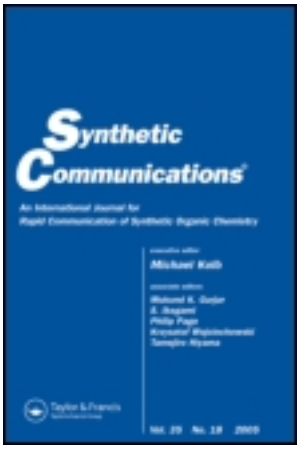

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NOVEL ONE-POT SYNTHESIS OF AZIRIDINES CARRYING SYDNONE MOIETY AND THEIR BIOLOGICAL STUDIES

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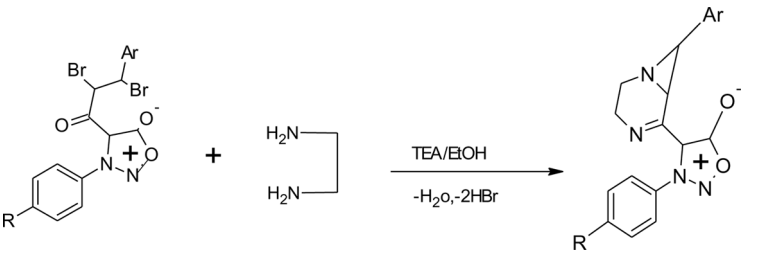
GRAPHICAL ABSTRACT



Abstract *A novel series of 5-(3-arylsydnon-4-yl)-7-aryl-1,4-diazabicyclo[4,1,0]hept-4-enes* ***3a–l*** *were prepared in a one-pot synthesis by the reaction of 2,3-dibromo-1-(3-arylsydnon-4-yl)-3-arylpropan-1-one* ***1a–l*** *and 1,2-diaminoethane. The newly synthesized compounds were screened for their antibacterial and antifungal activity.*

Keywords Aziridine; biological activity; one-pot synthesis; sydnone derivatives

INTRODUCTION

Aziridines are simple nitrogen-containing three-membered heterocycles, one of the most valuable classes in organic chemistry, because of their use in syntheses of many nitrogen-containing biologically active molecules.[1–3] Many naturally occurring aziridine derivatives exhibit antitumor and antibiotic activity.[4,5]

Sydnones are a well-defined novel class of mesoionic compounds consisting of a 1,2,3-oxadiazole ring system and are valuable synthetic intermediates.[6] Because of their mesoionic character, they have been widely studied since their discovery. Interest in sydnone derivatives has been encouraged by the discovery that they exhibit various pharmacological activities.[7,8]

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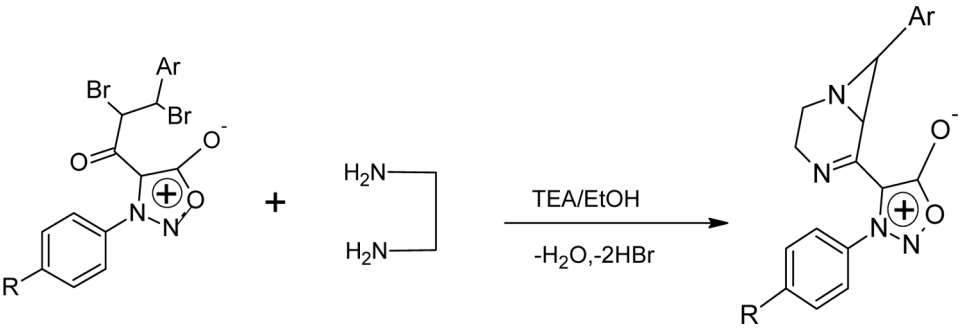
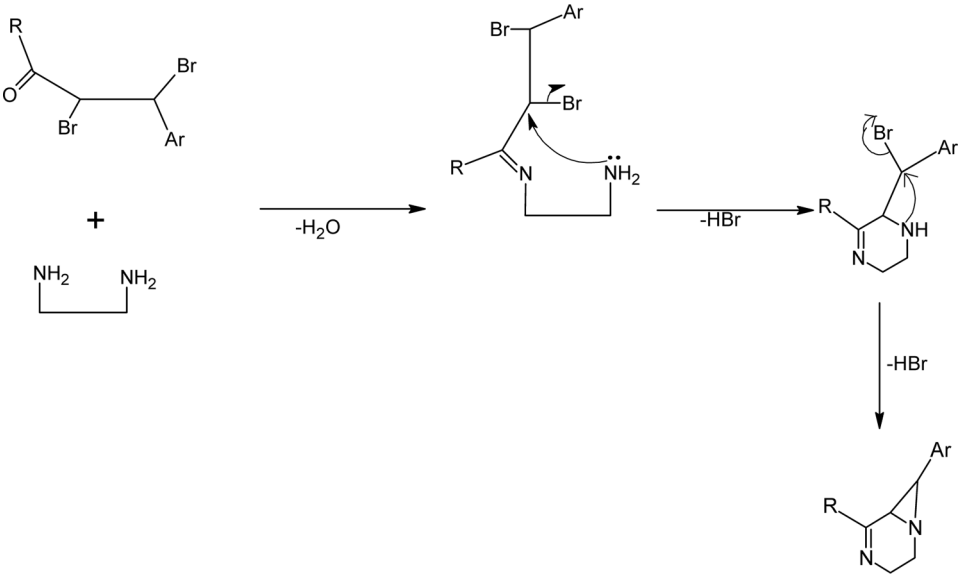


Scheme 1.



Scheme 2.

Prompted by these observations and in continuation of our research in sydnone chemistry,[9–12] we studied the mode of addition between 2,3-dibromo-1-(3-arylsydnone-4-yl)-3-arylpropane-1-ones **1** with ethylen diamine. Surprisingly, such reactions resulted in the formation of a hitherto-unreported novel series of aziridines containing a sydnone moiety (Scheme 1). A probable mechanism for the formation of aziridines is outlined in Scheme 2.

RESULTS AND DISCUSSION

The starting material, 2,3-dibromo-1-(3-arylsydnon-4-yl)-3-arylpropan-1-one **1a–l**, was prepared by the bromination of 1-(3-arylsydnone-4-yl)-3-aryl-2-propene-1-one.[12] These propenones were in turn prepared by the condensation of appropriate

Table 1. Characterization data of 5-(3-arylsydnon-4-yl)-7-aryl-1,4-diazabicyclo[4,1,0]hept-4-enes **3a–l**

Compound	R	Ar	Mol. formula	Yield (%)	MP (°C)	Nature of the solid	Analysis (%) found (calculated)		
							C	H	N
3a	H	Phenyl	$C_{19}H_{16}N_4O_2$	57	160–62	Brown shining needles	68.60 (68.67)	4.77 (4.81)	16.79 (16.86)
3b	H	4-Chlorophenyl	$C_{19}H_{15}ClN_4O_2$	63	152–54	Pale yellow crystals	62.11 (62.21)	4.05 (4.09)	15.22 (15.28)
3c	H	4-Bromophenyl	$C_{19}H_{15}BrN_4O_2$	63	144–46	Brown powder	55.68 (55.60)	3.60 (3.65)	13.71 (13.65)
3d	H	3,4-Methylenedioxyphenyl	$C_{20}H_{16}N_4O_4$	56	163–64	Brown crystals	63.71 (63.82)	4.19 (4.25)	14.82 (14.89)
3e	CH_3	Phenyl	$C_{20}H_{18}N_4O_2$	64	158–60	Brown shining crystals	69.25 (69.36)	5.15 (5.25)	16.13 (16.18)
3f	CH_3	4-Chlorophenyl	$C_{20}H_{17}ClN_4O_2$	61	182–84	Pale yellow crystals	63.17 (63.08)	4.40 (4.46)	14.78 (14.71)
3g	CH_3	4-Bromophenyl	$C_{20}H_{17}BrN_4O_2$	60	177–79	Light yellow crystals	56.72 (56.60)	4.07 (4.00)	13.15 (13.20)
3h	CH_3	3,4-Methylenedioxyphenyl	$C_{21}H_{18}N_4O_4$	69	175–76	Light yellow crystals	64.70 (64.61)	4.55 (4.61)	14.28 (14.35)
3i	$-OCH_3$	Phenyl	$C_{20}H_{18}N_4O_3$	65	138–39	Yellow powder	66.17 (66.29)	4.94 (4.97)	15.41 (15.46)
3j	$-OCH_3$	4-Chlorophenyl	$C_{20}H_{17}ClN_4O_3$	58	167–69	Brown crystals	60.62 (60.53)	4.21 (4.28)	14.04 (14.12)
3k	$-OCH_3$	4-Bromophenyl	$C_{20}H_{17}BrN_4O_3$	64	143–45	Brown powder	54.66 (54.54)	3.82 (3.86)	12.66 (12.72)
3l	$-OCH_3$	3,4-Methylenedioxyphenyl	$C_{21}H_{18}N_4O_5$	62	155–56	Light brown needles	62.13 (62.06)	4.39 (4.43)	13.72 (13.79)

aldehydes with 3-substituted-4-acetylsydnones.[12] 3-Substituted-4-acetylsydnone was prepared according to the procedure reported in the literature.[13]

The reaction between 2,3-dibromo-1-(3-arylsydnon-4-yl)-3-arylpropan-1-one **1a–l** with ethylene diamine **2** in the presence of triethyl amine in ethanol medium resulted in the formation of 5-(3-arylsydnon-4-yl)-7-aryl-1,4-diazabicyclo[4,1,0]hept-4-enes **3a–l**. All the newly synthesized compounds were characterized by spectral and analytical data. The characterization data of the newly synthesized compounds are given in Table 1.

The infrared (IR) spectra of these compounds showed an absorption band around 1754–1765 cm^{-1} for the carbonyl group of sydnone moiety. The ^1H NMR spectra (300 MHz) ($CDCl_3$) of aziridine **3g** showed a singlet at δ 2.35 integrating for three protons for the methyl group. The methylene protons at C-2 are found to be magnetically nonequivalent as they are prochiral. The signals corresponding to these two protons appeared as multiplets centered at δ 2.70 and δ 3.44, integrating for one proton each. The methylene protons at C-3 also appeared to be magnetically nonequivalent (diastereotopic) because of the restricted rotation and the signals due to these protons also appeared as multiplets centered at δ 3.21 and δ 3.80, integrating for one proton each. The two methine protons at C-7 and C-6 appeared as two doublets at δ 2.90 and δ 3.30, each integrating for one proton. The *ortho*- and *meta*-protons of *p*-tolyl group appeared as two doublets centered at δ 7.03 and δ 7.21, integrating for two protons each. Similarly the *ortho*- and *meta*-protons of *p*-bromophenyl group appeared as two doublets centered at δ 7.34 and δ 7.40, each integrating for two protons.

Further the mass spectrum [liquid chromatography–mass spectrometry (LCMS)] of this compound showed the $M^+ + 1$ peak and the corresponding isotopic peak at m/z 425/427, consistent with the molecular formula $C_{20}H_{17}BrN_4O_2$. Fragment peak at m/z 367 is due to the loss of -NO and -CO from the molecular ion, which is characteristic of sydnone-containing molecule. Base peak was observed at m/z 91 because of the formation of tropylium cation.

BIOLOGICAL ACTIVITY

The newly synthesized compounds **3a–l** were subjected for in vitro antibacterial and antifungal studies by the cup–plate[14] method against both Gram-positive and Gram-negative bacteria. Antibacterial activity was determined against *S. aureus* (ATCC-25923) and *K. pneumoniae* and antifungal activity was studied against *A. niger* and *C. albicans* (NCIM-NO. 3100). Ciprofloxacin and ciclopiroxolamine were employed as standard drugs. Dimethyl formamide (DMF) was used as solvent control. Among them, compounds **3c**, **3d**, and **3l** showed considerable antibacterial and antifungal activities. The results of antibacterial and antifungal studies are summarized in Table 2.

CONCLUSION

In conclusion, we studied the reaction of sydnone dibromides with ethylene dibromides to get a novel series of aziridines, namely 5-(3-arylsydnon-4-yl)-7-aryl-1,4-diazabicyclo[4,1,0]hept-4-enes **3a–l**, in a one-pot reaction, and the yields ranged from 53% to 69%.

Table 2. Antibacterial and antifungal activity data of 5-(3-arylsydnon-4-yl)-7-aryl-1,4-diazabicyclo [4,1,0]hept-4-enes **3a–l**

	Antibacterial activities[a] (diameter of zone of inhibition in mm)		Antifungal activities[b] (diameter of zone of inhibition in mm)	
Compound	*S. aureus*	*K. pneumoniae*	*A. niger*	*C. albicans*
3c	20	18	20	24
3d	18	22	26	26
3f	14	10	10	14
3g	15	12	—	10
3h	—	09	10	16
3j	12	18	20	18
3k	—	—	—	—
3l	20	22	18	24
Solvent control DMF	—	—	—	—
Ciprofloxacin	20	22	—	—
Ciclopiroxolamine	—	—	24	26

Notes. Diameter of the cup, 5 mm; amount of the sample used, 25 μg/cup; and solvent control, dimethyl formamide.

[a]Ciprofloxacin used as standard.

[b]Ciclopiroxolamine used as standard.

EXPERIMENTAL

Melting points were determined using the open capillary method and are uncorrected. All compounds were analyzed satisfactorily for C, H, N (Vairo-EL Elementar III model analyzer). Infrared (IR) spectra (KBr pellet) were recorded on a Perkin-Elmer 983 or Jasco Fourier transform (FT) IR 430 spectrophotometer. The ^{1}H NMR spectra were recorded on a Bruker AC 300 F (300-MHz) NMR spectrometer using dimethylsulfoxide (DMSO-d_6) as solvent and tetramethylsilane (TMS) as an internal standard. The chemical shift values are expressed in δ scale downfield from TMS, and proton signals are indicated as s, singlet; d, doublet; and m, multiplet. Mass spectra of synthesized compounds were recorded on a Jeol JMS-D 300 mass spectrometer or LC/MS (API 3000, Applied Bio systems) operating at 70 eV.

Preparation of 2,3-Dibromo-1-(3-arylsydnon-4-yl)-3-arylpropan-1-one 1a–l

1-(3-Arylsydnon-4-yl)-3-aryl-2-propen-1-ones (0.01 mol) was dissolved in glacial acetic acid (20 ml) by gentle warming. A solution of bromine in glacial acetic acid (30% w/v) was added to it with constant stirring until the yellow color of the bromine persisted. The reaction mixture was stirred at room temperature for 1–2 h. The solid separated was filtered, washed with methanol, and dried. It was then recrystallized from ethanol.

Preparation of 5-(3-Arylsydnon-4-yl)-7-aryl-1,4-diazabicyclo[4,1,0] hept-4-enes 3a–l

A mixture of 2,3-dibromo-1-(3-arylsydnon-4-yl)-3-arylpropan-1-one **1a–l** (0.01 mol), ethylenediamine (0.01 mol), and triethylamine (0.05 mol) was dissolved in 15 ml ethanol by heating. The clear solution was allowed to stand at room temperature for 4–6 days. The progress of the reaction was monitored by thin-layer chromatography (TLC). The solid separated was collected by filtration and recrystallized from ethanol to get pure 5-(3-arylsydnon-4-yl)-7-aryl-1,4-diazabicyclo[4,1,0]hept-4-enes **3a–l** in 53–69% yield.

The characterization data of compounds **3a–l** are given in Table 1.

Compound 3a. IR (KBr disc): $\gamma_{(C=O\ sydnone)}$ 1761 cm^{-1}, $\gamma_{(C=N)}$ 1605 cm^{-1}. ^1H NMR (300 MHz) $CDCl_3$, δ, 2.61 (m, 1H, C_2-H); δ 3.05 (d, 1H, C_7-H); δ 3.31 (m, 1H, C_3-H); δ 3.42 (d, 1H, C_6-H); δ 3.48–3.60 (m, 1H, C_2-H); δ 3.68–3.78 (m, 1H, C_3-H); δ 7.1–7.4 (m, 10H, Ar-H). Mass: m/z, 333 ($M^+ + 1$) (MF: $C_{19}H_{16}N_4O_2$).

Compound 3b. IR (KBr disc): $\gamma_{(C=O\ sydnone)}$ 1764 cm^{-1}, $\gamma_{(C=N)}$ 1602 cm^{-1}. ^1H NMR (300 MHz) $CDCl_3$, δ, 2.65–2.71 (m, 1H, C_2-H); δ 2.78 (d, 1H, C_7-H); δ 3.08 (m, 1H, C_3-H); δ 3.28 (d, 1H, C_6-H); δ 3.41–3.48 (m, 1H, C_2-H); δ 4.23–4.54 (m, 1H, C_3-H); δ 6.91 (d, 2H, *ortho* protons of *p*-chlorophenyl); δ 7.28 (d, 2H, *meta* protons of *p*-chlorophenyl); δ 7.05–7.40 (m, 5H, Ar-H). Mass: m/z, 367/369 ($M^+ + 1$ & $M^+ + 3$ peak) (MF: $C_{19}H_{15}ClN_4O_2$).

Compound 3c. IR (KBr disc): $\gamma_{(C=O\ sydnone)}$ 1760 cm^{-1}, $\gamma_{(C=N)}$ 1594 cm^{-1}. ^1H NMR (300 MHz) DMSO-d_6, δ, 2.65–2.74 (m, 1H, C_2-H); δ 2.81 (d, 1H, C_7-H); δ 3.06–3.18 (m, 1H, C_3-H); δ 3.28 (d, 1H, C_6-H); δ 3.35–3.47 (m, 1H, C_2-H); δ 4.31–4.64 (m, 1H, C_3-H); δ 6.91 (d, 2H, *ortho* protons of *p*-bromophenyl); δ 7.32 (d, 2H, *meta* protons of *p*-bromophenyl); δ 7.10–7.30 (m, 5H, Ar-H). Mass: m/z, 411/413 ($M^+ + 1$ & $M^+ + 3$ peak) (MF: $C_{19}H_{15}BrN_4O_2$).

Compound 3d. IR (KBr disc): $\gamma_{(C=O\ sydnone)}$ 1758 cm^{-1}, $\gamma_{(C=N)}$ 1598 cm^{-1}. ^1H NMR (300 MHz) DMSO-d_6, δ 2.58–2.66 (m, 1H, C_2-H); δ 2.71 (d, 1H, C_7-H); δ 2.96–3.18 (m, 1H, C_3-H); δ 3.31 (d, 1H, C_6-H); δ 3.50–3.60 (m, 1H, C_2-H); δ 4.10–4.35 (m, 1H, C_3-H); δ 4.54 (s, 2H, O-CH_2-O); δ 6.96–7.41 (m, 8H, Ar-H). Mass: m/z, 377 ($M^+ + 1$) (MF: $C_{20}H_{16}ClN_4O_4$).

Compound 3e. IR (KBr disc): $\gamma_{(C=O\ sydnone)}$ 1756 cm^{-1}, $\gamma_{(C=N)}$ 1595 cm^{-1}. ^1H NMR (300 MHz) $CDCl_3$, δ, 2.32 (s, 3H, CH_3); δ, 2.70 (m, 1H, C_2-H); δ, 2.97 (d, 1H, C_7-H); δ, 3.24 (m, 1H, C_3-H); δ, 3.33 (d, 1H, C_6-H); δ, 3.38-3.52 (m, 1H, C_2-H); δ, 3.76–3.84 (m, 1H, C_3-H); δ, 7.19 (d, 2H, *ortho*-protons of *p*-tolyl); δ, 7.34 (d, 2H, *meta*-protons of *p*-tolyl); δ, 7.12–7.28 (m, 5H, Ar-H). Mass: m/z, 347 ($M^+ + 1$) (MF$C_{20}H_{18}N_4O_2$).

Compound 3f. ^1H NMR (300 MHz) $CDCl_3$, δ, 2.28 (s, 3H, CH_3); δ 2.46 (m, 1H, C_2-H); δ 2.80 (d, 1H, C_7-H); δ 3.15 (m, 1H, C_3-H); δ 3.30 (d, 1H, C_6-H); δ 3.46–3.59 (m, 1H, C_2-H); δ 3.60–3.69 (m, 1H, C_3-H); δ 7.15 (d, 2H, o-protons of *p*-tolyl); δ 7.26 (d, 2H, m-protons of *p*-tolyl); δ 7.34 (d, 2H, o-protons of *p*-chlorophenyl); δ 7.54 (d, 2H, m-protons of *p*-chlorophenyl). Mass: m/z, 381/383 ($M^+ + 1$ and $M^+ + 3$ peaks) (MF$C_{20}H_{17}ClN_4O_2$).

Compound 3h. IR spectra (KBr disc): $\gamma_{(C=O\ sydnone)}$ 1749 cm^{-1}, $\gamma_{(C=N)}$ 1605 cm^{-1}. ^1H NMR (300 MHz) $CDCl_3$, δ, 2.25 (s, 3H, CH_3); δ 2.48–2.56 (m, 1H, C_2-H); δ 2.75 (d, 1H, C_7-H); δ 2.90–3.10 (m, 1H, C_3-H); δ 3.40 (d, 1H, C_6-H); δ 3.49–3.68 (m, 2H, C_2-H & C_3-H); δ 4.49 (s, 2H, -O-CH_2-O); δ 7.10 (d, 2H,o-protons of *p*-tolyl); δ 7.25–7.52 (m, 5H, remaining aromatic protons). Mass: m/z, 391 ($M^+ + 1$) (MF $C_{21}H_{18}N_4O_4$).

Compound 3i. IR spectra (KBr disc): $\gamma_{(C=O\ sydnone)}$ 1753 cm^{-1}, $\gamma_{(C=N)}$ 1589 cm^{-1}. ^1H NMR (300 MHz) $CDCl_3$, δ, 2.61–2.68 (m, 1H, C_2-H); δ 2.83 (d, 1H, C_7-H); δ 3.23–3.36 (m, 1H, C_3-H); δ 3.41 (d, 1H, C_6-H); δ 3.52–3.58 (m, 1H, C_2-H); δ 3.83 (s, 3H, -OCH_3); δ 4.32–4.65 (m, 1H, C_3-H); δ, 7.06 (d, 2H, *ortho* protons of *p*-anisyl); δ 7.28 (d, 2H, *meta*-protons of p-anisyl); δ 7.31–7.53 (m, 5H, Ar-H). Mass: m/z, 363 ($M^+ + 1$) (MF $C_{20}H_{18}N_4O_3$).

Compound 3j. IR spectra (KBr disc): $\gamma_{(C=O\ sydnone)}$ 1759 cm^{-1}, $\gamma_{(C=N)}$ 1593 cm^{-1}. ^1H NMR (300 MHz) $CDCl_3$, δ, 2.70–2.74 (m, 1H, C_2-H); δ, 2.86 (d, 1H, C_7-H); δ, 3.17–3.20 (m, 1H, C_3-H); δ, 3.31 (d, 1H, C_6-H); δ 3.45–3.50 (m, 1H, C_2-H); δ 3.79 (s, 3H, -OCH_3); δ 4.43–4.79 (m, 1H, C_3-H); δ 6.87 (d, 2H, o-protons of *p*-chlorophenyl); δ 7.07 (d, 2H, *ortho*-protons of *p*-anisyl); δ 7.24 (d, 2H, *meta*-protons of *p*-anisyl); δ 7.38 (d, 2H, m-protons of *p*-chlorophenyl). Mass: m/z, 397/399 ($M^+ + 1$ and $M^+ + 3$ peak) (MF $C_{20}H_{17}ClN_4O_3$).

Compound 3k. IR spectra (KBr disc): $\gamma_{(C=O\ sydnone)}$ 1757 cm^{-1}, $\gamma_{(C=N)}$ 1604 cm^{-1}. ^1H NMR (300 MHz) $CDCl_3$, δ, 2.58–2.64 (m, 1H, C_2-H); δ 2.86 (d, 1H, C_7-H); δ 3.21–3.34 (m, 1H, C_3-H); δ 3.41 (d, 1H, C_6-H); δ 3.48–3.71 (m, 2H, C_2-H & C_3-H); δ 3.91 (s, 3H, -OCH_3); δ 6.90 (d, 2H, *ortho*-protons of *p*-bromophenyl); δ 7.10 (d, 2H, *ortho*-protons of *p*-anisyl); δ 7.31 (d, 2H, *meta*-protons of *p*-anisyl); δ 7.42 (d, 2H, *meta*-protons of *p*-bromophenyl). Mass: m/z, 441/443 ($M^+ + 1$ and $M^+ + 3$ peak) (MF $C_{20}H_{17}BrN_4O_3$).

Compound 3l. IR spectra (KBr disc): $\gamma_{(C=O\ sydnone)}$ 1758 cm^{-1}, $\gamma_{(C=N)}$ 1595 cm^{-1}. ^1H NMR (300 MHz) $CDCl_3$, δ, 2.68–2.70 (m, 1H, C_2-H); δ 2.89 (d, 1H, C_7-H); δ 3.01–3.21 (m, 1H, C_3-H); δ 3.34 (d, 1H, C_6-H); δ 3.42–3.54 (m, 1H, C_2-H); δ 3.94 (s, 3H, -OCH_3); δ 4.21–4.54 (m, 1H, C_3-H); δ 4.61 (s, 2H, O-CH_2-O); δ 7.14 (d, 2H, *ortho*-protons of *p*-anisyl); δ 7.42–7.61 (m, 5H, *meta*-protons of *p*-anisyl & Ar-H). Mass: m/z, 407 ($M^+ + 1$) (MF $C_{21}H_{18}N_4O_5$).

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