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Synthesis of Some 2-Thioxo-imidazolidin-4-one Derivatives and its Antimicrobial Activity

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Abstract: Series of newly prepared 3-{[2,6-bis(4-substituted phenyl)-1-methylpiperidin-4- ylidene] amino}- 2-thioxo-imidazolidin-4-one derivatives (**3a-3f)** have been synthesized by the cyclization of compound **(2a-2f)**, ethyl chloro acetate and fused sodium acetate**.** The chemical structures were confirmed by IR, ^{1}H NMR and elemental analysis. The synthesized compounds were screened for their antimicrobial activity against four antibacterial and four antifungal organisms.

Keywords: 2,6-Diphenylpiperidine-4-one, 2-Thioxo-imidazolidin-4-one, Antimicrobial activity.

Introduction

Hydantoins [imidazolidin-2,4–dione and 2-thioxo–imidazolin-4-one] are belongs to heterocyclic compound, which has a wide range of biological and pharmacological properties such as antimicrobial activity (antifungal, antibacterial)[1], antitumor[2], anti-inflammatry[2], anti HIV[3], anti-hypertensive[4], hydantoin exhibits diverse biological activities, such as anticonvulsant[5], antifungal activities[6], antithyroidal[7], antiviral[8], anti HIV[9], tuber culosis[10], anti arrhythmic[11] and anti convulsant[12].

Many piperidine derivatives are found possessing pharmacological activities like anaesthetic activity[14] and antimicrobial activity[15]. 2–Thioxo-imidazolindin-4-one was prepared from the reaction of aromatic aldehydes and thiosemicarbazide to give alkyl thiosemicarbazone followed by cyclization with ethyl chloroacetate in the presence of fused sodium acetate[13]. Above method was followed in the present study, thiosemicarbazide react with 2,6-diphenyl piperidin-4-one to give 2,6-disubstituted phenyl-piperidine-4-thiosemicarbazone followed by cyclization with ethyl chloro acetate and fused sodium acetate.

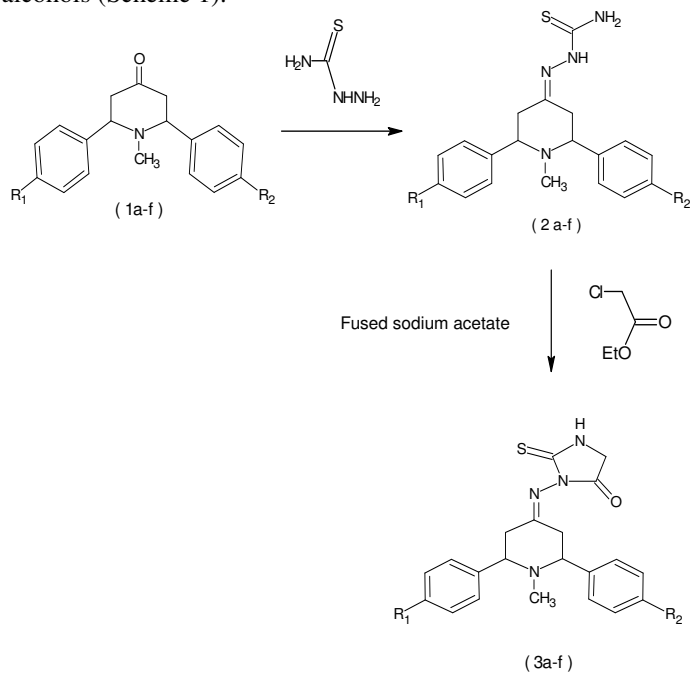
Major role of this study is to synthesis and screen for antimicrobial activity of series of 3-{[2,6-bis (4-substituted phenyl)-1-methylpiperidin-4-ylidene] amino}-2-thioxo-imidazolidin-4-one **(3a-3f).**

Experimental

Melting points were recorded in open capillary tubes and are uncorrected. IR(cm^{-1}) was recorded in KBr on a FT-IR shimadzu 8201 pc (4000-400 cm^{-1}) and ^1H NMR and Elemental analysis (C,H,N and S) was undertaken using an Elemental analyzer model vario EL III. The purity of the compounds was checked by thin layer chromatography (TLC) with silica gel plates.

General procedure for synthesis of 1-methyl-2,6-diphenylpiperidin-4-thiosemicarbazone **(2a-2f)**

A mixture of 1-methyl-2,6-disubstituted phenyl-piperidin-4-one (0.01 mol) and thiosemicarbazide (0.01 mol) in ethanol was heated under reflux for 6 h. The reaction mixture was cooled and poured into crushed ice. The resulting solid produced was filtered, dried and recrystallized from suitable alcohols (Scheme 1).



Scheme 1. Synthesis of 4-thioxo-imidazolidin-2-one derivatives

1-Methyl-2,6-diphenylpiperidin-4-thiosemicarbazone **(2a)**

IR(KBr,cm^{-1}): 3475(NH_2), 3060(Ar-CH str), 2960(NH), 1616(C=N), 1495(C=S), 727(N-C-N); ^1H NMR-(DMSO-d6, δ (ppm)):11.01 (s, 1H, =N-NH), 7.23-6.56 (m,4H,Ar-H), 6.73(s,1H,NH_2), 3.74 (s, 2H, 2,6-H in pipridine ring), 2.26 (s,3H, N-CH_3), 2.17(s,2H, 3,5-H in pipridine ring); Elemental analysis: Calculated for $C_{19}H_{22}N_4S$: C,67.36; H,6.50; N,16.54; S, 9.45; Found: C, 67.34; H, 6.57; N, 16.52; S, 9.48%.

2,6-Bis(4-chlorophenyl)-1-methylpiperidin-4-thiosemicarbazone **(2b)**

IR(KBr, cm^{-1}): 3432(NH_2), 3022(Ar-Ch Str), 2961(NH), 1632(C=N), 1423(C=S), 1082(N-C-N), 811(Ar–Cl); ^1H NMR-(DMSO-d6,δ(ppm)):11.21(s,1H, =N-NH), 7.81-7.20 (m,4H,Ar-H),

7.15(s,2H,NH_2), 3.68 (s, 2H, 2,6-H in pipridine ring), 2.18 (s,3H, N-CH_3), 2.14(s,2H, 3,5-H in pipridine ring); Elemental analysis: Calculated for $C_{19}H_{20}Cl_2N_4S$: C, 55.97; H,4.90;N,13.74;S,7.85 ; Found: C, 55.94; H, 4.87; N, 13.71 S, 7.81%.

2, 6-Bis (4-hydroxy phenyl)-1-methylpiperidin-4-one thiosemicarbazone **(2c)**

IR(KBr, cm^{-1}): 3473(NH_2), 3121(Ar-CH Str), 2931 (NH), 1626 (C=N), 1450(Ar-OH str), 1136 (C=S), 1122(N-C-N); ^{1}H NMR- (DMSO-d6, δ (ppm)) : 11.96(s, 1H,Ar-OH), 10.91(s, 1H, =N-NH), 7.51-7.34(m,4H,Ar-H), 7.20(s,2H,NH_2), 3.54 (s, 2H, 2,6-H in pipridine ring) 2.28 (s,3H, N-CH_3), 2.20(s,2H, 3,5-H in pipridine ring); Elemental analysis: Calculated for $C_{19}H_{22}N_4O_2S$: C,33.12; H,5.01; N,14.05; S,8.02; Found: C,33.09; H,5.04;N,14.02; S,8.04%.

2,6-Bis(4- methoxyphenyl)-1-methylpiperidin-4-one thiosemicarbazone **(2d)**

IR(KBr,cm^{-1}): 3465(NH_2), 3145(Ar-H), 2902(NH), 1675 (C=N), 1138(C=S), 1022(N-C-N); ^{1}H NMR-(DMSO-d6, δ (ppm)) : 11.12 (s, 1H, =N-NH), 7.61-7.49 (m,4H,Ar-H), 7.30 (s,2H,NH_2), 4.12 (s,3H,Ar-CH_3O), 3.54 (s, 2H, 2,6-H in pipridine ring) 2.39 (s,3H, *N*-CH_3); 2.20(s,2H, 3,5-H in pipridine ring); Elemental analysis: Calculated for $C_{19}H_{22}N_4S$: C,63.36; H,6.53; N,14.57; S,8.44; Found: C,63.34; H,6.50; N,14.50; S,8.48%.

2,6-Bis(4-nitro phenyl)-1-methylpiperidin-4-one thiosemicarbazone **(2e)**

IR(KBr,cm^{-1}): 3445(NH_2), 3092 (Ar-H), 2960(NH),1617 (C=N), 1550(Ar-NO_2), 1131(C=S), 1042(N-C-N);^{1}H NMR-(DMSO-d6, δ (ppm)):11.24(s, 1H, =N-NH),7.59-7.49(m,4H,Ar-H), 7.32 (s,2H,NH_2), 3.45 (s, 2H, 2,6-H in pipridine ring), 2.23 (s,3H, N-CH_3); 2.11(s,2H, 3,5-H in pipridine ring); Elemental analysis: Calculated for $C_{19}H_{20}N_6O_4S$: C,53.21; H,4.66; N,19.60; S,7.46 ; Found: C, 53.27; H, 4.63; N, 19.57; S, 7.42%.

2,6-Bis(4-dimethyl amine phenyl)-1-methylpiperidin-4-one thiosemicarbazone **(2f)**

IR(KBr, cm^{-1}): 3388(NH_2), 3112(Ar-H), 2927(NH), 1676 (C=N), 1127(C=S), 1052(N-C-N); ^{1}H NMR- (DMSO-d6, δ(ppm)): 11.30 (s,1H,=N-NH), 7.51-7.47(m,4H,Ar-H), 7.39 (s,2H,NH_2), 2.72(s,6H,Ar-N(CH_3)$_2$), 3.88 (s, 2H, 2,6-H in pipridine ring), 2.28 (s,3H, N-CH_3); 2.17(s,2H, 3,5-H in pipridine ring); Elemental analysis: Calculated for $C_{23}H_{32}N_6S$: C,65.00; H,7.53;N,19.78;S,7.53; Found: C, 65.05; H, 7.57; N, 19.75; S, 7.55%.

General procedure for synthesis of 3-[(1-methyl-2, 6-diphenylpiperidin-4-ylidene) amino]-2-thioxo-imidazolidin-4-one **(3a-3f)**

A mixture of compound 3-[(1-Methyl-2,6-disubstituted phenylpiperidin-4-ylidene)amino]-2-thioxo-imidazolidin-4-one **(2a-2f)** (0.1 mol), ethyl chloroacetate (0.1 mol) and fused sodium acetate (0.1 mole) in ethanol, the mixture was heated under reflux for 6 h. The reaction mixture was cooled and poured into crushed ice. The resulting solid product was filtered, dried and recryatallized from absolute ethanol (Table 1).

Table 1. Characterization data of the compounds **(3a-3f)**

Compd.no	R1	R2	m.p °C	Yield %
3a	- H	-H	231	54
3b	-Cl	-Cl	240	59
3c	-OH	-OH	252	57
3d	-OCH_3	-OCH_3	211	51
3e	-NO_2	-NO_2	227	48
3f	-N(CH_3)$_2$	-N(CH_3)$_2$	238	57

3-[(1-Methyl-2, 6-diphenylpiperidin-4-ylidene) amino]-2-thioxo-imidazolidin-4-one ***(3a)***

IR(KBr cm^{-1}): 3084(NH),1722(C=O), 1664 (C=N),1495(C=S); ^{1}H NMR -(DMSO-d6, δ (ppm)): δ10.32(s,1H NH), 7.58-7.21(m,4H,Ar-H), 3.90(s,2H, $5CH_2$), 3.54 (s, 2H, 2,6-H in pipridine ring), 2.41(s,2H,3,5-H in pipridine ring) 2.18 (s,3H, N-CH_3), Elemental analysis: Calculated for $C_{21}H_{22}N_4OS$: C,66.58; H,5.81;N,14.79;S,16.90; Found: C, 66.55; H, 5.79; N, 14.75; S, 16.88%.

3-{[2,6-Bis(4-chlorophenyl)-1-methylpiperidin-4-ylidene]amino}-2-thioxo-imidazolidin-4-one **(3b)**

IR(KBr, cm^{-1}): 3021(NH), 1723(C=O), 1666(C=N), 1520(C=S), 751 (Ar–Cl); ^{1}H NMR-(DMSO-d6, δ (ppm)): δ10.23(s,1H NH), 7.58-7.31(m,4H,Ar-H), 3.42(s,2H, $5CH_2$), 3.54 (s, 2H, 2,6-H in pipridine ring), 2.41(s,2H,3,5-H in pipridine ring), 2.12 (s,3H, N-CH_3); Elemental analysis: Calculated for For $C_{21}H_{20}Cl_2N_4OS$: C,56.32; H,4.47;N,12.51;S,7.15; Found: C,56.30; H,4.42; N,12.54; S,7.12%.

3-{[2,6-Bis(4-hydroxy phenyl)-1-methylpiperidin-4-ylidene]amino}-2-thioxo-imidazolidin-4-one **(3c)**

IR(KBr, cm^{-1}): 3032(NH), 1722(C=O), 1664 (C=N), 1459(Ar-OH), 1432(C=S); ^{1}H NMR-(DMSO-d6, δ (ppm)): δ11.21 (s,1H,Ar-OH), δ10.11(s,1H, NH), 7.58-7.11(m,4H,Ar-H), 4.21(s,2H, $5CH_2$), 3.54 (s, 2H, 2,6-H in pipridine ring), 2.20 (s,3H, N-CH_3); 2.41(s,2H,3,5-H in pipridine ring), 2.20 (s,3H, N-CH_3); Elemental analysis: Calculated for $C_{21}H_{22}N_4O_3S$:C, 61.39; H,5.35;N,13.64;S,7.79; Found: C,61.28; H,5.32; N,13.61; S,7.75%.

3-{[2,6-Bis(4-methoxy phenyl)-1-methylpiperidin-4-ylidene]amino}-2-thioxo-imidazolidin-4-one **(3d)**

IR(KBr, cm^{-1}): 3051(NH), 1783(C=O), 1675 (C=N), 1432 (C=S); ^{1}H NMR-(DMSO-d6, δ (ppm)): δ10.67(s,1H NH), 7.44-7.21(m,4H,Ar-H), 4.12(s, 3H,Ar-OCH_3), 4.07(s,2H, CH_2), 3.54 (s, 2H, 2,6-H in pipridine ring), 2.48 (s,3H, N-CH_3); 2.41(s,2H,3,5-H in pipridinering); Elemental analysis: Calculated for $C_{23}H_{26}N_6O_3S$:C,62.93; H,5.92;N,19.15;S,7.29; Found: C,62.90; H,5.93; N,19.12; S,7.25%.

3-{[2,6-Bis(4-nitro phenyl)-1-methylpiperidin-4-ylidene]amino}-2-thioxo-imidazolidin-4-one **(3e)**

IR(KBr , cm^{-1}): 3014(NH),1742(C=O), 1674(C=N),1553(Ar-NO_2),1438(C=S); ^{1}H NMR -(DMSO-d6, δ (ppm)): δ10.29(s,1H NH), 7.28-6.97(m,4H,Ar-H), 3.97(s,2H, $5CH_2$), 2.14 (s,3H, N-CH_3); 2.41(s,2H,3,5-H in pipridine ring), 3.54 (s, 2H, 2,6-H in pipridine ring); Elemental analysis: Calculated for $C_{21}H_{20}N_6O_5S$:C,53.79; H,4.26;N,17.93;S,6.83; Found: C, 53.75; H, 4.21; N, 17.90 S, 6.80%.

3-{[2,6-Bis(4-dimethylamine phenyl)-1-methylpiperidin-4-ylidene]amino}-2-thioxo-imidazolidin-4-one **(3f)**

IR(KBr,cm^{-1}): 3045(NH), 1736(C=O), 1652 (C=N), 1437(C=S); ^{1}H NMR(DMSO-d6, δ(ppm)): 10.69(s,1H NH), 7.42-7.30(m,4H,Ar-H), 3.72(s,2H, $5CH_2$), 3.54 (s, 2H, 2,6-H in pipridine ring), 2.79(s,6H,Ar-N(CH_3)$_2$), 2.41(s,2H,3,5-H in pipridine ring) , 2.28 (s,3H, N-CH_3); Elemental analysis: Calculated for $C_{25}H_{32}N_6OS$: C,64.56; H,6.88;N,18.07;S,6.88; Found: C, 64.54; H, 6.85; N, 18.02; S, 6.82%.

Results and Discussion

The IR spectrum of compounds **(2a-2f)**, show an absorption band at 3488-3432, 1676-1616, 1138-1127 cm^{-1} due to corresponding to the NH_2, C=N and C=O groups respectively. The IR spectrum

of compounds **(3a-3f)**, show an absorption band at 3014-3084, 1783-1722, 1652-1675 and 1432-1520 cm^{-1} due to corresponding to the NH, C=O, C=N and C=S groups respectively.

The ^1H NMR spectrum of compounds (**2a-2f)**, show a singlet at δ 11.30-10.91 ppm attributable to C=N-NH protons. The compounds **(3a-3f)** have very important signal at δ 10.69-10.11 and 4.27 -3.97 ppm corresponding to the NH, CH_2 N protons respectively.

Antimicrobial activity

In vitro antibacterial screening

The compounds **(3a-3f)** were evaluated for their *in vitro* antibacterial activity against *Staphylococcus aureus* (MTCC-96), *Enterococcus faecalis* (MTCC-439), *Escherchia coli* (MTCC-739), *Pseudomonas aeruginosa* (MTCC-2453) by agar dilution method[18,19] was performed using Mueller –Hinton agar (Hi-Media) medium. Each compound was tested at a concentration of 100 µg/mL in DMSO. The zone of inhibition was measured after 24 h incubation at 37 ºC. Inhibition zone of the compounds clearly indicate the **(3f)** compound was highly active against *S.aureus*. The results are presented in Table 2. Inhibition of the compounds **(3a-3f)** were clearly observed in NO_2 substituted at benzaldehyde containing compound **(3e)** showed maximum antibacterial potency. Compound (**3c)** has nearly activity against *Staphylococcus aureus*, *Enterococcus faecalis* and compound (**3d)** has less activity compared with norfloxacin against all bacterial organisms.

Table 2. Antibacterial activity of the compounds **(3a-3f)**

Compounds	*S. aureus*	*E.faecalis*	*E. coli*	*P. aeruginosa*
3a	20	14	16	13
3b	19	12	20	16
3c	21	13	20	8
3d	12	-	18	-
3e	22	13	21	15
3f	23	8	13	10
Standard	22	15	24	21

Zone of the inhibition measured in (mm). Indicate bacteria's are resistant to the compound 10 µg/mL Norfloxacin is used as the standard drug 100 µg/mL

In vitro antifungal screening

The compounds **(3a-3f)** were evaluated for their *in vitro* antifungal activity against *Aspergillus niger*, *Candia albicans, Aspergillus fumigatus* and *Cryptococcus neoformans* using an agar dilution method[20] with sabouraud's dextrose agar (Hi-Media). Each compound was tested at a concentration of 100 µg/mL in DMSO. The zone of inhibition was measured after incubating at 37 °C for 24 h**.** It was evident from screening results that only 4-OH phenyl substituted compound **(3c)** has remarkably enhanced the antifungal action. When compared to ketoconazole, compound **(3b)** is moderately active against all antifungal organisms**.** Compounds **(3a, 3d, 3e and 3f)** are less active against all antifungal organisms. All compounds are compared with ketoconazole the results are presented in Table 3.

Conclusion

The series of compound **(3a-3f)** 2-thioxo-imidazolidin-4-one derivatives were synthesized and screened for their antimicrobial activity. The compound **(3f)** has highly anti bacterial activity against *S.aureus* compared with norfloxacin standard and compound **(3c)** has highly antifungal activity aganist *A. niger* and *A.fumigates* compared with a ketoconazole standard.

Table 3. Antifungal activity of the compounds **(3a-3f)**

Compounds	*A. niger,*	*C.albicans*	*A .fumigatus*	*Cr.neoformans*
3a	12	10	12	13
3b	19	19	14	16
3c	24	23	18	14
3d	13	12	16	14
3e	8	10	12	8
3f	12	8	-	-
Standard	22	24	16	18

Zone of the inhibition measured in (mm). Indicate fun gals are resistant to the compound 100 µg/mL Ketoconazole is used as the standard 100 µg/mL

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