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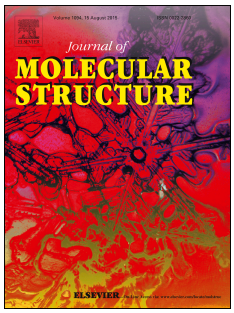

Stereoselective synthesis and spectral studies of some benzotriazolylacetyl hydrazones of 3–alkyl–2,6–diarylpiperidin–4–ones

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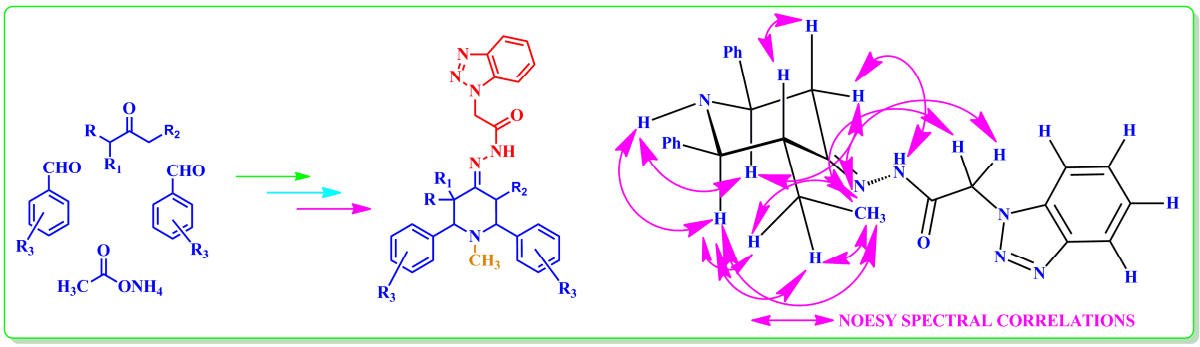
Graphical Abstract



STEREOSELECTIVE SYNTHESIS AND SPECTRAL STUDIES OF SOME BENZOTRIAZOLYLACETYL HYDRAZONES OF 3–ALKYL–2,6–DIARYLPIPERIDIN–4–ONES

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Abstract

An effort to include biologically potent benzotriazole nucleus into piperidine ring is achieved through hydrazone formation. The characterization of the synthesized compounds was carried out using FT-IR, ^{1}H &^{13}C NMR, ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, NOESY spectral techniques and GC-Mass spectrum. The spectral assignments were done without ambiguity using 2D-NMR techniques. The conformational preference of the piperidine ring deduced from the spectral studies is 'chair'. The diastereotopic nature of the methylene protons/methyl groups present in the molecules is revealed clearly in their spectral pattern observed.

Key Words: Piperidin-4-one, benzotriazolyl acetichyrazide, 1D & 2D NMR spectra.

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1. Introduction

Functionalized piperidines and their derivatives are important pharmacophores which are present in many pharmaceuticals [1]. Substituted piperidines particularly 2– and/or 2,6–disubstituted piperidines are synthetically important [2-20] as they exhibit wide spectrum of biological activities [6]. Likewise 3,5–disubstituted piperidines are important fundamentally as backbones for alkaloids, [21] high affinity agonists of human GABA–A receptors,[4b] farnesyl–protein transferase inhibitors [23] and continue to be basic moieties in pharmaceutical research and have been target molecules in organic synthesis [24–40].

4–Piperidone is an important derivative as well as an intermediate in the manufacture of certain chemicals and pharmaceutical drugs [41-43] such as fentanyl, carfentanyl and ramifentanyl. Further, compounds with 4–piperidone nucleus show desirable biological properties *viz.* antiviral [44], antitumor [45], central nervous system stimulant [46], analgesic [47], anticancer [48] and antimicrobial activity [49].

Hydrazones are having remarkable physiological and biological activities and also found application as insecticides, anticoagulants, antitumor agents, antioxidants and plant growth regulators [50-55]. Metal complexes formed from hydrazone ligands are having application in non–liner optics, sensors, medicine etc [56]. Several anti–inflammatory, antinociceptive, and antiplatelet active drugs contain hydrazone and acylhydrazone moieties as core pharmacophore units in their structure [57].

Azoles are forming a crucial part in the history of heterocyclic chemistry and also been used as synthons in synthetic organic chemistry. The growing interest in the research of azole chemistry is pertaining to the versatility of azole groups in chemotherapeutical activity. Reports are available about the benzotriazole derivatives which are potent in biological activity [58,59]. The role of benzotriazole derivatives as a precursor in organic syntheses [60,61],antiprotozoal [62], antimicrobial [63], anticonvulsant, anti–inflammatory [64] and anti–tumor [65] agents has been proven by several researchers. Having these facts in mind, we have designed and

synthesized a new series of biologically significant compounds with piperidine and benzotriazole moieties connected through potent hydrazone functionality. The structural elucidation of these compounds has been done by 1-D and 2-D NMR spectral techniques and the data are interpreted.

2. Experimental

2.1 General

All the solvents used for recrystallization and thin layer chromatography were of analytical grade and used without further purification. All reactions were monitored by thin layer chromatography on silica gel precoated aluminum sheets (Type 60 GF254, Merck). All the final compounds were purified by column chromatography with silica gel (100-200 mesh) and pet ether: ethyl acetate eluent system in 95:5 % (v/v) ratio. The melting points were recorded in open capillaries and are uncorrected. Elemental analysis of compounds have been carried out on a C, H, N analyzer type 1180(Carlo-Erba) and the report is shown in **Table S1**. FT-IR spectra were recorded on an AVATAR-330 FT-IR spectrometer (Thermo Nicolet) using KBr (pellet form). Mass spectra were recorded on a Varian Saturn 2000 GC-MS/MS spectrometer using electron impact technique. Samples were prepared by dissolving about 1 mg of compound in 5 mL of spectral grade methanol/acetone. ^{1}H and ^{13}C NMR spectra for all the compounds were recorded at 400 MHz and 100 MHz, in a Bruker ULTRASHIELD 400 PLUS instrument, using deuterated chloroform/deuterated DMSO as the solvent by taking about 10 mg and 50 mg of compound respectively for recording ^{1}H NMR and ^{13}C NMR spectra. Tetramethylsilane (TMS) was used as an internal reference for all NMR spectra, with chemical shifts reported in δ units (parts per million) relative to the standard. ^{1}H NMR splitting patterns are designated as singlet (s), broad singlet (bs), doublet (d), doublet of doublet (dd), triplet (t) and multiplet (m). Coupling constants are expressed in Hertz (Hz).

2.2 Synthesis of Benzotriazolyl hydrazones of 3–alkyl–2,6–diaryl piperidin–4–ones (25–38)

The parent compounds (**1-11**) were synthesized by Mannich condensation of aromatic aldehydes, ketones and ammonium acetate in ethanol [66]. The benzotriazolyl acetic hydrazide was prepared by following the procedure reported in the literature [67]. Further, compounds **1–3**

were methylated by methyl iodide in the presence of K_2CO_3 and acetone at refluxing conditions (**12-14**).

The title compounds **15–28** were prepared as follows: A mixture of 3–alkyl–2,6–diarylpiperidin–4–ones (2 mmol) and benzotriazolylacetic hydrazide (2mmol) in ethanol (10 mL) was heated to reflux for 3–6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solid product separated on cooling was collected by filtration and washed well with water (**Scheme 1**). Pure sample was obtained by recrystallization from 1:1 mixture of ethanol and ethyl acetate. Yield: 72 -87 %

3. Results and Discussion

A series of new benzotriazolylacetyl hydrazones of 3–alkyl–2,6–diarylpiperidin–4–ones has been prepared (**Scheme 1**) in good to excellent yields by the condensation of benzotriazolylacetic hydrazide with piperidin–4–ones. A higher degree of diastereoselectivity (selective formation of *E* isomer) was achieved owing to the presence of alkyl substituent adjacent to the carbonyl group which decides the orientation of the hydrazone moiety (–NH–N=) as *anti* with respect to it. Therefore the diastereoselectivity of the reaction is ascertained as substrate controlled. The numbering of carbon atoms in the compounds is shown in **Fig.1** and the protons are numbered accordingly. The newly synthesized hydrazones were characterized by IR, Mass, ^{1}H NMR, ^{13}C NMR, ^{1}H–^{1}H COSY, ^{1}H–^{13}C COSY and NOESY spectral techniques. The signals in the ^{1}H NMR spectra are assigned based on their chemical shift values, splitting pattern, coupling constants and correlations in the 2–D NMR spectra for compound **16** and for other compounds the signals were assigned by comparing chemical shift values of them with the former. The ^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY unraveled the problems during assignment of the signals in ^{1}H and ^{13}C NMR spectra.

3.1 Spectral Characterization and Analysis

3.1.1 Analysis of IR and Mass spectra

Infrared spectra of the synthesized compounds exhibited significant absorptions pertaining to the functional groups present such as imino (C=N), carbonyl (C=O), and the absorption frequencies (in cm^{-1}) are presented in **Table 1**. Mass spectrum of compound **25** has

shown $(M+H)^+$ value = 439.40. FT–IR and LC–Mass spectra of the synthesized compounds are shown through **Fig. S1 - S15.**

3.1.2 Analysis of ^{1}H NMR spectra

The ^{1}H NMR spectra of compounds **15–28** are shown through **Fig. S16 - S29**. Among the fourteen benzotriazolyl hydrazones synthesized, compound **16** is chosen as a representative to discuss about the spectral features. The numbering scheme given to compound **16** and its analogues is shown in **Fig. 1.** The ^{1}H NMR spectral data of compounds **15** to **28** are listed in **Table 2**.

In the ^{1}H NMR spectrum of compound **16 (Fig. 2),** the methyl protons of the C3–Et group, NH proton of the piperidine ring, proton of the –CONH–moiety (H8) and aromatic protons are observed at 0.89 (s), 1.85 (bs), 9.28 (s) and 7.32–7.47ppm(m). The methylene protons of the C3–Et group are observed as separate signals at 1.31 (m) and 1.66 ppm (m) due to their diastereotopic nature which is also evidenced from the cross peaks displayed between Me protons and the methylene protons in the ^{1}H–^{1}H COSY spectrum (**Fig. S30, Fig. 3** and **Table 4**). Likewise, the resonance of H3a proton at 2.48ppm (m) is ascertained by the correlations among this proton and the methylene protons previously described. Further, another cross peak exhibited by H3 proton with the doublet at 3.65ppm (J =9.6 Hz) revealed that the latter one is due to H2a proton.

The three protons H5a, H5e and H6a, forming an AMX spin system of coupling are detectable at 2.12ppm (t, J =12.4 Hz), 2.84ppm (d, J =13.6 Hz) and 3.76ppm (d, J =12 Hz). The diastereotopic methylene protons $H10_A$ and $H10_{B,}$ constituting an AB system of spin coupling with second order spectral characteristics are observed in the deshielded portion of the spectrum at 5.91 ppm (d, J =17.6 Hz) and 5.75 ppm (d, J =18.4 Hz) respectively. An isolated doublet found in the aromatic region of the spectra at 8.05ppm (J =7.2 Hz) is identified as that belongs to one of the proton of the benzotriazole nucleus (H4') from the literature reports [68-70] available for similar molecules.

3.1.3 Analysis of ^{13}C NMR spectrum

The ^{13}C NMR spectra of compounds **15–28** are displayed in **Fig. S31 – S44** and **Table 3** enlists the ^{13}C chemical shifts of the same. In the ^{13}C NMR spectrum of compound **16 (Fig. 4)**, the resonance of amido carbonyl carbon (C9) is observed at 167.6 ppm and the *ipso* carbons of

the phenyl rings have shown their resonance at 142.2 ppm and 142.6 ppm respectively while the resonance of imino carbon (C4) is observed at 156.2 ppm.

From the $^{1}H–^{13}C$ COSY spectrum of compound **16** (**Fig. S45, Table 4** and **Fig. 5**), the signal of methyl carbon of the C3–Et group is assigned based on its correlation with corresponding protons at 12.0 ppm. Similarly, the methylene carbon atoms bearing diastereotopic hydrogens at 3rd, 5th and 10th positions of the molecule are found to show cross peaks with respective protons at 19.0, 36.0 and 49.2 ppm and thereby those signals are assigned to them unambiguously. The C3, C6 and C2 carbons are also exhibited cross peaks at 52.0, 60.7 and 67.5 ppm respectively. In the aromatic region of the spectrum, the resonances observed at 109.7, 120.6, 123.9, 127.9, 133.9 and 146.0 are assigned to C7', C4', C5', C6', C7a' and C3a' respectively based on the spectra data reported for similar compounds in the literature [68-70] and correlations observed in the $^{1}H–^{13}C$ spectrum. All the aromatic carbons belong to aryl groups at C2 and C6 carbons shown their signals between 126.5–155.9 ppm collectively.

3.1.4 Stereochemistry

In substituted piperidine derivatives, the relative stereochemistry of the protons/substituents is determined conveniently by extracting coupling constants of the coupled protons. The relationship between the magnitude of coupling constant and the dihedral angle is given by Karplus equation and it applies well to these six membered cyclic systems. From that relation we know that the magnitude of vicinal coupling constant exceeding 10 Hz indicates the *trans* axial orientation of the coupled protons and thereby the equatorial orientation of the substituents. The values less than 10 Hz represent axial–axial or axial–equatorial or equatorial–equatorial relationship between the coupled protons.

In this case, the coupling between H2–H3 protons and H5–H6 protons are respectively 9.6 Hz ($^{3}J_{2a,3a}$) and 12 Hz ($^{3}J_{5a,6a}$). This observation supports a chair conformation for the piperidine ring in which all the substituents *i.e*. phenyl and methyl groups are equatorially oriented. Equatorial orientation of the bulky groups like phenyl provide stability to the molecule than at axial positions because it avoids the 1,3–diaxial interaction among the axial groups.

As the molecule of study contains a double bond at C4 carbon, there arises the possibility of existence of geometrical isomerism. The configuration about the C=N bond could be either *Z* or *E* depending upon the relative orientation of the hydrazone moiety with respect to the C3–

alkyl substituent. ^{13}C NMR spectroscopy provides sufficient light regarding this matter in such a way that the increased shielding of the carbon which lies *syn* to the hydrazone moiety reveals the configuration. For compound **26**, the chemical shift values of C5 and C3 carbons differ by about 16 ppm (δ_{C5}=52.0 ppm and δ_{C3}=36.0 ppm) indicating that the configuration as *E* with respect to the C3–Et group.

The NOESY spectrum of compound **16 (Fig. S46, Table 4** and **Fig.6),** exhibits correlation between methyl, methylene protons of the C3–Et group, H6a, piperidine NH and H2a protons which are lying in the same side of the piperidine ring. The $H10_A$ and $H10_B$ protons show cross peaks with methyl protons of the C3–Et group in the NOESY indicate their spatial proximity with the C3–Et group. The H8 (CONH) proton is also found to be close with H5a and H5e protons which reiterate the previous conclusion about the configuration.

4. Conclusion

A series of novel benzotriazolylacetyl hydrazones of 3–alkyl–2,6–diarylpiperidin–4–ones were synthesized stereoselectively and characterized by IR, Mass, ^1H NMR, ^{13}C NMR, ^1H–^1H COSY, ^1H–^{13}C COSY and NOESY spectra. The configuration of the molecules about the newly formed imino bond and the preferred conformation of the heterocyclic ring were established through ^1H, ^{13}C NMR NOESY and spectra.

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STEREOSELECTIVE SYNTHESIS AND SPECTRAL STUDIES OF SOME BENZOTRIAZOLYLACETYL HYDRAZONES OF 3–ALKYL–2,6–DIARYLPIPERIDIN–4–ONES

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Table Captions

Table 1 Significant IR absorption frequencies (cm^{-1}) and $(M+H)^+$ values of compounds **15–28**

Table 2 ^1H chemical shifts, splitting pattern and coupling constant values of compounds **15–28**

Table 3 ^{13}C chemical shift values of compounds **15–28**

Table 4 ^1H–^1H COSY, ^1H–^{13}C COSY and NOESY correlations of compound **16**

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Table 1 Significant IR absorption frequencies (cm^{-1}) and $(M+H)^+$ values of compounds **25–38**

Compound	–NH–	>C=O	>C=N–	Others	Mass(Observed) $(M+H)^+$
15	3199	1694	1599	—	439.40
16	3199	1687	—	—	—
17	3207	1682	1603	–	—
18	3088	1683	1613	—	—
19	—	1684	1611	1173 (C–O)	—
20	3199	1697	1615	748 (C–Cl)	—
21	3098	1688	1616	1354 (NO_2)	—
22	3108	1684	1618	738 (C–Cl)	—
23	3218	1683	1603	1490 (C–F)	—
24	3201	1694	1615	746 (C–Br)	–
25	—	1690	—	1126 (C–O)	—
26	3203	1685	1599	—	—
27	3208	1687	1637	—	—
28	1687	1687	1627	—	—

Table 2 ^{1}H chemical shifts, splitting pattern and coupling constant values of compounds **15–28**

Compound	CONH	$H10_A$ & $H10_B$	H6a	H2a	H5e	H3a	H5a	NH/NCH_3	Others
15	8.74 (s)	5.84 (d) *J* =17.6 Hz 5.75 (d) *J* =17.2 Hz	3.82 (d) *J* =11.2 Hz	3.50 (d) *J* =10 Hz	2.77 (d) *J* =13.2 Hz	2.57 (m)	2.17 (t) *J* =13.6 Hz, 12.4 Hz	Signal Merged With HOD signal	C3–Me 0.89 (d) *J* =5.2 Hz Aromatic 8.01 (d) *J* =8 Hz, 7.19–7.44 (m)
16	9.28 (s)	5.91 (d) *J* =17.6 Hz 5.75 (d)*J* =18.4 Hz	3.76 (d) *J* =12 Hz	3.65 (d) *J* =9.6 Hz	2.84 (d) *J* = 13.6 Hz	2.48 (m)	2.12 (t) *J* =12.4 Hz 12 Hz	1.85 (bs)	C3–Me 0.89 (s)CH*H* 1.31 (m)C*H*H 1.66 (m)Aromatic7.32 (s)7.36 (d)*J* = 4.8 Hz7.47 (s)8.05 (d)*J* =7.2 Hz
17	9.05 (s)	5.80 (d) *J* =17.2 Hz 5.88 (d) *J* =18 Hz	3.75 (s)	3.75 (s)	2.68 (d)	——	2.31 (d)	1.82 (bs0	C3–Me 1.09 (s)C3–Me' 1.21 (s)Aromatic6.69 (d)*J* =4 Hz7.04 (s)7.32–7.49 (m)7.58 (d)*J* =6.4 Hz8.06 (d)*J* =6.8 Hz
18	8.94 (s)	5.89 (d) *J* =17.6 Hz 5.80 (d) *J* =18 Hz	3.79 (d) *J* =11.6 Hz	3.50 (d) *J* =10 Hz	2.79 (d) *J* =14 Hz	2.58 (m)	2.16 (t) *J* =12.8 Hz *J* =12.4 Hz	1.97 (bs)	C3–Me 0.94 (d)*J* =4.8 Hz Aromatic $ArCH_3$ 2.33 (s)$ArCH_3$' 2.35 (s)7.13 (d)*J* =7.2 Hz7.17 (d)*J* =6.8 Hz7.27 (d)*J* =9.2 Hz7.35 (d)*J* =7.2 Hz7.49 (s)8.07 (d)*J* =8 Hz
19	9.20	5.87 (d)	3.70 (d)	3.45 (d)	2.78 (d)	2.52 (m)	2.08 (t)	1.89 (bs)	C3–Me 0.92 (d) *J* =5.2 Hz

Compound	CONH	$H10_A$ & $H10_B$	H6a	H2a	H5e	H3a	H5a	NH/NCH_3	Others
	(s)	*J* =17.6 Hz 5.77 (d) *J* =17.6 Hz	*J* =11.6 Hz	*J* =10 Hz	*J* =13.2 Hz		*J* =12.8 Hz 12.4 Hz		Aromatic $ArOCH_3$ 3.79 (s) $ArOCH_3$' 3.81 (s) 6.82 (d)*J* =7.2 Hz 6.89 (d) *J* =7.2 Hz 7.25 (d) *J* =7.6 Hz 7.37 (d) *J* =6.8 Hz 7.47 (s) 8.05 (d) *J* =7.6 Hz
20	9.97 (s)	5.80 (s)	4.30 (bs) Merged with H2a	4.30 (bs) Merged with H6a	3.21 (s)	2.59 (m) Merged with solvent signal	2.03 (bs) Merged with NH signal	2.03 (bs) Merged with H5a signal	C3–Me 0.96 (s) Aromatic 7.28 (s) 7.47 (s) 7.73 (s) 7.99 (s)
21	9.98 (s)	5.92 (d) *J* =17.6 Hz 5.75 (d) *J* =18 Hz	3.74 (d) *J* =11.6 Hz	3.64 (d) *J* =9.6 Hz	2.99 (d) *J* =13.6 Hz	2.59 (m)	2.00 (t) *J* =12.8 Hz 12.4 Hz	1.78 (bs)	C3–Me 0.93 (d) *J* =5.6 Hz Aromatic 7.30 (s) 7.41 (d) *J* =8.4 Hz 7.52 *J* =6.4 Hz 7.59 (d) *J* =7.2 Hz 7.75 (s) 7.85 (d) *J* =6.4 Hz 7.92 (d) *J* =8 Hz 8.09 (d) 7.6 Hz 8.38 (s)
22	10.9 (s)	5.86 (d) *J* =18.8 Hz 5.80 (d) *J* =18 Hz	3.91 (d) *J* =11.2 Hz	3.56 (d) *J* =10 Hz	3.38 (d) *J* =14 Hz	2.54 (m) Merged with solvent signal	2.06 (t) *J* =13.2 Hz 12. 4 Hz	2.17 (bs)	C3–Me 0.93 (d) *J* =5.6 Hz Aromatic 7.31 (d) *J* =8.4 Hz 7.35 (s) 7.39 (d) *J* =6.8 Hz 7.45 (s) 7.49 (d) *J* =7.6 Hz 7.58 (d) *J* =8 Hz 7.67 (s) 8.08 (d)

Compound	CONH	$H10_A$ & $H10_B$	H6a	H2a	H5e	H3a	H5a	NH/NCH_3	Others
23	9.15 (s)	5.89 (d) *J* =18 Hz 5.789d) *J* =17.2 Hz	3.77 (d) *J* =10.8 Hz	3.52 (d) *J* =9.6 Hz	2.81 (d) *J* =13.6 Hz	2.53 (m)	2.10 (t) *J* =12.8 Hz	2.00 (bs)	*J* =8 Hz C3–Me 0.93 (d)*J* =4.8 Hz Aromatic 6.99 (t) *J* =7.6 Hz 7.06 (t) *J* =7.6 Hz 7.33 (s) 7.37 (s 7.44 (s) 7.49 (s) 8.06 (d) *J* =8 Hz
24	11.06 (s)	5.86 (d) *J* =16.8 Hz 5.81 (d) *J* =18 Hz	3.90 (d) *J* =11.2 Hz	3.55 (d) *J* =10 Hz	3.41 (d) *J* =13.6 Hz	2.53 (m) Merged with solvent signal	2.04 (t) *J* =12.4 Hz 12 Hz	2.35 (bs)	C3–Me 0.94 (d) *J* =4.8 Hz Aromatic 7.41 (t) *J* =7.6 Hz 7 .46 (s)7.50 (d) *J* =8 Hz 7.61 (d) *J* =8 Hz 7.85 (s) 8.02 (d) *J* =7.2 Hz
25	9.10 (s)	5.91 (s) *J* =17.6 Hz 5.80 (d) *J* =17.6 Hz	3.72 (bs)	3.44 (d) *J* =10.4 Hz	2.85 (d) *J* =13.2 Hz	2.57 (m)	2.16 (t) *J* =12.4 Hz 12 Hz	1.90 (bs)	C3–Me 0.98 (d)*J* =4.8 Hz Aromatic 6.64 (s) 6.70 (s) 7.37 (s) 7.50 (s) 7.86 (s) 8.06 (d) *J* =8 Hz
26	9.21 (s)	5.82 (d) *J* = 14.8 Hz 5.65 (d) *J* =14.8 Hz	2.97 (bs)	2.81 (bs)	2.73 (bs) Merged with H3a signal	2.66 (bs) Merged with H5e signal	2.18 (bs)	1.68 (s)	C3–Me 0.84 (s) Aromatic 7.27 (s) 7.39 (d) *J* =7.6 Hz 8.07 (d) *J* =6.8 Hz

Compound	CONH	$H10_A$ & $H10_B$	H6a	H2a	H5e	H3a	H5a	NH/NCH_3	Others
27	9.49 (s)	5.84 (d) *J* =16.4 Hz 5.58 (d) *J* =17.6 Hz	2.89(m)Merged with H2a signal	2.89(m) Merged with H6a signal	2.70 (d)	2.49 (m)	2.06 (bs)	1.62 (s)	C*H*H 1.20 (m) CH*H* 1.54 (m) C3–Me 0.84 (s) Aromatic7.2 (s) 7.30 (s) 7.38 (s) 7.40 (s) 7.49 (s) 8.06 (d)*J* =7.6 Hz
28	8.85 (s)	5.90 (d) *J* =18 Hz 5.81 (d) *J* =18 Hz	3.09 (s) Merged with H2a signal	3.09 (s) Merged with H6a signal	2.63 (d) *J* =14 Hz	——	2.50 (t) *J* =10 Hz	1.76 (s)	C3–Me 1.00 (s) C3–Me' 1.30 (s) Aromatic 7.264–7.37 (m) 7.51 (s) 8.08 (d) *J* =6 Hz

Table 3 ^{13}C chemical shift values of compounds **15–28**

Compound	C2	C3	C4	C5	C6	C9	C10	Aromatic	Others
15	69.1	45.1	156.8	36.1	60.5	167.7	49.3	*ipso* 142.4,143.2 Others 109.9–133.9,145.7	C3–Me 12.2
16	67.5	52.0	155.9	36.0	60.7	167.6	49.2	*ipso* 142.2, 142.6 Others 109.7–133.9,146.0	C3–Me 12.0 CH_2 19.0
17	70.4	43.5	161.1	31.9	60.8	168.1	49.3	*ipso* 140.0, 143.1 Others 109.8–133.9,146.0	C3–Me 21.0 C3–Me' 22.7
18	68.9	45.3	157.2	35.7	60.5	167.5	49.3	*ipso* 139.3, 139.8 Others 109.7–137.6, 144.8, 146.0	C3–Me 21.1 Ar–Me 21.1
19	68.5	45.4	157.8	35.7	59.8	168.0	49.2	*ipso* 134.7, 135.1, 30 159.1, 159.2 Others 109.9–133.9, 144.8, 145.9	C3–Me 12.2 Ar–OCH_3 55.2, Ar–OCH_3' 55.3
20	62.3	44.8	155.0	33.7	56.0	167.4	49.0	*ipso* 139.3, 139.7 Others 109.7–133.2,145.2	C3–Me 11.2
21	68.1	45.1	156.2	35.6	59.2	168.7	49.1	*ipso* 148.2, 148.4,144.4, 144.6 Others 109.6–144.3,145.7	C3–Me 12.0
22	67.9	44.7	155.7	35.7	59.3	167.4	48.9	*ipso* 141.2, 141.4 Others 109.6–133.5	C3–Me 11.7
23	68.3	45.4	156.9	35.8	59.8	168.0	49.2	*ipso* 138.0, 138.4, 161.0, 161.2, 163.6 Others109.6–133.9, 146.0	C3–Me 12.1
24	67.9	44.5	155.6	35.8	59.2	167.5	48.9	*ipso* 141.6, 142.4 Others 110.1–133.6, 144.0, 145.1	C3–Me 11.9
25	69.5	45.3	156.7	35.7	60.8	167.8	49.2	*ipso* 153.2, 153.3, 137.4, 137.6,137.8, 138.4	C3–Me 12.2 $ArOCH_3$ 56.1,

26	77.1	44.3	155.5	36.0	68.5	167.1	48.6	Others 103.4–133.9, 144.8, 146.0 *ipso* 142.1, 143.2 Others 109.4–133.2, 145.0	$ArOCH_3$' 56.2 C3–Me 12.4 N–Me 40.6
27	75.6	51.8	155.4	36.3	68.7	167.9	49.1	*ipso* 142.2, 143.4 Others 110.0–133.9	C3–Et Me 12.0 CH_2 19.7 N–Me 41.3
28	79.2	43.2	160.2	32.4	69.5	167.7	49.3	*ipso* 139.2, 143.8 Others 109.8–133.9,144.8,146.0	C3–Me 22.3 C3–Me' 23.6 N–Me 42.5

Table 4 ^{1}H–^{1}H COSY, ^{1}H–^{13}C COSY and NOESY correlations of compound **16**

^{1}H chemical shifts in ppm	**Correlations in the ^{1}H–^{1}H COSY (^{1}H chemical shifts in ppm)**	**Correlations in the ^{1}H–^{13}C COSY(^{13}C chemical shifts in ppm)**	**NOESY correlations**
9.28 (CONH)	—	—	1.85, 2.84
8.05 (H7')	7.32–7.47	109.7	7.32–7.37
7.32–7.47 (Aromatic hydrogens)	8.05	120.1, 128.7	
5.91 & 5.75 ($H10_A$ & $H10_B$)	5.75, 5.91	49.2	0.89, 7.47
3.76 (H6a)	2.12, 2.84	60.7	1.85, 2.12, 2.84,7.32–7.37
3.65 (H2a)	2.48	67.4	0.89, 1.31, 1.66, 1.85
2.84 (H5e)	2.12, 3.76	36.0	2.12, 3.76, 7.32–7.37, 9.28
2.48 (H3a)	1.31, 1.66, 3.65	52.0	0.89, 1.31, 1.66, 2.12, 3.65,7.47
2.12 (H5a)	2.84, 3.76	36.0	2.48, 2.84, 3.76, 7.32–7.37
1.85 (NH)	—	—	3.76, 7.32–7.37, 9.28
1.66 C*H*H (C3–Et)	0.89, 1.31, 2.48	19.0	0.89, 1.31, 2.48, 3.65
1.31 CH*H* (C3–Et)	0.89, 1.66, 2.48	19.0	0.89, 1.66, 2.48, 3.65, 7.47
0.89 CH_3 (C3–Et)	1.31, 1.66	12.0	1.31, 1.66, 2.48, 3.65, 5.75, 5.91, 7.47

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Figures and Scheme Captions

Fig.1 Numbering pattern followed for compounds **15–28** to explain NMR spectra

Fig. 2 ^{1}H NMR spectrum of compound **16**

Fig. 3 ^{1}H-^{1}H COSY spectral correlations of compound **16**

Fig. 4 ^{13}C NMR spectrum of compound **16**

Fig. 5 ^{1}H-^{13}C COSY spectral correlations of compound **16**

Fig. 6 NOESY spectral correlations of compound **16**

Scheme 1 Synthetic scheme of benzotriazolylacetyl hydrazones **15–28**

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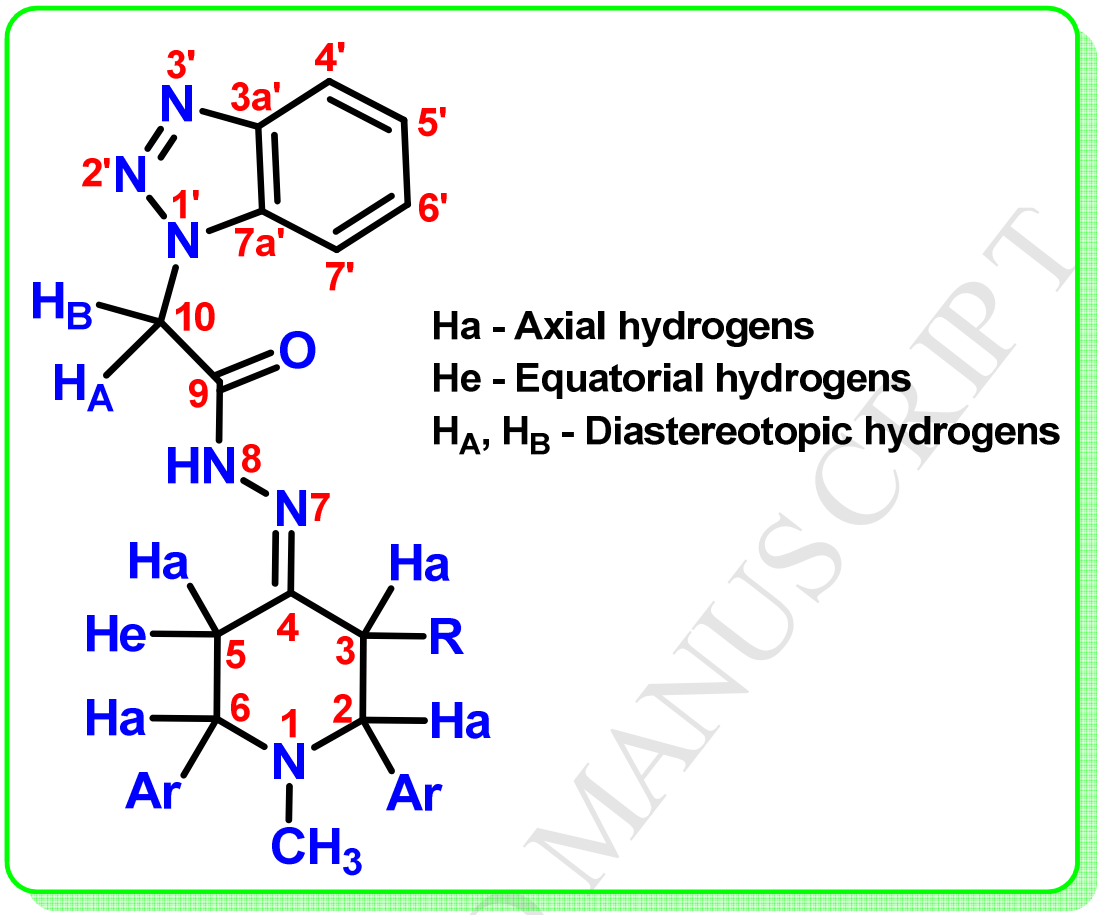


Fig.1 Numbering pattern followed for compounds **15–28** to explain NMR spectra

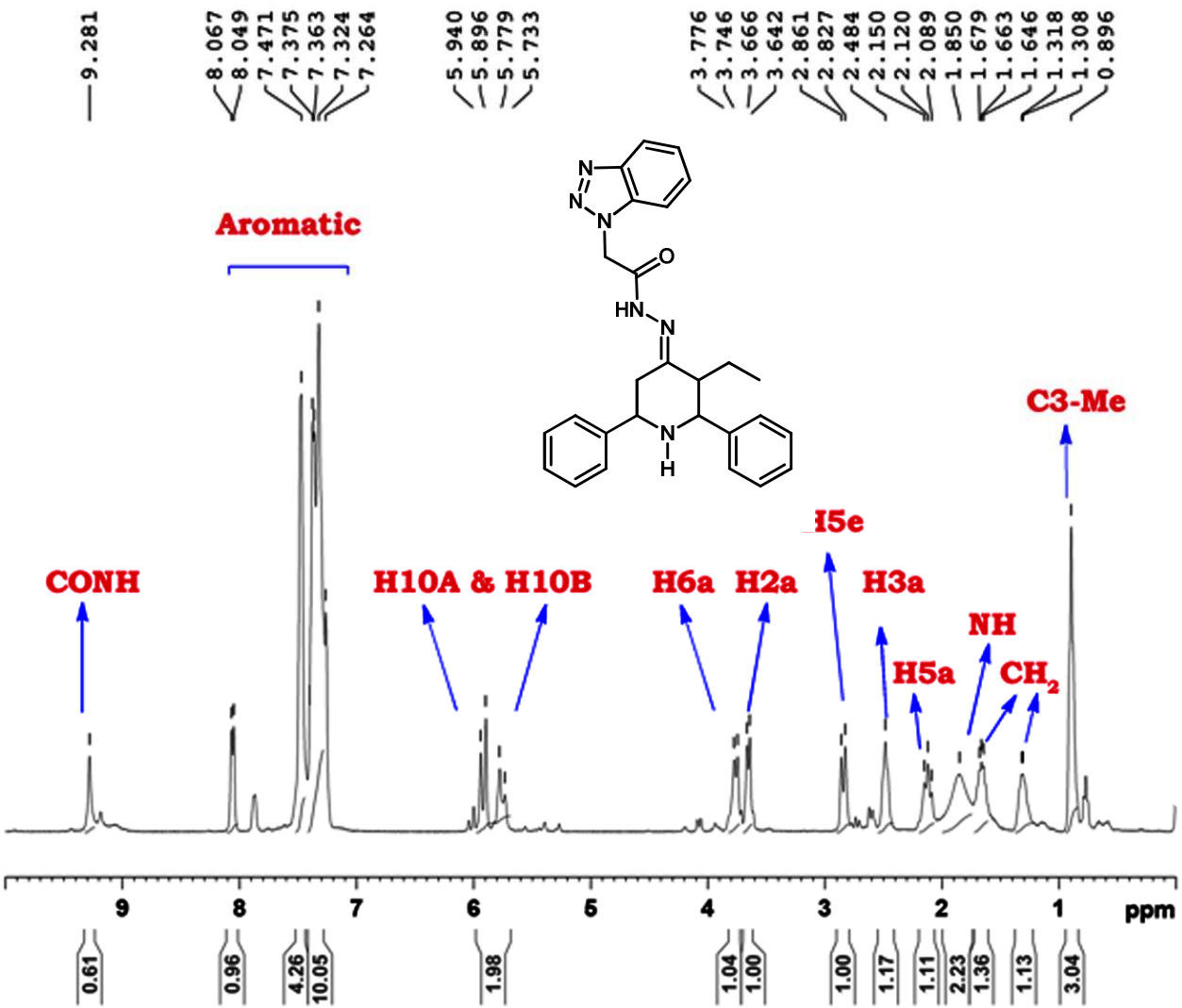


Fig. 2 ^{1}H NMR spectrum of compound **16**

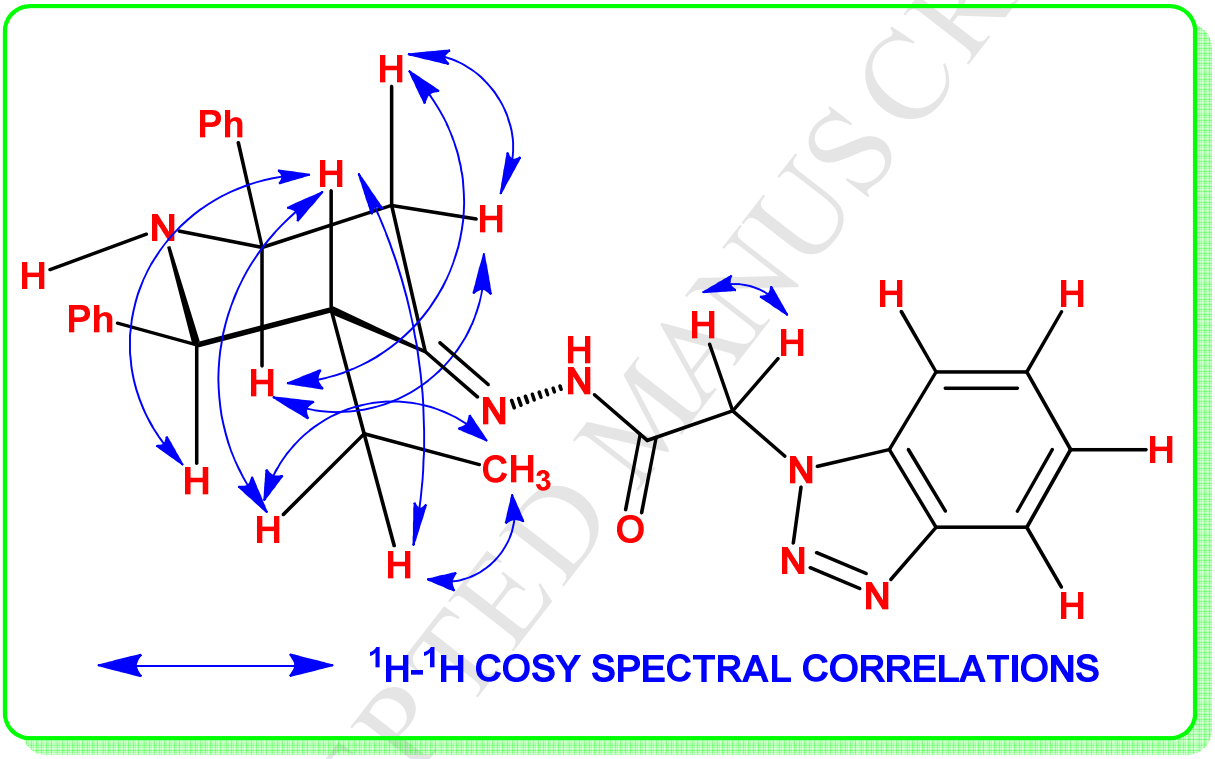


Fig. 3 ^{1}H-^{1}H COSY spectral correlations of compound **16**

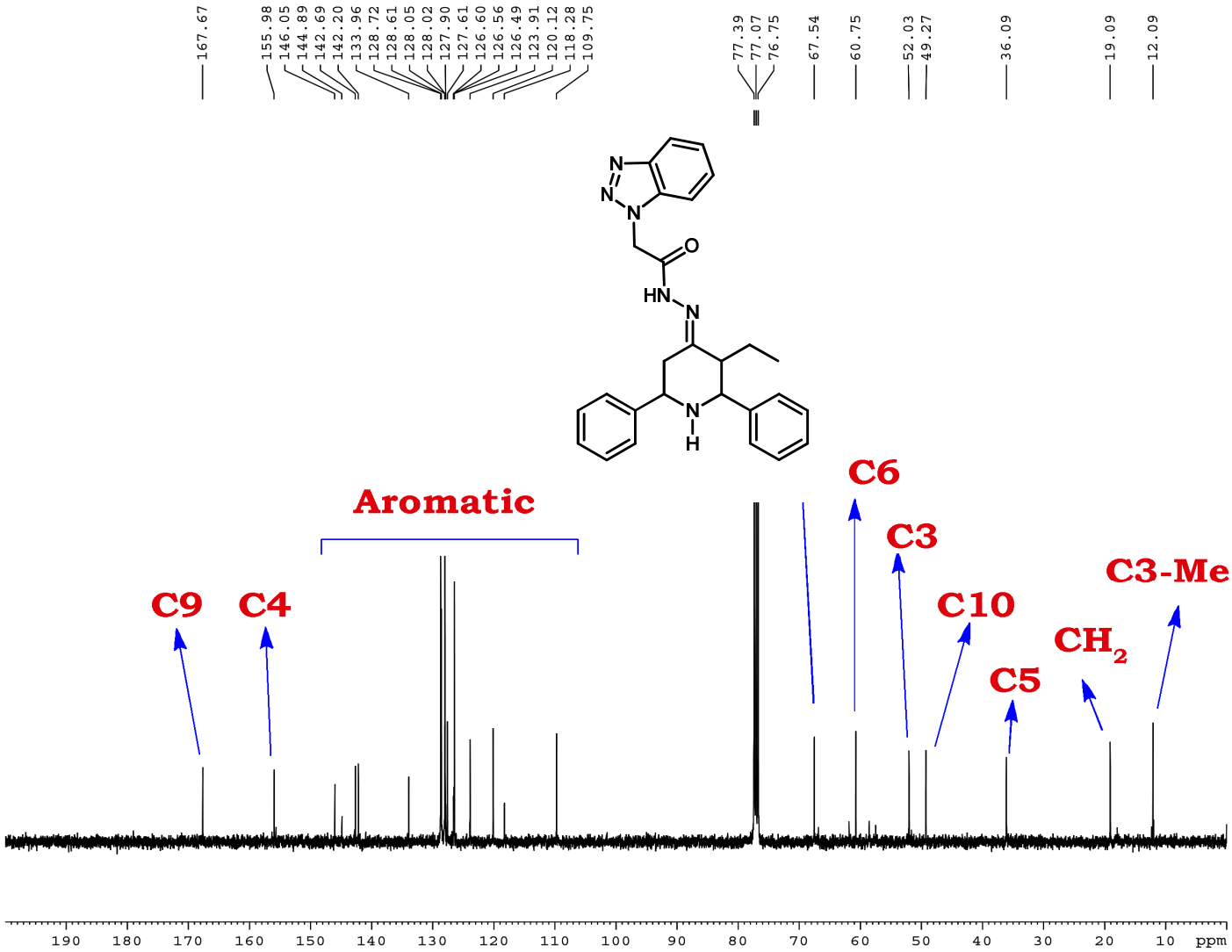


Fig. 4 ^{13}C NMR spectrum of compound **16**

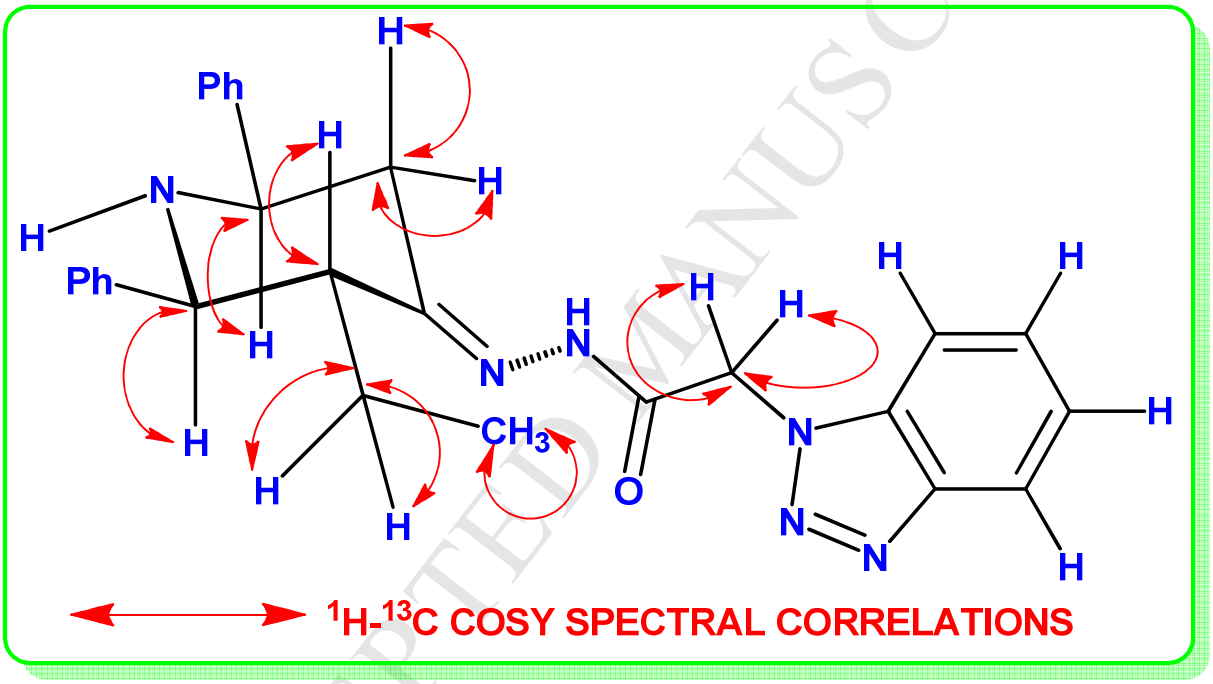


Fig. 5 ^{1}H-^{13}C COSY spectral correlations of compound **16**

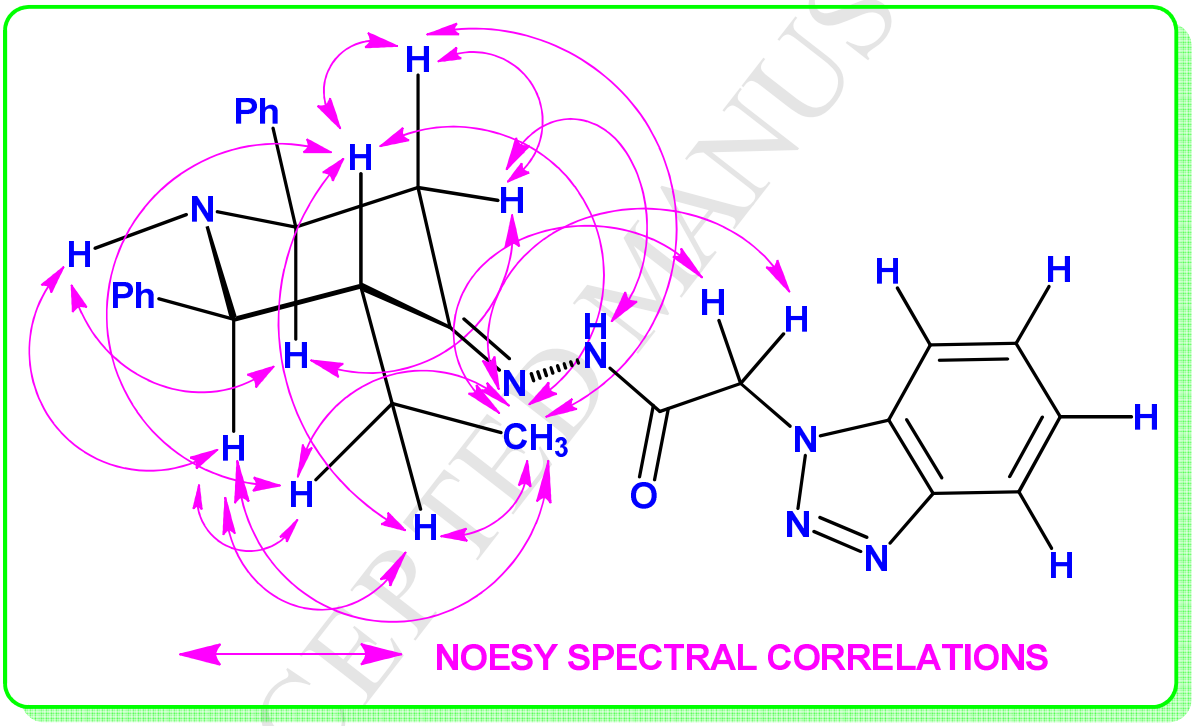
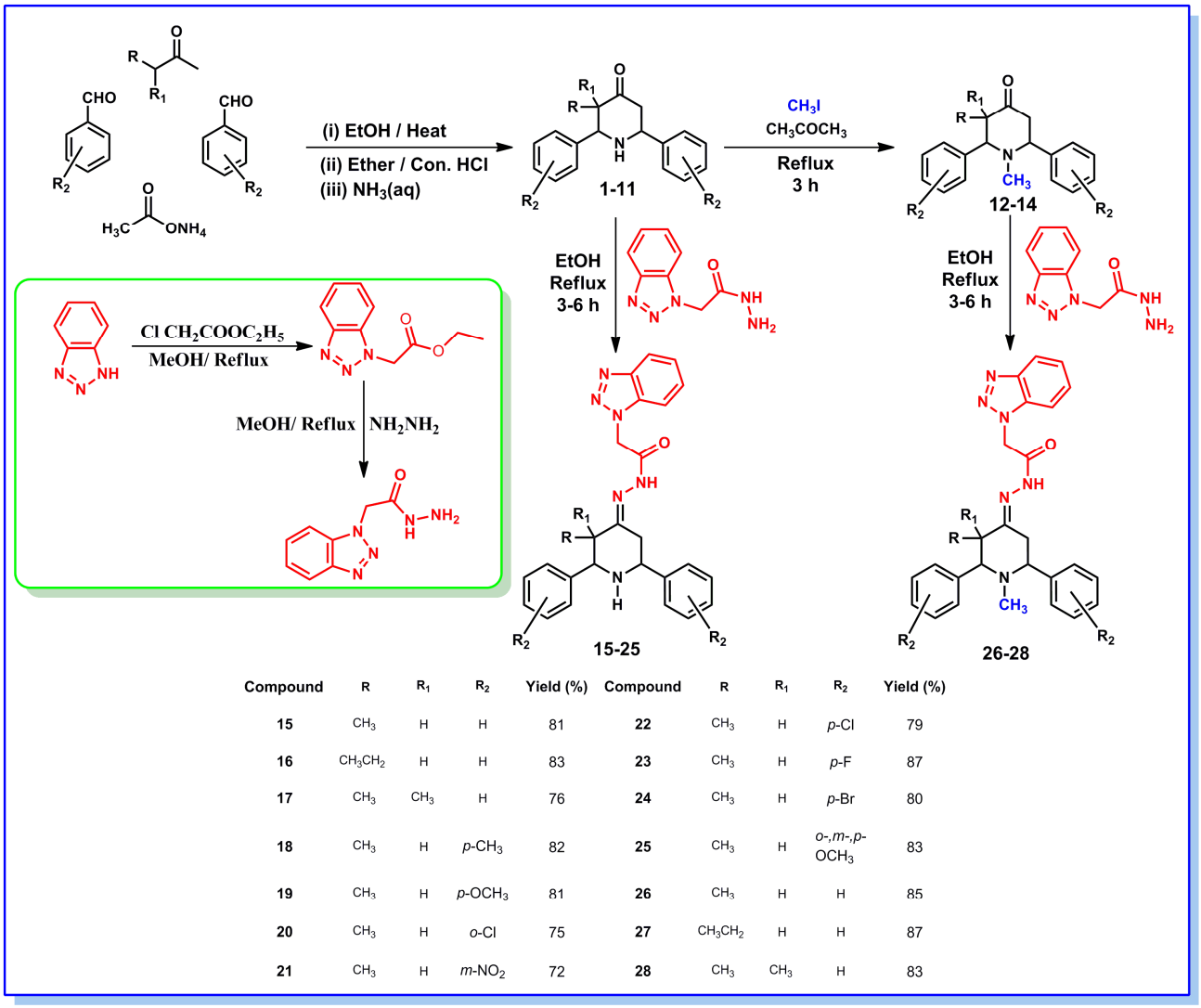


Fig. 6 NOESY spectral correlations of compound **16**



Compound	R	R_1	R_2	Yield (%)	Compound	R	R_1	R_2	Yield (%)
15	CH_3	H	H	81	**22**	CH_3	H	*p*-Cl	79
16	CH_3CH_2	H	H	83	**23**	CH_3	H	*p*-F	87
17	CH_3	CH_3	H	76	**24**	CH_3	H	*p*-Br	80
18	CH_3	H	*p*-CH_3	82	**25**	CH_3	H	*o*-,*m*-,*p*-OCH_3	83
19	CH_3	H	*p*-OCH_3	81	**26**	CH_3	H	H	85
20	CH_3	H	*o*-Cl	75	**27**	CH_3CH_2	H	H	87
21	CH_3	H	*m*-NO_2	72	**28**	CH_3	CH_3	H	83

Scheme 1 Synthetic scheme of benzotriazolylacetyl hydrazones **15–28**

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HIGHLIGHTS

- Selective synthesis of bio pertinent benzotriazole and piperidine containing molecules
- Characterization of the compounds through various spectral techniques
- 2D-NMR for unambiguous spectral assignments of signals
- Establishment of stereochemistry through spectral data

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