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ORIGINAL PAPER

Synthesis, complete NMR spectral assignments, and antifungal screening of new 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one oxime derivatives

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Abstract A series of differently substituted 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one oximes have been synthesized and their ^{1}H and ^{13}C NMR chemical shifts have been unambiguously assigned using H,H-COSY, NOESY, HSQC, and HMBC spectral data. On the basis of the NMR studies, irrespective of the nature and position of the substituents, all reported compounds exist in twin-chair conformation with equatorial disposition of the phenyl groups at C-2 and C-4 of the 3-azabicyclononane moiety. Among the synthesized oxime derivatives, compounds with halo-substituents at *ortho*/*para* positions of the phenyl showed good antifungal profile against all tested organisms.

Keywords 2,4-Diaryl-3-azabicyclo[3.3.1]nonan-9-one oxime · *O*-Methyloxime · N-Methylation · 2D NMR · Conformation · Antifungal activity

Introduction

The broad spectrum of biological activity, for example antifungal, antibacterial, analgesic, narcotic antagonism, antitussive, anti-inflammatory, sedative, antipyretic, antiphologistic, calcium antagonist, and hypotensive, and local anaesthetic activity of 3-azabicyclononanes has occupied much attention in the recent past [1–6]. The 3-azabicyclononane pharmacophore is present in numerous naturally abundant diterpenoid/norditerpenoid alkaloids and is responsible for their wide variety of pharmacological actions. Because the biological activity depends mainly on the stereochemistry of the molecules, it is very important to establish the configuration and conformation of the synthesized molecules; in this respect, NMR spectroscopy is a versatile tool for structural and stereochemical analysis of organic compounds [7–11].

Stereochemical investigations have been carried out on a few synthesized 3-azabicyclononane moieties with different substituents [12–19]. However, there are lacunae in the synthesis, spectral assignments, and stereochemistry of the 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one oximes and oxime ethers. Hence, in this study, a series of 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one oximes, 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one oxime, and 2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one *O*-methyloxime were synthesized with various electron donating/withdrawing substituents at *ortho*/*meta*/*para* positions of the phenyl groups at C-2 and C-4. Further, because of the antifungal efficacy of oxime derivatives of nitrogen heterocycles [20–22], the synthesized oxime derivatives **17–33** were screened for their antifungal activity against a panel of fungal strains.

Results and discussion

Synthesis

According to Scheme 1, all the compounds were synthesized, and characterized by use of their analytical and spectral data (IR, ^{1}H NMR, ^{13}C NMR, and MS). For the

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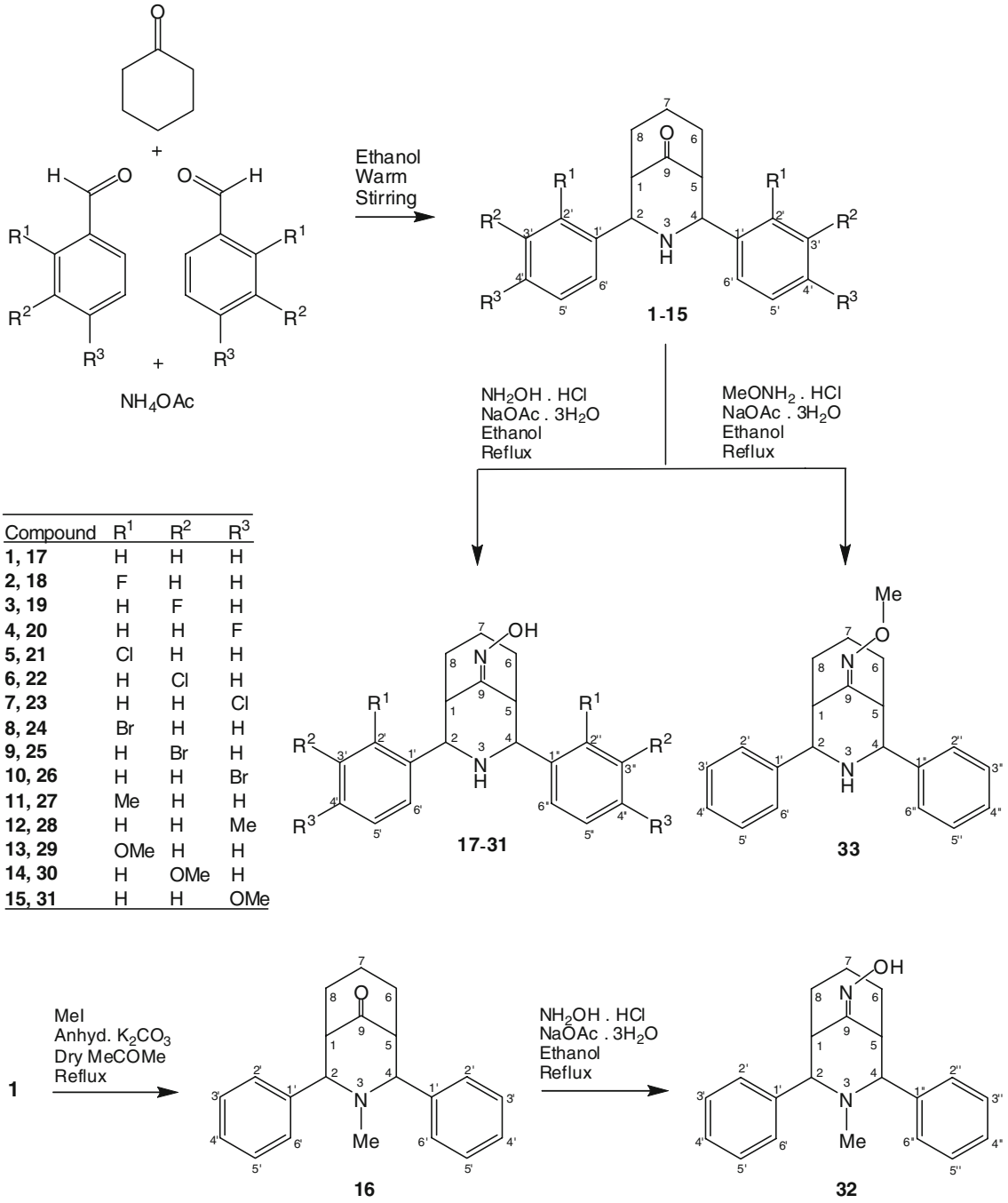

Compound	R^1	R^2	R^3
1, 17	H	H	H
2, 18	F	H	H
3, 19	H	F	H
4, 20	H	H	F
5, 21	Cl	H	H
6, 22	H	Cl	H
7, 23	H	H	Cl
8, 24	Br	H	H
9, 25	H	Br	H
10, 26	H	H	Br
11, 27	Me	H	H
12, 28	H	H	Me
13, 29	OMe	H	H
14, 30	H	OMe	H
15, 31	H	H	OMe

Scheme 1

representative compound **19**, H,H-COSY, NOESY, HSQC, and HMBC were recorded to assign all the signals unambiguously, and to establish the stereochemistry. The H,H-COSY/NOESY and HSQC/HMBC correlations are reproduced in Tables 1 and 2. Most of the synthesized 3-azabicyclic ketones **1–16** are reported for the first time, and for a few of the previously reported compounds complete ^{1}H and ^{13}C spectral data are not available. Hence, the complete ^{1}H and ^{13}C spectral assignments of **1–16** were carried out; for unambiguous assignment, H,H-COSY and HSQC have been recorded for compounds **5**, **6**, **8**, **9**, **11**, **13**, and **14**.

Assignment of proton chemical shifts and stereochemistry

In **19**, the broad singlet at 8.55 ppm (1H) has neither H,H-correlation nor NOE with any other protons and it has no

Table 1 Correlations in the H,H-COSY and NOESY spectra of **19**

Signal (δ (ppm))	Correlations in H,H-COSY	Correlations in NOESY
8.55 (br s, 1H, N–OH)	–	–
7.34 (m, 6H, H-2′/2″, H-5′/5″, H-6′/6″)	7.00	4.40 (s), 4.33 (s), 3.58, 2.72, 2.56 (w), 1.81–1.71
7.00 (t, 2H, H-4′/4″)	7.34	–
4.40 (s, 1H, H-2a)	2.56, 1.60–1.49 (w)	7.34[a] (s), 4.33, 2.56 (s), 1.81–1.71 (w)
4.33 (s, 1H, H-4a)	3.58, 1.60–1.49 (w)	7.34[b] (s), 4.40, 3.58 (s), 1.81–1.71 (w)
3.58 (br s, 1H, H-5)	4.33 (s), 2.56 (w), 1.81–1.71[c] (w), 1.60–1.49[d]	7.34[b] (s), 4.33 (s), 1.81–1.71, 1.60–1.49
2.72 (m, 1H, H-7a)	1.81–1.71, 1.41	7.34[a] (w), 1.41
2.56 (br s, 1H, H-1)	4.40 (s), 3.58 (w), 1.81–1.71[e] (w), 1.69–1.49[f]	7.34[a] (w), 4.40 (s), 1.60–1.49 (w)
1.81–1.71 (m, 3H, H-6e, H-8e, NH)	3.58 (w), 2.72, 1.60–1.49	7.34[a] (w),1.60–1.49
1.60–1.49 (m, 2H, H-6a, H-8a)	4.40 (w), 4.33 (w), 3.58, 2.56, 1.81–1.72, 1.41 (w)	1.81–1.71
1.41 (quin, 1H, H-7e)	2.72	2.72 (s)

s, strong correlation; w, weak correlation

[a] Correlation with the lower frequency region of the multiplet (H-2′/2″)

[b] Correlation with the higher frequency region of the multiplet (H-5′/5″, H-6′/6″)

[c] Correlation with the lower frequency region of the multiplet (H-6e)

[d] Correlation with the lower frequency region of the multiplet (H-6a)

[e] Correlation with the higher frequency region of the multiplet (H-8e)

[f] Strong correlation with the higher frequency region of the multiplet (H-8a) and weak correlation with H-6a

Table 2 Correlations in the HSQC and HMBC spectra of **19**

Signal (δ (ppm))	Correlations in HSQC	Correlations in HMBC
8.55 (br s, 1H, N–OH)	–	–
7.34 (m, 6H, H-2′/2″, H-5′/5″, H-6′/6″)	130.14[a], 130.07[a], 122.77, 122.64, 114.18[b], 114.07[b], 113.95[b], 113.85[b]	164.40, 161.96 (α, β, γ), 145.07, 145.01 (α, β), 122.27, 122.64 (α), 114.48–114.27 (α, β)
7.00 (t, 2H, H-4′/4″)	114.48, 114.27	164.40, 161.96 (α),122.27, 122.64 (β), 114.18–113.85 (β)
4.40 (s, 1H, H-2a)	65.07	145.13, 145.07, 145.01 (α), 122.27, 122.64 (β), 114.18–113.85 (β), 43.10 (β), 28.16 (β)
4.33 (s, 1H, H-4a)	63.10	145.13, 145.07, 145.01 (α), 122.27, 122.64 (β), 114.18–113.85 (β), 36.27 (α), 26.66 (β)
3.58 (br s, 1H, H-5)	36.27	–
2.72 (m, 1H, H-7a)	21.61	28.16 (α), 26.66 (α)
2.56 (br s, 1H, H-1)	43.10	–
1.81–1.71 (m, 3H, H-6e, H-8e, NH)	28.16[a], 26.66[b]	165.00 (β), 43.10 (α), 36.27 (α), 28.16 (β), 26.66 (β), 21.61 (α)
1.60–1.49 (m, 2H, H-6a, H-8a)	28.16[a], 26.66[b]	65.07 (β), 63.10 (β), 43.10 (α), 36.27 (α), 21.61 (α)
1.41 (quin, 1H, H-7e)	21.61	43.10 (β), 36.27 (β), 28.16 (α), 26.66 (α)

α: α-Correlation; β: β-correlation; γ: γ-correlation

[a] Correlation with the higher frequency region of the multiplet

[b] Correlation with the lower frequency region of the multiplet

correlation with any carbon signals. Also, it disappeared in the D_2O exchange ^1H NMR spectrum; consequently, the broad singlet is unequivocally assigned to the oxime proton. According to the D_2O exchange NMR, the multiplet at 1.81–1.71 ppm corresponding to three protons is reduced to two protons, because of D_2O exchange, which indicates that the NH proton resonance also overlapped the multiplet.

There are two broad singlets at 3.58 (1H) and 2.56 (1H) ppm with the half-width $W_{1/2}$ of 11.36 and 11.60 Hz, respectively. The broad singlet nature and half-width values suggest that they are due to the bridgehead protons H-1 and H-5. Further, the observed weak correlation between 3.58 and 2.56 ppm strongly implies that the correlation is due to long-range coupling between the

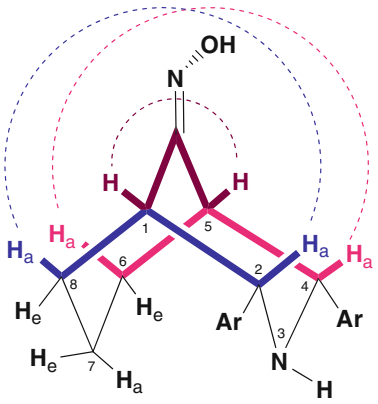

Fig. 1 Correlations between the protons that are in "W" arrangements, from the H,H-COSY spectrum of **19**

bridgehead protons because of the "W" arrangement of those protons (Fig. 1).

The difference between H-1 and H-5, i.e., $\Delta\delta$, is 1.02 ppm whereas in the corresponding bicyclic ketone, the bridgehead protons H-1 and H-5 appear together at 2.49 ppm (2H) as a broad singlet with a $W_{1/2}$ of 11.54 Hz. Because of allylic interaction ($A^{1,3}$) between the N–O and C(5)-H bonds (Fig. 2), the H-5 proton is deshielded, the deshielding magnitude is quite large (1.09 ppm). But there is no change in another bridgehead proton H-1, except for slight deshielding of 0.07 ppm. The positions, appearance, spectral width, and correlations strongly suggest that the signals at 3.58 and 2.56 ppm are due to the bridgehead protons H-5 (*syn* α) and H-1 (*anti* α). Though the bridgehead protons appear as two separate signals, both are broad singlets and their half-widths are also similar to that of its precursor. Hence, this suggests that the bicyclic oxime also adopts the twin-chair conformation.

The signals at 4.40 and 4.33 ppm are due to benzylic protons and they only have correlations with the bridgehead protons H-1 and H-5; hence, we can unequivocally assign the

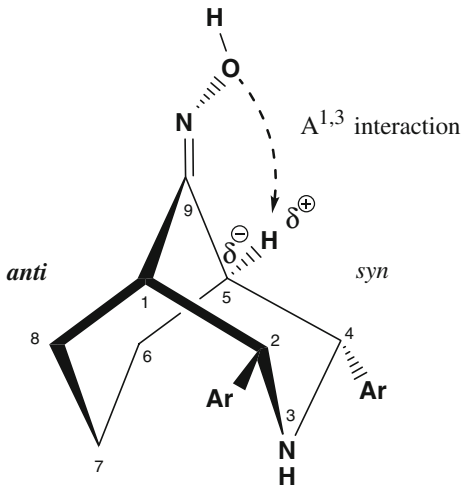

Fig. 2 Interaction between the N–O and C(5)-H bonds

signals to H-2 and H-4. Further, they have close proximity (NOE) with each other, hence indicating their orientation as axial. Except for axial orientation of the protons at C-2 and C-4, there is otherwise no possibility of NOE between them in the chair conformation. As a consequence of the observed NOE, we can conclude that the orientation of the phenyl groups on the same carbons should be equatorial. Moreover, 1,3-diequatorial orientation of the bulkier substituents is more favorable in the chair conformation. Further, the observed strong NOE of the *ortho* protons with H-7a/H-8e/H-6e also supports the equatorial orientation of the phenyl groups and the twin-chair conformation.

In addition to the "W" correlation, both H-1 and H-5 have correlations with the multiplets at 1.81–1.71 (3H, due to overlapped NH) and 1.60–1.49 (2H) ppm. It is usually observed that the chemical shift difference of protons in the cyclohexane chair conformation is positive ($\Delta\delta_{eq,ax} = \delta_{eq} - \delta_{ax}$, is $\sim$0.3 ppm), owing to the leading hyperconjugation of the C–C single bond [23]. The multiplets with average difference of 0.22 ppm suggest that they are due to C-6 and C-8 protons. Specifically, the lower and higher frequency regions of both multiplets have correlations with H-5 and H-1. Hence, the lower and higher-frequency regions of the multiplets are assigned to H-6e/6a and H-8e/8a. Further, the assignments and chair conformation of the cyclohexane part are confirmed by their NOE (Fig. 3).

A strong correlation between the proton resonances at 2.72 (m, 1H) and 1.41 (quin, 1H) ppm clearly confirms that the signals are due to C-7 protons, and the multiplet only correlates with H-6a/H-8a and H-6e/H-8e. The NOE between the multiplet and the aryl protons supports attribution of the multiplet to H-7a (endocyclic proton, which is spatially very close to the *ortho* protons), hence, the 1.41 ppm quintet is attributed to H-7e. But the difference

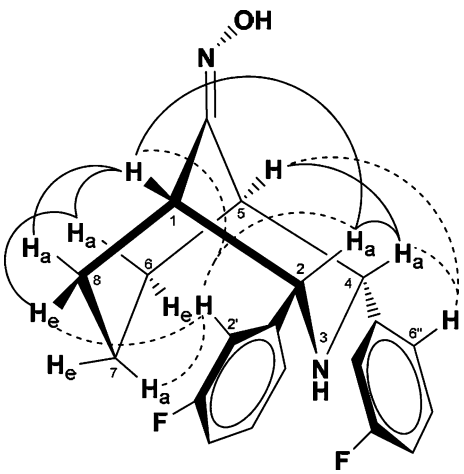

Fig. 3 Twin-chair conformation with equatorial orientation of the phenyl groups at C-2 and C-4; supported by the NOE observed in the NOESY spectrum of **19**. For clarity, the NOE between the *ortho* and ring protons is shown by *dashed lines*

between H-7a and H-7e is quite large (1.31 ppm), moreover, in contrast with other cyclohexane ring protons, H-7a appears at almost twice the chemical shift magnitude of H-7e. This is neither in accordance with the hyperconjugation effect of the C–C single bond of the cyclohexane in the chair conformation nor only because of the magnetic anisotropy of the nitrogen lone pair [12, 13]. Hence, it should be mainly because of the steric interaction implied by the endocyclic bond. Thus the steric interaction polarizes C–H(7a) bond and, as a result, H-7a acquires positive charge and C-7 acquires negative charge. Hence, H-7a is deshielded and C-7 is shielded; as a consequence, H-7e also shielded by ~0.4 ppm more than the other equatorial protons H-6e/H-8e.

Of the two sets of aryl signals, a multiplet centered at 7.34 (6H) and a triplet at 7.00 (2H) ppm, the triplet has no NOE with any of the protons in the molecule whereas it has H,H-correlation with the higher-frequency region of the multiplet. Hence the triplet is assigned to *para* protons (H-4′/4″). The lower-frequency region of the multiplet has NOE with H-1/H-2a/H-7a/H-8e whereas the higher-frequency region has NOE with H-4a/H-5. Accordingly, the lower and higher-frequency regions are assigned to the *ortho* protons H-2′/2″ and H-6′/6″, respectively.

Overall, the chemical shifts, splitting pattern, H,H-correlation, and NOE suggest that the compound is in twin-chair conformation with equatorial orientation of the phenyl groups, as depicted in Fig. 3. Further, the twin-chair conformation is evidenced by the $W_{1/2}$ of H-1 and H-5; these values are in good agreement with the corresponding ketone and with literature values for the flattened twin-chair conformation of similar bicycles. If one of the cycles adopts a boat conformation, the resonances for the bridgehead protons H-1 and H-5 should be apparent doublets with coupling constants of about 18 Hz [12]. In addition, the observed long-range couplings between H-2a and H-8a and between H-4a and H-6a are due to the "W" arrangement of those protons and this is only possible when the bicycle is in the twin-chair conformation (Fig. 1). Apart from this, the correlations support the axial orientation of the protons at C-2 and C-4.

The order of chemical shift magnitude of the bicyclic protons of **19** is H-2a > H-4a > H-5 > H-7a > H-1 > H-8e > H-6e > H-8a > H-6a > H-7e. Similarly, ^{1}H NMR signals of other bicyclic oximes **17–31** and oxime ether **33** are assigned and summarized in the Experimental section whereas in the *N*-Me derivative **32**, because of the introduction of electron-donating methyl group on the heterocyclic ring nitrogen of **17**, both the benzylic protons H-2a and H-4a are shielded by 0.81 and 0.80 ppm but the methinic protons H-1 and H-5 are shielded by 0.13 and 0.14 ppm, respectively. Also, the benzylic carbons (α to the ring nitrogen) are deshielded by 10.03 and 10.12 ppm but the methinic and *ipso* carbons (β to the ring nitrogen)/C-9 (γ to the ring nitrogen) are respectively deshielded and shielded by around 1 ppm. In **32**, vicinal coupling constants $J_{2a,1} = 3.28$ and $J_{4a,5} = 2.92$ Hz are appreciably higher than corresponding non-*N*-Me oxime **17**; for **17**, vicinal coupling constants are 1.44 and 1.84 Hz. The higher magnitude of coupling constants for **32** is because of the lower electronegativity of the NMe group than that of NH. Besides, owing to the higher population of *N*-Me equatorial conformations [13], the interaction between the nitrogen lone pair and the *ortho* protons will be increased and, as a consequence, one set of the *ortho* protons is deshielded by 0.24 ppm relative to its non-*N*-Me analogue and appears as a broad singlet at 7.83 ppm (2H).

Careful analysis of the ^{1}H NMR data reveals that the benzylic and bridgehead protons of the *ortho* substituted compounds are more deshielded than their *meta*/*para* analogues. The deshielding of H-1/H-5 and H-2a/H-4a is, respectively, about 0.1–0.3 and 0.2–0.4 ppm for all compounds, except **24**, because of a solvent effect. The maximum deshielding is observed for Cl-substituted compound **21**, because of its higher electronegativity (H-1/H-5 and H-2a/H-4a are 0.33/0.34 and 0.42/0.43 ppm, respectively) and lower for methyl substituted compound **27** (H-1/H-5 and H-2a/H-4a are 0.08/0.09 and 0.18/0.19 ppm, respectively) than for their respective *para* analogues **23** and **28**. Moreover in *ortho* substituted compounds, the *ortho* protons, i.e., H-6′/66″, are experiencing unusual deshielding and appear as a separate signal at around 8 ppm compared to the same *ortho* protons in **17**. The deshielding is not only due to the electronic effect of the *ortho* substituent, because such deshielding is not observed in *para*/*meta* compounds; moreover, the effect is more for halogen substituents, where the halogen atom prefers to be syn to the benzylic proton to avoid dipole–dipole interaction between C–X and C–N bonds. As an outcome, the *ortho* protons H-6′/6″ are deshielded by the nitrogen lone pair.

In **24**, the oxime and NH protons appear at abnormally higher frequencies than in the rest of the compounds. This deshielding is because of the effect of DMSO solvent. The oxygen atom in the sulfoxide may be interacting with the protons in the oxime and NH. Owing to this, the oxime and NH protons are deshielded by 2 ppm compared with analogous compounds.

Assignment of carbon chemical shifts

All the carbon signals of the representative compound **19** were unambiguously assigned using HSQC and HMBC spectra. The carbon signals from 21.61 to 65.07 ppm have cross peaks with the bicyclic ring protons; carbon signals between 114.27 and 130.14 ppm show cross peaks with

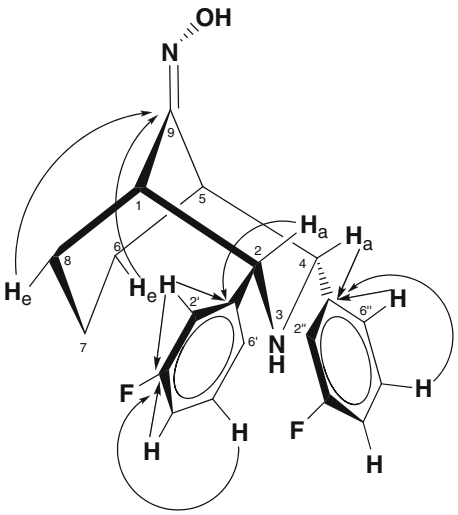

Fig. 4 Typical connectivities found in the HMBC spectrum of **19**

phenyl protons and, hence, are assigned unambiguously. However, signals beyond 130.14 ppm have no correlations in the HSQC spectrum and, hence, they were assigned with the help of HMBC correlations (Fig. 4). The carbon signals of all other oximes/oxime ether are assigned by comparison with oxime **19** and summarized in the Experimental section. The HSQC and HMBC correlations are reproduced in Table 2.

Effect of oximation/oximination

Because C=N is less polar than C=O, the electronegativity of the C=N group of our synthesized oximes/oxime ether **17–33** must be less than that of the C=O group of their precursors **1–16**. In general, because of the decrease in the electronegativity of a particular group in the ring skeleton, the α-carbons are shielded and the *β*- and *γ*-carbons are deshielded [24]. Accordingly in oximes **17–32** and oxime ether **33**, the α-carbons are shielded. Specifically, in our compounds, the shielding of a *syn* α-carbon is more pronounced (∼17–18 ppm) than that of an *anti* α-carbon (∼10–11 ppm) because of the interaction between N–O and *syn* α C–H bonds (Fig. 2). Owing to this, the *syn* α-proton (H-5) acquires an appreciable positive charge and the C-5 carbon acquires negative charge; hence, the *syn* α-carbon is more shielded than the *anti* α-carbon by ∼7 ppm.

According to the general pattern, in **17–33** the *anti* *β*-carbons are deshielded but the *syn* *β*-carbons are shielded. This contrast is because of the transmittance of excess negative charge from the *syn* α-carbon to the *syn* *β*-carbon. This negative charge results in shielding of the *syn* *β*-carbon, hence this effect prevails over the deshielding produced by the electronegativity effect. For the same reason, the *syn* *γ*-carbon experiences less deshielding than the *anti* *γ*-carbon; however, it is not enough to overcome the deshielding produced by the electronegativity effect. The effects of oximation/oximination on the ring carbons are summarized in Table 3.

As a consequence of the N–O and C(5)-H interaction, the oximation effect is strong fo the α-protons and less for the *β*-protons. Especially, the *syn* α-proton H-5 is deshielded by 1 ppm compared with the corresponding 3-azabicyclo[3.3.1]nonan-9-ones. Furthermore, the difference between α-protons ($\Delta\delta_{5,1}$) is quite large and found to be above 1 ppm whereas the difference between *β*-protons ($\Delta\delta_{2a,4a}$) is only ≤0.1 ppm.

Table 3 ^{13}C chemical shift difference between 3-azabicyclo[3.3.1]nonan-9-ones **1–16** and their corresponding oxime derivatives **17–33** [($\delta_{3\text{-ABN-9-one}} - \delta_{\text{oxime/oxime ether}}$) (ppm)]

Compounds	C-1	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-1′	C-1″
17	10.75	−0.87	1.13	17.50	2.42	−0.48	0.94	51.74	−1.27	−1.22
18	10.66	−0.96	0.86	17.46	2.69	−0.39	1.12	51.92	−1.10	−1.00
19	10.68	−0.88	1.09	17.51	2.48	−0.44	0.98	51.48	−1.25	−1.19
20	10.66	−0.92	1.08	17.50	2.40	−0.48	0.92	51.66	−1.23	−1.16
21	10.66	−1.18	0.62	17.29	2.81	−0.34	1.18	56.34	−1.26	−1.22
22	10.63	−0.96	1.02	17.39	2.47	−0.45	0.98	51.48	−1.25	−1.19
23	10.67	−0.91	1.09	17.54	2.43	−0.46	0.96	51.59	−1.22	−1.17
24[a]	9.98	−1.87	−0.06	16.75	1.84	−1.13	0.34	54.07	−2.89	−2.84
25	10.73	−0.85	1.15	17.31	2.52	−0.38	1.02	54.10	−1.13	−1.09
26	10.64	−0.97	1.05	17.51	2.43	−0.47	0.94	51.52	−1.24	−1.19
27	10.88	−1.27	0.65	17.64	2.68	−0.41	1.16	51.53	−1.30	−1.30
28	10.97	−0.89	1.08	17.75	2.39	−0.37	0.90	51.93	−1.12	−1.05
29	10.66	−0.94	0.83	17.48	2.57	−0.47	1.03	53.70	−1.31	−1.31
30	10.77	−0.89	1.09	17.66	2.38	−0.48	0.91	52.29	−1.33	−1.28
31	10.86	−0.81	1.20	17.60	2.40	−0.49	0.93	52.03	−1.38	−1.33
32	10.70	−1.22	0.69	17.31	2.39	−0.90	0.93	51.75	−1.02	−0.97
33	10.89	−0.82	1.16	16.98	2.37	−0.38	0.90	53.49	−1.30	−1.20

A negative sign denotes deshielding

[a] Deviation is because of the effect of solvent; oxime **24** was recorded in DMSO-d_6 whereas its corresponding ketone **8** was recorded in $CDCl_3$

Table 4 Antifungal profile of the synthesized oxime derivatives by the disc diffusion method

Compound	*Candida albicans*	*Candida*-6	*Candida*-51	*Rhizopus* sp.	*Aspergillus niger*	*Aspergillus flavus*
17	− −	− − −	− − −	− − −	− − −	− − −
18	+ +	+ + +	+ + +	+	+ + +	+ +
19	−	+	+ + +	− −	+ +	−
20	+ +	+ +	+ + +	+	+ + +	+
21	+ + +	+ +	+ + +	+ +	+	+ + +
22	+ +	−	+ +	+	− −	+ +
23	+ + +	+ +	+ +	+ +	+ +	+ + +
24	+	+	+ + +	+	+ +	+
25	−	− −	+	−	−	+
26	+	−	+ +	+	+	+ + +
27	+	+	+	+ +	−	+
28	−	+	−	+	+	+
29	+	+	+	+	+ +	−
30	+	−	− −	+	−	− −
31	+	−	+ +	+	+	−
32	+	− −	− −	+	− −	− − −
33	+	− − −	−	− −	− −	− − −
Ketoconazole	+ + +	+ + +	+ + +	+ +	+ + +	+ + +

Activity index: − − − : ≤3 mm; − − : ≤6 mm; − : ≤10 mm; + : ≤15 mm; + + : ≤20 mm; + + + : ≤25 mm; Ketoconazole has activity in the range 19–23 mm against all strains; DMSO has activity of ≤1 mm for all strains

Antifungal activity

All synthesized oxime derivatives **17–33** were screened for their antifungal activity against a panel of fungal strains—*Candida albicans, Candida*-6*, Candida*-51*, Rhizopus* sp.*, Aspergillus niger,* and *Aspergillus flavus*—by the disc diffusion method using ketoconazole as positive reference standard. Ketoconazole has an inhibition range of 19–23 mm against all treated strains whereas the negative solvent control DMSO has ≤1 mm of inhibition zone. Table 4 provides in vitro antifungal profile of the synthesized oxime derivatives. Compound **17** with unsubstituted phenyl groups on either sides of the secondary amino group has no activity against all strains; however, replacement of H by a methyl group at the ring nitrogen in **32** or the oxime functionality of **33** has improved activity; in particular, their activity is noticeable against *C. albicans*. But more surprisingly, the activity is abruptly increased when incorporating the halogen substituents on the phenyl groups of **17**. Specifically, the fluoro/chloro/bromo substituents at *ortho*/*para* positions (**18**, **20**, **21**, **23**, **24**, and **26**) inhibit the growth of the tested fungal strains significantly.

Conclusion

All compounds (**1–33**) were characterized by use of their IR, mass, and NMR spectral data. Based on the 1D and 2D NMR data, complete proton/carbon chemical shifts and stereochemistry of the synthesized compounds were established. All compounds exist in the twin-chair conformation with equatorial orientation of the aryl substituents at C-2 and C-4. The observed effect on the ring carbons/their associated protons due to oximation and N-methylation are significant, whereas there are no significant changes due to O-methylation.

According to the preliminary screening carried out by the disc diffusion method, oxime derivatives with electron-withdrawing substituents at the *ortho*/*para* position of the phenyl groups at C-2 and C-4 of the 3-azabicyclononane pharmacophore had remarkable activity against all tested fungal strains.

Experimental

All reported melting points were taken in open capillaries. FT-IR spectra were recorded on a Perkin–Elmer Spectrum GX FT-IR spectrophotometer. Electron-impact mass spectra (EIMS) were recorded with a Jeol JMS-700 mass spectrometer, whereas chemical ionization mass spectra (CIMS) were recorded with a Pesciex API 3000 series mass spectrometer. Elemental analyses were performed with an Heraeus Carlo Erba 1108 CHN analyzer; results were found to be in good agreement with the calculated values. Unless otherwise stated, all reagents and solvents used were of high grade and purchased from Aldrich and Alfa Aesar.

Recording of NMR spectra

All 1D NMR spectra of synthesized compounds were recorded on a Jeol JNM ECP 400 NMR spectrometer at 294 K. The ^{1}H and ^{13}C NMR spectra were measured from 0.03 and 0.05 M solutions, respectively, in $CDCl_3$ with TMS as internal reference in 5 mm NMR tubes for all compounds except **24**, which was recorded in DMSO-d_6 because of its insolubility in $CDCl_3$. The pulse conditions were as follows: ^{1}H NMR spectra: SF 399.78 MHz, AQ 2.73 s, NS 32, DS 0, SW 5,998.8 Hz, pulse 4.65 μs, angle 45°, width 9.3 μs, DR 0.366 Hz, RD 5 s, RG 13, data points 16,384, pre scan delay 1 s; ^{13}C NMR spectra: SF 100.52 MHz, AQ 1.25 s, NS 250, DS 4, SW 26,178.01 Hz, Pulse 3.13 μs, angle 30°, width 9.4 μs, DR 0.798 Hz, RD 1 s, RG 25, data points 32,768, pre scan delay 1 s.

All 2D NMR spectra were recorded on a Jeol JNM ECP 400 NMR spectrometer at 294 K using 0.05 M solutions in $CDCl_3$ with TMS in a 5 mm NMR tube. The pulse conditions were as follows: SF of protons and carbons are 399.78 and 100.52 MHz for all experiments; H,H-COSY: Spectral width of 3,815.3 Hz was used in both dimensions and the acquisition data points were 1,024 × 256, NS 60, AQ 0.26 s (X), 67.09 ms (Y), P1, P2 90°, RD 1 s, RG 14, G. selection 1:1, G. shape sine, G. type 2, DR 3.72 (X), 14.90 Hz (Y), DS 4 (X), 0 (Y), pre scan delay 0.1 s; NOESY: Spectral width of 3,815.3 Hz was used in both dimensions and the number of data points were 1,024 × 73, mixing time 700 ms, NS 16, AQ 0.26 s (X), 33.54 ms (Y), RD 7 s, RG 11, G. shape sine, G. type 2, DR 3.72 (X), 52.26 Hz (Y), DS 4 (X), 0 (Y), pre scan delay 1 s; HSQC: Spectral width of 3,815.3 Hz in X and 18,181.8 Hz in Y was used. The experiment was optimized for C–H coupling of 140.0 Hz. Acquisition data size was 1,024 points, and the number of increments for evolution was 512. The number of scans per increment was 4, with a 2.0 s delay between transients, AQ 0.26 (X), 28.16 (Y), DS 4 (X), 0 (Y), RG 31, G. recover 0.1 ms, pre scan delay 0.1 ms; HMBC: The conditions were very similar to those used in the HSQC experiment, and long-range ^{13}C, ^{1}H chemical shift correlations were obtained by optimizing for a coupling of 8 Hz. The acquisition data size was 1,024 points, and the number of increments for evolution was 256. The number of scans per increment was 8 with a 2.0 s delay between transients.

The ^{1}H and ^{13}C chemical shift values are given as δ (ppm) and referred to TMS, via the solvent signals (^{1}H, residual $CHCl_3$ at 7.26 ppm; ^{13}C, $CHCl_3$ at 77.16 ppm). Coupling constants J are reported in Hz. The expansions for the abbreviations used are s: singlet, br s: broad singlet, d: doublet, dd: doublet of doublet, ddd: doublet of doublet of doublet, dt: doublet of triplet, t: triplet, td: triplet of doublet, q: quartet, quin: quintet, m: multiplet, SF: spectrometer frequency, AQ: acquisition time, NS: number of transients, DS: dummy scans, SW: spectral width, DR: digital resolution, RD: relaxation delay, RG: receiver gain.

Synthesis of 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones ***1–15***

A mixture of cyclohexanone, substituted benzaldehyde, and ammonium acetate in 1:2:1.5 ratio in ethanol was very gently warmed and stirred until the completion of the reaction. The crude products formed were filtered and washed with an ethanol–ether (1:5) mixture. Then the bicyclic ketones were recrystallized from ethanol–chloroform–acetone to obtain the pure compounds. In this study, we optimized the reaction conditions to afford higher yields of 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones, absolutely as a single product and as a single isomer, without the chalcone byproduct when using 1.5 equiv of NH_4OAc for 1 equiv cyclohexanone with moderate stirring at ~30–35 °C during the entire course of reaction.

2,4-Diphenyl-3-azabicyclo[3.3.1]nonan-9-one
(**1**, $C_{20}H_{21}NO$)
Yield: 49%; m.p.: 185 °C; IR (KBr): $\bar{\nu} = 3{,}315$ (N–H stretching), 3,057, 3,026, 2,926, 2,857, 2,794 (C–H stretching), 1,708 (C=O stretching), 1,598 (C=C stretching-Ph), 1,491, 1,454, 1,433, 1,373, 1,346, 1,302, 1,283, 1,257, 1,236, 1,165, 1,127, 1,071, 1,024, 1,005, 929, 853, 779, 760, 722, 701, 675 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.54$ (d, $J = 7.32$ Hz, H-2′, H-6′), 7.39 (t, $J = 7.52$ Hz, H-3′, H-5′), 7.30 (t, $J = 7.32$ Hz, H-4′), 4.39 (d, $J = 2.40$ Hz, H-2a, H-4a), 2.89 (m, H-7a), 2.47 (br s, H-1, H-5), 1.93 (dd, $J = 5.86$, 1.46 Hz, H-8e), 1.90 (dd, $J = 5.88$, 1.48 Hz, H-6e), 1.87 (br s, NH), 1.74–1.64 (m, H-6a, H-8a), 1.38 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 217.58$ (C-9), 141.37 (C-1′), 128.61 (C-3′, C-5′), 127.62 (C-4′), 126.96 (C-2′, C-6′), 64.81 (C-2, C-4), 54.05 (C-1, C-5), 29.14 (C-6, C-8), 21.21 (C-7) ppm; MS (EI): $m/z = 291.2$ (M^+).

2,4-Bis(2-fluorophenyl)-3-azabicyclo[3.3.1]nonan-9-one
(**2**, $C_{20}H_{19}F_2NO$)
Yield: 52%; m.p.: 187 °C; IR (KBr): $\bar{\nu} = 3{,}310$ (N–H stretching), 3,068, 3,039, 2,973, 2,933, 2,857, 2,826 (C–H stretching), 1,735, 1,716 (C=O stretching), 1,611, 1,581 (C=C stretching-Ph), 1,486, 1,455, 1,436, 1,380, 1,348, 1,277, 1,255, 1,221, 1,173, 1,130, 1,090, 1,033, 1,003, 979, 948, 927, 893, 881, 845, 814, 763, 751, 735, 687, 666, 573 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.95$ (dt, $J = 7.32$, 1.84 Hz, H-6′), 7.33–7.22 (m, H-4′, H-5′), 7.07 (dd, $J = 8.04$, 1.38 Hz, H-3′), 4.80 (s, H-2a, H-4a), 2.85 (m, H-7a), 2.63 (br s, H-1, H-5), 1.93 (dd, $J = 5.86$, 1.46 Hz, H-8e), 1.89 (dd, $J = 5.86$, 1.46 Hz, H-6e), 1.82–1.72 (m, H-6a, H-8a), 1.65 (br s, NH), 1.39 (quin, H-7e)

ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 216.48$ (C-9), 161.08, 158.62 (C-2′), 128.44, 128.40 (C-4′), 129.09, 129.01 (C-6′), 128.32 (C-1′), 124.22, 124.18 (C-5′), 115.81, 115.60 (C-3′), 57.51 (C-2, C-4), 51.30 (C-1, C-5), 29.82 (C-6, C-8), 21.12 (C-7) ppm; MS (EI): $m/z = 327.14$ (M^+).

2,4-Bis(3-fluorophenyl)-3-azabicyclo[3.3.1]nonan-9-one (**3**, $C_{20}H_{19}F_2NO$)

Yield: 46%; m.p.: 192 °C; IR (KBr): $\bar{\nu} = 3{,}315$ (N–H stretching), 3,073, 2,978, 2,930, 2,910, 2,852, 2,815 (C–H stretching), 1,712 (C=O stretching), 1,614, 1,589 (C=C stretching-Ph), 1,488, 1,462, 1,443, 1,381, 1,344, 1,325, 1,270, 1,255, 1,237, 1,171, 1,141, 1,123, 1,071, 1,024, 1,003, 971, 937, 889, 857, 823, 777, 746, 698, 661, 625, 574 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$–7.27 (m, H-2′, H-5′, H-5′), 7.02 (dt, $J = 7.80$, 1.80 Hz, H-4′), 4.42 (d, $J = 1.60$ Hz, H-2a, H-4a), 2.80 (m, H-7a), 2.49 (br s, H-1, H-5), 1.94 (d, $J = 4.80$ Hz, H-8e, NH), 1.90 (d, $J = 5.20$ Hz, H-6e), 1.78–1.68 (m, H-6a, H-8a), 1.42 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 216.48$ (C-9), 164.40, 161.95 (C-3′), 143.88, 143.82 (C-1′), 130.31, 130.23 (C-5′), 122.58, 122.56 (C-6′), 114.75, 114.54 (C-2′), 114.04, 113.82 (C-4′), 64.19 (C-2, C-4), 53.78 (C-1, C-5), 29.14 (C-6, C-8), 21.17 (C-7) ppm; MS (EI): $m/z = 327.14$ (M^+).

2,4-Bis(4-fluorophenyl)-3-azabicyclo[3.3.1]nonan-9-one (**4**, $C_{20}H_{19}F_2NO$)

Yield: 48%; m.p.: 198 °C; IR (KBr): $\bar{\nu} = 3{,}310$ (N–H stretching), 3,073, 2,973, 2,924, 2,852 (C–H stretching), 1,708 (C=O stretching), 1,603 (C=C stretching-Ph), 1,506, 1,459, 1,440, 1,336, 1,285, 1,220, 1,156, 1,130, 1,092, 1,014, 925, 895, 848, 822, 796, 765, 714, 692, 661 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.51$ (dd, $J = 8.44$, 5.52 Hz, H-2′, H-6′), 7.10 (t, $J = 8.60$ Hz, H-3′, H-5′), 4.40 (d, $J = 2.20$ Hz, H-2a, H-4a), 2.83 (m, H-7a), 2.44 (br s, H-1, H-5), 1.92 (d, $J = 5.48$ Hz, H-8e), 1.88 (d, $J = 5.48$ Hz, H-6e, NH), 1.76–1.67 (m, H-6a, H-8a), 1.41 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 216.90$ (C-9), 163.46, 161.01 (C-4′), 136.94, 136.92 (C-1′), 128.49, 128.41 (C-2′, C-6′), 115.61, 115.40 (C-3′, C-5′), 64.17 (C-2, C-4), 53.95 (C-1, C-5), 28.97 (C-6, C-8), 21.15 (C-7) ppm; MS (CI): $m/z = 328.0$ ($M + 1$).

2,4-Bis(2-chlorophenyl)-3-azabicyclo[3.3.1]nonan-9-one (**5**, $C_{20}H_{19}Cl_2NO$)

Yield: 57%; m.p.: 218 °C; IR (KBr): $\bar{\nu} = 3{,}305$ (N–H stretching), 3,063, 2,973, 2,931, 2,905, 2,852, 2,821 (C–H stretching), 1,720, 1,706 (C=O stretching), 1,589, 1,567 (C=C stretching-Ph), 1,467, 1,434, 1,373, 1,341, 1,270, 1,236, 1,194, 1,168, 1,131, 1,076, 1,045, 1,032, 1,000, 950, 927, 893, 882, 845, 777, 764, 749, 735, 700, 664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.05$ (dd, $J = 8.00$, 1.20 Hz, H-6′), 7.39 (dt, $J = 7.00$, 1.60 Hz, H-3′, H-5′), 7.27 (dt, $J = 7.60$, 1.80 Hz, H-4′), 4.85 (d, $J = 2.40$ Hz, H-2a, H-4a), 2.88 (m, H-7a), 2.77 (br s, H-1, H-5), 1.90 (d, $J = 4.80$ Hz, H-8e), 1.87 (dd, $J = 4.80$, 1.60 Hz, H-6e), 1.81–1.71 (m, H-6a, H-8a), 1.66 (br s, NH), 1.41 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 216.34$ (C-9), 138.17 (C-1′), 132.69 (C-2′), 130.17 (C-6′), 128.90 (C-3′), 128.78 (C-4′), 126.92 (C-5′), 61.01 (C-2, C-4), 49.67 (C-1, C-5), 29.65 (C-6, C-8), 20.93 (C-7) ppm; MS (EI): $m/z = 359.08$ (M^+).

2,4-Bis(3-chlorophenyl)-3-azabicyclo[3.3.1]nonan-9-one (**6**, $C_{20}H_{19}Cl_2NO$)

Yield: 56%; m.p.: 180 °C; IR (KBr): $\bar{\nu} = 3{,}315$ (N–H stretching), 2,984, 2,926, 2,887, 2,805 (C–H stretching), 1,711 (C=O stretching), 1,593, 1,572 (C=C stretching-Ph), 1,433, 1,346, 1,276, 1,239, 1,126, 1,071, 945, 890, 790, 769, 697, 662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.54$ (s, H-6′), 7.40 (d, $J = 7.68$ Hz, H-2′), 7.34 (t, $J = 7.70$ Hz, H-4′), 7.30 (td, $J = 7.68$ Hz, H-5′), 4.38 (s, H-2a, H-4a), 2.80 (m, H-7a), 2.47 (br s, H-1, H-5), 1.93 (dd, $J = 5.88$, 1.48 Hz, H-8e), 1.90 (br s, NH, H-6e), 1.77–1.68 (m, H-6a, H-8a), 1.42 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 216.35$ (C-9), 143.16 (C-1′), 134.67 (C-3′), 130.01 (C-5′), 127.97 (C-2′), 127.02 (C-6′), 125.18 (C-4′), 64.23 (C-2, C-4), 53.66 (C-1, C-5), 29.05 (C-6, C-8), 21.18 (C-7) ppm; MS (EI): $m/z = 359.08$ (M^+).

2,4-Bis(4-chlorophenyl)-3-azabicyclo[3.3.1]nonan-9-one (**7**, $C_{20}H_{19}Cl_2NO$)

Yield: 47%; m.p.: 174 °C; IR (KBr): $\bar{\nu} = 3{,}314$ (N–H stretching), 3,063, 2,921, 2,852, 2,800 (C–H stretching), 1,709 (C=O stretching), 1,590 (C=C stretching-Ph), 1,489, 1,438, 1,404, 1,340, 1,294, 1,241, 1,194, 1,163, 1,133, 1,088, 1,012, 924, 880, 856, 823, 807, 777, 720, 691, 655, 630 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.48$ (d, $J = 8.44$ Hz, H-2′, H-6′), 7.38 (d, $J = 8.80$ Hz, H-3′, H-5′), 4.39 (d, $J = 2.20$ Hz, H-2a, H-4a), 2.80 (m, H-7a), 2.44 (br s, H-1, H-5), 1.90 (d, $J = 4.76$ Hz, H-8e), 1.87 (d, $J = 4.76$ Hz, H-6e, NH), 1.76–1.66 (m, H-6a, H-8a), 1.40 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 216.64$ (C-9), 139.63 (C-1′), 133.43 (C-4′), 128.88 (C-2′, C-6′), 128.28 (C-3′, C-5′), 64.17 (C-2, C-4), 53.77 (C-1, C-5), 29.00 (C-6, C-8), 21.14 (C-7) ppm; MS (EI): $m/z = 359.08$ (M^+).

2,4-Bis(2-bromophenyl)-3-azabicyclo[3.3.1]nonan-9-one (**8**, $C_{20}H_{19}Br_2NO$)

Yield: 51%; m.p.: 214 °C; IR (KBr): $\bar{\nu} = 3{,}305$ (N–H stretching), 3,068, 2,968, 2,933, 2,900, 2,857, 2,826 (C–H stretching), 1,719, 1,703 (C=O stretching), 1,585, 1,564 (C=C stretching-Ph), 1,462, 1,434, 1,370, 1,340, 1,320, 1,269, 1,257, 1,234, 1,194, 1,171, 1,134, 1,076, 1,040, 1,021, 1,000, 961, 945, 921, 890, 880, 845, 775, 763, 747,

730, 696, 675, 665, 601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.02$ (dd, $J = 7.88$, 1.64 Hz, H-6′), 7.57 (dd, $J = 8.06$, 1.10 Hz, H-3′), 7.42 (dt, $J = 7.52$, 1.10 Hz, H-5′), 7.18 (dt, $J = 7.52$, 1.64 Hz, H-4′), 4.77 (s, H-2a, H-4a), 2.88 (m, H-7a), 2.79 (br s, H-1, H-5), 1.90 (dd, $J = 6.40$, 1.28 Hz, H-8e), 1.86 (dd, $J = 5.16$, 1.08 Hz, H-6e), 1.81–1.71 (m, H-6a, H-8a), 1.67 (s, NH), 1.40 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 216.17$ (C-9), 139.56 (C-1′), 133.54 (C-3′), 129.28 (C-6′), 129.19 (C-4′), 127.51 (C-5′), 122.97 (C-2′), 63.38 (C-2, C-4), 49.59 (C-1, C-5), 29.54 (C-6, C-8), 20.90 (C-7) ppm; MS (EI): $m/z = 446.98$ (M^+).

2,4-Bis(3-bromophenyl)-3-azabicyclo[3.3.1]nonan-9-one (**9**, $C_{20}H_{19}Br_2NO$)

Yield: 47%; m.p.: 180 °C; IR (KBr): $\bar{\nu} = 3{,}310$ (N–H stretching), 3,063, 2,973, 2,931, 2,852 (C–H stretching), 1,710 (C=O stretching), 1,588, 1,564 (C=C stretching-Ph), 1,470, 1,434, 1,383, 1,344, 1,297, 1,278, 1,241, 1,197, 1,168, 1,126, 1,063, 1,034, 995, 942, 890, 840, 790, 767, 748, 733, 699, 680, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.68$ (s, H-2′), 7.46 (d, $J = 8.08$ Hz, H-4′, H-6′), 7.28 (t, $J = 7.68$ Hz, H-5′), 4.37 (d, $J = 2.20$ Hz, H-2a, H-4a), 2.79 (m, H-7a), 2.47 (br s, H-1, H-5), 1.93 (d, $J = 4.76$ Hz, H-8e), 1.89 (d, $J = 4.40$ Hz, H-6e, NH), 1.77–1.68 (m, H-6a, H-8a), 1.40 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 216.20$ (C-9), 143.41 (C-1′), 130.92 (C-2′), 130.31 (C-5′), 129.93 (C-4′), 125.64 (C-6′), 122.91 (C-3′), 64.20 (C-2, C-4), 53.64 (C-1, C-5), 29.03 (C-6, C-8), 21.18 (C-7) ppm; MS (EI): $m/z = 447.0$ (M^+).

2,4-Bis(4-bromophenyl)-3-azabicyclo[3.3.1]nonan-9-one (**10**, $C_{20}H_{19}Br_2NO$)

Yield: 55%; m.p.: 198 °C; IR (KBr): $\bar{\nu} = 3{,}310$ (N–H stretching), 3,057, 2,984, 2,921, 2,852, 2,800, 2,763 (C–H stretching), 1,705 (C=O stretching), 1,603, 1,572 (C=C stretching-Ph), 1,486, 1,449, 1,438, 1,400, 1,370, 1,340, 1,323, 1,294, 1,278, 1,241, 1,192, 1,163, 1,134, 1,105, 1,071, 1,008, 963, 924, 880, 857, 818, 806, 774, 717, 681, 658, 634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.54$ (d, $J = 8.40$ Hz, H-2′, H-6′), 7.42 (d, $J = 8.44$ Hz, H-3′, H-5′), 4.37 (d, $J = 1.49$ Hz, H-2a, H-4a), 2.79 (m, H-7a), 2.44 (br s, H-1, H-5), 1.91 (d, $J = 4.76$ Hz, H-8e), 1.87 (br s, H-6e, NH), 1.76–1.66 (m, H-6a, H-8a), 1.40 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 216.48$ (C-9), 140.12 (C-1′), 131.80 (C-3′, C-5′), 128.61 (C-2′, C-6′), 121.51 (C-4′), 64.17 (C-2, C-4), 53.67 (C-1, C-5), 28.99 (C-6, C-8), 21.12 (C-7) ppm; MS (EI): $m/z = 448.0$ (M + 1).

2,4-Bis(2-methylphenyl)-3-azabicyclo[3.3.1]nonan-9-one (**11**, $C_{22}H_{25}NO$)

Yield: 51%; m.p.: 194 °C; IR (KBr): $\bar{\nu} = 3{,}305$ (N–H stretching), 3,052, 3,021, 2,973, 2,929, 2,852 (C–H stretching), 1,714, 1,700 (C=O stretching), 1,610, 1,581 (C=C stretching-Ph), 1,478, 1,457, 1,428, 1,375, 1,344, 1,310, 1,289, 1,273, 1,222, 1,160, 1,136, 1,060, 1,043, 987, 908, 893, 861, 821, 783, 760, 736, 723, 672, 620, 574 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.00$ (d, $J = 8.00$ Hz, H-6′), 7.31 (dt, $J = 6.96$, 1.02 Hz, H-5′), 7.23–7.17 (m, H-3′, H-4′), 7.18 (dt, $J = 7.52$, 1.64 Hz, H-4′), 4.60 (d, $J = 1.48$ Hz, H-2a, H-4a), 3.01 (m, H-7a), 2.50 (br s, H-1, H-5), 2.34 (s, Me-C-2′), 1.99 (dd, $J = 6.24$, 1.28 Hz, H-8e), 1.96 (d, $J = 5.12$ Hz, H-6e), 1.79–1.69 (m, H-6a, H-8a), 1.63 (br s, NH), 1.42 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 217.77$ (C-9), 139.09 (C-1′), 134.87 (C-2′), 130.91 (C-3′, C-4′), 127.25 (C-6′), 126.05 (C-5′), 61.42 (C-2, C-4), 50.82 (C-1, C-5), 29.36 (C-6, C-8), 21.13 (C-7), 19.15 (Me-C-2′) ppm; MS (EI): $m/z = 319.19$ (M^+).

2,4-Bis(4-methylphenyl)-3-azabicyclo[3.3.1]nonan-9-one (**12**, $C_{22}H_{25}NO$)

Yield: 57%; m.p.: 160 °C; IR (KBr): $\bar{\nu} = 3{,}315$ (N–H stretching), 3,024, 2,939, 2,859 (C–H stretching), 1,714 (C=O stretching), 1,599, 1,564 (C=C stretching-Ph), 1,508, 1,442, 1,311, 1,267, 1,197, 1,154, 1,139, 1,062, 958, 909, 868, 817, 758, 730, 706, 660, 608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.43$ (d, $J = 8.04$ Hz, H-2′, H-6′), 7.21 (d, $J = 7.68$ Hz, H-3′, H-5′), 4.37 (d, $J = 2.20$ Hz, H-2a, H-4a), 2.89 (m, H-7a), 2.44 (br s, H-1, H-5), 2.36 (s, Me-C-4′), 1.95 (dd, $J = 5.86$, 1.46 Hz, H-8e), 1.92 (dd, $J = 5.32$, 1.64 Hz, H-6e, NH), 1.75–1.65 (m, H-6a, H-8a), 1.37 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 217.99$ (C-9), 138.46 (C-1′), 137.22 (C-4′), 129.29 (C-3′, C-5′), 126.90 (C-2′, C-6′), 64.71 (C-2, C-4), 54.21 (C-1, C-5), 29.18 (C-6, C-8), 21.27 (C-7), 21.22 (Me-C-4′) ppm; MS (EI): $m/z = 319.20$ (M^+).

2,4-Bis(2-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-one (**13**, $C_{22}H_{25}NO_3$)

Yield: 49%; m.p.: 217 °C; IR (KBr): $\bar{\nu} = 3{,}300$ (N–H stretching), 3,073, 2,934, 2,831 (C–H stretching), 1,711 (C=O stretching), 1,598, 1,585 (C=C stretching-Ph), 1,488, 1,459, 1,436, 1,391, 1,373, 1,336, 1,283, 1,244, 1,232, 1,192, 1,161, 1,134, 1,106, 1,071, 1,050, 1,026, 941, 906, 847, 760, 746, 696, 673, 649, 602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.95$ (dd, $J = 7.50$, 1.26 Hz, H-6′), 7.28 (dt, $J = 7.68$, 1.08 Hz, H-4′), 7.05 (t, $J = 7.52$ Hz, H-5′), 6.88 (d, $J = 8.04$ Hz, H-3′), 4.79 (d, $J = 2.20$ Hz, H-2a, H-4a), 3.81 (s, OMe-C-2′), 2.89 (m, H-7a), 2.67 (br s, H-1, H-5), 1.90 (d, $J = 5.12$ Hz, H-8e), 1.87 (d, $J = 5.48$ Hz, H-6e), 1.74–1.65 (m, H-6a, H-8a), 1.45 (br s, NH), 1.31 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 219.21$ (C-9), 156.21 (C-2′), 129.71 (C-1′), 128.17 (C-4′), 127.79 (C-6′), 120.33 (C-5′), 110.25 (C-3′), 58.12 (C-2, C-4), 55.21 (OMe-C-2′), 50.36

(C-1, C-5), 30.08 (C-6, C-8), 21.01 (C-7) ppm; MS (EI): $m/z = 351.19$ (M^+).

2,4-Bis(3-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-one (**14**, $C_{22}H_{25}NO_3$)

Yield: 56%; m.p.: 160 °C; IR (KBr): $\bar{\nu} = 3{,}310$ (N–H stretching), 3,073, 2,933, 2,930, 2,826 (C–H stretching), 1,708 (C=O stretching), 1,609, 1,583 (C=C stretching-Ph), 1,485, 1,440, 1,373, 1,339, 1,272, 1,231, 1,192, 1,144, 1,128, 1,079, 1,044, 1,005, 995, 953, 894, 859, 806, 778, 748, 715, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.31$ (t, $J = 7.86$ Hz, H-5′), 7.12 (m, H-2′, H-6′), 6.84 (ddd, $J = 7.96$, 2.38, 0.86 Hz, H-4′), 4.37 (d, $J = 2.20$ Hz, H-2a, H-4a), 3.84 (s, OMe-C-3′), 2.86 (m, H-7a), 2.48 (br s, H-1, H-5), 1.97 (dd, $J = 5.68$, 1.48 Hz, H-8e), 1.93 (dd, $J = 4.76$, 1.48 Hz, H-6e), 1.90 (s, NH), 1.75–1.65 (m, H-6a, H-8a), 1.38 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 217.55$ (C-9), 159.83 (C-3′), 143.03 (C-1′), 129.61 (C-5′), 119.27 (C-6′), 112.97 (C-2′), 114.6 (C-4′), 64.65 (C-2, C-4), 55.29 (OMe-C-3′), 54.03 (C-1, C-5), 29.23 (C-6, C-8), 21.18 (C-7) ppm; MS (EI): $m/z = 351.18$ (M^+).

2,4-Bis(4-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-one (**15**, $C_{22}H_{25}NO_3$)

Yield: 45%; m.p.: 174 °C; IR (KBr): $\bar{\nu} = 3{,}307$ (N–H stretching), 3,005, 2,968, 2,933, 2,831 (C–H stretching), 1,705 (C=O stretching), 1,610, 1,584 (C=C stretching-Ph), 1,553, 1,509, 1,452, 1,344, 1,301, 1,289, 1,247, 1,163, 1,131, 1,026, 966, 871, 831, 814, 792, 764, 737, 695, 684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.46$ (d, $J = 8.80$ Hz, H-2′, H-6′), 6.93 (d, $J = 8.80$ Hz, H-3′, H-5′), 4.34 (d, $J = 2.56$ Hz, H-2a, H-4a), 3.28 (s, OMe-C-4′), 2.88 (m, H-7a), 2.41 (br s, H-1, H-5), 1.96 (d, $J = 4.40$ Hz, H-8e), 1.92 (d, $J = 4.76$ Hz, H-6e), 1.87 (br s, NH), 1.74–1.64 (m, H-6a, H-8a), 1.38 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 217.88$ (C-9), 158.98 (C-4′), 136.51 (C-1′), 132.27 (C-2′, C-6′), 113.89 (C-3′, C-5′), 64.36 (C-2, C-4), 55.29 (OMe-C-4′), 54.24 (C-1, C-5), 29.05 (C-6, C-8), 21.22 (C-7) ppm; MS (EI): $m/z = 351.18$ (M^+).

3-Methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one (**16**, $C_{21}H_{23}NO$)

A mixture of 2.914 g 2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one (**1**, 0.01 mol), 2 g anhydrous potassium carbonate, and 1.42 g iodomethane (0.01 mol) in 30 cm^3 dry acetone was heated under reflux for 3 h in an inert atmosphere. Removal of acetone by distillation, dilution with water, and treatment with aqueous ammonia afforded the corresponding N-methylated 3-azabicyclononan-9-one **16**. Yield: 78%; m.p.: 198 °C; IR (KBr): $\bar{\nu} = 3{,}057$, 3,026, 2,926, 2,857, 2,794 (C–H stretching), 1,710 (C=O stretching), 1,599 (C=C stretching-Ph), 1,490, 1,454, 1,434, 1,373, 1,346, 1,300, 1,283, 1,257, 1,236, 1,165, 1,127, 1,070, 1,025, 1,001, 930, 853, 779, 761, 712, 675, 630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.81$ (br s, H-2′, H-6′), 7.57 (d, $J = 7.36$ Hz, H-2′, H-6′), 7.39–7.28 (m, H-3′, H-5′), 3.74 (d, $J = 3.36$ Hz, H-2a, H-4a), 2.91 (m, H-7a), 2.42 (br s, H-1, H-5), 1.97 (s, NMe), 1.92 (dt, $J = 5.92$, 1.48 Hz, H-6e, H-8e), 1.69–1.60 (m, H-6a, H-8a), 1.46 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 216.96$ (C-9), 140.76 (C-1′), 128.58 (C-3′, C-5′), 127.59 (C-4′), 127.33 (C-2′, C-6′), 74.49 (C-2, C-4), 54.67 (C-1, C-5), 29.65 (C-6, C-8), 20.27 (C-7) ppm; MS (EI): $m/z = 305.2$ (M^+).

Synthesis of 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one oximes ***17–32***

To a hot solution of the corresponding 2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one (0.005 mol) in ethanol, 0.417 g hydroxylamine hydrochloride (0.006 mol) and 2.04 g sodium acetate trihydrate (0.015 mol) were added and the mixture was heated under reflux until completion of the reaction. After that, water was added to the concentrated reaction mixture, and the precipitated oxime was separated by filtration, washed with excess water, and dried. The crude oxime obtained was purified by recrystallization from ethanol.

2,4-Diphenyl-3-azabicyclo[3.3.1]nonan-9-one oxime (**17**, $C_{20}H_{22}N_2O$)

Yield: 90%; m.p.: 196 °C; IR (KBr): $\bar{\nu} = 3{,}311$ (N–H stretching), 3,080, 3,063, 3,022, 2,960, 2,931, 2,894, 2,857, 2,800 (C–H stretching), 1,668 (C=N stretching), 1,598 (C=C stretching-Ph), 1,491, 1,451, 1,432, 1,345, 1,263, 1,251, 1,240, 1,175, 1,144, 1,068, 1,029, 1,000, 964, 938, 893, 852, 819, 782, 750, 702, 683, 633, 593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.53$ (br s, N–OH), 7.59 (dd, $J = 11.72$, 7.68 Hz, H-2′, H-2″, H-6′, H-6″), 7.40 (dt, $J = 7.32$, 1.84 Hz, H-3′ H-3″, H-5′, H-5″), 7.30 (dt, $J = 7.32$, 1.84 Hz, H-4′, H-4″), 4.40 (d, $J = 1.44$ Hz, H-2a), 4.34 (d, $J = 1.84$ Hz, H-4a), 3.58 (br s, $W_{1/2} = 9.56$ Hz, H-5), 2.82 (m, H-7a), 2.55 (br s, $W_{1/2} = 9.88$ Hz, H-1), 1.80–1.72 (m, H-6e, H-8e, NH), 1.58–1.46 (m, H-6a, H-8a), 1.39 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 165.84$ (C-9), 142.64/142.59 (C-1′/C-1″), 128.52 (C-3′, C-3″, C-5′, C-5″), 127.39 (C-4′, C-4″), 127.20/127.08 (C-2′, C-6′/C-2″, C-6″), 65.68 (C-2), 63.68 (C-4), 43.30 (C-1), 36.55 (C-5), 28.20 (C-8), 26.72 (C-6), 21.69 (C-7) ppm; MS (EI): $m/z = 307.2$ (M + 1).

2,4-Bis(2-fluorophenyl)-3-azabicyclo[3.3.1]nonan-9-one oxime (**18**, $C_{20}H_{20}F_2N_2O$)

Yield: 92%; m.p.: 191 °C; IR (KBr): $\bar{\nu} = 3{,}303$ (N–H stretching), 3,068, 3,039, 2,965, 2,936, 2,911, 2,857 (C–H stretching), 1,670 (C=N stretching), 1,613, 1,586 (C=C stretching-Ph), 1,487, 1,453, 1,432, 1,382, 1,337, 1,278,

1,259, 1,232, 1,173, 1,138, 1,099, 1,080, 1,039, 996, 941, 895, 822, 754, 680, 636, 609, 568 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.91$ (dt, $J = 7.32$, 1.80 Hz, H-6′, H-6″), 7.74 (br s, N–OH), 7.32–7.21 (m, H-4′, H-4″, H-5′, H-5″), 7.10–7.04 (m, H-3′ H-3″), 4.73 (s, H-2a), 4.68 (s, H-4a), 3.73 (br s, $W_{1/2} = 11.00$ Hz, H-5), 2.75 (m, H-7a), 2.68 (br s, $W_{1/2} = 11.36$ Hz, H-1), 1.78–1.70 (m, H-6e, H-8e), 1.63–1.52 (m, H-6a, H-8a, NH), 1.39 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 164.56$ (C-9), 161.38, 158.92/161.36, 158.90 (C-2′/C-2″), 129.44, 129.40/129.32 (C-1′/C-1″), 128.84/128.76 (C-6′/C-6″), 128.52, 128.48/128.43, 128.39 (C-4′/C-4″), 124.17, 124.13/124.10 (C-5′/C-5″), 115.71/115.50 (C-3′/C-3″), 58.47 (C-2), 56.65 (C-4), 40.64 (C-1), 33.84 (C-5), 28.70 (C-8), 27.13 (C-6), 21.51 (C-7) ppm; MS (ES): $m/z = 342.2$ (M^+).

2,4-Bis(3-fluorophenyl)-3-azabicyclo[3.3.1]nonan-9-one oxime (**19**, $C_{20}H_{20}F_2N_2O$)

Yield: 86%; m.p.: 219 °C; IR (KBr): $\bar{\nu} = 3{,}307$ (N–H stretching), 3,068, 3,039, 2,969, 2,931, 2,907, 2,861, 2,833, 2,808 (C–H stretching), 1,668 (C=N stretching), 1,611, 1,589 (C=C stretching-Ph), 1,484, 1,447, 1,432, 1,376, 1,341, 1,325, 1,288, 1,267, 1,254, 1,177, 1,141, 1,123, 1,070, 1,000, 967, 938, 923, 887, 864, 833, 798, 782, 754, 707, 680, 648, 609, 592, 572 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.55$ (br s, N–OH), 7.34 (m, H-2′, H-2″, H-5′, H-5″, H-6′, H-6″), 7.00 (t, $J = 7.72$ Hz, H-4′ H-4″), 4.40 (s, H-2a), 4.33 (s, H-4a), 3.58 (br s, $W_{1/2} = 11.36$ Hz, H-5), 2.72 (m, H-7a), 2.56 (br s, $W_{1/2} = 11.60$ Hz, H-1), 1.81–1.71 (m, H-6e, H-8e, NH), 1.60–1.49 (m, H-6a, H-8a), 1.41 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 165.00$ (C-9), 164.40, 161.96 (C-3′, C-3″), 130.14/130.07 (C-5′/C-5″), 122.77/122.64 (C-6′/C-6″), 114.48/114.27 (C-4′/C-4″), 114.18, 114.07/113.95, 113.85 (C-2′/C-2″), 65.07 (C-2), 63.10 (C-4), 43.10 (C-1), 36.27 (C-5), 28.16 (C-8), 26.66 (C-6), 21.61 (C-7) ppm; MS (CI): $m/z = 343.2$ (M + 1).

2,4-Bis(4-fluorophenyl)-3-azabicyclo[3.3.1]nonan-9-one oxime (**20**, $C_{20}H_{20}F_2N_2O$)

Yield: 88%; m.p.: 204 °C; IR (KBr): $\bar{\nu} = 3{,}296$ (N–H stretching), 3,068, 3,031, 3,006, 2,977, 2,927, 2,899, 2,861, 2,804, 2,771 (C–H stretching), 1,675 (C=N stretching), 1,603 (C=C stretching-Ph), 1,506, 1,455, 1,440, 1,343, 1,323, 1,295, 1,263, 1,216, 1,155, 1,144, 1,094, 1,014, 1,001, 944, 928, 895, 827, 796, 749, 724, 695, 669, 627, 609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.72$ (br s, N–OH), 7.54 (m, H-2′, H-2″, H-6′, H-6″), 7.09 (dt, $J = 8.62$, 1.84 Hz, H-3′, H-3″, H-5′, H-5″), 4.37 (s, H-2a), 4.31 (s, H-4a), 3.53 (br s, $W_{1/2} = 9.16$ Hz, H-5), 2.74 (m, H-7a), 2.50 (br s, $W_{1/2} = 9.12$ Hz, H-1), 1.84 (br s, NH), 1.80–1.70 (m, H-6e, H-8e), 1.59–1.47 (m, H-6a, H-8a), 1.40 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 165.24$ (C-9), 163.39, 160.95 (C-4′, C-4″), 138.17/138.10 (C-1′/C-1″), 128.68, 128.60, 128.57, 128.49 (C-2′, C-2″, C-6′, C-6″), 115.51, 115.30 (C-3′, C-3″, C-5′, C-5″), 65.09 (C-2), 63.09 (C-4), 43.26 (C-1), 36.45 (C-5), 28.05 (C-8), 26.57 (C-6), 21.63 (C-7) ppm; MS (EI): $m/z = 342.16$ (M^+).

2,4-Bis(2-chlorophenyl)-3-azabicyclo[3.3.1]nonan-9-one oxime (**21**, $C_{20}H_{20}Cl_2N_2O$)

Yield: 87%; m.p.: 256 °C; IR (KBr): $\bar{\nu} = 3{,}311$ (N–H stretching), 3,055, 2,965, 2,932, 2,857, 2,824 (C–H stretching), 1,674 (C=N stretching), 1,592, 1,568 (C=C stretching-Ph), 1,465, 1,435, 1,374, 1,343, 1,275, 1,257, 1,238, 1,193, 1,173, 1,144, 1,082, 1,047, 1,033, 998, 937, 895, 819, 760, 749, 735, 707, 688, 669, 635, 600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.01$ (d, $J = 7.68$ Hz, H-6′, H-6″), 7.41–7.35 (m, H-3′ H-3″, H-5′, H-5″), 7.26 (dt, $J = 5.88$, 1.84 Hz, H-4′, H-4″), 7.13 (br s, N–OH), 4.78 (s, H-2a), 4.73 (s, H-4a), 3.87 (br s, $W_{1/2} = 11.16$ Hz, H-5), 2.83 (s, H-1), 2.79 (m, H-7a), 1.71 (dt, $J = 20.52$, 4.76 Hz, H-6e, H-8e), 1.63–1.51 (m, H-6a, H-8a, NH), 1.40 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 160.00$ (C-9), 139.43/139.39 (C-1′/C-1″), 132.96 (C-2′, C-2″), 130.05 (C-6′, C-6″), 128.94/128.86 (C-3′/C-3″), 128.54 (C-4′, C-4″), 126.88/126.82 (C-5′/C-5″), 62.19 (C-2), 60.39 (C-4), 39.01 (C-1), 32.38 (C-5), 28.47 (C-8), 26.81 (C-6), 21.27 (C-7) ppm; MS (ES): $m/z = 375.1$ (M + 1).

2,4-Bis(3-chlorophenyl)-3-azabicyclo[3.3.1]nonan-9-one oxime (**22**, $C_{20}H_{20}Cl_2N_2O$)

Yield: 95%; m.p.: 197 °C; IR (KBr): $\bar{\nu} = 3{,}308$ (N–H stretching), 2,952, 2,925, 2,854, 2,800 (C–H stretching), 1,666 (C=N stretching), 1,594, 1,574 (C=C stretching-Ph), 1,467, 1,454, 1,432, 1,375, 1,342, 1,286, 1,257, 1,203, 1,139, 1,094, 1,076, 1,001, 933, 905, 899, 867, 787, 777, 725, 716, 703, 680, 645, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.99$ (br s, N–OH), 7.56 (d, $J = 8.44$ Hz, H-6′, H-6″), 7.45 (dd, $J = 15.76$, 7.68 Hz, H-2′, H-2″), 7.36–7.26 (m, H-4′, H-4″), 4.35 (s, H-2a), 4.29 (s, H-4a), 3.56 (br s, $W_{1/2} = 8.80$ Hz, H-5), 2.71 (m, H-7a), 2.53 (br s, $W_{1/2} = 9.16$ Hz, H-1), 1.78–1.70 (m, H-6e, H-8e, NH), 1.59–1.48 (m, H-6a, H-8a), 1.42 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 164.87$ (C-9), 144.41/144.35 (C-1′/C-1″), 134.57 (C-3′, C-3″), 129.91/129.89 (C-5′/C-5″), 127.74 (C-2′, C-2″), 127.23/127.13 (C-6′/C-6″), 125.38/125.24 (C-4′/C-4″), 65.19 (C-2), 63.21 (C-4), 43.03 (C-1), 36.27 (C-5), 28.07 (C-8), 26.58 (C-6), 21.63 (C-7) ppm; MS (EI): $m/z = 374.1$ (M^+).

2,4-Bis(4-chlorophenyl)-3-azabicyclo[3.3.1]nonan-9-one oxime (**23**, $C_{20}H_{20}Cl_2N_2O$)

Yield: 94%; m.p.: 183 °C; IR (KBr): $\bar{\nu} = 3{,}298$ (N–H stretching), 2,960, 2,927, 2,907, 2,894, 2,845 (C–H stretching), 1,672 (C=N stretching), 1,594 (C=C stretching-Ph),

1,489, 1,454, 1,432, 1,411, 1,341, 1,294, 1,255, 1,236, 1,168, 1,138, 1,089, 1,014, 998, 942, 936, 910, 893, 872, 816, 779, 721, 685, 656, 619 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.18$ (br s, N–OH), 7.51 (dd, $J = 11.72, 8.36$ Hz, H-2′, H-2″, H-6′, H-6″), 7.37 (dd, $J = 8.44, 2.20$ Hz, H-3′, H-3″, H-5′, H-5″), 4.36 (s, H-2a), 4.30 (s, H-4a), 3.53 (br s, $W_{1/2} = 9.92$ Hz, H-5), 2.70 (m, H-7a), 2.50 (br s, $W_{1/2} = 10.28$ Hz, H-1), 1.77–1.69 (m, H-6e, H-8e), 1.58–1.46 (m, H-6a, H-8a, NH), 1.40 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 165.05$ (C-9), 140.85/140.80 (C-1′/C-1″), 133.17 (C-4′, C-4″), 128.78, 128.75 (C-2′, C-2″, C-6′, C-6″), 128.49/128.37 (C-3′, C-5′/C-3″, C-5″), 65.08 (C-2), 63.08 (C-4), 43.10 (C-1), 36.23 (C-5), 28.04 (C-8), 26.57 (C-6), 21.60 (C-7) ppm; MS (EI): $m/z = 375.1$ (M + 1).

2,4-Bis(2-bromophenyl)-3-azabicyclo[3.3.1]nonan-9-one oxime (**24**, $C_{20}H_{20}Br_2N_2O$)
Yield: 91%; m.p.: 237 °C; IR (KBr): $\bar{\nu} = 3{,}290$ (N–H stretching), 3,068, 2,993, 2,965, 2,931, 2,899, 2,849 (C–H stretching), 1,671 (C=N stretching), 1,584, 1,563 (C=C stretching-Ph), 1,464, 1,434, 1,372, 1,342, 1,321, 1,257, 1,197, 1,171, 1,140, 1,082, 1,043, 1,021, 997, 947, 921, 894, 868, 816, 782, 749, 728, 687, 662, 633, 599 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 10.35$ (s, N–OH), 8.04 (t, $J = 6.38$ Hz, H-6′, H-6″), 7.62 (d, $J = 8.08$ Hz, H-3′, H-3″), 7.50 (t, $J = 7.32$ Hz, H-5′, H-5″), 7.25 (t, $J = 7.32$ Hz, H-4′, H-4″), 4.45 (s, H-2a), 4.38 (s, H-4a), 3.69 (br s, $W_{1/2} = 10.28$ Hz, H-5), 2.97 (br s, NH), 2.76 (m, H-7a), 2.65 (br s, $W_{1/2} = 10.24$ Hz, H-1), 1.51 (dd, $J = 12.84, 4.76$ Hz, H-6e, H-8e), 1.46–1.33 (m, H-6a, H-8a), 1.28 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, DMSO-d_6): $\delta = 162.10$ (C-9), 142.45/142.40 (C-1′/C-1″), 134.24 (C-3′, C-3″), 131.20/131.09 (C-6′/C-6″), 130.36 (C-4′, C-4″), 129.04/128.96 (C-5′/C-5″), 123.62/123.56 (C-2′/C-2″), 65.25 (C-2), 63.44 (C-4), 39.61 (C-1), 32.84 (C-5), 29.20 (C-8), 27.70 (C-6), 22.03 (C-7) ppm; MS (EI): $m/z = 463.0$ (M + 1).

2,4-Bis(3-bromophenyl)-3-azabicyclo[3.3.1]nonan-9-one oxime (**25**, $C_{20}H_{20}Br_2N_2O$)
Yield: 87%; m.p.: 188 °C; IR (KBr): $\bar{\nu} = 3{,}307$ (N–H stretching), 2,961, 2,923, 2,853 (C–H stretching), 1,670 (C=N stretching), 1,592, 1,567 (C=C stretching-Ph), 1,471, 1,454, 1,436, 1,427, 1,370, 1,341, 1,321, 1,288, 1,259, 1,195, 1,142, 1,088, 1,069, 1,017, 953, 930, 895, 851, 790, 776, 725, 704, 683, 667, 638, 603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.69$ (d, $J = 11.36$ Hz, H-2′, H-2″, N–OH), 7.50 (dd, $J = 13.56, 7.72$ Hz, H-6′, H-6″), 7.44 (d, $J = 7.72$ Hz, H-4′, H-4″), 7.27 (dt, $J = 7.68, 1.84$ Hz, H-5′, H-5″), 4.33 (d, $J = 2.20$ Hz, H-2a), 4.28 (d, $J = 2.56$ Hz, H-4a), 3.55 (br s, $W_{1/2} = 9.34$ Hz, H-5), 2.69 (m, H-7a), 2.52 (br s, $W_{1/2} = 9.36$ Hz, H-1), 1.75 (dt, $J = 18.72, 5.52$ Hz, H-6e, H-8e), 1.60–1.47 (m, H-6a, H-8a, NH), 1.41 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 164.68$ (C-9), 144.54/144.50 (C-1′/C-1″), 130.63 (C-2′, C-2″), 130.13, 129.98 (C-4′, C-4″), 130.07 (C-5′, C-5″), 122.78 (C-3′, C-3″), 65.05 (C-2), 63.05 (C-4), 42.91 (C-1), 36.33 (C-5), 28.01 (C-8), 26.51 (C-6), 21.56 (C-7) ppm; MS (EI): $m/z = 462.0$ (M^+).

2,4-Bis(4-bromophenyl)-3-azabicyclo[3.3.1]nonan-9-one oxime (**26**, $C_{20}H_{20}Br_2N_2O$)
Yield: 85%; m.p.: 192 °C; IR (KBr): $\bar{\nu} = 3{,}298$ (N–H stretching), 2,960, 2,925, 2,911, 2,903, 2,849, 2,800 (C–H stretching), 1,672 (C=N stretching), 1,588 (C=C stretching-Ph), 1,486, 1,453, 1,433, 1,407, 1,370, 1,341, 1,296, 1,259, 1,263, 1,169, 1,137, 1,097, 1,071, 1,010, 998, 909, 891, 874, 815, 776, 763, 749, 719, 685, 646, 616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.98$ (br s, N–OH), 7.52 (dd, $J = 8.14, 2.02$ Hz, H-2′, H-2″, H-6′, H-6″), 7.45 (dd, $J = 11.72, 8.40$ Hz, H-3′, H-3″, H-5′, H-5″), 4.34 (s, H-2a), 4.28 (s, H-4a), 3.53 (br s, $W_{1/2} = 9.56$ Hz, H-5), 2.69 (m, H-7a), 2.49 (br s, $W_{1/2} = 10.28$ Hz, H-1), 1.76–1.67 (m, H-6e, H-8e, NH), 1.58–1.46 (m, H-6a, H-8a), 1.39 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 164.96$ (C-9), 141.36/141.31 (C-1′/C-1″), 131.71 (C-3′, C-3″, C-5′, C-5″), 128.85, 128.73 (C-2′, C-2″, C-6′, C-6″), 121.27 (C-4′, C-4″), 65.10 (C-2), 63.12 (C-4), 43.03 (C-1), 36.16 (C-5), 28.05 (C-8), 26.56 (C-6), 21.59 (C-7) ppm; MS (CI): $m/z = 463.0$ (M + 1).

2,4-Bis(2-methylphenyl)-3-azabicyclo[3.3.1]nonan-9-one oxime (**27**, $C_{22}H_{26}N_2O$)
Yield: 91%; m.p.: 221 °C; IR (KBr): $\bar{\nu} = 3{,}296$ (N–H stretching), 3,068, 3,026, 2,965, 2,935, 2,853, 2,812 (C–H stretching), 1,679 (C=N stretching), 1,601 (C=C stretching-Ph), 1,484, 1,455, 1,429, 1,377, 1,346, 1,292, 1,273, 1,255, 1,175, 1,143, 1,081, 1,049, 1,003, 955, 934, 894, 866, 823, 800, 755, 743, 731, 689, 679, 639, 604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.97$ (t, $J = 6.96$ Hz, H-6′, H-6″), 7.65 (br s, N–OH), 7.30 (t, $J = 6.96$ Hz, H-5′, H-5″), 7.23–7.17 (m, H-3′, H-3″), 4.55 (s, H-2a), 4.48 (s, H-4a), 3.64 (br s, $W_{1/2} = 8.98$ Hz, H-5), 2.92 (m, H-7a), 2.56 (br s, $W_{1/2} = 9.56$ Hz, H-1), 2.41 (s, Me-C-2′), 2.38 (s, Me-C-2″), 1.80 (dt, $J = 15.18, 4.76$ Hz, H-6e, H-8e), 1.66 (br s, NH), 1.60–1.48 (m, H-6a, H-8a), 1.42 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 166.24$ (C-9), 140.39 (C-1′, C-1″), 135.26/135.18 (C-2′/C-2″), 130.79 (C-4′, C-4″), 127.24/127.18 (C-3′/C-3″), 127.06 (C-5′, C-5″), 126.07/125.99 (C-6′/C-6″), 62.69 (C-2), 60.77 (C-4), 39.94 (C-1), 33.18 (C-5), 28.20 (C-8), 26.68 (C-6), 21.54 (C-7), 19.38, 19.18 (Me-C-2′, Me-C-2″) ppm; MS (EI): $m/z = 334.2$ (M^+).

2,4-Bis(4-methylphenyl)-3-azabicyclo[3.3.1]nonan-9-one oxime (**28**, $C_{22}H_{26}N_2O$)
Yield: 90%; m.p.: 186 °C; IR (KBr): $\bar{\nu} = 3{,}304$ (N–H stretching), 3,027, 2,961, 2,939, 2,859, 2,815 (C–H

stretching), 1,671 (C=N stretching), 1,598 (C=C stretching-Ph), 1,506, 1,444, 1,310, 1,271, 1,195, 1,156, 1,142, 1,060, 960, 909, 868, 817, 760, 732, 707, 660, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.61$ (br s, N–OH), 7.45 (dd, $J = 10.94$, 7.68 Hz, H-2′, H-2″, H-6′, H-6″), 7.20 (dd, $J = 7.72$, 2.16 Hz, H-3′, H-3″, H-5′, H-5″), 4.37 (s, H-2a), 4.29 (s, H-4a), 3.55 (br s, $W_{1/2} = 9.18$ Hz, H-5), 2.80 (m, H-7a), 2.48 (br s, $W_{1/2} = 9.12$ Hz, H-1), 2.380 (s, Me-C-4′), 2.377 (s, Me-C-4″), 1.80–1.70 (m, H-6e, H-8e, NH), 1.58–1.47 (m, H-6a, H-8a), 1.38 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 166.06$ (C-9), 139.58/139.51 (C-1′/C-1″), 136.65/136.63 (C-4′/C-4″), 129.21 (C-3′, C-3″, C-5′, C-5″), 126.97/127.02 (C-2′, C-6′/C-2″, C-6″), 65.60 (C-2), 63.63 (C-4), 43.24 (C-1), 36.46 (C-5), 28.28 (C-8), 26.79 (C-6), 21.64 (C-7), 19.83, 19.81 (Me-C-4′, Me-C-4″) ppm; MS (EI): $m/z = 334.2$ (M^+).

2,4-Bis(2-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-one oxime (**29**, $C_{22}H_{26}N_2O_3$)
Yield: 89%; m.p.: 221 °C; IR (KBr): $\bar{\nu} = 3{,}303$ (N–H stretching), 3,002, 2,952, 2,936, 2,923, 2,837 (C–H stretching), 1,674 (C=N stretching), 1,601, 1,585 (C=C stretching-Ph), 1,489, 1,460, 1,435, 1,378, 1,339, 1,298, 1,284, 1,259, 1,235, 1,169, 1,142, 1,080, 1,050, 1,026, 1,025, 996, 940, 926, 895, 821, 793, 745, 690, 639, 599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.93$ (d, $J = 6.96$ Hz, H-6′, H-6″), 7.27 (t, $J = 7.02$ Hz, H-4′, H-4″), 7.13 (br s, N–OH), 7.05 (t, $J = 6.96$ Hz, H-5′, H-5″), 6.89 (dd, $J = 7.86$, 4.76 Hz, H-3′, H-3″), 4.73 (s, H-2a), 4.67 (s, H-4a), 3.86 (s, OMe-C-2′), 3.83 (s, OMe-C-2″), 3.76 (br s, $W_{1/2} = 8.44$ Hz, H-5), 2.81 (m, H-7a), 2.72 (br s, $W_{1/2} = 9.16$ Hz, H-1), 1.73 (t, $J = 13.92$ Hz, H-6e, H-8e, NH), 1.56–1.45 (m, H-6a, H-8a), 1.32 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 165.51$ (C-9), 156.61/156.59 (C-2′, C-2″), 131.02 (C-1′, C-1″), 127.97 (C-4′, C-4″, C-6′, C-6″), 120.42 (C-5′/C-5″), 110.39/110.24 (C-3′/C-3″), 59.06 (C-2), 57.29 (C-4), 55.57, 55.39 (O OMe-C-2′, OMe-C-2″), 39.70 (C-1), 32.88 (C-5), 29.05 (C-8), 27.51 (C-6), 21.48 (C-7) ppm; MS (EI): $m/z = 366.2$ (M^+).

2,4-Bis(3-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-one oxime (**30**, $C_{22}H_{26}N_2O_3$)
Yield: 92%; m.p.: 176 °C; IR (KBr): $\bar{\nu} = 3{,}305$ (N–H stretching), 2,969, 2,926, 2,854, 2,808, 2,783 (C–H stretching), 1,658 (C=N stretching), 1,607, 1,593, 1,582 (C=C stretching-Ph), 1,487, 1,464, 1,450, 1,433, 1,370, 1,339, 1,315, 1,274, 1,249, 1,233, 1,191, 1,181, 1,151, 1,139, 1,109, 1,083, 1,048, 1,041, 1,025, 995, 950, 942, 921, 903, 883, 845, 801, 774, 752, 702, 689, 649, 600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.32$ (dt, $J = 7.68$, 2.56 Hz, H-5′, H-5″, N–OH), 7.16 (dt, $J = 10.62$, 2.20 Hz, H-2′, H-2″, H-6′, H-6″), 6.84 (td, $J = 7.32$ Hz, H-4′, H-4″), 4.35 (d, $J = 2.56$ Hz, H-2a), 4.29 (d, $J = 2.20$ Hz, H-4a), 3.85 (s, OMe-C-3′), 3.84 (s, OMe-C-3″), 3.57 (br s, $W_{1/2} = 8.44$ Hz, H-5), 2.77 (m, H-7a), 2.53 (br s, $W_{1/2} = 8.24$ Hz, H-1), 1.79 (dt, $J = 14.64$ Hz, H-6e, H-8e), 1.55–1.45 (m, H-6a, H-8a, NH), 1.38 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 165.26$ (C-9), 159.834/159.826 (C-3′/C-3″), 144.27/144.26 (C-1′/C-1″), 129.55/129.51 (C-5′/C-5″), 119.62/119.44 (C-6′/C-6″), 113.10/113.01 (C-2′/C-2″), 112.37/112.28 (C-4′/C-4″), 65.54 (C-2), 63.56 (C-4), 55.40, 55.38 (OMe-C-3′, OMe-C-3″), 43.26 (C-1), 36.37 (C-5), 28.32 (C-8), 26.85 (C-6), 21.66 (C-7) ppm; MS (EI): $m/z = 366.2$ (M^+).

2,4-Bis(4-methoxyphenyl)-3-azabicyclo[3.3.1]nonan-9-one oxime (**31**, $C_{22}H_{26}N_2O_3$)
Yield: 94%; m.p.: 195 °C; IR (KBr): $\bar{\nu} = 3{,}306$ (N–H stretching), 2,985, 2,959, 2,940, 2,923, 2,861, 2,835 (C–H stretching), 1,679 (C=N stretching), 1,610, 1,584 (C=C stretching-Ph), 1,509, 1,465, 1,457, 1,439, 1,348, 1,325, 1,299, 1,259, 1,241, 1,179, 1,170, 1,142, 1,103, 1,084, 1,036, 1,000, 934, 896, 822, 790, 745, 729, 698, 689, 667, 630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.05$ (br s, N–OH), 7.50 (t, $J = 10.20$ Hz, H-2′, H-2″, H-6′, H-6″), 6.94 (t, $J = 8.44$ Hz, H-3′, H-3″, H-5′, H-5″), 4.33 (s, H-2a), 4.27 (s, H-4a), 3.830 (s, OMe-C-4′), 3.826 (s, OMe-C-4″), 3.51 (br s, $W_{1/2} = 10.24$ Hz, H-5), 2.81 (m, H-7a), 2.47 (br s, $W_{1/2} = 9.88$ Hz, H-1), 1.75 (t, J = 15.40 Hz, H-6e, H-8e, NH), 1.59–1.47 (m, H-6a, H-8a), 1.40 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 165.85$ (C-9), 158.78 (C-4′, C-4″), 134.83/134.78 (C-1′/C-1″), 128.19, 128.07 (C-2′, C-6″), 113.77 (C-3′, C-3″, C-5′, C-5″), 65.17 (C-2), 63.16 (C-4), 55.34 (OMe-C-4′, OMe-C-4″), 43.38 (C-1), 36.64 (C-5), 28.12 (C-8), 26.65 (C-6), 21.71 (C-7) ppm; MS (CI): $m/z = 367.2$ (M + 1).

3-Methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one oxime (**32**, $C_{21}H_{24}N_2O$)
Yield: 85%; m.p.: 206 °C; IR (KBr): $\bar{\nu} = 3{,}030$, 2,962, 2,930, 2,856, 2,780 (C–H stretching), 1,653 (C=N stretching), 1,601 (C=C stretching-Ph), 1,492, 1,450, 1,356, 1,220, 1,143, 1,042, 920, 873, 801, 756, 701, 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.30$ (br s, N–OH), 7.83 (br s, H-6′, H-6″), 7.57 (d, $J = 8.80$ Hz, H-2′, H-2″), 7.40–7.27 (m, H-3′, H-3″, H-4′, H-4″, H-5′, H-5″), 3.59 (d, $J = 3.28$ Hz, H-2a), 3.54 (d, $J = 2.92$ Hz, H-4a), 3.44 (br s, $W_{1/2} = 10.12$ Hz, H-5), 2.78 (m, H-7a), 2.42 (br s, $W_{1/2} = 9.94$ Hz, H-1), 1.89 (s, *N*-Me), 1.68–1.58 (m, H-6e, H-8e), 1.45–1.33 (m, H-6a, H-8a, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 165.21$ (C-9), 141.78/141.73 (C-1′/C-1″), 128.48, 128.41 (C-3′, C-3″, C-5′, C-5″), 127.41 (C-4′, C-4″), 127.17/127.11 (C-2′, C-6′/C-2″, C-6″), 75.71 (C-2), 73.80 (C-4), 43.97 (C-1), 43.80 (*N*-Me), 37.36 (C-5), 28.72 (C-8), 27.26 (C-6), 21.17 (C-7) ppm; MS (EI): $m/z = 320.2$ (M^+).

2,4-Diphenyl-3-azabicyclo[3.3.1]nonan-9-one O-methyloxime (**33**, $C_{21}H_{24}N_2O$)

A mixture of 1.457 g 2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one (**1**, 0.005 mol), 0.50 g methoxylamine hydrochloride (0.006 mol), and 2.04 g sodium acetate trihydrate (0.015 mol) in ethanol was heated under reflux. After completion of the reaction, the contents of the flask were concentrated, water was added, and the mixture was extracted with ether. The ethereal layer was dried with anhydrous sodium sulfate to afford the crude product. Then, the crude oxime ether **33** was purified by column chromatography on neutral alumina using petroleum ether (b.p.: 40–60 °C)/*n*-hexane, 1:2, as eluent. Yield: 91%; m.p.: 124 °C; IR (KBr): $\bar{\nu} = 3{,}310$ (N–H stretching), 3,067, 3,022, 2,971, 2,929, 2,894, 2,857, 2,806 (C–H stretching), 1,660 (C=N stretching), 1,598 (C=C stretching-Ph), 1,492, 1,451, 1,431, 1,345, 1,265, 1,250, 1,241, 1,175, 1,145, 1,068, 1,030, 1,001, 964, 938, 895, 852, 820, 782, 750, 706, 685, 633, 590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.56$ (t, $J = 6.96, 5.12$ Hz, H-2′, H-2″, H-6′, H-6″), 7.37 (t, $J = 7.32$ Hz, H-3′, H-3″, H-5′, H-5″), 7.27 (t, $J = 7.32, 6.96$ Hz, H-4′, H-4″), 4.34 (s, H-2a), 4.26 (s, H-4a), 3.91 (s, OMe), 3.44 (br s, $W_{1/2} = 10.28$ Hz, H-5), 2.77 (m, H-7a), 2.48 (br s, $W_{1/2} = 9.88$ Hz, H-1), 1.79–1.74 (m, H-8e, NH), 1.68 (dd, $J = 15.04, 4.40$ Hz, H-6e), 1.54–1.40 (m, H-6a, H-8a), 1.34 (quin, H-7e) ppm; ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 164.90$ (C-9), 142.67/142.57 (C-1′/C-1″), 128.43/128.38 (C-3′, C-5′/C-3″, C-5″), 127.26 (C-4′, C-4″), 127.08/126.94 (C-2′, C-6′/C-2″, C-6″), 65.63 (C-2), 63.65 (C-4), 61.26 (OMe), 43.16 (C-1), 37.07 (C-5), 28.24 (C-8), 26.77 (C-6), 21.59 (C-7) ppm; MS (ES): $m/z = 320.2$ (M^+).

Antifungal analysis

The antifungal activity [25] of the synthesized oximes was tested using Sabouraud dextrose agar (SDA) medium. The sterilized (autoclaved at 120 °C for 30 min) medium was inoculated (1 cm^3/100 cm^3 of medium) with a suspension of the microorganism (matched to McFarland barium sulfate standard) and poured into Petri dishes to give a depth of 3–4 mm. Paper discs impregnated with the test compounds (1 mg/cm^3 in dimethyl sulfoxide) were placed on the solidified medium. The plates were pre incubated for 1 h at room temperature and incubated at 37 ± 1 °C for about 48 h for antifungal activity. Ketoconazole (100 µg/disc) was used as positive reference standard. Negative controls were also prepared by impregnating discs of the same size with DMSO solvent.

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References

1. Jeyaraman R, Avila S (1981) Chem Rev 81:149
2. Hardick DJ, Blagbrough IS, Cooper G, Potter BVL, Critchley T, Wonnacott S (1996) J Med Chem 39:4860
3. Paterson D, Nordberg A (2000) Prog Neurobiol 61:75
4. Bryant DL, Free RB, Thomasy SM, Lapinsky DJ, Ismail KA, McKay SB, Bergmeier SC, McKay DB (2002) Neurosci Res 42:57
5. Barker D, Lin DH, Carland JE, Chu CP, Chebib M, Brimble MA, Savage GP, McLeod MD (2005) Bioorg Med Chem 13:4565
6. Parthiban P, Aridoss G, Rathika P, Ramkumar V (2009) Bioorg Med Chem Lett 19:6981
7. Aridoss G, Balasubramanian S, Parthiban P, Kabilan S (2007) Spectrochim Acta Part A 68:1153
8. Parthiban P, Balasubramanian S, Aridoss G, Kabilan S (2008) Spectrochim Acta Part A 70:11
9. Parthiban P, Ramachandran R, Aridoss G, Kabilan S (2008) Magn Reson Chem 46:780
10. Parthiban P, Rani M, Kabilan S (2009) Monatsh Chem 140:287
11. Parthiban P, Aridoss G, Rathika P, Ramkumar V, Kabilan S (2009) Bioorg Med Chem Lett 19:2981
12. Iriepa I, Madrid AI, Galvez E, Bellanato J (2003) J Mol Struct 651–653:579 and references cited therein
13. Arias-Perez MS, Alejo A, Galvez E, Perez SM, Santos MJ (1995) J Mol Struct 349:169
14. Arias MS, Smeyers YG, Fernandez MS, Smeyers NJ, Galvez E, Fonseca I, Aparicio JS (1994) J Org Chem 59:2565
15. Goodall KJ, Brimble MA, Barker D (2006) Magn Reson Chem 44:980
16. Polonski T, Pham M, Milewska MJ, Gdaneic M (1996) J Org Chem 61:3766
17. Parthiban P, Ramkumar V, Kim MS, Lim KT, Jeong YT (2008) Acta Cryst E 64:1586
18. Parthiban P, Thirumurugan K, Ramkumar V, Pazhamalai S, Jeong YT (2008) Acta Cryst E 64:1708
19. Parthiban P, Ramkumar V, Santan HD, Kim JT, Jeong YT (2008) Acta Cryst E 64:1710
20. Rameshkumar N, Veena A, Ilavarasan R, Adiraj M, Shanmugapandiyan P, Sridhar SK (2003) Biol Pharm Bull 26:188
21. Balasubramanian S, Aridoss G, Parthiban P, Ramalingan C, Kabilan S (2006) Biol Pharm Bull 29:125
22. Parthiban P, Balasubramanian S, Aridoss G, Kabilan S (2005) Med Chem Res 14:523
23. Klod S, Koch A, Kleinpeter E (2002) J Chem Soc Perkin Trans 2:1506
24. Lambert JB, Netzel DA, Sun HN, Lilianstorm KK (1976) J Am Chem Soc 98:3778
25. Gillespie SH (1994) Medical microbiology-illustrated. Butterworth–Heinemann, London, p 234