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Synthesis and Antimicrobial Evaluation of Trisubstituted Purine coupled with Phthalamide Derivative of Amino Acids at C2 position.

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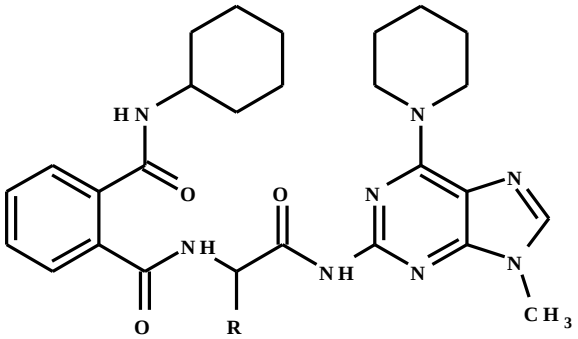
Abstract : *A novel series of trisubstituted purine compounds coupled with amino acids derivative at the C2 position was synthesized. The compounds were synthesized by coupling of 9-methyl-6-(piperidin-1-yl)-9H-purin-2-amine with N-Phthaloyl or carboxamide derivatives of amino acids using phosphorous oxychloride in pyridine. The synthesized compounds were characterized using IR, Mass, NMR and screened for their in vitro antimicrobial activity against microorganism S. aureus, E. coli, P. aeruginosa S. typhimurium F. oxysporum and A. alternata. All of these compounds showed moderate to good activity.*

Keywords - *Trisubstituted purine, carboxamide, antimicrobial activity, phosphorous oxychloride.*

I. INTRODUCTION

2, 6, 9- trisubstituted purine (TSP) have broad biomedical value as therapeutics at it can alter interactions with nucleic acids and proteins. TSP derivatives can act as cell cycle dependent kinase inhibitor (CDK inhibitor)[1-4], inhibitors of microtubule assembly[5], inhibitors of Src tyrosine kinase[6], potent heat shock protein 90 (Hsp90) inhibitor[7], potent signal transducer and activator of transcription (Stat3) binding inhibitor[8], inhibitors of P38 mitogen-activated protein (p38a MAP kinase)[9]. They can also act as antiviral[10], antitumor[11], sulfotransferase[12], phosphodiesterase[13], adenosine receptor antagonists[14], use for treatment of autoimmune diseases[15] and modulators of multidrug resistance[16]. The introduction of substituent at the 2-position of purine can leads to very important biologically active compounds. One of the prominent functionalized substituent of high biological relevance is undoubtedly an amino acid derivative. Such compounds may display biological activity and be used as building blocks in the synthesis of chemically and enzymatically stable nucleic acids–peptide/protein conjugates. In this connection, we have synthesized phthalamide derivative of trisubstituted purine **(Figure1, Scheme 2, 7a-f)** and characterized using IR, ^{1}H, ^{13}C –NMR, mass analysis and screened for their *in vitro* antimicrobial activity.



R = -H, -CH_3, -CH (CH_3)$_2$, -CH_2CH (CH_3)$_2$, -CH_2Ph, -CH_2Ph (pOBn)

Fig. 1: Structure of phthalamide derivative of trisubstituted purine **7a-f.**

1.2 Experimental

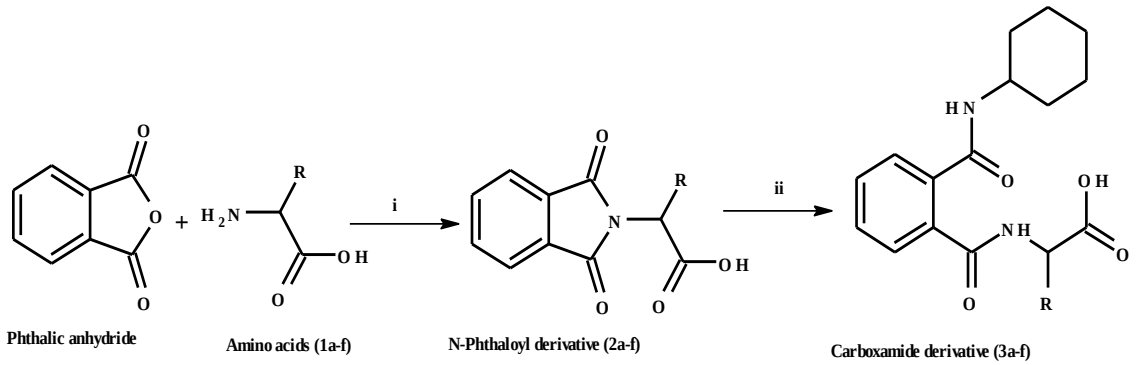
Reagents, instrumentation, and measurements:

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.

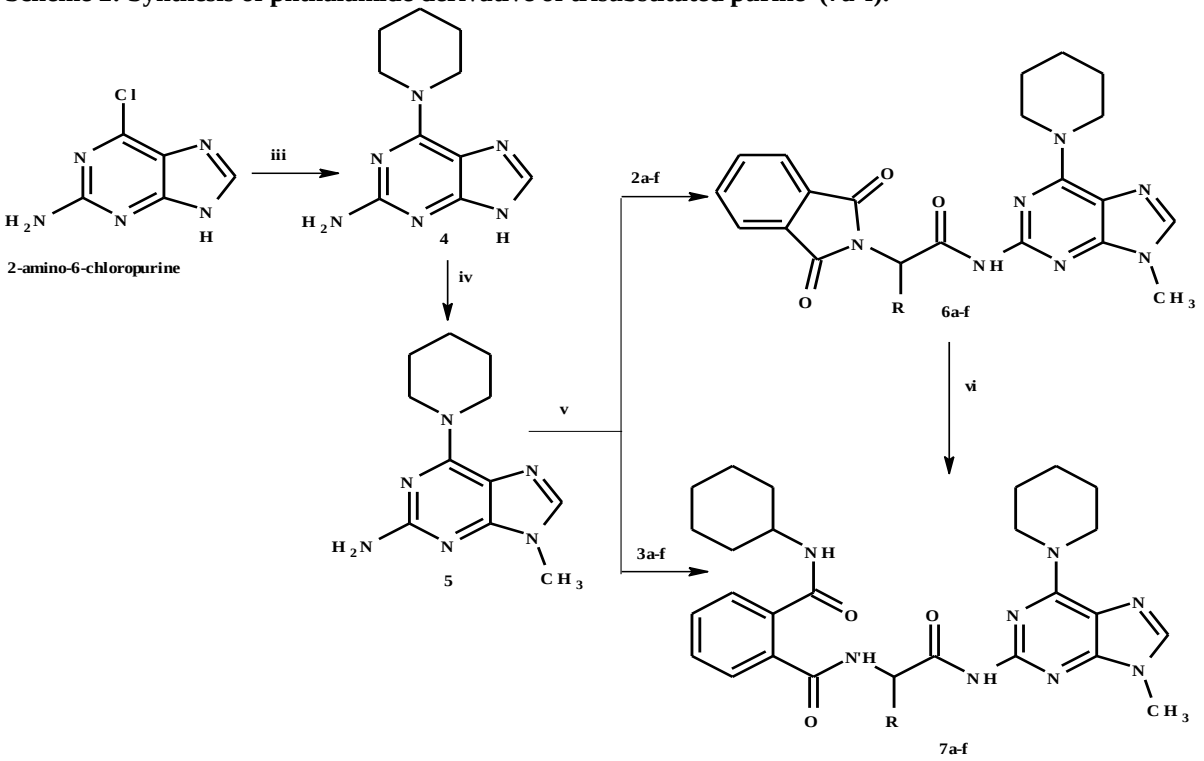
Biological Assay: 10 mm borer was used to prepare the cup in agar plate seeded with an appropriate microorganism. Four cups per plate at four corners and at equidistance were made. A 10 µL test sample was transferred with help of micropipette per well. Plates were immediately kept at 4^0C in refrigerator for 1 hr. and then shifted to BOD incubator. The plates were incubated at 35^0C± 0.5^0C for 24 hrs. Zone of inhibition was measured after 24 hrs of incubation and further evaluated for their (MIC) by using twofold serial dilution method. DMF alone was used as control at the same concentration and showed no zone of inhibition. A loopful of culture was inoculated from the stock slant culture in 5 mL of Hi-sensitivity test broth (Muller-Hinton broth) and broth was incubated at 35^0C± 0.5^0C in BOD incubator for 18-20 hrs. After incubation, a loopful of actively growing culture was inoculated into 10 mL of Hi-sensitivity broth. The broth was incubated at 35^0C± 0.5^0C for 6-8 hrs. This culture was used for the inoculation of Hi-sensitivity test agar plates. Control experiments were also performed.

1.2.1: Scheme 1 Synthesis of N-Phthaloyl and carboxamide derivatives of amino acid 3a-f



Reaction condition and reagents: i. TEA, toluene, reflux, 3 h, 80-95% ; (ii) Cyclohexylamine, DCM: MeOH, RT, 10-12h, 60-75 %.

Scheme 2: Synthesis of phthalamide derivative of trisubstituted purine (7a-f).



R = -H, -CH_3, -CH (CH_3)$_2$, -CH_2CH (CH_3)$_2$, -CH_2Ph, -CH_2Ph (pOBn)

Reaction conditions and reagents: iii) Piperidine, K_2CO_3, Reflux, 5 h, 63 %; iv) MeI, 40% TBAOH, DCM, RT, 1 h, 53 %; v) $POCl_3$, pyridine, -15°C to RT, 10 h, 40-65% ; vi) Cyclohexylamine, DMF, RT, 10-12h, 55-65 %.

1.2.2: ***General procedure for the synthesis of carboxamide derivatives of amino acid (3a-f)***

In RBF fitted with Dean-stark apparatus and a reflux condenser, phthalic acid anhydride (1.48 g, 10 mmol) and appropriate amino acids (1a-f) (10 mmol) were refluxed in toluene and 0.1 ml triethylamine for 3 h. Solvent was removed under reduced pressure to get sticky oily reaction mass followed by addition of water. The reaction mass was acidified with hydrochloric acid and stirred for 30 minutes to get solid. The solid obtained was filtered, washed with water and dried to get compound N-Phthaloyl derivatives 2a-f. Further it dissolved in methanol: dichloromethane (1:2) mixture and cyclohexylamine (20 mmol) was added. Reaction Mixture was stirred at room temperature for 10-12 h. and then solvent was removed under reduced pressure. The oily residue obtained was triturated with hexane and then stirred in ethyl acetate: hexane mixture to get respective carboxamide 3a-f (Scheme 1). Physical characteristic data of synthesized compounds is summarized in Table-1

Synthesis of 6- piperidine -9H-purin-2-amine 4:

2-Amino-6-chloro purine (2-ACP) (10 mmol), piperidine (15 mmol) and K_2CO_3 (20 mmol) were heated in 30 ml n-butanol 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. Crude product was recrystallized from ethanol to get purified product (Scheme 2).

9-methyl-6-(piperidin-1-yl)-9H-purin-2-amine 5:

6-amino-9H-purin-2-amine 4 (10 mmol) dissolved in 50 ml dichloromethane. 40% aqueous tetrabutylammonium hydroxide (10 ml) and methyl iodide (20 mmol) was added and stirred for 1 h. Organic layer was separated out, washed with water and solvent was removed under reduced pressure to get crude product. Crude was purified by crystallization in ethanol.

Synthesis of phthalamide derivative of trisubstituted purine 7a-f:

N-Phthaloyl derivatives 2a-f (10 mmol) and 9-methyl-6-(piperidin-1-yl)-9H-purin-2-amine 5 (10 mmol) were dissolved in anhydrous pyridine. The solution was cooled to −15 ℃ and $POCl_3$ (11 mmol) was added drop wise under vigorous stirring. The reaction mixture then stirred at −15 ℃ for 30 minutes. The solution was allowed to warm to room temperature and then stirred for 10-12 h 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 further dissolved in DMF, cyclohexylamine (20 mmol) was added to it and stirred at room temperature for 10-12 h. Solvent was removed 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 7a-f (Scheme 2). Similarly, carboxamide derivative 3a-f and 9-methyl-6-(piperidin-1-yl)-9H-purin-2-amine 5 will give direct desired product 7a-f. (Scheme 2)

N-Cyclohexyl-N'-[1-(9-methyl-6-piperidin-1-yl-9H-purin-2-ylcarbamoyl)-methyl]-Phthalamide 7a

Yield: 53 %; off white solid ; mp: 116-118 ^oC; MF: $C_{27}H_{34}N_8O_3$; MW: 518.61; IR (KBr, cm^{-1}): 3455 (N-H), 2939 (C-H), 1713, 1686 (C=O), 1630 (C=N), 1570, 1455 (C=C), 1341 (C–N); MS (*m*/*z*): $[MH]^+$ 519.31 ; ^1H NMR ($CDCl_3$, 500MHz): δ = 8.08 (s, 1H, Ar-CH), 7.91 (dd, 2H, Ar-CH), 7.89 (dd, 2H, Ar-CH), 7.6 (s, 1H, -CONH), 4.53 (s, 2H, $-CH_2$), 4.19 (br, 4H, $-NCH_2$), 3.76 (s, 3H, $-NCH_3$), 2.83 (m, 1H, -NCH), 1.72-1.67 (m, 6H, $-CH_2$), 1.64-1.07 (m, 1H, $-CH_2$); ^{13}C NMR ($CDCl_3$, 125MHz): δ = 167.58 (>C=O), 153.50 (C_2), 152.5-152.43 (C_4 & C_6), 138.53(C_8), 133.81 (C_{21} & C_{26}) , 132.22 (C_{23} & C_{24}), 123.61 (C_{22} & C_{25}), 116.46 (C_5), 53.15 (C_{29}), 45.96 (C_{11} & C_{15}), 40.31 (C_{18}), 29.93 (C_{10}), 31.84 (C_{30} & C_{34}), 26.1(C_{12} & C_{14}), 24.74 (C_{31} & C_{33}), 24.61 (C_{32}), 24.5 (C_{13}),

N-Cyclohexyl-N'-[1-(9-methyl-6-piperidin-1-yl-9H-purin-2-ylcarbamoyl)-ethyl]-Phthalamide 7b

Yield: 45 %; white solid ; mp: 120-122 ^oC; MF: $C_{28}H_{36}N_8O_3$; MW: 532.63; IR (KBr, cm^{-1}): 3425 (N-H), 2956 (C-H), 1699, 1685 (C=O), 1620 (C=N), 1591, 1465 (C=C), 1370 (C–N); MS (*m*/*z*): $[MH]^+$ 433.33; ^1H NMR ($CDCl_3$, 500MHz): δ = 8.11 (s, 1H, Ar-CH), 7.88 (dd, 2H, Ar-CH), 7.85 (dd, 2H, Ar-CH), 7.61 (s, 1H, -CONH), 4.66 (q, 1H, -CH), 4.2 (br, 4H, $-NCH_2$), 3.77 (s, 3H, $-NCH_3$), 2.81 (m, 1H, -NCH), 1.71-1.65 (m, 6H, $-CH_2$), 1.64-1.07 (m, 13H, $-CH_2$ & $-CH_3$); ^{13}C NMR ($CDCl_3$, 125MHz): δ = 169.15 (>C=O), 153.74 (C_2), 152.0-151.71 (C_4 & C_6), 138.26(C_8), 134.3 (C_{21} & C_{26}) , 132.21 (C_{23} & C_{24}), 123.11 (C_{22} & C_{25}), 117.04 (C_5), 54.33 (C_{29}), 54.00 (C_{18}), 45.74 (C_{11} & C_{15}), 31.16 (C_{30} & C_{34}), 29.85 (C_{10}), 26.09 (C_{12} & C_{14}), 24.76 (C_{31} & C_{33}), 24.45 (C_{32}), 22.86 (C_{13}), 18.5 (C_{35}).

N-Cyclohexyl-N'-[2-methyl-1-(9-methyl-6-piperidin-1-yl-9H-purin-2-ylcarbamoyl)-propyl]-Phthalamide 7c

Yield: 61 % ; white solid; mp: 102-104 ^{o}C; MF: $C_{30}H_{40}N_8O_3$; MW: 560.69 ; IR (KBr, cm^{-1}): 3296 (N-H), 2965 (C-H), 1720, 1690 (C=O), 1618 (C=N), 1585, 1465 (C=C), 1388 (C–N); MS (*m*/*z*): $[MH]^+$ 561.39 ; ^{1}H NMR ($CDCl_3$, 500MHz): δ = 8.1 (s, 1H, Ar-CH), 7.89 (dd, 2H, Ar-CH), 7.86 (dd, 2H, Ar-CH), 7.62 (s, 1H, -CONH), 4.64 (d, 1H, -CH), 4.22 (br, 4H, -NCH_2), 3.75 (s, 3H, -NCH_3), 2.88 (m, 1H, -CH), 2.84 (m, 1H, -NCH), 1.7-1.63 (m, 6H, -CH_2), 1.64-0.9 (m, 19H, -CH_2 & -CH_3); ^{13}C NMR ($CDCl_3$, 125MHz): δ = 167.83 (>C=O), 153.82 (C_2), 151.98-151.79 (C_4 & C_6), 138.24 (C_8), 134.21 (C_{21} & C_{26}) , 131.79 (C_{23} & C_{24}), 123.56 (C_{22} & C_{25}), 116.92 (C_5), 53.66 (C_{29}), 52.61 (C_{18}), 43.34 (C_{11} & C_{15}), 31.00 (C_{30} & C_{34}), 29.75 (C_{10}), 29.46 (C_{35}), 26.22 (C_{12} & C_{14}), 24.71 (C_{31} & C_{33}), 24.43 (C_{32}), 22.9 (C_{13}), 20.93-19.51 (C_{36} & C_{37}).

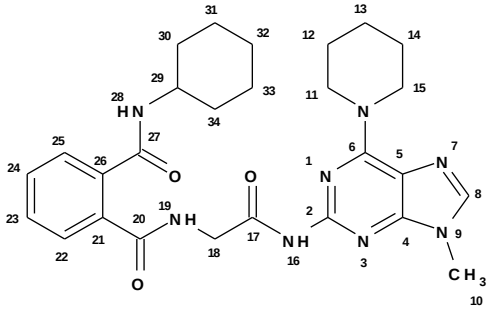
N-Cyclohexyl-N'-[3-methyl-1-(9-methyl-6-piperidin-1-yl-9H-purin-2-ylcarbamoyl)-butyl]-Phthalamide 7d:
Yield: 55 %; off white solid; mp: 111-113 ^{o}C; MF: $C_{31}H_{42}N_8O_3$; MW: 574.71 IR (KBr, cm^{-1}): 3499 (N-H), 3065 (C-H), 1711, 1635 (C=O), 1612 (C=N), 1566, 1460 (C=C), 1391 (C–N); MS (*m*/*z*): $[MH]^+$ 575.33 ; ^{1}H NMR ($CDCl_3$, 500MHz): δ = 8.15 (s, 1H, Ar-CH), 7.88 (dd, 2H, Ar-CH), 7.86 (dd, 2H, Ar-CH), 7.61 (s, 1H, -CONH), 4.88 (s, 1H, -CH), 4.22 (br, 4H, -NCH_2), 3.76 (s, 3H, -CH_3), 2.93 (m, 1H, -CH), 2.88 (m, 1H, -CH), 1.75-0.8 (m. 22H, -CH_2 & -CH_3); ^{13}C NMR ($CDCl_3$, 125MHz): δ = 168.21 (>C=O), 153.83 (C_2), 152.24-151.61 (C_4 & C_6), 138.8 (C_8), 134.33 (C_{21} & C_{26}) , 131.85 (C_{23} & C_{24}), 123.62 (C_{22} & C_{25}), 116.91 (C_5), 56.22 (C_{18}), 54.33 (C_{29}), 45.33 (C_{11} & C_{14}), 31.00 (C_{30} & C_{34}), 29.77 (C_{10}), 26.36 (C_{35}), 26.25 (C_{12} & C_{14}), 24.9 (C_{13}), 24.74 (C_{31} & C_{33}), 24.43 (C_{32}),17.60 (C_{36}), 11.16 (C_{37} & C_{38}).

N-Cyclohexyl-N'-[1-(9-methyl-6-piperidin-1-yl-9H-purin-2-ylcarbamoyl)-2-phenyl ethyl]-Phthalamide 7e:
Yield: 48 %; off white solid; mp: 98-100 ^{o}C; MF: $C_{34}H_{40}N_8O_3$; MW: 608.73 ; IR (KBr, cm^{-1}): 3465 (N-H), 2975 (C-H), 1720, 1633 (C=O), 1615 (C=N), 1565, 1460 (C=C), 1377 (C–N); MS (*m*/*z*): $[MH]^+$ 609.56; ^{1}H NMR ($CDCl_3$, 500MHz): δ = 8.09 (s, 1H, -CH), 7.79 (dd, 2H, Ar-CH), 7.7 (dd, 2H, Ar-CH), 7.61 (s, 1H, -CONH), 7.27-7.12 (m, 5H, Ar-CH), 5.1 (s, 1H, -CH), 4.22 (br, 4H, -NCH_2), 3.77 (s, 3H,-NCH_3), 3.27-3.22 (dd, 2H, -CH_2), 2.84 (m, 1H, -NCH), 1.82-1.08 (m. 16H, -CH_2); ^{13}C NMR ($CDCl_3$, 125MHz): δ = 169.73 (>C=O), 153.88 (s, C_2), 152.2-151.79 (C_4 & C_6), 138.85 (C_{38}), 136.28 (C_8), 134.55 (C_{21} & C_{26}) , 130.45 (C_{23} & C_{24}), 128.75 (C_{39} & C_{43}), 128.32 (C_{40} & C_{42}), 126.19 (C_{41}), 123.4(C_{22} & C_{25}), 117.05 (C_5), 56.32 (s, C_{18}), 50.2 (C_{29}), 45.74 (C_{11} & C_{15}), 37.75 (C_{35}), 31.12 (C_{30} & C_{34}), 29.79 (C_{10}), 26.28 (C_{12} & C_{14}), 24.81 (C_{13}), 24.74 (C_{31} & C_{33}), 24.43 (C_{32}),

N-[2-(4-Benzyloxyphenyl)-1-(9-methyl-6-piperidin-1-yl-9H-purin-2-ylcarbamoyl)-2-ethyl]-N'-cyclohexyl Phthalamide 7f:
Yield: 50 %; off white solid; m.p: 66-68 ^{o}C; MF: $C_{41}H_{46}N_8O_4$; MW: 714.85; IR (KBr, cm^{-1}): 3488 (N-H), 2945 (C-H), 1716, 1635 (C=O), 1630 (C=N), 1572, 1470 (C=C), 1386 (C–N); MS (*m*/*z*): $[MH]^+$ 716.34; ^{1}H NMR ($CDCl_3$, 500MHz): δ = 8.11 (s, 1H, -CH), 7.80 (dd, 2H, Ar-CH), 7.71 (dd, 2H, Ar-CH), 7.61 (s, 1H, -CONH), 7.36-7.30 (m, 5H, Ar-CH), 7.09-7.07 (d, 2H, Ar-CH), 6.78-6.77 (d, 2H, Ar-CH), 5.2 (s, 1H, -CH), 4.95 (s, 2H, -CH_2), 4.19 (br, 4H, -NCH_2), 3.67 (s, 3H, -NCH_3), 3.54-3.46 (dd, 2H, -CH_2), 2.83 (m, 1H, -NCH), 1.85-1.02 (m, 16H, -CH_2); ^{13}C NMR ($CDCl_3$, 125MHz): δ = 168.3 (>C=O), 157.18 (C_{41}), 153.88 (C_2), 152.1-151.47 (C_4 & C_6), 138.79 (C_8), 117.04 (s, C_5, purine), 137.11(C_{44}), 133.61 (C_{21} & C_{26}), 132.05 (C_{38}) 131.26 (C_{23}& C_{24}), 129.72 (C_{39} & C_{43}), 128.5 (C_{46} & C_{48}), 127.85 (C_{45} & C_{49}), 127.49 (C_{22} & C_{25}), 122.99(C_{47}), 114.67 (C_{40} & C_{42}), 69.8 (C_{43}), 56.25 (C_{18}), 50.15 (C_{29}), 45.71 (C_{11} & C_{15}), 34.7 (C_{35}), 30.91 (C_{30} & C_{34}), 29.77 (C_{10}), 26.22 (C_{12} & C_{14}), 24.72 (C_{13}), 24.68 (C_{31} & C_{33}), 24.47 (C_{32}).

1.3: Results and Discussion

The amination of 2-amino-6-chloropurine can be achieved by various synthetic technique reported in the literature using solvent like ethanol, n-butanol [15], acetonitrile [17], 1,4- Dioxane, DMF[18] or DMSO[19] and base like triethylamine, *N*,*N*-dimethyl cyclohexylamine or diisopropylethylamine[20] at higher temperature. 9-methyl-6-(piperidin-1-yl)-9*H*-purin-2-amine 3 was synthesize by reaction of 2-ACP with piperidine using potassium carbonate (K_2CO_3) as base and n-butanol as solvent at reflux temperature followed by N9 methylation using 40% aq. solution of tetrabutylammonium hydroxide (TBAOH) [2] as base in dichloromethane .
For the synthesis of targeted molecule the best results were obtained with the non-classical coupling system phosphorous oxychloride ($POCl_3$) in pyridine [21]. Synthesis of N-Phthaloyl 2a-f and carboxamide derivatives 3a-f was carried out using reported method in literature [22]. 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}. On the basis of all the above facts, the compounds have been assigned structure as follows.



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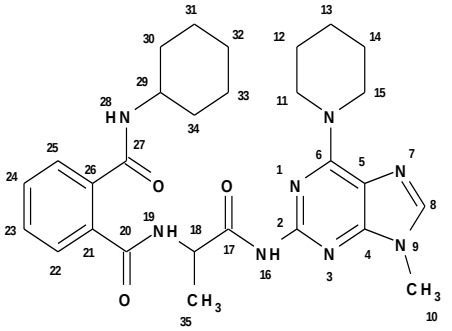

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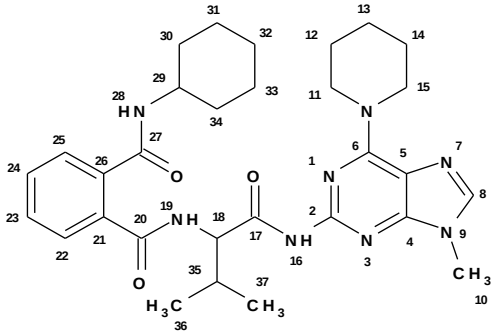

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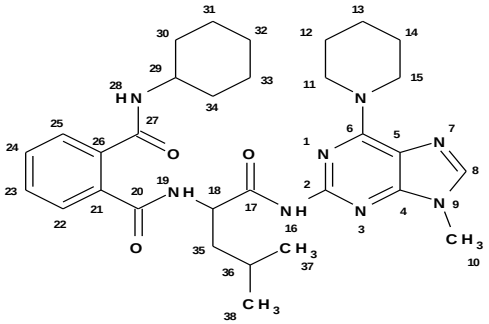

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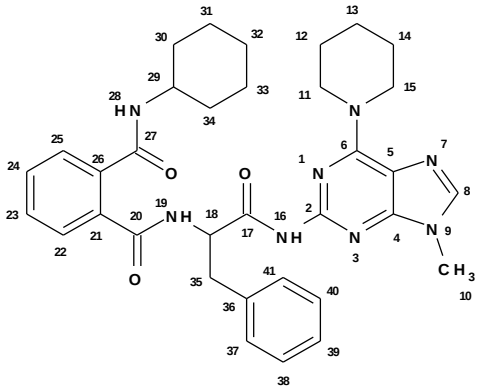

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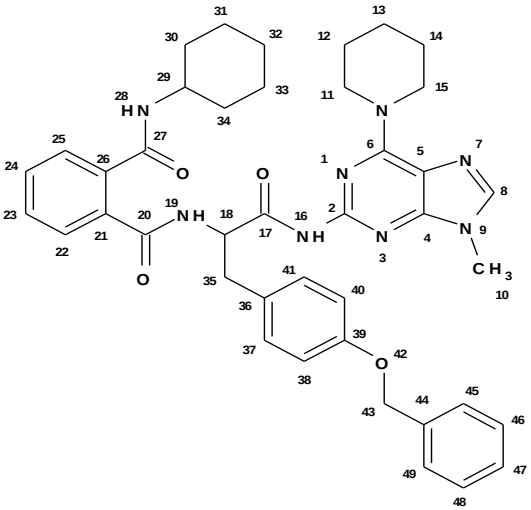

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1.3.1: Biological assays

All the synthesized compounds were evaluated *in vitro* for their antibacterial activities against *S. aureus as* examples of Gram positive bacteria and *E. coli, P. aeruginosa and S. typhimurium as* examples of Gram negative bacteria. They were also evaluated *in vitro* for their antifungal activities against the *F. oxysporum* and *A. alternate* fungal strains. The results were compared with the standard 0.3% Amplicilline and Chloramphenicol as antibacterial agent while Nystatin was used as reference drugs as antifungal agent. Results were summarized in Table 1.

TABLE 1. In *vitro* antimicrobial activities of all synthesized compounds

Compound code	Zone of inhibition in mm					
	Bacteria*				Fungi#	
	Gram +ve	Gram -ve				
	S. aureus	*E. coli*	*P. aeruginosa*	*S. typhi*	*F. oxysporum*	*A. alternata*
7a	18	10	11	10	49	38

7b	17	10	10	11	38	35
7c	13	7	8	9	22	26
7d	12	6	7	8	23	24
7e	20	11	12	11	53	33
7f	19	10	11	11	38	32
Amplicilline	20	11	-	-	-	-
Chloramphenicol	17	20	12	12	-	-
Nystatin	-	-	-	-	70	50

1.4: Conclusion

In summary, we have disclosed the rational design of a series phthalamide derivative of trisubstituted purine derivative by coupling of dicarboxamides of amino acid at C2 position of purine. Microbial analysis reveals that compound of glycine, phenylalanine and tyrosine are more biologically active and can be used as alternative biologically relevant molecules with broad biomedical value as therapeutics.

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