_8$), 113.67 (s, $C_5$), 45.71 (d, $–NCH_2$), 29.47 (s, $-9NCH_3$), 26.18 (d, –N-$CH_2$-**C**$H_2$), 24.87 (s, –N-$CH_2$-$CH_2$-**C**$H_2$).
**Synthesis of trisubstituted purine (8a-f):-**
Phthalimido derivative **(5a-f) /** Carboxamide derivative **(6a-f)** (10 mmol) and 9-methyl-6-(piperidin-1-yl)-9H-purin-2-amine **(3) (**2.3 g**,** 10 mmol) were dissolved in anhydrous pyridine. The solution was cooled to −15 °C and $POCl_3$ (1.6 g, 11 mmol) was added drop wise under vigorous stirring. The reaction mixture then was stirred at −15 °C for 30 minutes. The solution was allowed to warm to room temperature and then stirred for 10-12h at same temperature. The reaction was quenched by addition of crushed ice/water. The desired compound was extracted using ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography to obtain the desired trisubstituted purine **7a-f** & **8a-f (Scheme 1)**

Similarly**, 7a-f** (10 mmol) was dissolved in 30 ml DMF, cyclopropylamine (0.11 g, 20 mmol) was added to it and stirred at room temperature for 10-12 h. Solvent was distilled off under reduced pressure to get sticky solid. Water was added and stirred for 1 h. Solid was filtered off to get crude product. Further purified by column chromatography to obtain the desired trisubstituted purine **8a-f (Scheme 1)**

**N-Cyclopropyl-N'-[1-(9-methyl-6-piperidin-1-yl-9H-purin-2-ylcarbamoyl)-methyl]-Phthalamide (8a):** Yield: 48 %; off white solid ; mp: 139-141 $^{o}$C; molecular formula: $C_{24}H_{28}N_8O_3$; molecular weight: 476.53; IR (KBr, cm$^{-1}$): 3462 (N-H), 2941 (C-H), 1711, 1682 (C=O), 1627 (C=N), 1568, 1461 (C=C), 1335 (C–N); MS (*m*/*z*): $[MH]^+$ 477.20 ; $^1$H NMR ($CDCl_3$, 500MHz): δ = 8.11 (s, 1H, 8-CH, purine), 7.85 (m, 2H, Ar-CH), 7.72 (m, 2H, Ar-CH), 7.61 (s, 1H, -CONH), 4.63 (s, 2H, $-CH_2$, glycine αH), 4.24 (br, 4H, $-NCH_2$, piperidine ring), 3.75 (s, 3H, $-9NCH_3$, purine), 2.40 (m, 1H, -NCH, cyclopropyl ring), 1.72-1.67 (m. 6H, $-CH_2$, piperidine ring), 0.67-0.59 (m, 4H, $-CH_2$, cyclopropyl ring); $^{13}$C NMR ($CDCl_3$, 125MHz): δ = 168.21-167.83 (d, >C=O), 153.76 (s, $C_2$, purine), 151.98-153.7 (d, $C_4$ & $C_6$, purine), 138.24 (s, $C_8$, purine), 133.93 (d, Ar-C) , 132.31 (d, Ar-CH), 123.28 (d, Ar-CH), 116.92 (s, $C_5$, purine), 45.71 (d, $–NCH_2$, piperidine ring), 41.09 (s, **C**$H_2$, glycine α$CH_2$), 29.85 (s, $-9NCH_3$, Purine), 25.8 (d, $–N-CH_2-$**C**$H_2$, piperidine ring), 24.5 (s, $–N-CH_2-CH_2-$**C**$H_2$, piperidine ring). 22.71(s, -NCH, cyclopropyl ring), 4.10 (d, $-CH_2$, cyclopropyl ring).

**N-Cyclopropyl-N'-[1-(9-methyl-6-piperidin-1-yl-9H-purin-2-ylcarbamoyl)-ethyl]-Phthalamide (8b):** Yield: 52 %; white solid ; mp: 104-106 $^{o}$C; molecular formula: $C_{25}H_{30}N_8O_5$; molecular weight: 490.55; IR (KBr, cm$^{-1}$): 3419 (N-H), 2933 (C-H), 1712, 1694 (C=O), 1627 (C=N), 1593, 1456 (C=C), 1367 (C–N); MS (*m*/*z*): $[MH]^+$ 491.18; $^1$H NMR ($CDCl_3$, 500MHz): δ = 8.08 (s, 1H, 8-CH, purine), 7.88 (m, 2H, Ar-CH), 7.77 (m, 2H, Ar-CH), 7.61 (s, 1H, -CON**H**), 4.73 (s, 1H, -CH, Alanine αH), 4.28 (br, 4H, $-NCH_2$, piperidine ring), 3.73 (s, 3H, $-9NCH_3$, purine), 2.67 (m, 1H, -NCH, cyclopropyl ring), 1.75-1.6 (m. 6H, $-CH_2$, piperidine ring), 1.33 (d, 3H, $-CH_3$, Alanine), 0.72-0.57 (m, 4H, $-CH_2$, cyclopropyl ring); $^{13}$C NMR ($CDCl_3$, 125MHz): δ = 168.11-167.61 (d, >C=O), 153.83 (s, $C_2$, purine), 152.98-151.79 (d, $C_4$ & $C_6$, purine), 136.81 (s, $C_8$, purine), 134.16 (d, Ar-C) , 131.51 (d, Ar-CH), 123.48 (d, Ar-CH), 117.08 (s, $C_5$, purine), 45.9 (d, $–NCH_2$, piperidine ring), 54.0 (s, -**C**H, Alanine αC), 29.85 (s, $-9NCH_3$, Purine), 25.9 (d, $–N-CH_2-$**C**$H_2$, piperidine ring), 24.7 (s, $–N-CH_2-CH_2-$**C**$H_2$, piperidine ring). 22.8 (s, -NCH, cyclopropyl ring), 18.4 (s, $-CH_3$, Alanine), 6.8 (d, $-CH_2$, cyclopropyl ring).

**N-Cyclopropyl-N'-[2-methyl-1-(9-methyl-6-piperidin-1-yl-9H-purin-2-ylcarbamoyl)-propyl]-Phthalamide (8c):** Yield: 50 % ; white solid; mp: 78-80 $^{o}$C; molecular formula: $C_{27}H_{34}N_8O_3$; molecular weight: 518.61 ; IR (KBr, cm$^{-1}$): 3306 (N-H), 2957 (C-H), 1719, 1695 (C=O), 1621 (C=N), 1591, 1469 (C=C), 1384 (C–N); MS (*m*/*z*): $[MH]^+$ 519.32; $^1$H NMR ($CDCl_3$, 500MHz): δ = 8.09 (s, 1H, 8-CH, purine), 7.88 (m, 2H, Ar-CH), 7.74 (m, 2H, Ar-CH), 7.62 (s, 1H, -CO**NH**), 4.86 (s, 1H, -CH, Valine αH), 4.15 (br, 4H, $-NCH_2$, piperidine ring), 3.76 (s, 3H, $-9NCH_3$, purine), 2.85 (m, 1H, -CH, Valine), 2.78 (m, 1H, -NCH, cyclopropyl ring), 1.77-1.68 (m. 6H, $-CH_2$, piperidine ring), 1.18-0.92 (d, 6H, $-CH_3$, Valine) 0.73-0.59 (m, 4H, $-CH_2$, cyclopropyl ring); $^{13}$C NMR ($CDCl_3$, 125MHz): δ = 168.22-167.76 (d, >C=O), 153.83 (s, $C_2$, purine), 152.2-151.73 (d, $C_4$ & $C_6$, purine), 138.81 (s, $C_8$, purine), 134.3 (d, Ar-C) , 131.57 (d, Ar-CH), 123.66 (d, Ar-CH), 116.91 (s, $C_5$, purine), 45.5 (d, $–NCH_2$, piperidine ring), 57.51 (s, C**H**, Valine αC), 29.85 (s, $-9NCH_3$, Purine), 29.46 (s, CH, Valine), 26.09 (d, $–N-CH_2-$**C**$H_2$, piperidine ring), 24.73 (s, $–N-CH_2-CH_2-$**C**$H_2$, piperidine ring). 22.58 (s, -NCH, cyclopropyl ring), 20.93-19.51 (d, $-CH_3$, Valine), 6.38(d, $-CH_2$, cyclopropyl ring).

**N-Cyclopropyl-N'-[3-methyl-1-(9-methyl-6-piperidin-1-yl-9H-purin-2-ylcarbamoyl)-butyl]-Phthalamide (8d):**Yield: 52 %; off white solid; mp: 55-58 $^oC$; molecular formula: $C_{28}H_{36}N_8O_3$; molecular weight: 532.63 IR (KBr, $cm^{-1}$): 3493 (N-H), 3080 (C-H), 1722, 1629 (C=O), 1629 (C=N), 1568, 1464 (C=C), 1382 (C–N); MS (*m*/*z*): $[MH]^+$ 533.29 ; $^1H$ NMR ($CDCl_3$, 500MHz): δ = 8.2 (s, 1H, 8-CH, purine), 7.82 (m, 2H, Ar-CH), 7.7 (m, 2H, Ar-CH), 7.62 (s, 1H, -CON**H**), 4.85 (s, 1H, -CH, Leucine αH), 4.27 (br, 4H, $-NCH_2$, piperidine ring), 3.77 (s, 3H, $-9NCH_3$, purine), 2.9 (m, 1H, -CH, Leucine), 2.74 (m, 1H, -NCH, cyclopropyl ring), 1.75-1.61 (m. 8H, -$CH_2$, piperidine ring & Leucine), 1.51 (d, 6H, $-CH_3$, Leucine) 0.71-0.55 (m, 4H, $-CH_2$, cyclopropyl ring); $^{13}C$ NMR ($CDCl_3$, 125MHz): δ = 168.53-167.21 (d, >C=O), 153.74 (s, $C_2$, purine), 152-151.71 (d, $C_4$ & $C_6$, purine), 138.21 (s, $C_8$, purine), 133.64 (d, Ar-C) , 132.16 (d, Ar-CH), 123.02 (d, Ar-CH), 116.9 (s, $C_5$, purine), 45.1 (d, $–NCH_2$, piperidine ring), 60.18 (s, C**H**, Leucine αC), 29.76 (s, $-9NCH_3$, Purine), 26.23 (s, $-CH_2$, Leucine), 26.18 (d, $–N-CH_2-$**C**$H_2$, piperidine ring), 24.87 (s, $–N-CH_2-CH_2-$**C**$H_2$, piperidine ring). 22.8 (s, -NCH, cyclopropyl ring), 17.58 (s, -CH, Leucine), 11.16 (d, $-CH_3$, Leucine), 6.8(d, $-CH_2$, cyclopropyl ring).

**N-Cyclopropyl-N'-[1-(9-methyl-6-piperidin-1-yl-9H-purin-2-ylcarbamoyl)-2-phenyl ethyl]-Phthalamide (8e):** Yield: 65 %; off white solid; mp: 128-130 $^oC$; molecular formula: $C_{31}H_{34}N_8O_3$; Molecular Weight: 566.65 ; IR (KBr, $cm^{-1}$): 3482 (N-H), 2963 (C-H), 1718, 1631 (C=O), 1628 (C=N), 1571, 1463 (C=C), 1388 (C–N); MS (*m*/*z*): $[M+H^+]$ 567.65; $^1H$ NMR ($CDCl_3$, 500MHz): δ = 8.13 (s, 1H, 8-CH, purine), 7.64 (s, 1H, -CO**NH**), 7.47 (m, 2H, Ar-CH), 7.42 (m, 2H, Ar-CH), 7.3-7.09 (m, 5H, Ar-CH, Phenylalanine), 5.2 (s, 1H, -CH, Phenylalanine αH), 4.29 (br, 4H, $-NCH_2$, piperidine ring), 3.75 (s, 3H, $-9NCH_3$, purine), 3.4-3.36 (dd, 1H, $-CH_2$, Phenylalanine), 3.27-3.22(dd, 1H, $-CH_2$, Phenylalanine), 2.87 (m, 1H, -NCH, cyclopropyl ring), 1.76-1.56 (m. 8H, $-CH_2$, piperidine ring & Phenylalanine), 0.78-0.59 (m, 4H, $-CH_2$, cyclopropyl ring); $^{13}C$ NMR ($CDCl_3$, 125MHz): δ = 169.73-169.15 (d, >C=O), 153.83 (s, $C_2$, purine), 152.24-151.61 (d, $C_4$ & $C_6$, purine), 138.8 (s, 1H, Ar-C, Phenylalanine) 136.26 (s, $C_8$, purine), 134.23 (d, Ar-C) , 130.45 (d, Ar-CH), 128.88 (d, 1H, Ar-CH, Phenylalanine), 128.56 (d, 1H, Ar-CH, Phenylalanine), 127.81 (s, 1H, Ar-CH, Phenylalanine), 127.0 (d, Ar-CH), 117.05 (s, $C_5$, purine), 56.0 (s, **CH**, amide, Phenylalanine αC), 45.71 (d, $–NCH_2$, piperidine ring), 37.88 (s, $-CH_2$, Phenylalanine), 29.76 (s, $-9NCH_3$, Purine), 26.18 (d, $–N-CH_2-$**C**$H_2$, piperidine ring), 24.87 (s, $–N-CH_2-CH_2-$**C**$H_2$, piperidine ring). 23.16 (s, -NCH, cyclopropyl ring), 6.62-6.5 (d, $-CH_2$, cyclopropyl ring).

**N-[2-(4-Benzyloxyphenyl)-1-(9-methyl-6-piperidin-1-yl-9H-purin-2-ylcarbamoyl)-2- ethyl]-N'-cyclopropyl Phthalamide (8f):** Yield: 40 %; off white solid; m.p: 50-52 $^oC$; molecular Formula: $C_{38}H_{40}N_8O_4$; molecular weight: 672.77; IR (KBr, $cm^{-1}$): 3481 (N-H), 2956 (C-H), 1721, 1633 (C=O), 1623 (C=N), 1569, 1460 (C=C), 1381 (C–N); MS (*m*/*z*): $[MH]^+$ 673.45; $^1H$ NMR ($CDCl_3$, 500MHz): δ = 8.11 (s, 1H, 8-CH, purine), 7.73 (m, 2H, Ar-CH), 7.63 (m, 2H, Ar-CH), 7.61 (s, 1H, -CON**H**), 7.38-7.29 (m, 5H, Ar-CH, tyrosine), 7.095-7.079 (d, 2H, Ar-CH, -$OCH_2Ph$), 6.786-6.77 (d, 2H, Ar-CH, $-OCH_2Ph$), 5.1 (s, 1H, -CH, tyrosine αH), 4.69 (s, 2H, -$CH_2$, Tyrosine-OBn), 4.28 (br, 4H, $-NCH_2$, piperidine ring), 3.77 (s, 3H, $-9NCH_3$, purine), 3.54-3.42 (dd, 2H, $-CH_2$, Tyrosine), 2.81 (m, 1H, -NCH, cyclopropyl ring), 1.75-1.52 (m. 6H, $-CH_2$, piperidine ring), 0.77-0.57 (m, 4H, $-CH_2$, cyclopropyl ring); $^{13}C$ NMR ($CDCl_3$, 125MHz): δ = 168.7-168.3 (d, >C=O), 153.82 (s, $C_2$, purine), 152.21-151.74 (d, $C_4$ & $C_6$, purine), 138.81 (s, $C_8$, purine), 133.61 (d, Ar-C) , 131.26 (d, Ar-CH), 127.49 (d, Ar-CH), 117.04 (s, $C_5$, purine), 157.18, 137.08, 132.05, 128.5, 127.85,127.49, 114.67 (Ar-C, Tyrosine), 69.87 (s, $-CH_2$, -OC**H**$_2$Ph), 56.25 (s, C**H**, amide, Tyrosine αC), 45.71 (d, $–NCH_2$, piperidine ring), 34.7 (s, $-CH_2$, Tyrosine), 30.24

(s, -NCH, cyclopropyl ring), 29.85 (s, -9NCH$_3$, purine), 26.21 (d, –N-CH$_2$-**C**H$_2$, piperidine ring), 24.75 (s, –N-CH$_2$-CH$_2$-**C**H$_2$, piperidine ring). 6.64-6.31 (d, -CH$_2$, cyclopropyl ring).

**Table I:** Physical parameters of phthalimido derivatives of amino acids (**5a-f**)

| Sr. No | Product code | R | MP ($^0$C) | Molecular Formula | Molecular Weight | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | 5a | -H | 190 | $C_{10}H_7NO_4$ | 205 | 95 |
| 2 | 5b | $-CH_3$ | 136 | $C_{11}H_9NO_4$ | 219 | 91 |
| 3 | 5c | $-CH(CH_3)_2$ | 110 | $C_{13}H_{13}NO_4$ | 247 | 91 |
| 4 | 5d | $-CH_2CH(CH_3)_2$ | 143 | $C_{14}H_{15}NO_4$ | 261 | 95 |
| 5 | 5e | $-CH_2Ph$ | 180 | $C_{17}H_{13}NO_4$ | 295 | 90 |
| 6 | 5f | $-CH_2Ph$(p-OBn) | 92 | $C_{24}H_{19}NO_5$ | 401 | 80 |

**Table II:** Physical parameters of carboxamide derivatives of amino acids **(6a-f)**

| Sr. No | Product code | R | MP ($^0$C) | Molecular Formula | Molecular Weight | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | 6a | -H | 215 | $C_{13}H_{14}N_2O_4$ | 262 | 73 |
| 2 | 6b | $-CH_3$ | 140 | $C_{14}H_{16}N_2O_4$ | 276 | 79 |
| 3 | 6c | $-CH(CH_3)_2$ | 149 | $C_{16}H_{20}N_2O_4$ | 304 | 71 |
| 4 | 6d | $-CH_2CH(CH_3)_2$ | 158 | $C_{17}H_{22}N_2O_4$ | 318 | 70 |
| 5 | 6e | $-CH_2Ph$ | 163 | $C_{20}H_{20}N_2O_4$ | 352 | 78 |
| 6 | 6g | $-CH_2Ph$(p-OBn) | 120 | $C_{27}H_{26}N_2O_5$ | 458 | 60 |

**CONCLUSION:**

In summary, we have disclosed the rational design of a series of trisubstituted purine derivatives by coupling of dicarboxamides of amino acid at C2 position of purine. Method for the coupling of amino acid and its derivatives at C2 position of purine is not available too much in the literature.

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