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Spectral characterization of novel *bis* heterocycles comprising both piperidine and thiohydantoin nuclei

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Abstract A series of *bis* heterocycles comprising both piperidine and thiohydantoin nuclei namely 3-(3-alkyl-2,6-diarylpiperin-4-ylidene)-2-thioxoimidazolidin-4-ones is synthesized and characterized by melting point, elemental analysis, MS, FT–IR, one-dimensional NMR (^{1}H, D_2O exchanged ^{1}H and ^{13}C), two-dimensional HOMOCOSY, and NOESY spectroscopic data.

Keywords 3-alkyl-2 · 6-diarylpiperin-4-ones · 3-alkyl-2 · 6-diarylpiperin-4-one thiosemicarbazones · 3-(3-alkyl-2, 6-diarylpiperin-4-ylidene)-2-thioxoimidazolidin-4-ones · HOMOCOSY · NOESY

Introduction

Baliah et al. [1, 2] have reviewed the importance of piperidin-4-ones as intermediates in the synthesis of several physiologically active compounds. Similarly, Lijinsky and Taylor [3] have found that the presence of substituents at both the α-positions to that of N in piperidin-4-one is important to exert marked biological properties. Bioactive heterocyclic ring systems having 2,6-diaryl-piperidine-4-one nucleus with different substituents at 3- and 5-positions of the ring have aroused great interest due to their wide variety of biological properties [4–11]. Thiohydantoins are sulfur analogs of hydantoins with one or both carbonyl groups replaced by thiocarbonyl groups [12]. Among the known thiohydantoins, 2-thiohydantoins were most notably known due of their wide applications as hypolipidemic [13], anticarcinogenic [14], antimutagenic [15], antithyroidal [16] antiviral (e.g., against herpes simplex virus, HSV) [17], human immunodeficiency

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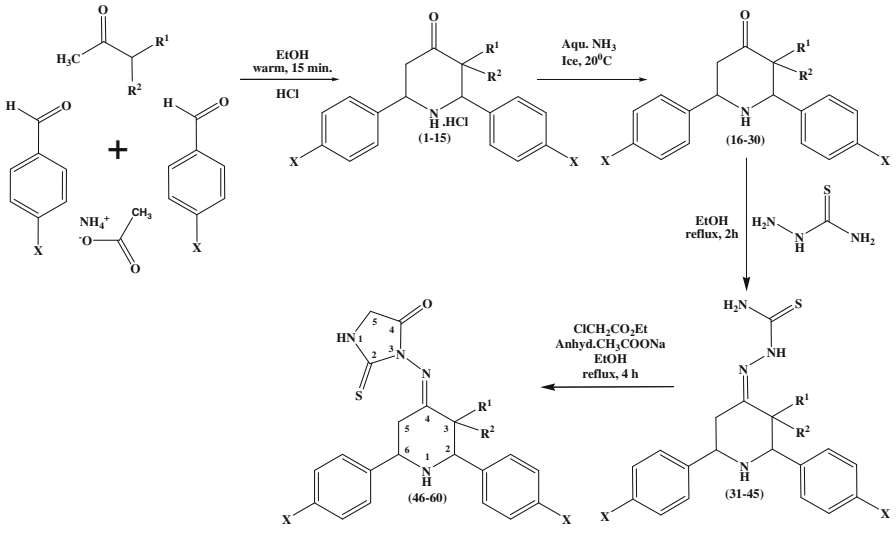
virus (HIV) [18], and tuberculosis [19]), antimicrobial (antifungal and antibacterial) [20], anti-ulcer and anti-inflammatory agents [21], as well as pesticides [22]. Additionally, 2-thiohydantoins have been used as reference standards for the development of C-terminal protein sequencing [23], as reagents for the development of dyes [24] and in textile printing, metal cation complexation, and polymerization catalysis [25]. In connection with our earlier work and as part of our ongoing research programme on synthesis of structurally diverse potent biologically active heterocycles [26–33], we planned to design a system that combines both bioactive piperidine and thiohydantoin components together to give a new series of *bis* heterocycles comprising both piperidine and thiohydantoin nuclei and their structural elucidation using spectroscopic techniques were discussed.

Results and discussion

In the present work, a new series of potent antimicrobial agents [34], *bis* heterocycles comprising both piperidine and thiohydantoin nuclei namely 3-(3-alkyl-2,6-diarylpiperin-4-ylidene)-2-thioxoimidazolidin-4-ones **46–60** was synthesized by the treatment of the respective thiosemicarbazones **31–45** with chloroethyl acetate and anhydrous sodium acetate in refluxing ethanol for 4 h. The synthetic route for the formation of compounds **46–60** is given in Scheme 1. The physical and analytical data are given in Table 1. The structures of all the synthesized compounds **46–60** are discussed with the help of m.p.'s, elemental analysis, FT–IR, MS, and one-dimensional NMR (^{1}H, ^{13}C) spectra.



Scheme 1 Synthetic route for the formation of 3-(3-substituted-2,6-diaryl-piperidin-4-ylideneamino)-2-thioxoimidazolidin-4-ones

Table 1 Physical and analytical characteristics of compounds **46-60**

Compounds	R^1	R^2	X	Yield (%)	m.p. (°C)	Elemental analysis (%)			m/z $(M+1)^{+\bullet}$ Molecular formula
						C Found (calculated)	H Found (calculated)	N Found (calculated)	
46	H	H	H	74	108	65.87	5.50	15.33	365
						(65.91)	(5.53)	(15.37)	$C_{20}H_{20}N_4OS$
47	H	H	F	78	103	59.97	4.50	13.96	400
						(59.99)	(4.53)	(13.99)	$C_{20}H_{18}F_2N_4OS$
48	H	H	Cl	67	167	55.41	4.15	12.91	432
						(55.43)	(4.19)	(12.93)	$C_{20}H_{18}Cl_2N_4OS$
49	H	H	OCH_3	72	158	62.20	5.66	13.17	424
						(62.24)	(5.70)	(13.20)	$C_{22}H_{24}N_4O_3S$
50	H	H	CH_3	70	142	67.30	6.15	14.23	392
						(67.32)	(6.16)	(14.27)	$C_{22}H_{24}N_4OS$
51	CH_3	H	H	75	171	66.60	5.82	14.76	378
						(66.64)	(5.86)	(14.80)	$C_{21}H_{22}N_4OS$
52	CH_3	H	F	78	182	60.81	4.82	13.48	414
						(60.85)	(4.86)	(13.52)	$C_{21}H_{20}F_2N_4OS$
53	CH_3	H	Cl	75	187	56.35	4.47	12.49	446
						(56.38)	(4.51)	(12.52)	$C_{21}H_{20}Cl_2N_4OS$
54	CH_3	H	OCH_3	72	182	62.95	5.95	12.68	438
						(62.99)	(5.98)	(12.78)	$C_{23}H_{26}N_4O_3S$
55	CH_3	H	CH_3	70	136	67.92	6.41	13.75	406
						(67.95)	(6.45)	(13.78)	$C_{23}H_{26}N_4OS$
56	CH_3	CH_3	H	76	148	67.28	6.14	14.21	392
						(67.32)	(6.16)	(14.27)	$C_{22}H_{24}N_4OS$
57	CH_3	CH_3	F	77	134	61.64	5.11	13.03	428
						(61.67)	(5.17)	(13.08)	$C_{22}H_{22}F_2N_4OS$
58	CH_3	CH_3	Cl	75	176	57.21	4.78	12.11	460
						(57.27)	(4.81)	(12.14)	$C_{22}H_{22}Cl_2N_4OS$
59	CH_3	CH_3	OCH_3	72	132	63.65	6.52	12.33	452
						(63.69)	(6.24)	(12.38)	$C_{24}H_{28}N_4O_3S$
60	CH_3	CH_3	CH_3	71	124	68.52	6.68	13.28	420
						(68.54)	(6.71)	(13.32)	$C_{24}H_{28}N_4OS$

In order to investigate the spectral assignments, compound **46** was chosen as a representative compound. IR spectrum of 3-(2,6-diphenylpiperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one **46** shows characteristic frequencies at 1,728, 1,215 cm^{-1} are due to the presence of the carbonyl group and the thiocarbonyl group. Absorption frequencies are in the region of 3,300–3,426 cm^{-1}, suggesting the presence of –NH groups. In addition, the absorption frequency at 1,635 cm^{-1} was due to C=N stretching vibration. Mass spectrum of compound **46** shows a molecular

ion peak at *m/z* 365.25 ($M^{+\bullet}+1$), which is consistent with the proposed molecular formula of **46**. The elemental analysis (C*cal* 65.87, C*obs* 65.91; H*cal* 5.53, H*obs* 5.50; N*cal* 15.37, N*obs* 15.33) are consistent with the proposed molecular formula ($C_{20}H_{20}N_4OS$) of **46**.

The assignments of signals in the ^{1}H NMR spectrum of compound **46** have been done based on total widths and spin multiplicities. There are two double doublet centered at 3.90 ppm and 4.17 ppm. Each signal corresponds to one proton. These two signals are due to the benzylic protons H_{2a} and H_{6a} (3.90/H_{2a}, 4.17/H_{6a}). Two coupling constants are extracted from the double doublet at 3.88–3.92 and the values are 11.76 Hz and 3.08 Hz. The lower value is due to the vicinal coupling of $J_{2a,3e}$ and the higher value corresponds to *trans* coupling of $J_{2a,3a}$. The two coupling constants are calculated from the double doublet at 4.15–4.19 ppm and the values are 11.88 Hz and 3.20 Hz. The lower value is due to the vicinal coupling of $J_{6a,5e}$ and the higher value is due to the *trans* coupling of $J_{6a,5a.}$ The double doublets observed at 2.41–2.37 ppm and 3.62–3.66 ppm are due to the equatorial methylenic protons H_{3e} and H_{5e}, respectively. A double doublet is expected for axial methylenic proton H_{5a}, but a multiplet is obtained at 2.43–2.52 ppm corresponds to H_{5a} proton. A double doublet at 2.37–2.41 ppm has two coupling constants and the coupling values are 2.96 Hz and 13.64 Hz. The lower value corresponds to vicinal coupling of $J_{3e,2a}$ and the higher value corresponds to geminal coupling of $J_{3e,3a}$. The two coupling constant values are extracted from the double doublet at 3.62–3.66 ppm. The lower value 2.96 Hz is due to vicinal coupling of $J_{5e,\ 6a}$ and the higher value 13.52 Hz is due to geminal coupling of $J_{5e,\ 5a}$. A sharp singlet observed at 3.80 ppm is due to the methylene protons of imidazolidine moiety. A double doublet is expected for axial methylenic proton H_{3a}, but a multiplet is obtained at 1.97–2.05 ppm corresponds to H_{3a} proton. The NH proton of piperidone moiety observed as a broad singlet at 2.83 ppm. The broad signal at 11.78 ppm is due to the NH proton of imidazolidine moiety. A multiplet appeared in the range of 7.23–7.50 ppm is due to aromatic ring protons at C-2 and C-6 positions.

In the ^{13}C NMR spectrum of **46**, resonances in the aliphatic range of 29.62, 37.30, 60.23, 61.12, and 43.64 ppm have been observed. The signals appearing at 29.62 and 37.30 ppm are due to C-3 and C-5 carbons, respectively. Among the signals at 60.23 ppm and 61.12 ppm for the benzylic carbons, the one at 60.23 ppm is due to C-2 and the signal at 61.12 ppm is due to C-6 carbon. 13C resonance at 43.64 ppm must be due to the methylene carbon of imidazolidine moiety (at C-5). The signal at 163.19 ppm is conveniently assigned to C=N carbon of piperidone moiety. The 13C resonance of carbonyl carbon and thiocarbonyl carbon at C-4 and C-2 of imidazolidine moiety appeared at 167.63 and 173.87 ppm (C=S/173.87; C=O/167.63), respectively. The *ipso* carbons appeared at 144.01 and 144.16 ppm. The signals appearing in the region of 126.51–128.15 are due to the aromatic carbons in two phenyl rings at C-2 and C-6 positions. All the above-mentioned assignments are further confirmed by HOMOCOSY and NOESY spectra.

In the HOMOCOSY spectrum of **46**, the signal at 3.90 ppm shows cross peaks with the signals at 2.01 ppm and 2.39 ppm. The signal at 4.17 ppm shows cross peaks with the signals at 2.48 and 3.64 ppm. Consequently, the signal at 3.90 ppm must be due to the benzylic proton H_{2a}. Since this can have coupling only with the

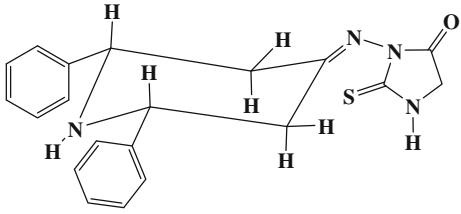


Fig. 1 3-(2,6-diphenylpiperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one **46** (Chair conformation)

H_{3e} and H_{3a} protons, the two signals at 2.01 ppm and 2.39 ppm are assigned to H_{3a} and H_{3e} proton, respectively. The signal at 4.17 ppm must be due to the benzylic proton H_{6a}, since this can have coupling with H_{5a} and H_{3e} protons. The two signals at 2.48 and 3.64 ppm are assigned to H_{5a} and H_{5e} protons, respectively. The individual assignments can be made by using its NOESY spectrum.

In the NOESY spectrum of **46**, the signals of benzylic proton (H_{2a},H_{6a}) have strong nOe with signals of methylene protons (H_{3e} and H_{5a} proton). Hence the signal at 3.90 ppm has strong nOe with the signal at 2.39 ppm. The signal at 4.17 ppm has strong nOe with the signal 2.48 ppm. From this, it is concluded that the signal at 3.90 ppm must be due to the benzylic proton H_{2a}. The signal at 4.17 ppm must be due to the benzylic proton H_{6a}. The signals at 2.39 ppm and 2.48 ppm must be due to H_{3e} and H_{5a} proton, respectively. Moreover, an interesting observation from the NOESY spectrum of compound **46** is that signal at 11.78 ppm has strong nOe with the signal at 2.01 ppm. Hence, the signal at 11.78 must be due to NH proton of imidazolidine moiety and the signal at 2.01 ppm must be due to H_{3a} proton. The signal at 3.80 ppm has strong nOe with the signal at 2.01 ppm and 2.39 ppm. The signal at 3.80 ppm must be due to methylene proton of imidazolidine moiety. The signal at 2.39 ppm is due to H_{3e} proton. From the NOESY spectrum, we concluded that imidazolidine moiety of 46 present towards the H_{3a} and H_{3e} protons of piperidone moiety of **46**. From the view of nOes of –NH and CH_2 protons of imidazolidine moiety, the –NH signal (11.78 ppm) and CH2 signal (3.80 ppm) must be very close to methylene protons of piperidone moiety at C-3 position. Therefore, with reference to HOMOCOSY and NOESY correlations in compound **46**, the tentative assignments made for its ring and substituent protons are confirmed. It has been well proven that mostly and favorably 2,6-diarylpiperidin-4-one ring adopts chair conformation with all its substituents at equatorial disposition [1]. Moreover, equatorial disposition of the phenyl group at C-2 and C-6 makes the chair conformation more rigid, thereby preventing interconversion of one chair into another. Hence, based on the obtained chemical shifts and coupling constant values, normal chair conformation (Fig. 1) is proposed for compound **46**.

Two-dimensional HOMOCOSY and NOESY NMR spectral assignments for the synthesized 3-(3,3-dimethyl-2,6-diphenylpiperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one 56

Two singlets of two methyl protons at 0.97 and 1.19 ppm had a cross peak with the signal at 3.72 ppm. Hence, the signal at 3.72 ppm must be due to the H_{2a} proton. The double doublet at 4.15 ppm had cross peaks with the signal at 2.54 ppm and

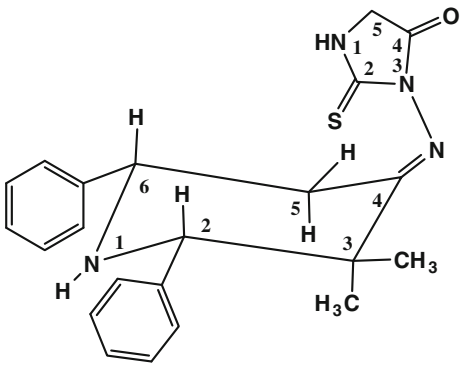


Fig. 2 Chair conformation Compound **56**

vice versa. This mutual correlation clearly showed that the signal at 4.15 ppm was due to the H_{6a} proton and the signal at 2.54 ppm must be due to the H_{5e} proton. The individual assignments can be made using its NOESY spectrum.

From the NOESY spectrum of compound **56,** it was interesting to note that the two methyl protons at 0.97 ppm and 1.19 ppm had nOe with protons at 3.72 ppm. This shows that the signal at 3.72 ppm should be due to the H_{2a} proton. The double doublet at 4.15 ppm had strong nOe with the proton at 2.54 ppm. This revealed that the signal at 2.54 ppm must be due to the H_{5e} proton. In addition, the signal at 3.91 ppm had strong nOe with the proton signal at 2.54 ppm and weak nOe with the proton signal at 3.21 ppm. Hence, the signal at 3.91 ppm must be due to methylene proton of imidazolidine moiety. The signal at 3.21 ppm must be due to the H_{5a} proton. NH proton signal (11.80 ppm) of imidazolidine moiety had strong nOe with methine proton signals at 2.54 and 3.21 ppm. This showed clearly that the NH and CH_2 protons of imidazolidine moiety must be very close to the methylene protons at C-5 position of piperidone moiety. Therefore, with reference to HOMOCOSY and NOESY correlations in compound **46,** the assignments made for its ring and substituent protons were confirmed. Hence, based on the obtained chemical shifts and coupling constant values, normal chair conformation (Fig. 2) was proposed for compound **56**.

Experimental

General remarks

We used TLC to assess the reactions and the purity of the products. All the reported melting points were taken in open capillaries and were uncorrected. IR spectra were recorded in KBr (pellet forms) on a Thermo Nicolet-Avatar–330 FT-IR spectrophotometer and noteworthy absorption values (cm^{-1}) alone are listed. One-dimensional ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker AMX 400 NMR spectrometer using DMSO-*d* as solvent. Two-dimensional HOMOCOSY and NOESY spectra were recorded at 500 MHz on a Bruker DRX 500 NMR spectrometer using DMSO-*d* as solvent. The electron

spray impact (ESI) positive (+ve) mass (MS) spectra were recorded on a Bruker Daltonics LC–MS spectrometer. Satisfactory microanalysis was obtained on a Carlo Erba 1106 CHN analyzer.

By adopting the literature precedent [2], 3-alkyl-2,6-diarylpiperidin-4-ones **16–30** and their thiosemicarbazones **31–45** were prepared.

Typical procedure for the synthesis of 3-(2,6-diphenylpiperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one 46

To a well-stirred solution of 2,6-diphenylpiperidin-4-one thiosemicarbazone **31** (5 mmol) and anhydrous sodium acetate (5 mmol) in 30 ml of ethanol, chloroethyl acetate (5 mmol) in 15 ml of ethanol was added drop-wise through the addition funnel for about 10 min. The reaction mixture was then refluxed further for 4 h. After completion of the reaction, the reaction mixture was poured into ice cold water and the solid mass was collected and recrystallized twice from ethanol to yield compound **46**. IR (KBr) (cm^{-1}): 3400, 3306, 3060, 3029, 2980, 2896, 2797, 1728, 1635, 1598, 1215, 701, 758, 1041; ^{1}H NMR (δ ppm): 1.97–2.05 (*m*, 1H, H_{3a}), 2.37–2.41 (*dd*, 1H, H_{3e}, $J_{3e,3a}$ = 13.64 Hz, $J_{3e,2a}$ = 2.96 Hz); 2.43–2.52 (*m*, 1H, H_{5a}), 2.83 (*s*, 1H, NH of piperidine), 3.62–3.66 (*dd*, H_{5e}, $J_{5e,5a}$ = 2.96 Hz, $J_{5e,6a}$ = 13.52 Hz), 3.80 (*s,* 2H, CH_2 of imidazolidine), 3.88–3.92 (*dd*, 1H, H_{2a}, $J_{2a,3e}$ = 3.08 Hz, $J_{2a,3a}$ = 11.76 Hz), 4.15–4.19 (*dd*, 1H, H_{6a}, $J_{6a,5e}$ = 3.20 Hz, $J_{6a,5a}$ = 11.88 Hz), 7.23–7.50 (*m*, 10H, Ar–H's), 11.78 (*s*, NH of imidazolidine); in the D_2O exchanged ^{1}H NMR spectrum, two peaks at 2.83 ppm and 11.78 ppm, which resonances are due to NH of piperidine and imidazolidine, respectively, disappeared; ^{13}C NMR (δ ppm): 29.6 C-3, 37.3 C-5, 43.6 CH_2 of imidazolidine, 60.2 C-2, 61.1 C-6, 126.5–128.1 Ar–C's, 144.0, 144.1 *ipso*-C, 163.1 C=N, 167.6 C=O, 173.8 C=S.

Compounds **47–60** were synthesized in a similar fashion.

*3-(2,6-bis(4-fluorophenyl)piperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one **47***

IR (KBr) (cm^{-1}): 3430, 3317, 3076, 3030, 2956, 2924, 2854, 1717, 1641, 1604, 1092, 835, 733, 519; ^{1}H NMR (δ ppm): 1.98–2.05 (*m*, 1H, H_{3a}), 2.39–2.44 (*dd*, 1H, H_{3e}, $J_{3e,3a}$ = 13.52 Hz, $J_{3e,2a}$ =2.96 Hz); 2.44–2.49 (*m*, 1H, H_{5a}), 2.86 (*s*, 1H, NH of piperidine), 3.51–3.55 (*dd*, 1H, H_{5e}, $J_{5e,5a}$ = 2.96 Hz, $J_{5e,6a}$ =13.40 Hz), 3.77 (*s*, 2H, CH_2 of imidazolidine), 3.85–3.89 (*dd*, 1H, H_{2a}, $J_{2a,3e}$ = 2.96 Hz, $J_{2a,3a}$ = 11.76 Hz), 4.16–4.20 (*dd*, 1H, H_{6a}, $J_{6a,5e}$ = 3.32 Hz, $J_{6a,5a}$ = 11.96 Hz), 7.18–7.37 (*m*, 8H, Ar–H's), 11.81 (*s*, 1H, NH of imidazolidine); ^{13}C NMR (δ ppm): 30.1 C-3, 38.2 C-5, 43.4 CH_2 of imidazolidine, 61.8 C-2, 62.9 C-6, 114.3–142.6 Ar–C's, 142.9, 159.6 *ipso*-C, 162.0 C=N, 166.7 C=O, 173.7 C=S.

*3-(2,6-bis(4-chlorophenyl)piperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one **48***

IR (KBr) (cm^{-1}): 3400, 3309, 3065, 3032, 2978, 2923, 2852, 1724, 1628, 1595, 1195, 1014, 826, 722, 676, 634; ^{1}H NMR (δ ppm): 1.98–2.05 (*m*, 1H, H_{3a}),

2.38–2.42 (*dd*, 1H, H_{3e}, $J_{3e,3a}$ =13.52 Hz, $J_{3e,2a}$ = 2.98 Hz); 2.43–2.48 (*m*, 1H, H_{5a}), 2.79 (*s*, 1H, NH of piperidine), 3.52–3.56 (*dd*, 1H, H_{5e}, $J_{5e,5a}$ = 3.08 Hz, $J_{5e,6a}$ = 13.42 Hz), 3.78 (*s*, 2H, CH_2 of imidazolidine), 3.87–3.91 (*dd*, 1H, H_{2a}, $J_{2a,3e}$ = 3.08 Hz, $J_{2a,3a}$ = 11.76 Hz), 4.15–4.19 (*dd*, 1H, H_{6a}, $J_{6a,5e}$ = 3.14 Hz, $J_{6a,5a}$ = 11.70 Hz), 7.30–7.58 (*m*, 8H, Ar–H's), 11.79 (*s*, 1H, NH of imidazolidine); ^{13}C NMR (δ ppm): 30.0 C-3, 38.8 C-5, 43.5 CH_2 of imidazolidine, 60.9 C-2, 61.2 C-6, 126.7–140.4 Ar–C's, 144.7, 145.3 *ipso*-C, 163.1 C=N, 166.8 C=O, 173.5 C=S.

3-(2,6-bis(4-methoxyphenyl)piperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one ***49***

IR (KBr) (cm^{-1}): 3400, 3306, 3065, 3020, 2962, 2924, 2853, 1728, 1630, 1601, 1251, 1031, 830, 749, 527; ^{1}H NMR (δ ppm): 1.97–2.04 (*m*, 1H, H_{3a}), 2.35–2.39 (*dd*, 1H, H_{3e}, $J_{3e,3a}$ = 13.52 Hz, $J_{3e,2a}$ = 2.96 Hz); 2.43–2.50 (*m*, 1H, H_{5a}), 2.89 (*s*, 1H, NH of piperidine), 3.48–3.53 (*dd*, 1H, H_{5e}, $J_{5e,5a}$ = 3.16 Hz, $J_{5e,6a}$ = 13.40 Hz), 3.59 (*s*, 6H, OCH_3 at the phenyl rings), 3.72 (*s*, 2H, CH_2 of imidazolidine), 3.87–3.91 (*dd*, 1H, H_{2a}, $J_{2a,3e}$ = 3.16 Hz, $J_{2a,3a}$ = 11.68 Hz), 4.13–4.17 (*dd*, 1H, H_{6a}, $J_{6a,5e}$ = 3.08 Hz, $J_{6a,5a}$ = 11.68 Hz), 7.19–7.42 (*m*, 8H, Ar–H's), 11.78 (*s*, 1H, NH of imidazolidine); ^{13}C NMR (δ ppm): 30.1 C-3, 37.0 C-5, 43.1 CH_2 of imidazolidine, 54.2 –OCH_3 at the phenyl rings, 60.2 C-2, 61.1 C-6, 127.3–144.0 Ar–C's, 144.1, 159.9, *ipso*-C, 162.3 C=N, 167.7 C=O, 173.8 C=S.

3-(2,6-dip-tolylpiperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one ***50***

IR (KBr) (cm^{-1}): 3403, 3308, 3063, 3018, 2960, 2921, 2850, 1727, 1631, 1600, 1249, 1023, 828, 742, 524; ^{1}H NMR (δ ppm): 1.97–2.05 (*m*, 1H, H_{3a}), 2.18 (*s*, 6H, CH_3 at the phenyl rings), 2.34–2.38 (*dd*, 1H, H_{3e}, $J_{3e,3a}$ = 13.50 Hz, $J_{3e,2a}$ = 2.97 Hz); 2.45–2.52 (*m*, 1H, H_{5a}), 2.84 (*s*, 1H, NH of piperidine), 3.49–3.52 (*dd*, 1H, H_{5e}, $J_{5e,5a}$ = 3.14 Hz, $J_{5e,6a}$ = 13.42 Hz), 3.76 (*s*, 2H, CH_2 of imidazolidine), 3.88–3.90 (*dd*, 1H, H_{2a}, $J_{2a,3e}$ = 3.14 Hz, $J_{2a,3a}$ = 11.66 Hz), 4.14–4.18 (*dd*, 1H, H_{6a}, $J_{6a,5e}$ = 3.07 Hz, $J_{6a,5a}$ = 11.66 Hz), 7.17–7.39 (*m*, 8H, Ar–H's), 11.76 (*s*, 1H, NH of imidazolidine); ^{13}C NMR (δ ppm): 22.2 –CH_3 at the phenyl rings, 30.3 C-3, 37.2 C-5, 43.3 CH_2 of imidazolidine, 60.1 C-2, 61.0 C-6, 127.1–143.9 Ar–C's, 144.1, 147.2, *ipso*-C, 162.8 C=N, 167.5 C=O, 173.5 C=S.

3-(3-methyl-2,6-diphenylpiperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one ***51***

IR (KBr) (cm^{-1}): 3420, 3311, 3063, 3031, 2978, 2933, 1713, 1634, 1600, 1232, 755, 702; ^{1}H NMR (δ ppm): 0.77–0.79 (*d*, 3H, CH_3 at C-3, $J_{CH3,3a}$ = 6.45 Hz), 2.05–2.11 (*m*, 1H, H_{5a}), 2.55–2.59 (*m*, 1H, H_{3a}), the signal for 1H, NH of piperidine merged with water peak, 2.69–2.79 (*m*, 1H, H_{5e}), 3.45–3.48 (*d*, 1H, H_{2a}, $J_{2a,3a}$ = 9.98 Hz), 3.54–3.58 (*dd*, 1H, H_{6a}, $J_{6a,5e}$ = 2.50 Hz, $J_{6a,5a}$ = 12.95 Hz), 3.76 (*s,* 2H, CH_2 of imidazolidine), 7.24–7.47 (*m*, 10H, Ar–H's), 11.71 (*s*, NH of imidazolidine); ^{13}C NMR (δ ppm): 11.9 –CH_3 at C-3, 32.5 C-5, 37.3 C-3, 44.4 CH_2 of imidazolidine, 60.4 C-6, 68.7 C-2, 126.5–128.1 Ar–C's, 144.9, 144.0, *ipso*-C, 163.1 C=N, 167.5 C=O, 173.8 C=S.

3-(2,6-bis(4-fluorophenyl)-3-methylpiperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one ***52***

IR (KBr) (cm^{-1}): 3412, 3304, 3071, 3030, 2985, 2931, 2869, 1717, 1635, 1597, 1221, 1030, 535, 836, 766; ^{1}H NMR (δ ppm): 0.78–0.80 (*d*, 3H, CH_3 at C-3, $J_{CH3,3a}$ = 6.58 Hz), 2.07–2.09 (*m*, 1H, H_{5a}), 2.54–2.59 (*m*, 1H, H_{3a}), the signal for 1H, NH of piperidine merged with water peak, 2.67–2.79 (*m*, 1H, H_{5e}), 3.46–3.48 (*d*, 1H, H_{2a}, $J_{2a,3a}$ = 10.61 Hz), 3.54–3.58 (*dd*, 1H, H_{6a}, $J_{6a,5e}$ = 2.46 Hz, $J_{6a,5a}$ = 12.46 Hz), 3.78 (*s,* 2H, CH_2 of imidazolidine), 7.12–7.51 (*m*, 8H, Ar–H's), 11.72 (*s*, NH of imidazolidine); ^{13}C NMR (δ ppm): 11.8 –CH_3 at C-3, 32.5 C-5, 37.2 C-3, 44.5 CH_2 of imidazolidine, 61.0 C-6, 67.7 C-2, 114.6–160.7 Ar–C's, 162.4, 162.5, *ipso*-C, 163.4 C=N, 169.2 C=O, 173.9 C=S.

3-(2,6-bis(4-chlorophenyl)-3-methylpiperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one ***53***

IR (KBr) (cm^{-1}): 3429, 3282, 3070, 3032, 2985, 2931, 1718, 1625, 1592, 1210, 1017, 897, 823; ^{1}H NMR (δ ppm): 0.77–0.79 (*d*, 3H, CH_3 at C-3, $J_{CH3,3a}$ = 6.57 Hz), 2.01–2.07 (*m*, 1H, H_{5a}), 2.53–2.57 (*m*, 1H, H_{3a}), the signal for 1H, NH of piperidine merged with water peak, 2.68–2.80 (*m*, 1H, H_{5e}), 3.46–3.48 (*d*, 1H, H_{2a}, $J_{2a,3a}$ = 10.82 Hz), 3.54–3.58 (*dd*, 1H, H_{6a}, $J_{6a,5e}$ =2.44 Hz, $J_{6a,5a}$ = 12.45 Hz), 3.90 (*s,* 2H, CH_2 of imidazolidine), 7.37–7.49 (*m*, 8H, Ar–H's), 11.74 (*s*, NH of imidazolidine); ^{13}C NMR (δ ppm): 11.8 –CH_3 at C-3, 31.8 C-5, 36.8 C-3, 44.3 CH_2 of imidazolidine, 61.0 C-6, 67.7 C-2, 128.0–131.7 Ar–C's, 141.8, 142.8 *ipso*-C, 160.8 C=N, 166.9 C=O, 171.5 C=S.

3-(2,6-bis(4-methoxyphenyl)-3-methylpiperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one ***54***

IR (KBr) (cm^{-1}): 3426, 3286, 3080, 2981, 2927, 1722, 1627, 1594, 1200, 1025, 897, 812, 744, 527; ^{1}H NMR (δ ppm): 0.78–0.80 (*d*, 3H, CH_3 at C-3, $J_{CH3,3a}$ = 6.45 Hz), 2.04–2.08 (*m*, 1H, H_{5a}), 2.55–2.59 (*m*, 1H, H_{3a}), the signal for 1H, NH of piperidine merged with water peak, 2.69–2.79 (*m*, 1H, H_{5e}), 3.46–3.48 (*d*, 1H, H_{2a}, $J_{2a,3a}$ = 10.72 Hz), 3.54–3.58 (*dd*, 1H, H_{6a}, $J_{6a,5e}$ = 2.56 Hz, $J_{6a,5a}$ = 12.87 Hz), 3.28 (*s*, 6H, OCH_3 at the phenyl rings), 3.78 (*s,* 2H, CH_2 of imidazolidine), 6.86–7.36 (*m*, 8H, Ar–H's), 11.82 (*s*, NH of imidazolidine); ^{13}C NMR (δ ppm): 11.9 –CH_3 at C-3, 32.5 C-5, 37.3 C-3, 44.6 CH_2 of imidazolidine, 54.9 –OCH_3 at the phenyl rings, 60.5 C-6, 68.1 C-2, 127.6–158.4 Ar–C's, 160.5, 163.1 *ipso*-C, 166.9 C=N, 169.7 C=O, 173.9 C=S.

3-(3-methyl-2,6-dip-tolylpiperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one ***55***

IR (KBr) (cm^{-1}): 3441, 3312, 3229, 3060, 2971, 2931, 1727, 1634, 1607, 1247, 1031, 542, 833, 753; ^{1}H NMR (δ ppm): 0.78–0.80 (*d*, 3H, CH_3 at C-3, $J_{CH3,3a}$ = 6.38 Hz), 2.01–2.07 (*m*, 1H, H_{5a}), 2.19 (*s*, 6H, CH_3 at the phenyl rings), 2.54–2.58 (*m*, 1H, H_{3a}), the signal for 1H, NH of piperidine merged with water peak, 2.69–2.79 (*m*, 1H, H_{5e}), 3.44–3.47 (*d*, 1H, H_{2a}, $J_{2a,3a}$ = 10.85 Hz), 3.54–3.58 (*dd*, 1H, H_{6a}, $J_{6a,5e}$ = 2.55 Hz,

$J_{6a,5a}$ = 12.89 Hz), 3.89 (*s,* 2H, CH_2 of imidazolidine), 7.10–7.33 (*m*, 8H, Ar–H's), 11.75 (*s*, NH of imidazolidine); ^{13}C NMR (δ ppm): 11.9 –CH_3 at C-3, 20.6 –CH_3 at the phenyl rings, 32.5 C-5, 37.0 C-3, 44.5 CH_2 of imidazolidine, 60.2 C-6, 68.4 C-2, 126.3–136.2 Ar–C's, 139.9, 140.9 *ipso*-C, 166.8 C=N, 169.6 C=O, 171.5 C=S.

3-(3,3-dimethyl-2,6-diphenylpiperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one ***56***

IR (KBr) (cm^{-1}): 3496, 3307, 3060, 3027, 2973, 2926, 2852, 1719, 1625, 1206, 1028, 758, 703; ^{1}H NMR (δ ppm): 0.97 (*s*, 3H, CH_3 at C-4), 1.19 (*s*, 3H, CH_3 at C-4), 2.52–2.56 (*dd*, 1H, H_{5e}, $J_{5e,5a}$ = 13.96 Hz, $J_{5e,6a}$ = 3.64 Hz), 2.75 (*s*, 1H, H_1); 3.18–3.25 (*m*, 1H, H_5a), 3.72 (*s*, 1H, H_{2a}), 3.91 (*s*, 2H, CH_2 of imidazolidine), 4.13–4.18 (*dd*, 1H, H_{6a}, $J_{6a,5e}$ = 3.64 Hz, $J_{6a,5a}$ = 14.44 Hz), 7.21–7.53 (*m*, 10H, H_{arom}), 11.80 (*s*, 1H, NH of imidazolidine); ^{13}C NMR (δ ppm): 20.4, 20.8 two CH_3 at C-4, 43.5 CH_2 of imidazolidine, 46.4 C-5, 48.8 C-3, 61.0 C-6, 69.8 C-2, 126.5–140.3 Arom-C's, 143.5, 144.2 *ipso* C's, 163.1 C=N, 167.3 C=O, 173.8 C=S.

3-(2,6-bis(4-fluorophenyl)-3,3-dimethylpiperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one ***57***

IR (KBr) (cm^{-1}): 3480, 3309, 3147, 3072, 2975, 2923, 1719, 1628, 1222, 836, 702, 656, 525; ^{1}H NMR (δ ppm): 0.96 (*s*, 3H, CH_3 at C-4), 1.18 (*s*, 3H, CH_3 at C-4), 2.53–2.58 (*dd*, 1H, H_{5e}, $J_{5e,5a}$ = 13.80 Hz, $J_{5e,6a}$ = 3.60 Hz), 2.80 (*s*, 1H, H_1); 3.19–3.27 (*m*, 1H, H_5a), 3.78 (*s*, 1H, H_{2a}), 3.92 (*s*, 2H, CH_2 of imidazolidine), 4.15–4.19 (*dd*, 1H, H_{6a}, $J_{6a,5e}$ = 3.60 Hz, $J_{6a,5a}$ = 14.44 Hz), 7.30–7.59 (*m*, 8H, H_{arom}), 11.79 (*s*, 1H, NH of imidazolidine); ^{13}C NMR (δ ppm): 20.3, 20.7 two CH_3 at C-4, 43.5 CH_2 of imidazolidine, 46.4 C-5, 48.8 C-3, 61.0 C-6, 69.9 C-2, 113.9–140.4 Arom-C's, 160.4, 160.6 *ipso* C's, 163.3 C=N, 166.9 C=O, 173.8 C=S.

3-(2,6-bis(4-chlorophenyl)-3,3-dimethylpiperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one ***58***

IR (KBr) (cm^{-1}): 3400, 3306, 3093, 3030, 2974, 2928, 2852, 1722, 1630, 1203, 1015, 827, 766, 523; ^{1}H NMR (δ ppm): 0.98 (*s*, 3H, CH_3 at C-4), 1.28 (*s*, 3H, CH_3 at C-4), 2.54-2.58 (*dd*, 1H, H_{5e}, $J_{5e,5a}$ = 13.92 Hz, $J_{5e,6a}$ = 3.64 Hz), 2.81 (*s*, 1H, H_1); 3.18–3.25 (*m*, 1H, H_5a), 3.77 (*s*, 1H, H_{2a}), 3.94 (*s*, 2H, CH_2 of imidazolidine), 4.16–4.21 (*dd*, 1H, H_{6a}, $J_{6a,5e}$ = 3.64 Hz, $J_{6a,5a}$ = 14.48 Hz), 7.37–7.89 (*m*, 8H, H_{arom}), 11.85 (*s*, 1H, NH of imidazolidine); ^{13}C NMR (δ ppm): 20.2, 20.8 two CH_3 at C-4, 43.4 CH_2 of imidazolidine, 46.0 C-5, 48.5 C-3, 61.4 C-6, 68.6 C-2, 113.4–139.2 Arom-C's, 158.8, 159.2 *ipso* C's, 163.2 C=N, 165.9 C=O, 173.5 C=S.

3-(2,6-bis(4-methoxyphenyl)-3,3-dimethylpiperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one ***59***

IR (KBr) (cm^{-1}): 3448, 3317, 3098, 3027, 2976, 2924, 2861, 1702, 1626, 1211, 1028, 818, 747, 519; ^{1}H NMR (δ ppm): 0.98 (*s*, 3H, CH_3 at C-4), 1.16 (*s*, 3H, CH_3 at

C-4), 2.54–2.58 (*dd*, 1H, H_{5e}, $J_{5e,5a}$ = 13.94 Hz, $J_{5e,6a}$ = 3.66 Hz), 2.76 (*s*, 1H, H_1); 3.19-3.25 (*m*, 1H, H_5a), 3.56 (*s*, 6H, OCH_3 at the phenyl rings),3.79 (*s*, 1H, H_{2a}), 3.91 (*s*, 2H, CH_2 of imidazolidine), 4.17–4.22 (*dd*, 1H, H_{6a}, $J_{6a,5e}$ = 3.66 Hz, $J_{6a,5a}$ = 14.50 Hz), 7.19–7.76 (*m*, 8H, H_{arom}), 11.79 (*s*, 1H, NH of imidazolidine); ^{13}C NMR (δ ppm): 20.3, 20.7 two CH_3 at C-4, 43.5 CH_2 of imidazolidine, 46.5 C-5, 48.9 C-3, 54.0 –OCH_3 at the phenyl rings, 61.0 C-6, 68.2 C-2, 126.4–141.1 Arom-C's, 141.3, 142.2 *ipso* C's, 163.1 C=N, 166.8 C=O, 173.8 C=S.

3-(3,3-dimethyl-2,6-dip-tolylpiperidin-4-ylideneamino)-2-thioxoimidazolidin-4-one ***60***

IR (KBr) (cm^{-1}): 3450, 3318, 3093, 3022, 2974, 2925, 2864, 1705, 1628, 1209, 1023, 817, 749, 516; ^{1}H NMR (δ ppm): 0.99 (*s*, 3H, CH_3 at C-4), 1.18 (*s*, 3H, CH_3 at C-4), 2.24 (*s*, 6H, CH_3 of phenyl rings), 2.55–2.59 (*dd*, 1H, H_{5e}, $J_{5e,5a}$ = 13.96 Hz, $J_{5e,6a}$ = 3.68 Hz), 2.77 (*s*, 1H, H_1); 3.19–3.26 (*m*, 1H, H_5a), 3.80 (*s*, 1H, H_{2a}), 3.92 (*s*, 2H, CH_2 of imidazolidine), 4.18–4.23 (*dd*, 1H, H_{6a}, $J_{6a,5e}$ = 3.68 Hz, $J_{6a,5a}$ = 14.52 Hz), 7.21–7.80 (*m*, 8H, H_{arom}), 11.80 (*s*, 1H, NH of imidazolidine); ^{13}C NMR (δ ppm): 20.3, 20.7 two CH_3 at C-4, 22.7 (–CH_3 of phenyl rings), 43.5 CH_2 of imidazolidine, 46.5 C-5, 48.9 C-3, 61.0 C-6, 68.2 C-2, 126.4–141.1 Arom-C's, 141.3, 142.2 *ipso* C's, 163.1 C=N, 166.8 C=O, 173.8 C=S.

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