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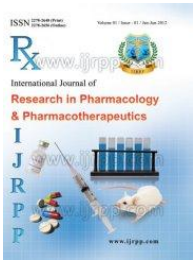

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Research article ***Open Access***

A work on synthesis & characterization of Piperidine-4-carbohydrazide derivatives with its antimicrobial evaluation of pharmaceutical interest.

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ABSTACT

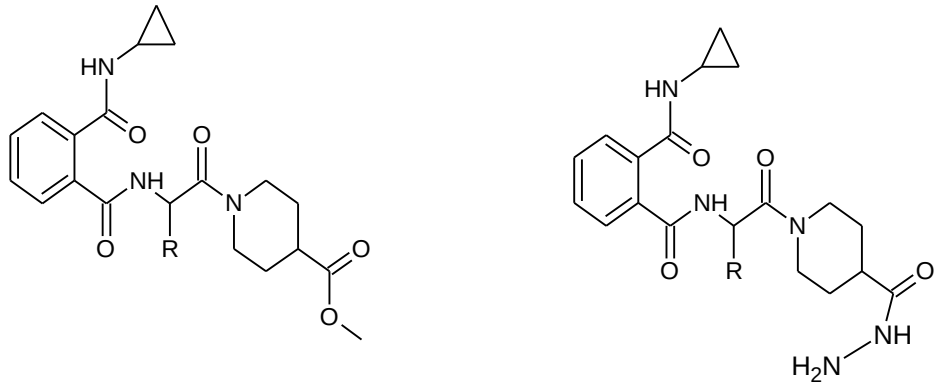
A series of piperidine-4-carboxylic acid methyl ester coupled with N-phthaloyl amino acids derivatives were synthesized, characterized and their antimicrobial properties were evaluated. These compounds were synthesized with dicyclohexylcarbodimide coupling of piperidine-4-carboxylic acid methyl ester with N-phthaloyl amino acids with N, N'-dicyclohexylcarbodiimide followed by ring opening reaction with cyclopropylamine and reaction of ester with hydrazine hydrate to obtain final compound characterized using IR, ^{1}H and ^{13}C-NMR and mass spectroscopy**.** The synthesized compounds were screened for their *in vitro* antimicrobial activity against *S. aurous, E. coli, P. aeruginosa, S. typhimurium, F. oxysporum and A. alternate*. Some of these compounds exhibited moderate to good activity, where as some were inactive.

Keywords: N-phthaloyl amino acids, Cyclopropylamine, Antimicrobial activity, DCC, Coupling**,** Hydrazine hydrate

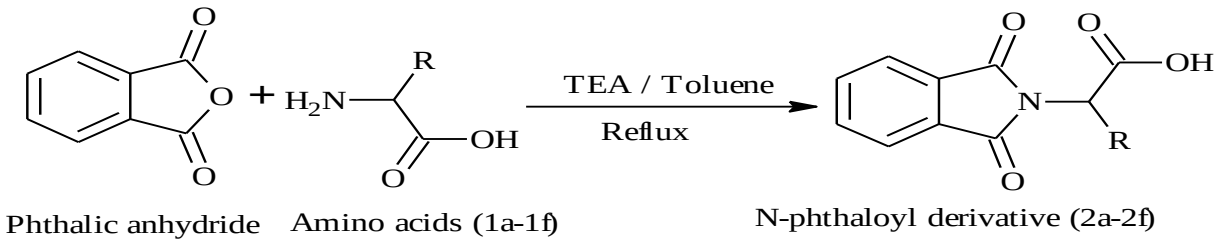
INTRODUCTION

Carbohydrazidederivatives are useful as preventives and therapeutic agents. It has been found that alkyl and aryl carboxamide derivatives show very good antibacterial, antiviral [1–2], anti-inflammatory/analgesic [3], anti-tuberculosis [4], anticancer [5], and respiratory analeptic [6] activities and offer an emerging target for the treatment of pain [7]. 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 ant metabolites. Currently there is a tendency to use amino acid/peptide residues during the prod rug design process. The literature reports that bioactive compounds shows enhanced activity when linked to amino acids [8–10]. The presence of an unusual amino acid has stimulated interest in new synthetic methodology and strategies to obtain a target structure. The goal of the present work was to synthesize 4-carbohydrazide derivatives bearing amino acids acid at position 2 of carboxamide and an amine at position 1 using amines such as cyclopropylamine. Methyl ester of isonipecotic acid is carried out using known general method i.e. using

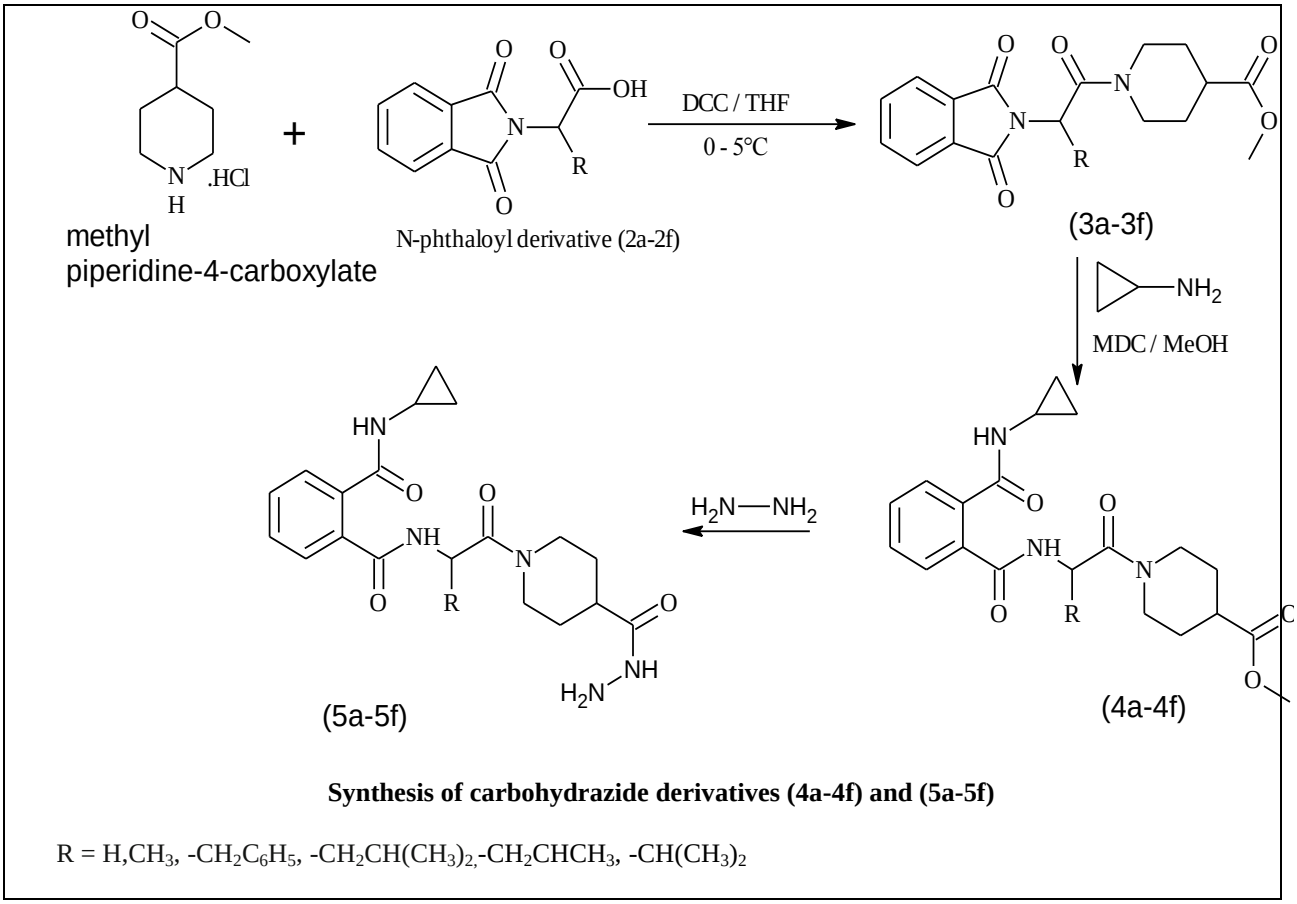
thionyl chloride and methanol at lower temperature (Scheme 1). N-phthaloyl derivative 2a-2f was synthesized according to known methods [11–13] (Scheme 2). Coupling is carried out using coupling reagent N,N'-dicyclohexylcarbodiimide (DCC) in tetrahydrofuran (THF) as solvent and triethylamine (TEA) as base. Final ring opening reaction is carried out using cyclopropylamine in dichloromethane (DCM) and methanol (MeOH) mixture as solvent at room temperature thisester is reacted with hydrazine hydrate to get final compounds 4a – 4f in reasonable yield [14 – 15].



Scheme 1: Synthesis of methyl ester of isonipecotic acid



Scheme 2: Synthesis of carbohydrazide derivative



Synthesis of carbohydrazide derivatives (4a-4f) and (5a-5f)

R = H,CH_3, -$CH_2C_6H_5$, -$CH_2CH(CH_3)_2$,-CH_2CHCH_3, -$CH(CH_3)_2$

EXPERIMENTAL CHEMICAL PART

All chemicals were purchased from commercial suppliers and used without further purification. Melting points (m.p.) were determined using a Veego VMP-PM melting point apparatus and are uncorrected. Mass spectra (MS) were recorded on a Waters Q-TOF instrument in only positive ion detection mode. The ^{1}H-NMR spectra were recorded on a Bruker Avance II 500 (500 MHz) instrument using either $CDCl_3$ / DMSO-*d*6 as solvent and TMS as internal reference. Chemical shifts are expressed as δ values (ppm). IR spectra were recorded on Perkin Elmer spectrum 100 FT-IR spectrophotometer. The course of reactions was monitored and the purity of synthesized compounds was checked by TLC using silica gel 60 F 254 Al-plates (Merck, Germany) in DCM-MeOH (9:1) solvent system and the spots were visualized under UV illumination.

Synthesis of methyl ester of isonipecotic acid

Isonipecotic acid (10 mmol) is suspended in methanol (10 vol) and cooled to 0 to 5°C. Thionyl chloride (15 mmol) is added slowly to below -5 °C. Stirring is continued till completion of reaction. Reaction is monitored using TLC. After completion of reaction, methanol is distilled off and resulting mass is dissolved in methanol and distilled off repeatedly to remove traces of thionyl chloride. Add acetone (5 vol) and distill out the solvent under vacuum at below 50ºC to get product, Isonipecotic acid methyl ester is used as such for next step.

Yield

95.0%; M.P.190-192°C (KBr,cm^{-1}): 3615 (NH), 3412 (OH), 1720 (COOH), 1610 (C=O), 1516 (C-N), 770 (1, 2-disubstitution); ^{1}H-NMR (500 MHz, $CDCl_3$, *δ* / ppm): δ = 9.2 (s,1H, HCl), 9.0 (s,1H,NH), 3.62 (s, 3H, -$COOCH_3$), 3.2-3.18 (m, 2H, >N-CH_2-), 2.92-2.86 (m, 2H, >N-CH2-), 2.7(m, 1H),1.98(m, 2H), 1.8-1.72 (m,2H) ; MS (*m/z*): 204.22 (M+Na)

Synthesis of n-phthaloyl amino acids (2a-2f) (general method)

In RBF fitted with Dean-stark apparatus and a reflux condenser, phthalic acid anhydride 10 mmol) and appropriate amino acids **(1a – 1f)** (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 a sticky oily mass. Water was added to this oily mass and the mixture was acidified with hydrochloric acid, and stirred for 30 min to get a solid product. This solid was filtered off, washed with water, and dried to get a target compound **(2a – 2f)**.

Synthesis of methyl 1-[(1, 3-dioxo-1, 3-dihydro-2h-isoindol-2-yl)] piperidine-4-carboxylate

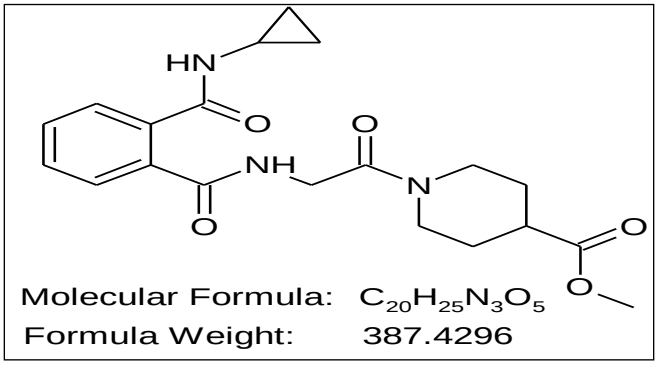
(3a – 3f)

In RBF fitted with reflux condenser, Methyl piperidine 4-carboxylate (10 mmol) and appropriate N-phthaloyl derivatives **(2a-2f)** were dissolve in THF and add(10 mmol) N,N'-dicyclohexylcarbodiimide (DCC) slowly to below 20 ^{o}C and reflux reaction mass till reaction completion. After completion of reaction removed the solvent under reduced pressure to get off white material. This material was crystallizing with ethanol: MDC mixture and stir for 60 min at below 10 ^{o}C. This solid material was filtered off, washed with ethanol:MDC mixture ,and dried to get a target compound **(3a-3f)**

Synthesis of piperidine-4-carbohydrazide derivatives (4a – 4f) (general method)

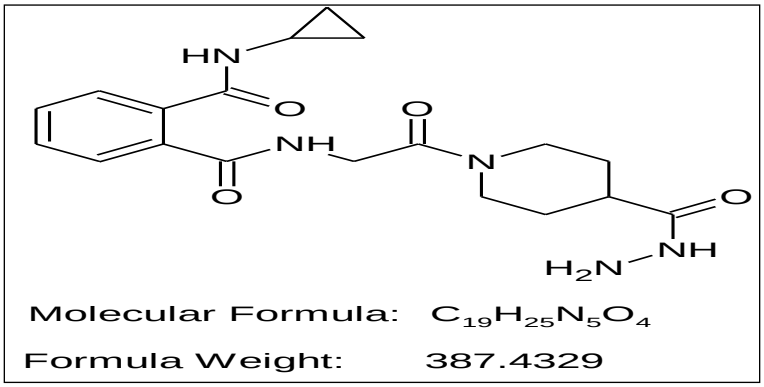
N-Phthaloyl amino acids derivatives **(2a-2f)** were dissolved in MeOH: MDC (1:2) mixture and cyclopropylamine **(**20 mmol) was added. Reaction mixture was stirred at room temperature for 10 – 12 h. The organic solvent was removed under reduced pressure and the obtained oily residue was triturated with hexane and then stirred in ethyl acetate – hexane mixture to get respective thisester is reacted with hydrazine hydrate to get final compounds **4a-4f** (Scheme 1).

1-[2-(2-cyclopropylcarbamoyl-benzoylamino)-acetyl]-piperidine-4-carboxylate (4a)



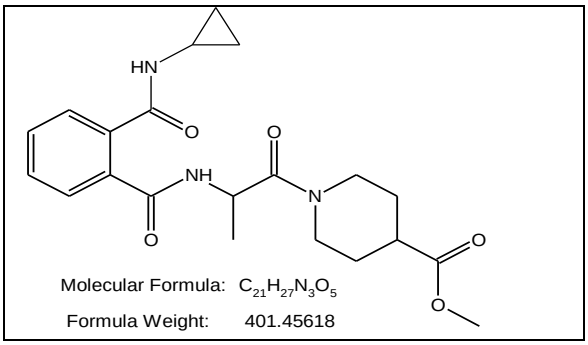
Yield (40.2%); M.P., 212°C; MF $C_{20}H_{25}N_3O_5$; M.W. .:387.4; IR (KBr, cm^{-1}) : 3455 (N-H), 2939 (C-H), 1713, 1686 (C=O): 1H NMR spectrum in $CDCl_3$ (δ ppm) ; 8.08 (s, 1H, Ar-CH), 7.91 (dd, 2H, Ar-CH), 7.89 (dd, 2H, Ar-CH), 7.6 (s, 1H, -CONH),4.53 (s, 2H, -CH2) 2.4 –2.37 (m, 1H, J13.5 Hz, J24.0 Hz, -NCH), 0.67 – 0.65(m, 2H, J11.5 Hz, J25.5 Hz,-CH_2), 0.59 – 0.55 (q, J11.5 Hz, J25.5 Hz, -CH_2); MS, (*m/z*): 410.1 (M + Na).

1-[2-(2-cyclopropylcarbamoyl-benzoylamino)-acetyl]-piperidine-4-carbohydrazide (5a)



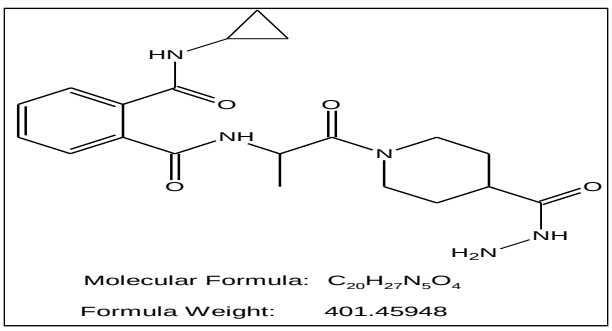
Yield, (55.5%); M.P.,188°C; $C_{20}H_{25}N_3O_5$; M.wt,387.5; IR (KBr, cm^{-1}): 3455 (N-H), 2939 (C-H), 1713, 1686 (C=O) 1H NMR spectrum in CDCl3 (δ ppm): δ = 7.80 (s, 1H, Ar-CH), 7.91 (dd, 2H, Ar-CH), 7.6 (s, 1H, -CONH)4.53 (s, 2H, -CH2) 2.4 –2.37 (m, 1H, N-CH), 0.59 – 0.55 (q, J11.5 Hz, J25.5 Hz, -CH2); MS, *(m/z): 410.2 (M + Na).*

1-[2-(2-cyclo-propylcarbamoyl-benzoylamino)-propionyl]-piperidine-4-carboxylate (4b)



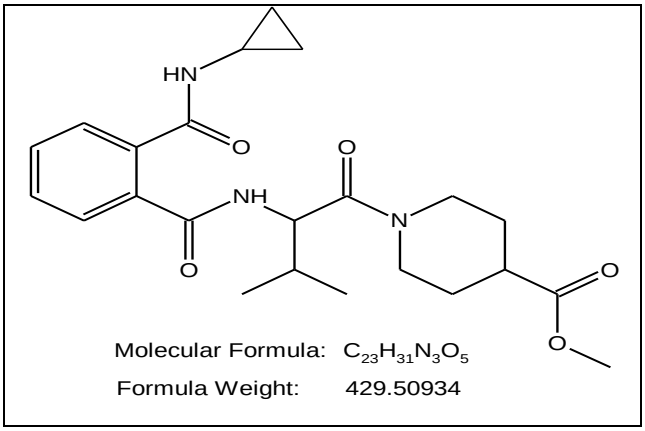
Yield, (27.2%); m.p.,169°C C21H27N3O5; M.wt,401.4; IR (KBr,cm^{-1}):1582, 465 (C=C), 1725,1730,1750 (C=O), 2947 (C-H), 3463 (N-H,);1H NMR spectrum in CDCl3 (ppm): 7.69 – 8.13 (dd, 2H, J13.0,Hz, J24.0, C6H4),2.32 ((s, 2H, J13.0 Hz, J24.0, Hz,4.7 (s, 2H, -CH), 1.48-1.40 (s, 3H, -CH3), 8.0 (s, 1H, J13.5 Hz, J24.0 Hz, -NH), 0.48-0.49(m, 2H, J11.5 Hz, J25.5 Hz,-CH2), 1.85-3.34(m, 10H, J11.5 Hz, J25.5 Hz, CH2), 3.67 (S, 1H, J13.5 Hz, J24.0 Hz, -OCH3), MS, (*m/z*): 424.5 *(M + Na).*

1-[2-(2-cyclo-propylcarbamoyl-benzoylamino)-propionyl]-piperidine-4-carbohydrazide (5b)



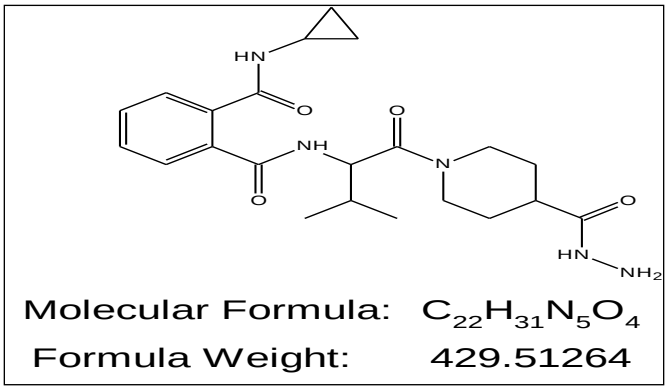
Yield, (28.5%); M.P.,210°C; C21H27N3O5; M.wt.,401.4; IR (KBr,cm^{-1}):1582, 465 (C=C), 1725,1730 (C=O), 2947 (CH), 3443,1690,1640 (NH,);1H NMR spectrum in CDCl3 (ppm): 7.60 – 8.13 (dd, 2H, J13.0 Hz, J24.0, C6H4),2.32 (s, 2H, J13.0 Hz, J24.0 Hz,4.7 (s, 2H, CH), 1.48-1.40 (s, 3H, CH3), 7.98 (s, 1H, J13.5 Hz, J24.0 Hz,N-H), 0.48,0.49 (m, 2H, J11.5 Hz, J25.5, Hz, -CH2), 1.74-3.34 (m, 10H, J11.5,Hz, J25.5 ,CH2), 2.0 (m, 1H, J11.5, J25.5 Hz, NH2); MS, (*m/z*): 424.5 *(M + Na).*

1-[2-(2-cyclopropylcarbamoyl-benzoylamino)-3-methyl-butyryl]-piperidine-4-carboxylate (4c)



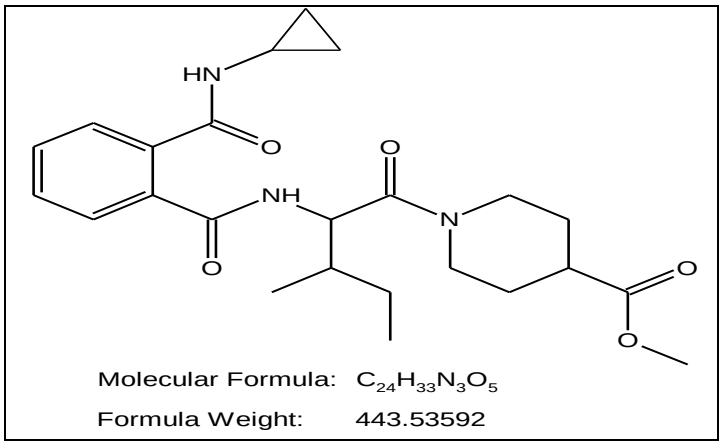
Yield, (23.2%); M.P., 139°C;$C_{23}H_{31}N_3O_5$; M.wt.,429.5; IR (KBr,cm^{-1}) : 1600, 465 (C=C), 1721,1750 (C=O), 2947 (C-H), 3450 (N-H,);1H NMR spectrum in CDCl3 (ppm): 7.60 – 8.13 (dd, 2H, J13.0 Hz, J24.0 Hz, C6H4),2.32 (s, 2H, J13.0 Hz, J24.0 Hz,4.7 (s, 2H, -CH), 2.8-3.3 (dd, 3H, -CH3), 8.0 – (s, 1H, J13.5 Hz, J24.0 Hz, -NH), 0.47-0.49 (m, 2H, J11.5 Hz, J25.5 Hz,-CH2), 1.74-3.34(m, 10H, J11.5 Hz, J25.5 Hz,-CH2), MS (*m/z*): 452.1 *(M + Na).*

1-[2-(2-cyclopropylcarbamoyl-benzoylamino)-3-methyl-butyryl]-piperidine-4- carbohydrazide. (5c)



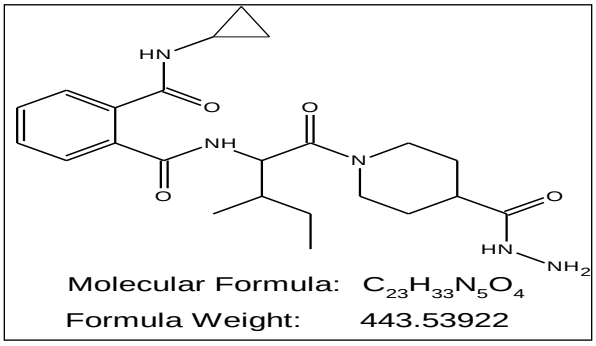
Yield,(32.3%); M.P.,193°C;$C_{23}H_{31}N_5O_4$; M.wt.,429.5;IR (KBr,cm^{-1}) : 1600, 465 (C=C), 1721,1750 (C=O), 2948 (C-H), 3450,1640 (N-H,);1H NMR spectrum in CDCl3 (ppm): 7.58 – 8.10 (dd, 2H, J13.0 Hz, J24.0 Hz, C6H4),2.32 (s, 2H, J13.0 Hz, J24.0 Hz,2.8-3.3 (dd, 3H, -CH3), 8.0 –2.0 (s, 1H, J13.5 Hz, J24.0 Hz, -NH,NH2), 0.47-0.49 (m, 2H, J11.5 Hz, J25.5 Hz,-CH2), 1.85-3.34 (m, 10H, J11.5 Hz, J25.5 Hz,-CH2), MS (*m/z*): 452.1 *(M + Na).*

1-[2-(2-cylopropyl carbamoyl-benzoylamino)-4-methyl-pentanoyl]-piperidine-4-carboxylate (4d):



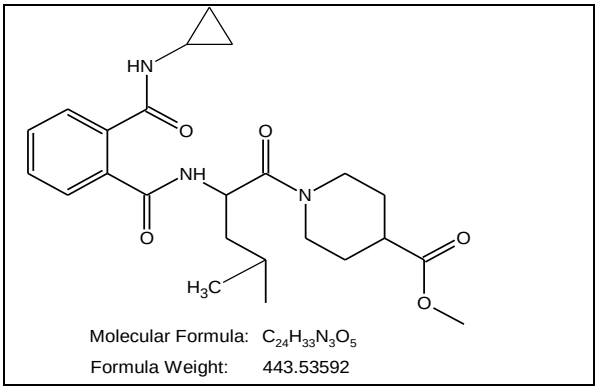
Yield, (26.5%); M.P., 136°C;$C_{24}H_{33}N_3O_5$; M.wt.,443.53; IR (KBr,cm^{-1}) : 1610, 465 (C=C), 1721,1750 (C=O), 2950 (C-H), 3463 (N-H,);1H NMR spectrum in CDCl3 (ppm) : 7.69 – 8.13 (dd, 2H, J13.0 Hz, J24.0 Hz, C6H4),2.33 (s, 2H, J13.0 Hz, J24.0 Hz),4.52-2.5 (s, 2H, -CH,CH), 1.06-0.96 (d, 3H, J7.5 Hz, -CH3), 1.29 (d, 3H, J7.5 Hz, -CH2); 2.8-3.34 (dd, 3H, -CH3), 8.0 (s, 1H, J13.5 Hz, J24.0 Hz, -NH), 0.47-0.49 (m, 2H, J11.5 Hz, J25.5 Hz,-CH2), 1.74-3.34 (m, 10H, J11.5 Hz, J25.5 Hz,-CH2), MS (*m/z*): 466.1(M + Na).

1-[2-(2-cylopropylcarbamoyl-benzoylamino)-4-methyl-pentanoyl]-piperidine-4-carbohydrazide.(5d)



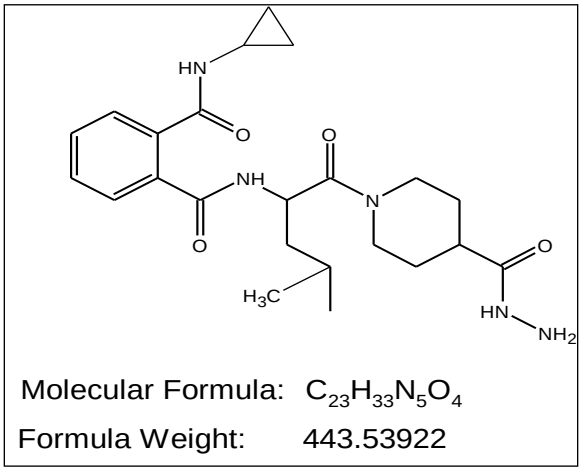
Yield, (22.4 %); M.P., 138°C;$C_{23}H_{33}N_5O_4$; M.wt.,443.53; IR (KBr,cm^{-1}) : 1599, 465 (C=C), 1721, (C=O), 2950 (C-H), 3463,1650 (N-H,);1H NMR spectrum in CDCl3 ppm: 7.69 – 8.13 (dd, 2H, J13.0 Hz, J24.0 Hz, C6H4),2.33 (s, 2H, J13.0 Hz, J24.0 Hz,-CH2),4.52-2.5 (s, 2H, -CH,CH), 1.06-0.96 (d, 3H, J7.5 Hz, -CH3), 3.26 (d, 3H, J7.5 Hz, -CH2); 1.74-3.34 (dd, 3H, -CH3), 8.0,2.0 – (s, 1H, J13.5 Hz, J24.0 Hz, -NH-NH2), 0.48-0.49 (m, 2H, J11.5 Hz, J25.5 Hz,-CH2), 1.74-3.34(m, 10H, J11.5 Hz, J25.5 Hz,-CH2), MS (*m/z*): 466.1 *(M + Na).*

1-[2-(2-cyclopropyl-carbamoyl-benzoylamino)-3-methyl-pentanoyl]-piperidine-4-carboxylate (4e)



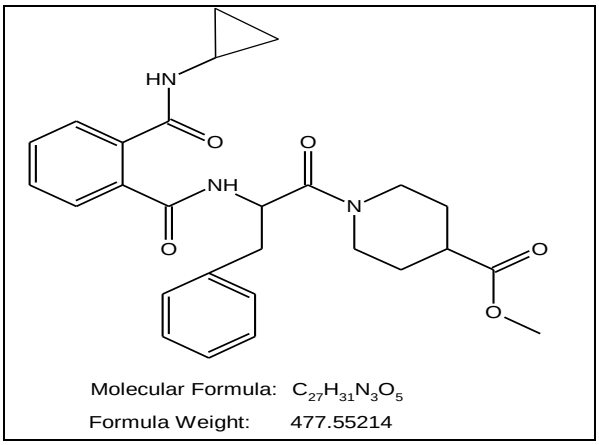
Yield, (21%); M.P.,.133°C;$C_{24}H_{23}N_3O_3$; M.wt,443.53; IR (KBr,cm^{-1}) : 1597, 465 (C=C), 1721,1750 (C=O), 2947 (C-H), 3460 (N-H,);1H NMR spectrum in CDCl3 (ppm): 7.69 – 8.13 (dd, 2H, J13.0 Hz, J24.0 Hz, C6H4),1.06-0.96 (d, 3H, J7.5 Hz, -CH3), 3.26 (d, 3H, J7.5 Hz, -CH2); 1.74-3.34 (dd, 3H, -CH3), 8.0, (s, 1H, J13.5 Hz, J24.0 Hz, -NH), 0.48-0.49 (m, 2H, J11.5 Hz, J25.5 Hz,-CH2), 1.74-3.34(m, 10H, J11.5 Hz, J25.5 Hz,-CH2), MS (*m/z*): 466.2 *(M + Na).*

1-[2-(2-cyclopropyl-carbamoyl-benzoylamino)-3-methyl-pentanoyl]-piperidine-4-carbohydrazide (5e)



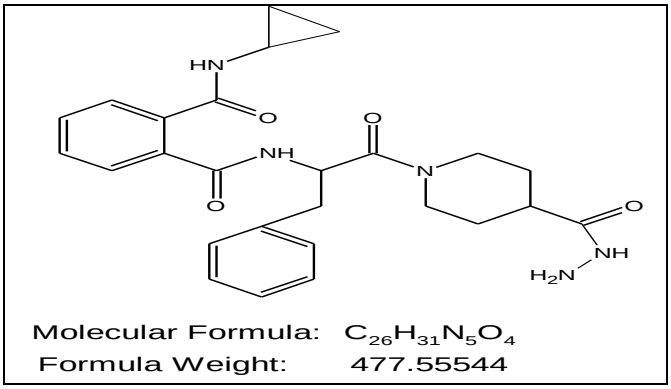
Yield, (30.2%); m.p..°C;$C_{23}H_{33}N_5O_4$; M.W.443.5; IR (KBr,cm^{-1}) : 1597, 465 (C=C), 1721,1750 (C=O), 2947 (C-H), 3462 (N-H,);1H NMR spectrum in CDCl3 (ppm): 7.69 – 8.13 (dd, 2H, J13.0 Hz, J24.0 Hz, C6H4),2.33 (s, 2H, J13.0 Hz, J24.0 Hz,-CH2),4.52-2.5 (s, 2H, -CH2), 1.46 (d, 3H, J7.5 Hz, -CH3), 3.26 (d, 3H, J7.5 Hz, -CH2); 1.74-3.34 (dd, 3H, -CH3), 8.0,2.0 – (s, 1H, J13.5 Hz, J24.0 Hz, -NH-NH2), 0.48-0.49 (m, 2H, J11.5 Hz, J25.5 Hz,-CH2), 1.74-3.34(m, 10H, J11.5 Hz, J25.5 Hz,-CH2), MS (*m/z*): 466.2(M + Na).

1-[2-(2-cyclopropyl-carbamoyl-benzoylamino)-3-phenyl-propionyl]-piperidine-4-carboxylate (4f)



Yield, (17.3%); M.P.,138°C; $C_{27}H_{31}N_2O_5$; M.wt,477.5; IR (KBr,cm^{-1}) : 1598, 465 (C=C), 1721,1750 (C=O), 2947 (C-H), 3463 (N-H,); 1H NMR spectrum in CDCl3 (ppm): 7.85 – 7.82 (dd, 2H, J13.0 Hz, J24.0 Hz, C6H4), 7.26 (dd, 2H, J13.0 Hz, J24.0 Hz,C6H4), 4.53 (s, H, -CH), 8.0 (s, 1H, J13.5 Hz, J24.0 Hz, -NH-), 0.48 – 0.49 (m, 2H, J11.5 Hz, J25.5 Hz,-CH2), 1.87 (q, J11.5 Hz, J25.5 Hz, -CH2); MS (*m/z*): 500.2 *(M + Na).*

1-[2-(2-cyclopropyl-carbamoyl-benzoylamino)-3-phenyl-propionyl]-piperidine-4-carbohydrazide. (5f)



Yield, (18.2%); M.P.211°C; $C_{26}H_{31}N_5O_4$; M.wt.,477.5; IR (KBr,cm^{-1}) : 1597, 465 (C=C), 1721,1750 (C=O), 2947 (C-H), 3462 (N-H,);1H NMR spectrum in CDCl3 (ppm): 7.69 – 8.13 (dd, 2H, J13.0 Hz, J24.0 Hz, C6H4),2.33 (s, 2H, J13.0 Hz, J24.0 Hz,-CH2),7.26 (dd, 2H, J13.0 Hz, J24.0 Hz, C6H5),1.87 (s, 2H, -CH2), 3.26 (d, 4H, J7.5 Hz, -CH2); 1.74-3.34 (dd, 3H, -CH3), 8.0,2.0 (s, 1H, J13.5 Hz, J24.0 Hz, -NH-NH2), 0.48-0.49 (m, 2H, J11.5 Hz, J25.5 Hz,-CH2), 1.74-3.34 (m, 10H, J11.5 Hz, J25.5 Hz,-CH2), MS (*m/z*): 500.4 *(M + Na).*

EXPERIMENTAL BIOLOGICAL PART

Preliminary testing of the antibacterial activity of the newly synthesized compounds was performed by the disc diffusion method using Muller Hinton Agar (MHA) medium. In hard glass screw cap test tube, sterile slants of MHA were prepared. Stored pure cultures were transferred to the freshly prepared MHA slants separately for each organism using sterilized inoculating loop. In this way, four test tubes were freshly prepared for each bacterial pathogen. Freshly prepared pure culture tubes slants were used for inoculation of nutrient broths. These tubes were

incubated at (35±2°C) for 24 hours to get bacterial suspensions used to study antibacterial activity. The microorganisms were spared on the surface of MHA plate. Five wells of equal size were created using gel puncher (4 mm) in each plate. These wells were then filled with 10 µL of each sample) and labeled accordingly. DMSO was used as a solvent. The micro-organisms of *Staphylococcus aureus* NCIM 2127 (*S. aureus*), *Escherichia coli* NCIM 2065 (*E. coli*), *Pseudomonas aeruginosa* NCIM-2036 (*P. aeruginosa)* and *Salmonella typhimurium* NCIM 2501 (*S. typhimurium*) were purchased from the National Chemical Laboratory (NCL), Pune, India.

RESULTS AND DISCUSSION

All the synthesized compounds were characterized using various spectroscopic techniques. IR spectra showed characteristic bands of amide 1709-1722cm^{-1} and carbonyl 1733-1712cm^{-1}. Stretching frequencies of -$COOCH_3$ and hydrazide groups were in the range of 1735-3200 cm^{-1}. The 1H spectrum was carried out at 500 MHz and showed characteristics pattern of peaks. Aromatic protons of phthalamide ring appeared at 7.85 –7.66 ppm. Electron ionization mass spectrometric fragmentation pattern of all compounds was the same.

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 I. *In vitro*antimicrobial activities of all synthesized compounds

Compound code	Zone of inhibition in mm					
	Bacteria				Fungi	
	Gram +ve	Gram -ve				
	S. *aurous*	E. *coli*	P. *aeruginosa*	S. *typhi*	*F. oxysporum*	*A. alternata*
3a	18	10	11	10	49	38
3b	17	10	10	11	38	35
3c	13	7	8	9	22	26
3d	12	6	7	8	23	24
3e	20	11	12	11	53	33
3f	19	10	11	11	38	32
Amplicilline	20	11	-	-	-	-
Chloramphenicol	17	20	12	12	-	-
Nystatin	-	-	-	-	70	50

CONCLUSION

In summary, we have disclosed the rational design of a series of potent piperidine carbohydrazide derivatives (3a-3f and 4a-4f). The biological data indicate that carbohydrazide having cyclopropyl group are more active than the carbohydrazide group.

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REFERENCES

[1]. S.Pande P. Utale ,Gholse S, Tekade P and Gunjate J, An efficient Synthesis of Trisubstituted Purine via Unusual coupling of N-Phthaloyl Derivatives of Amino Acids, International Journal of ChemTech Research, 5(6), 2013, 3023-31.
[2]. X. He, A. Alian, R. Stroud, and P. R. Ortiz de Montellano, *J. Med. Chem*., 49(21), 2006, 6308 – 6323.
[3]. F. Schiaffella, R. Fringuelli, V. Cecchetti, et al., *Farmaco*, 44(11), 1989, 1031 – 1044.
[4]. C. Dittrich, V. Dieras, P. Kerbrat, et al., *Investig. New Drugs: J.New Anticancer Agents*, 21(3), 2003, 347–352.
[5]. G. M. Keating, A. Santoro, *Drugs*, 69(2), 2009, 223 – 240.
[6]. F. J. Torriani, M. Rodriguez-Torres, J. K. Rockstroh, et al., *New Engl. J. Med*., 351(5), 2004, 438 – 450.
[7]. Y. K. Jong, J. S. Hee, H. L. Sung, et al., *Bioorg. Med. Chem.Lett*., 19(1), 2009, 142 –145.
[8]. S. Sidique, R. Ardecky, Y. Su, et al., *Bioorg. Med. Chem. Lett*., 19 **(**1), 2009, 222 – 225.
[9]. A. C. Leite, K. P. da Silva, I. A. de Souza, et al., *Eur. J. Med. Chem*., 39(12), 2004, 1059 – 1065.
[10]. X. Collin, J. Robert, G. Wielgosz, et al., *Eur. J. Med. Chem*., 36 (7–8), 2001, 639–649.
[11]. A. A. Abdel-Aziz, *Eur. J. Med. Chem*., 42(5), 2007, 614 – 626.
[12]. CK.Belwal and Joshi KA, Pharmacological examination and synthesis of some Schiff bases and thiazolidinone derivatives of 5-amino-1H-imidazole-4-carboxamide, Der Pharma Chemica, 4(5), 2012, 1873-78.
[13]. E. Moreno, S. Ancizu, S. Perez-Silanes, et al., *Eur. J. Med. Chem*., 45(10), 2010, 4418 – 4426.
[14]. M. Ohkubo, A. Kuno, H. Sakai, and H. Takasugi, *Chem. Pharm. Bull*, 43(6), 1995, 947 – 954.
[15]. Jigisha A. Modi, (2012), Design, synthesis of some 2, 6, 9- trisubstituted purinyl thioureido derivatives and evaluation of antimicrobial activity, Med Chem. Res 1660-1664.