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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of some pyrazolylaldehyde *N*-isonicotinoyl hydrazones and 2,5-disubstituted 1,3,4-oxadiazoles as DNA photocleaving agents

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Abstract In search of potential biologically active compounds, some novel 2,5-disubstituted 1,3,4-oxadiazole derivatives have been prepared conveniently via oxidation of newly synthesized pyrazolylaldehyde *N*-isonicotinoyl hydrazones by (diacetoxyiodo)benzene in dichloromethane under mild reaction conditions. Compounds were obtained in excellent yields, and their structures have been established on the basis of their FT-IR, ^{1}H, ^{13}C NMR, and mass spectral data. The DNA photocleavage potential for all the synthesized compounds was evaluated using agarose gel electrophoresis. It has been observed that oxadiazole derivatives showed a significant level of DNA photocleavage activity when compared with their corresponding hydrazones, and some modifications in the basic structure may lead to construct some potential chemotherapeutic agents in future.

Keywords Pyrazole · Oxadiazole · Hydrazone · Isonicotine · DNA photocleavage · (Diacetoxyiodo)benzene

Introduction

Isoniazid, a heterocyclic compound containing pyridine moiety, is still being considered as one of the leading pharmacophore in the development of potential bioactive compounds (Judge *et al.,* 2012a). Compounds containing isoniazid moiety possess a wide range of biological significance as anti-mycobacterial (Nikaljea *et al.,* 2012), antimicrobial (Deep *et al.,* 2012), anticancer (Kumar *et al.,* 2011), anti-tubercular (Sriram *et al.,* 2011, 2012), analgesic (Deodhar *et al.,* 2012), and anti-viral and antifungal agents (Judge *et al.*, 2012b). Pyridine nucleus is a basic unit of many drugs, vitamins, dyes, insecticides, and herbicides (Elguero *et al.*, 1996). Some isonicotinoyl hydrazones are known to exhibit anti-tubercular (Sousa *et al.*, 2014; Ríkova *et al.*, 2011), antitumor (Martins *et al.*, 1999), DNA-binding, and photocleavage activity (Gowda *et al.*, 2013).

On the other hand, azoles derivatives are well known for their great biological (Kaur *et al.*, 2014; Lu *et al.*, 2012; Bondock *et al.*, 2013) and medicinal significance (Kumar *et al.,* 2013a; Hassan *et al.*, 2012). Among azoles, substituted pyrazoles have possessed a broad spectrum of biological properties such as anti-tumor (Mohareb *et al.*, 2012), anti-tubercular (Ravala *et al.*, 2011), antioxidant (Al-Ayed, 2011), anti-inflammatory (Kumar *et al.*, 2013b; Bekhit *et al.*, 2009), anti-bacterial (Kumar *et al.*, 2005), anti-obesity (Gupta *et al.*, 2011), and antidepressant (Aziz *et al.*, 2009) activities. Similarly, 2,5-disubstituted 1,3,4-oxadiazoles and their derivatives have proven their role as bioactive agents and thus play an important role in the field of medicinal chemistry. These compounds in particular are well known for their great biological potential specifically in the presence of some other potent heterocycles. Several, 1,3,4-oxadiazoles derivatives have shown biological and pharmacological activities like antifungal (Merugu *et al.*, 2011; Chandrakantha *et al.*, 2010), anticancer (Dash *et al.*, 2011), immunosuppressive (Zhang *et al.*, 2012; Tang *et al.*, 2012), and antimicrobial (Bakht *et al.*, 2010; Joshi and Parikh, 2014).

In recent years, attention has been paid to evaluate the DNA photocleavage potential of some azoles such as oxadiazoles

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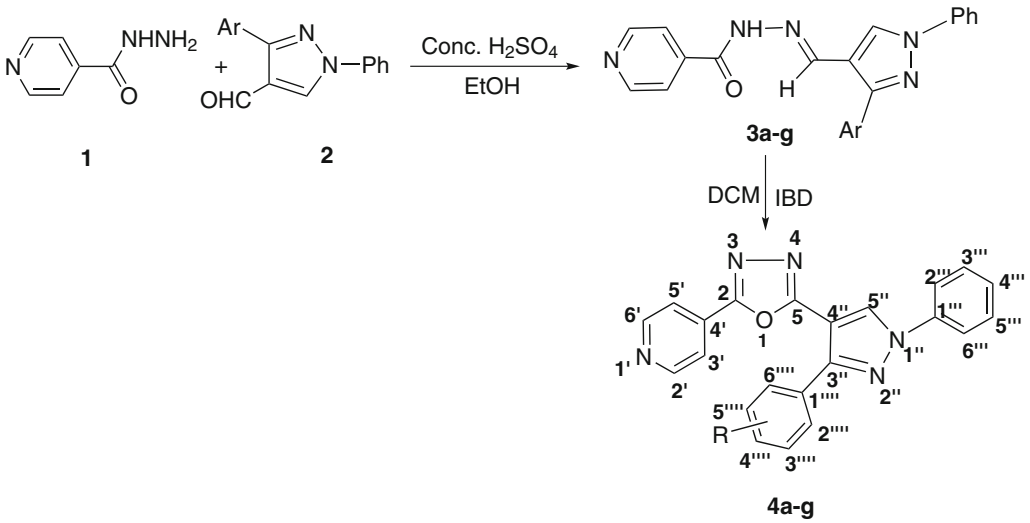
(Kulkarni *et al.*, 2011; Hanumanagoud and Basavaraja, 2012; Taj *et al.*, 2012) or heteroaryl-linked hydrazones (Gowda *et al.*, 2013) may be because of their binding or interacting ability with the DNA structure. Therefore, such nitrogen-containing heterocyclic compounds could be used as probes for DNA structure, potential chemotherapeutic and diagnostic agents (Kurdekar *et al.*, 2011). DNA is a site where most of the chemotherapeutic drugs act and interact, which may result in DNA photocleavage leading to inhibition or death of cancerous cells (Raman and Raja, 2007). In light of the above facts, it was decided to synthesize some novel pyrazole-linked isonicotinoyl hydrazones which were further converted into 2,5-disubstituted 1,3,4-oxadiazoles under mild conditions and evaluate their DNA photocleavage activity. In past years, organic synthesis has acquired various advantages such as shorter reaction time and higher regio-selectivity (Aggarwal *et al.*, 2007, Gupta *et al.*, 2014; Pal *et al.*, 2014), use of greener solvents or reagents with low toxicity profile. In this concern, organoiodine (III) reagents like (Diacetoxyiodo)benzene (DIB), hydroxy tosyloxy iodobenzene (HTIB). etc. are well known for their non-toxic and eco-friendly behavior in organic synthesis (Vorvoglis, 1997; Zhdankin, 2009). Due to low toxicity and selective nature (Kumar, 2012; Yang and Dai, 1993), these reagents have been extensively used for the synthesis of various heterocycles such as triazoles, oxadiazoles, etc. Herein also, some disubstituted 1,3,4-oxadiazoles were prepared using DIB.

Result and discussion

Chemistry

It has already been reported in the literature that disubstituted 1,3,4-oxadiazoles were synthesized using different reagents like phosphorus oxychloride (Jha *et al.*, 2010), phosphorus pentaoxide (Rostamizadeh and Ghamkhar, 2008), and acetic anhydride (Oliveira *et al.*, 2012), etc. which are toxic in nature. In continuation of our interest to synthesize biologically active compounds, herein, we report the synthesis of some novel pyrazole-linked isonicotinoyl hydrazones which on oxidative transformation by iodobenzene diacetate (IBD) in dichloromethane under mild conditions gave 2,5-disubstituted 1,3,4-oxadiazoles (Scheme 1).

The pyrazolylaldehyde isonicotinoyl hydrazones **3** were obtained by the condensation of **1** with substituted 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **2** in ethanol and dichloromethane (DCM) in the presence of a catalytic amount of concentrated sulfuric acid under reflux conditions as adopted by Prakash *et al.* (2010, 2011) for different derivatives. The final products (**4**) were obtained in 88–92 % yields with high purity by oxidative cyclization of **3** in the presence of 1.1 equivalent of IBD under mild conditions (Scheme 1). Various 1,3,4-oxadiazole derivatives were also prepared via oxidation of substituted hydrazones such as *N*-acylhydrazones (Yang and Dai, 1993) with 1.1 equivalent of (diacetoxyiodo)benzene in dichloromethane at room temperature. In the present investigation, total fourteen novel compounds were prepared and characterized on the basis of FT-IR, ^{1}H, ^{13}C NMR, and mass spectral data. The absorption bands for –NH and –C=O stretching vibration appeared in the IR spectra of the compounds **3a–g** at 3421 and 1665 cm^{-1}, respectively. The compounds **3a–g** displayed two singlets due to 5-H of pyrazole ring and N=CH around at δ 9.05 and 8.59, respectively. In ^{1}H NMR spectra of **3a–g**, the characteristic downfield signal at δ 11.97 is attributed to the *N*H proton, and rest of the protons exhibit multiplet in the aromatic region. The chemical shifts in ^{13}C NMR spectra at around δ



Scheme 1 Synthesis of isonicotinoyl hydrazones **(3a–g)** and oxadiazoles **(4a–g)**

142.0–142.4, 127.2, and 161.1 correspond to N=CH, pyrazole-5, and carbonyl carbons, respectively.

The structures of the final products (**4**) were established by comparing FT-IR, ^{1}H, and ^{13}C NMR spectral data with those of the compounds **3a–g**. The FT-IR spectrum of **4** was transparent in the region of –NH and –C=O stretching and thus confirmed the successful oxidation of **3** into **4**. Disappearance of chemical shifts at δ 8.59–8.66 (N=CH) and 11.91–11.99 (*N*H) in ^{1}H NMR spectrum of each product (**4a–g**) confirmed the oxidative transformation of isonicotinoyl hydrazones into 2,5-disubstituted 1,3,4-oxadiazoles. The ^{13}C NMR spectra displayed signals at around δ 160.2, 161.5 for oxadiazole carbons and other signals at δ 150.8, 105.5 and 131.6 correspond to pyrazole ring carbon-3″, 4″, 5″, respectively. In ^{13}C NMR spectrum, disappearance of a signal in range of δ 142.0–142.4 due to N=CH functionality further confirmed the formation of titled compounds.

The ^{1}H and ^{13}C correlation of compound **3** or **4** was assigned on the basis of DEPT-135, COSY, HSQC, and ROESY experiments. In the ^{13}C NMR spectrum, 16 carbon signals were appeared. Further, the DEPT-135 spectra showed only 10 signals corresponding to methine carbons and other six quaternary carbons. The HSQC spectrum of compound **3** indicated that 5′ and 6′-H resonated at δ 9.05 and 8.59, respectively, with the corresponding carbon signals of C-5′ and C-6′ at δ 127.2 and 142.2, respectively. In the same spectrum, two set of protons 2, 6-H and 3, 5-H appeared at δ 8.78 and 7.83, respectively, which gave correlation by carbon signals of carbons 2, 6 and 3, 5 at δ 150.3 and, 121.5, respectively.

Furthermore, the correlation between carbons and protons in spectrum of the compound **4** was also estimated by HSQC spectrum. In this case, protons 5″ and 2‴, 6‴-H gave signals at δ 9.48 and 8.02, respectively, along with cross-signals by the carbons, C-5″ and C-2‴, 6‴ at δ 131.6 and 118.9, respectively. Moreover, 2′, 6′ and 3′, 5′-H protons shared signals at δ 8.84 and 7.90, respectively, which gave correlation with carbons, C-2′, 6′ and C-3′, 5′ at δ 150.9 and 119.98. The disappearance of NMR signal at δ 142.2 also indicated the formation of oxadiazole.

The COSY spectra have shown well correlation between protons with adjacent protons. It has been observed from ^{1}H NMR and COSY spectra that signals at δ 7.83 and 8.78 correspond to pyridine ring, while 6′-H and –NH signals at δ 8.59 and 11.97 did not show coupling with any other proton.

The formation of compound **4** was also confirmed on the basis of disappearance of signals at δ 8.59 and 11.97. The COSY spectra indicated that the signals at δ 7.90 and 8.84 correspond to pyridine ring. However, the pyrazole proton, 5″-H is resonated at δ 9.48.

ROESY experiment

The stereochemistry of the compound **3** or **4** was established by analyzing the ROESY spectra. The ROESY spectra of isonicotinoyl hydrazones **3** have shown a clear space interaction between the –NH proton with 6′ and 3, 5-H protons. The protons 5′-H and 6′-H showed a close relationship in space with 2″, 6″ and 2‴, 6‴-H, respectively. The four possible configurations for **3a** are given in Fig. 1.

The configuration **I** was in full agreement with the observation drawn from the ROESY spectra. Therefore, the confirmed structure of compound **3** should be of type-**I**. The ROESY experiment also provided a great help for assigning the structure of compound **4** in which the spectra were clearly showing the ROEs between 5″-H with 2‴, 6‴-H. Further, the proton signals due to 2⁗ and 6⁗-H are

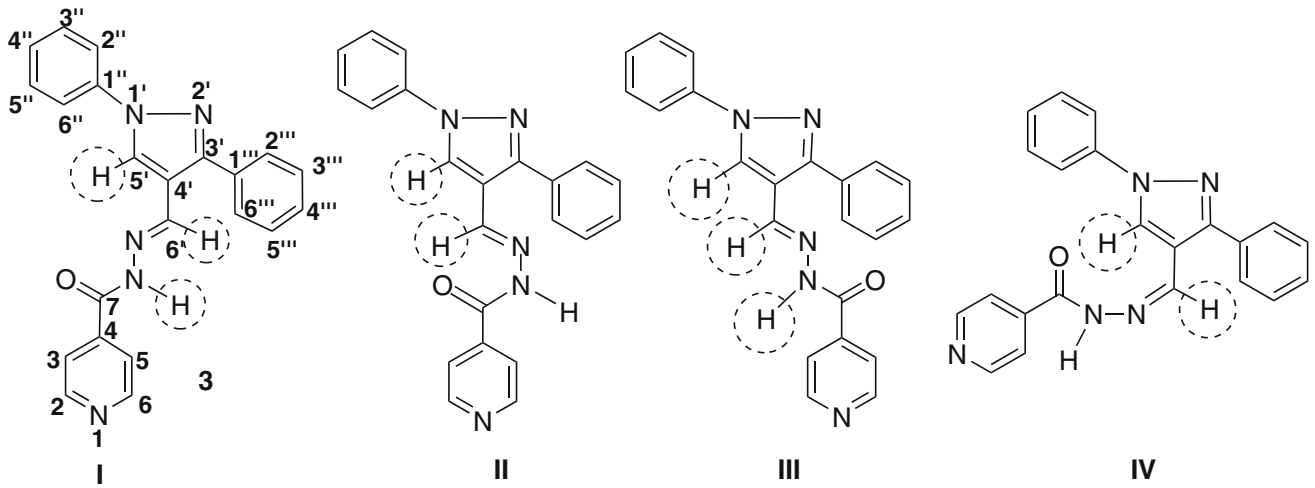


Fig. 1 Possible configurations of isonicotinoyl hydrazone **3a**

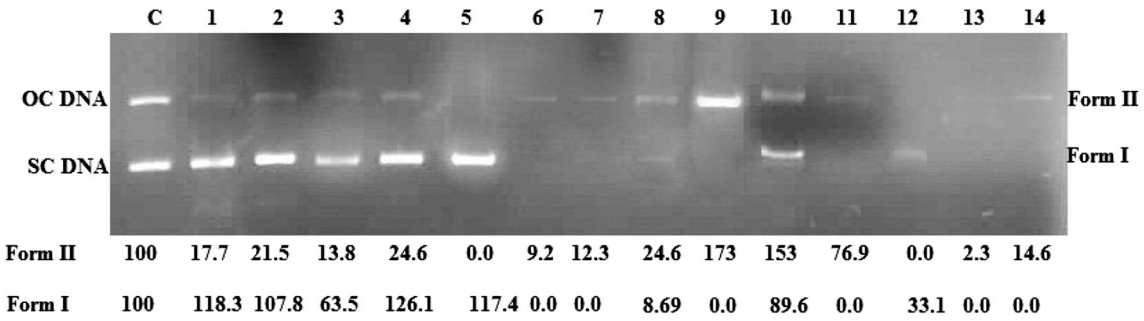


Fig. 2 Plasmid DNA photocleavage picture

shifted to higher value because of the anisotropic effect of oxygen atom of the oxadiazole formed after cyclization of the corresponding hydrazone compound.

Biological evaluation

Plasmid DNA photocleavage study

Figure 2: Lane C: Control plasmid DNA + UV + DMSO, Lane 1 DNA + 40 μg **3a**, Lane 2 DNA + 40 μg **3b**, Lane 3 DNA + 40 μg **3c**, Lane 4 DNA + 40 μg **3d**, Lane 5 DNA + 40 μg **3e**, Lane 6 DNA + 40 μg **3f**, Lane 7 DNA + 40 μg **3g**, Lane 8 DNA + 40 μg **4a**, Lane 9 DNA + 40 μg **4b**, Lane 10 DNA + 40 μg **4c**, Lane 11 DNA + 40 μg **4d**, Lane 12 DNA + 40 μg **4e**, Lane 13 DNA + 40 μg **4f**, Lane 14 DNA + 40 μg **4g**, respectively.

The DNA photocleavage study was performed using agarose gel electrophoresis, and the overall pattern is shown in Fig. 2. No DNA cleavage was observed for negative control (lane C). A significant change in intensity of DNA Forms (I, II) in case of isonicotinoyl hydrazones as well as oxadiazoles in comparison with untreated DNA indicated some kinds of fragmentations or interactions caused by the compounds. In case of isonicotinoyl hydrazones, compounds **3a, 3b, 3d,** and **3e** (Lane 1, 2, 4, and 5, respectively), the intensity of Form I of *p*BR322 DNA was found to be increased, while Form II was either decreased or completely diminished as compared to the control (Lane C). However, compound **3c** (Lane 3) decreased the intensity of both the forms in comparison with control. The compounds **3f** and **3g** (Lane 6 and 7) were found responsible to a significant decrease in intensity of Form II and complete disappearance of Form I, whereas for oxadiazoles (**4**), the intensity of open circular DNA (Form II) was found to be increased to a large extent in comparison with control in cases of compounds **4b** and **4c** (Lane 9 and 10, respectively). However, rest of the oxadiazoles (**4a**, **4d**–**g**) was responsible for either complete disappearance of Form I or highly reduced value of its intensity. It has been observed in case of oxadiazoles intensity of Form I is either decreased or diminished to a great extent in comparison with hydrazones.

In case of hydrazone **3b** in which nitro group is present at *para*-position of phenyl ring attached to pyrazole moiety, both the forms of DNA appeared with low intensity in comparison with control. On the other hand, its corresponding oxadiazole (**4b**) was found to be the most effective agent due to its selective nature to convert the Form I into Form II to a large extent. The most effective nature of oxadiazole nucleus was further indicated by the results of other oxadiazoles in comparison with hydrazones (Fig. 2). The hydrazones (**3f–g**) as well as their corresponding oxadiazoles (**4f–g**) bearing bromo or methyl substitution at *para*-position of phenyl ring attached to pyrazole ring completely degraded the Form I and reduced intensity of Form II to a large extent in comparison with control. The hydrazone bearing fluoro substitution is responsible for converting the Form II to Form I; however, its corresponding oxadiazole was found to be responsible for diminishing the Form I and reducing the intensity of Form II. The overall results observed from the present study have indicated that oxadiazole derivatives possessed more potential for DNA photocleavage as compared to isonicotinoyl hydrazones.

Conclusion

In present investigation, we have reported the synthesis of some novel unsymmetrical 1,3,4-oxadiazole derivatives via oxidative cyclization of some newly synthesized isonicotinoyl hydrazones using IBD as a mild oxidizing agent and thus extended potential of organoiodine (III) reagents in heterocycles synthesis. Structures of the synthesized compounds have been established by rigorous analysis of their NMR spectral data. The DNA photocleavage potential was evaluated for all the synthesized compounds using agarose gel electrophoresis. A significant change in intensity of both the Forms (I and II) of *p*BR322 DNA was observed in case of isonicotinoyl hydrazones as

well as oxadiazoles. Compounds **3c**, **3f, 3g**, **4b**, and **4d–g** have emerged as the most active DNA photocleaving agents among all the synthesized compounds. Furthermore, the present study have indicated that oxadiazole derivatives possessed more potential for DNA photocleavage as compared to isonicotinoyl hydrazones and some modifications in the basic structure may lead to construct some potential chemotherapeutic agents in future.

Experimental

Chemistry-materials and methods

Melting points of all compounds were determined in open capillary using digital melting point apparatus and are uncorrected. IR spectra were recorded as KBr disks on a PerkinElmer Spectrophotometer in the 4000–450 cm^{-1} range. Both ^{1}H and ^{13}C NMR ($CDCl_3$/DMSO-d_6) spectra of the synthesized compounds were recorded on a Bruker Advance at 400 and 100 MHz, respectively. Chemical shifts were measured relative to internal standard TMS ($\delta = 0$) on δ scale (ppm). Mass spectra were recorded on Agilent Mass Spectrometer, and carbon, nitrogen, hydrogen contents were analyzed using LECO 9320 analyzer. Isoniazid **1** (Manjunatha *et al.*, 2010), 4-formylpyrazoles (**2**) (Rajput and Rajput, 2011) utilized in present investigation were synthesized according to the literature methods.

*Synthesis of Isonicotinoyl hydrazones (**3a–g**)*

General procedure A solution of an appropriate 4-formylpyrazole derivative (**2**, 0.01 mol) in dichloromethane was added to an ethanolic solution of isoniazid (**1**, 0.01 mol). One drop of concentrated sulfuric acid was added to the reaction mass and refluxed it for 40–45 min till completion of reaction. The reaction was monitored by thin-layer chromatography. The excess of solvent was evaporated and then cooled to room temperature. The obtained product was filtered, washed with alcohol, and recrystallized from ethanol. Noted m.p. and submitted to analysis.

N-Isonicotinoyl-N′-(1′,3′-diphenyl-4′-pyrazolylmethylidene)hydrazine (**3a**) Yield 92 %; mp 195–197 °C; $R_f = 0.09$ [ethylacetate: hexane (1:1)]; IR (KBr) υ_{max}: 3427 (N–H str.), 1668 (C=O str.) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz,): $\delta = 11.97$ (1H, s, H–N, D_2O exchangeable), 9.05 (1H, s, H-5′), 8.79 (2H, d, $J = 3.6$ Hz, H-2, H-6), 8.59 (1H, s, H-6′), 8.04 (2H, d, $J = 7.6$ Hz, H-2″, H-6″), 7.83 (2H, d, $J = 3.2$ Hz, H-3, H-5), 7.75 (2H, d, $J = 6.8$ Hz, H-2‴, H-6‴), 7.39–7.55 (6H, m, H-3″, H-4″, H-5″ & H-3‴, H-4‴, H-5‴); ^{13}C NMR (DMSO-d_6, 100 MHz,): $\delta = 161.1$ (C, C-7), 152.1 (C, C-3′), 150.3 (CH, C-2, C-6), 142.2 (CH, C-6′), 140.5 (C, C-1″), 139.0 (C, C-4), 131.9 (C, C-1‴), 129.6 (CH, C-3‴, C-5‴), 128.8 (CH, C-3″, C-5″), 128.7 (C, C-4‴), 128.4 (CH, C-2‴, C-6‴), 127.2 (CH, C-5′), 127.0 (CH, C-4″), 121.5 (CH, C-3, C-5), 118.8 (CH, C-2″, C-6″), 116.6 (C, C-4′); MS (ESI) m/z: 368.14 $(M + 1)^+$; Anal. Calcd. for $C_{22}H_{17}N_5O$: C, 71.91; H, 4.63; N, 19.07. Found: C, 71.89; H, 4.62; N, 19.05.

N-Isonicotinoyl-N′-[3′-(4‴-nitrophenyl)-1′-phenyl-4′-pyrazolylmethylidene]hydrazine (**3b**) Yield 87.5 %; mp 256–257 °C; $R_f = 0.05$ [ethylacetate: hexane (1:1)]; IR (KBr) υ_{max}: 3430 (N–H str.), 1667 (C=O str.), 1540 (NO_2 asymmetric str.), 1351 (NO_2 symmetric str.) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz,): $\delta = 11.99$ (1H, s, H–N, D_2O exchangeable), 9.01 (1H, s, H-5′), 8.77 (2H, d, $J = 5.9$ Hz, H-2, H-6), 8.66 (1H, s, H-6′), 8.36 (2H, d, $J = 8.4$ Hz, H-3‴, H-5‴), 8.14 (2H, d, $J = 8.0$ Hz, H-2‴, H-6‴), 8.00 (2H, d, $J = 8.4$ Hz, H-2″, H-6″), 7.85 (2H, d, $J = 5.9$ Hz, H-3, H-5), 7.37–7.57 (3H, m, H-3″, H-4″, H-5″); ^{13}C NMR (DMSO-d_6, 100 MHz,): $\delta = 161.1$ (C, C-7), 150.6 (C, C-3′), 150.1 (CH, C-2, C-6), 146.3 (C, C-4‴), 142.1 (CH, C-6′), 140.4 (C, C-1″), 138.8 (C, C-4), 137.1 (C, C-1‴), 128.6 (CH, C-3″, C-5″), 127.5 (CH, C-5′), 127.0 (CH, C-4″), 126.4 (CH, C-2‴, C-6‴), 124.5 (CH, C-3‴, C-5‴), 121.4 (CH, C-3, C-5), 118.7 (CH, C-2″, C-6″), 116.6 (C, C-4′); MS (ESI) m/z: 413.13 $(M + 1)^+$; Anal. Calcd. for $C_{22}H_{16}N_6O_3$: C, 64.06; H, 3.88; N, 20.38. Found: C, 64.05; H, 3.86; N, 20.35.

N-Isonicotinoyl-N′-[3′-(4‴-methoxyphenyl)-1′-phenyl-4′-pyrazolylmethylidene]hydrazine (**3c**) Yield 88.4 %; mp 209–210 °C; $R_f = 0.04$ [ethylacetate: hexane (1:1)]; IR (KBr) υ_{max}: 3421 (N–H str.), 1665 (C=O str.) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz,): $\delta = 11.91$ (1H, s, H–N, D_2O exchangeable), 8.92 (1H, s, H-5′), 8.77 (2H, d, $J = 5.2$ Hz, H-2, H-6), 8.59 (1H, s, H-6′), 7.98 (2H, d, $J = 8.0$ Hz, H-2″, H-6″), 7.85 (2H, d, $J = 5.6$ Hz, H-3, H-5), 7.68 (2H, d, $J = 8.0$ Hz, H-2‴, H-6‴), 7.35–7.54 (3H, m, H-3″, H-4″, H-5″), 7.07 (2H, d, $J = 8.0$ Hz, H-3‴, H-5‴), 3.86 (3H, s, 4‴-OC**H**$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz,): $\delta = 161.2$ (C, C-7), 159.2 (C, C-4‴), 150.6 (C, C-3′), 150.1 (CH, C-2, C-6), 142.0 (CH, C-6′), 140.4 (C, C-1″), 138.9 (C, C-4), 128.4 (CH, C-3″, C-5″), 127.8 (CH, C-5′), 127.4 (CH, C-2‴, C-6‴), 126.9 (CH, C-4″), 121.3 (CH, C-3, C-5), 120.3 (C, C-1‴), 118.8 (CH, C-2″, C-6″), 116.6 (C, C-4′), 114.3 (CH, C-3‴, C-5‴), 55.3 (CH_3, OCH_3); MS (ESI) m/z: 398.15 $(M + 1)^+$; Anal. Calcd. for $C_{23}H_{19}N_5O_2$: C, 69.49; H, 4.78; N, 17.62. Found: C, 69.48; H, 4.77; N, 17.59.

N′-[3′-(4‴-Fluorophenyl)-1′-phenyl-4′-pyrazolylmethylidene]-N-isonicotinoylhydrazine (**3d**) Yield 84 %; mp 258–259 °C; $R_f = 0.14$ [ethylacetate: hexane (1:1)]; IR (KBr) υ_{max}: 3422 (N–H str.), 1663 (C=O str.) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz,): $\delta = 11.92$ (1H, s, H–N, D_2O exchangeable), 8.95 (1H, s, H-5′), 8.77 (2H, d, $J = 5.0$ Hz, H-2, H-6), 8.59 (1H, s, H-6′), 7.98 (2H, d, $J = 8.0$ Hz, H-2″, H-6″), 7.50–7.85 (6H, m, H-3″, H-5″, H-2‴, H-6‴ & H-3, H-5), 7.28–7.38 (3H, m, H-3‴, H-5‴ & H-4″); ^{13}C NMR (DMSO-d_6, 100 MHz,): $\delta = 161.4$ (C, d, $^1J_{C\text{-}F} = 245.3$ Hz, C-4‴), 161.2 (C, C-7), 150.7 (C, C-3′), 150.1 (CH, C-2, C-6), 141.9 (CH, C-6′), 140.5 (C, C-1″), 138.9 (C, C-4), 129.6 (C, d, $^3J_{C\text{-}F} = 8.3$ Hz, C-2‴, C-6‴), 128.8 (C, C-1‴), 128.5 (CH, C-3″, C-5″), 127.7 (CH, C-5′), 127.0 (CH, C-4″), 121.5 (CH, C-3, C-5), 118.7 (CH, C-2″, C-6″), 116.6 (C, C-4′), 116.0 (C, d, $^2J_{C\text{-}F} = 21.6$ Hz, C-3‴, C-5‴); MS (ESI) m/z: 386.13 $(M + 1)^+$; Anal. Calcd. for $C_{22}H_{16}FN_5O$: C, 68.55; H, 4.15; N, 18.17. Found: C, 68.54; H, 4.14; N, 18.15.

N′-[3′-(4‴-Chlorophenyl)-1′-phenyl-4′-pyrazolylmethylidene]-N-isonicotinoylhydrazine (**3e**) Yield 89.3 %; mp 247–248 °C; $R_f = 0.11$ [ethylacetate: hexane (1:1)]; IR (KBr) υ_{max}: 3430 (N–H str.), 1668 (C=O str.) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz,): $\delta = 11.93$ (1H, s, H–N, D_2O exchangeable), 8.96 (1H, s, H-5′), 8.77 (2H, d, $J = 5.8$ Hz, H-2, H-6), 8.59 (1H, s, H-6′), 7.98 (2H, d, $J = 8.0$ Hz, H-2″, H-6″), 7.79–7.85 (4H, m, H-2‴, H-6‴ & H-3, H-5), 7.35–7.56 (5H, m, H-3‴, H-5‴ & H-3″, H-4″, H-5″); ^{13}C NMR (DMSO-d_6, 100 MHz,): $\delta = 161.0$ (C, C-7), 150.6 (C, C-3′), 150.0 (CH, C-2, C-6), 141.9 (CH, C-6′), 140.4 (C, C-1″), 138.9 (C, C-4), 133.5 (C, C-4‴), 130.8 (CH, C-2‴, C-6‴), 130.0 (C, C-1‴), 129.5 (CH, C-3‴, C-5‴), 128.5 (CH, C-3″, C-5″), 127.6 (CH, C-5′), 126.9 (CH, C-4″), 121.4 (CH, C-3, C-5), 118.8 (CH, C-2″, C-6″), 116.7 (C, C-4′); MS (ESI) m/z: 402.10 $(M + 1)^+$, 404.10 $(M + 2)^+$ in the ratio showing typical chlorine isotope profile (3:1); Anal. Calcd. for $C_{22}H_{16}ClN_5O$: C, 65.82; H, 3.99; N, 17.45. Found: C, 65.78; H, 3.97; N, 17.41.

N′-[3′-(4‴-Bromophenyl)-1′-phenyl-4′-pyrazolylmethylidene]-N-isonicotinoylhydrazine (**3f**) Yield 89.4 %; mp 239–240 °C; $R_f = 0.16$ [ethylacetate: hexane (1:1)]; IR (KBr) υ_{max}: 3433 (N–H str.), 1665 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz,): $\delta = 11.93$ (1H, s, H–N, D_2O exchangeable), 8.99 (1H, s, H-5′), 8.77 (2H, d, $J = 5.9$ Hz, H-2, H-6), 8.58 (1H, s, H-6′), 7.99 (2H, d, $J = 8.0$ Hz, H-2″, H-6″), 7.83 (2H, d, $J = 5.8$ Hz, H-3, H-5), 7.37–7.76 (7H, m, H-3‴, H-5‴, H-Ph″ & H-2‴, H-6‴); ^{13}C NMR (DMSO-d_6, 100 MHz,): $\delta = 160.0$ (C, C-7), 150.6 (C, C-3′), 150.0 (CH, C-2, C-6), 142.0 (CH, C-6′), 140.5 (C, C-1″), 138.9 (C, C-4), 132.7 (CH, C-3‴, C-5‴), 129.9 (C, C-1‴), 128.5 (CH, C-3″, C-5″), 127.9 (CH, C-5′), 127.5 (CH, C-2‴, C-6‴), 127.0 (CH, C-4″), 123.9 (C, C-4‴), 121.3 (CH, C-3, C-5), 118.7 (CH, C-2″, C-6″), 116.5 (C, C-4′); MS (ESI) m/z: 446.05 $(M + 1)^+$, 448.05 $(M + 2)^+$ in the ratio showing typical bromine isotope profile (1:1); Anal. Calcd. for $C_{22}H_{16}BrN_5O$: C, 59.32; H, 3.59; N, 15.73. Found: C, 59.30; H, 3.58; N, 15.69.

N-Isonicotinoyl-N′-[3′-(4‴-methylphenyl)-1′-phenyl-4′-pyrazolylmethylidene]hydrazine (**3g**) Yield 90 %; mp 199–200 °C; $R_f = 0.07$ [ethylacetate: hexane (1:1)]; IR (KBr) υ_{max}: 3426 (N–H str.), 1666 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz,): $\delta = 9.93$ (1H, s, H–N, D_2O exchangeable), 8.74 (2H, d, $J = 5.2$ Hz, H-2, H-6), 8.61 (1H, s, H-5′), 8.42 (1H, s, H-6′), 7.45–7.80 (9H, m, H-Ph″, H-2‴, H-6‴ & H-3, H-5), 7.25 (2H, d, $J = 8.0$ Hz, H-3‴, H-5‴), 2.17 (3H, s, 4‴-C**H**$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz,): $\delta = 161.1$ (C, C-7), 152.1 (C, C-3′), 150.2 (CH, C-2, C-6), 142.4 (CH, C-6′), 140.5 (C, C-1″), 139.0 (C, C-4), 138.0 (C, C-4‴), 129.4 (CH, C-2‴, C-6‴), 129.2 (CH, C-3‴, C-5‴), 129.1 (C, C-1‴), 128.5 (CH, C-3″, C-5″), 126.9 (CH, C-5′), 126.8 (CH, C-4″), 121.4 (CH, C-3, C-5), 118.7 (CH, C-2″, C-6″), 116.5 (C, C-4′), 20.8 (C, CH_3); MS (ESI) m/z: 382.16 $(M + 1)^+$; Anal. Calcd. for $C_{23}H_{19}N_5O$: C, 72.41; H, 4.98; N, 18.36. Found: C, 72.40; H, 4.96; N, 18.32.

Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles

General procedure IBD (0.011 mol) was added in a lot-wise manner to the suspension or solution of an appropriate isonicotinoyl hydrazone (**3**, 0.01 mol) in dichloromethane under stirring. The reaction mass was further stirred for 1. 0 h, and the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated and residues were triturated with petroleum ether twice to obtain crude product (**4**) which was recrystallised from ethanol.

2-(1″,3″-Diphenyl-pyrazol-4″-yl)-5-(pyridin-4′-yl)-1,3,4-oxadiazole (**4a**) Yield 91 %; mp 177–178 °C; $R_f = 0.22$ [ethylacetate: hexane (1:1)]; IR (KBr) υ_{max}: transparent in the region of (N–H str.) and (C=O str.), 1251 (C–O str.) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz,): $\delta = 9.48$ (1H, s, H-5″), 8.85 (2H, d, $J = 5.4$ Hz, H-2′, H-6′), 8.03 (2H, d, $J = 8.0$ Hz, H-2‴, H-6‴), 7.99 (2H, d, $J = 7.6$ Hz, H-2⁗, H-6⁗), 7.91 (2H, d, $J = 5.6$ Hz, H-3′, H-5′), 7.43–7.59 (6H, m, H-3‴, H-4‴, H-5‴ & H-3⁗, H-4⁗, H-5⁗); ^{13}C NMR (DMSO-d_6, 100 MHz,): $\delta = 161.6$ (C, C-5), 160.2 (C, C-2), 150.9 (CH, C-2′, C-6′), 150.8 (C, C-3″), 138.6 (C, C-4′), 131.6 (CH, C-5″), 131.3 (C, C-1‴), 130.3 (C, C-1⁗), 129.7 (CH, C-3⁗, C-5⁗), 129.1 (C, C-4⁗), 128.8 (CH, C-2⁗, C-6⁗), 128.2 (CH, C-3‴, C-5‴), 127.5 (CH, C-4‴), 120.0 (CH, C-3′, C-5′), 118.9 (CH, C-2‴, C-6‴), 105.5 (C, C-4″); MS (ESI) m/z: 366.13 $(M + 1)^+$; Anal. Calcd. for

$C_{22}H_{15}N_5O$: C, 72.30; H, 4.11; N, 19.17. Found: C, 72.28; H, 4.10; N, 19.15.

2-[3″-(4‴″-Nitrophenyl)-1″-phenyl-pyrazol-4″-yl]-5-(pyridin-4′-yl)-1,3,4-oxadiazole (**4b**) Yield 88.5 %; mp 241–242 °C; $R_f = 0.18$ [ethylacetate: hexane (1:1)]; IR (KBr) υ_{max}: transparent in the region of (N–H str.) and (C=O str.), 1543 (NO_2 symmetric str.), 1349 (NO_2 asymmetric str.), 1247 (C–O str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz,): δ = 9.52 (1H, s, H-5″), 8.87 (2H, d, $J = 5.2$ Hz, H-2′, H-6′), 8.39 (2H, d, $J = 7.8$ Hz, H-3‴″, H-5‴″), 8.18 (2H, d, $J = 8.0$ Hz, H-2‴″, H-6‴″), 8.06 (2H, d, $J = 8.0$ Hz, H-2‴, H-6‴), 7.99 (2H, d, $J = 5.4$ Hz, H-3′, H-5′), 7.46–7.62 (3H, m, H-3‴, H-4‴, H-5‴); ^{13}C NMR (DMSO-d_6, 100 MHz,): δ = 161.5 (C, C-5), 160.1 (C, C-2), 150.8 (CH, C-2′, C-6′), 150.7 (C, C-3″), 145.7 (C, C-4‴″), 138.7 (C, C-4′), 137.2 (C, C-1‴″), 131.4 (CH, C-5″), 130.5 (C, C-1‴), 129.6 (CH, C-2‴″, C-6‴″), 127.5 (CH, C-3‴, C-5‴), 126.7 (CH, C-3‴″, C-5‴″), 126.3 (CH, C-4‴), 119.8 (CH, C-3′, C-5′), 118.7 (CH, C-2‴, C-6‴), 105.3 (C, C-4″); MS (ESI) m/z: 411.1 $(M + 1)^+$; Anal. Calcd. for $C_{22}H_{14}N_6O_3$: C, 64.37; H, 3.41; N, 20.48. Found: C, 64.36; H, 3.39; N, 20.45.

2-[3″-(4‴″-Methoxyphenyl)-1″-phenyl-pyrazol-4″-yl]-5-(pyridin-4′-yl)-1,3,4-oxadiazole (**4c**) Yield 90 %; mp 195–196 °C; $R_f = 0.15$ [ethylacetate: hexane (1:1)]; IR (KBr) υ_{max}: transparent in the region of (N–H str.) and (C=O str.), 1249 (C–O str.) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz,): δ = 8.83 (2H, d, $J = 5.6$ Hz, H-2′, H-6′), 8.71 (1H, s, H-5″), 7.83–7.94 (6H, m, H-3′, H-5′, H-2‴″, H-6‴″-H & H-2‴, H-6‴), 7.39–7.56 (3H, m, H-3‴, H-4‴, H-5‴), 7.05 (2H, d, $J = 7.2$ Hz, H-3‴″, H-5‴″), 3.91 (3H, s, 4‴″-OC**H**$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz,): δ = 161.5 (C, C-5), 160.5 (C, C-2), 159.7 (C, C-4‴″), 151.0 (CH, C-2′, C-6′), 150.9 (C, C-3″), 138.7 (C, C-4′), 131.8 (CH, C-5″), 130.5 (C, C-1‴), 128.6 (CH, C-2‴″, C-6‴″), 128.5 (CH, C-3‴, C-5‴), 126.9 (CH, C-4‴), 120.1 (CH, C-3′, C-5′), 119.1 (C, C-1‴″), 118.9 (CH, C-2‴, C-6‴), 114.2 (CH, C-3‴″, C-5‴″), 105.4 (C, C-4″), 55.3 (CH_3, OCH_3); MS (ESI) m/z: 396.2 $(M + 1)^+$; Anal. Calcd. for $C_{23}H_{17}N_5O_2$: C, 69.84; H, 4.30; N, 17.71. Found: C, 69.82; H, 4.30; N, 17.69.

2-[3″-(4‴″-Fluorophenyl)-1″-phenyl-pyrazol-4″-yl]-5-(pyridin-4′-yl)-1,3,4-oxadiazole (**4d**) Yield 89.3 %; mp 237–238 °C; $R_f = 0.38$ [ethylacetate: hexane (1:1)]; IR (KBr) υ_{max}: transparent in the region of (N–H str.) and (C=O str.), 1253 (C–O str.) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz,): δ = 8.85 (2H, d, $J = 5.4$ Hz, H-2′, H-6′), 8.72 (1H, s, H-5″), 7.83–7.97 (6H, m, H-3′, H-5′, H-2‴″, H-6‴″ & H-2‴, H-6‴), 7.20–7.57 (5H, m, H-3‴″, H-5‴″ & H-3‴, H-4‴, H-5‴); ^{13}C NMR (DMSO-d_6, 100 MHz,): δ = 162.3 (C, d, $^1J_{C\text{-}F} = 246.1$ Hz, C-4‴″), 161.5 (C, C-5), 160.2 (C, C-2), 150.9 (CH, C-2′, C-6′), 150.8 (C, C-3″), 138.6 (C, C-4′), 131.9 (CH, C-5″), 130.6 (C, C-1‴), 130.4 (C, d, $^3J_{C\text{-}F} = 8.4$ Hz, C-2‴″, C-6‴″), 129.8 (C, C-1‴″), 128.4 (CH, C-3‴, C-5‴), 127.6 (CH, C-4‴), 120.1 (CH, C-3′, C-5′), 118.9 (CH, C-2‴, C-6‴), 115.8 (C, d, $^2J_{C\text{-}F} = 21.5$ Hz, C-3‴″, C-5‴″), 105.3 (C, C-4″); MS (ESI) m/z: 384.1 $(M + 1)^+$; Anal. Calcd. for $C_{22}H_{14}FN_5O$: C, 68.91; H, 3.65; N, 18.27. Found: C, 68.90; H, 3.64; N, 18.25.

2-[3″-(4‴″-Chlorophenyl)-1″-phenyl-pyrazol-4″-yl]-5-(pyridin-4′-yl)-1,3,4-oxadiazole (**4e**) Yield 91.2 %; mp 214–215 °C; $R_f = 0.35$ [ethylacetate: hexane (1:1)]; IR (KBr) υ_{max}: transparent in the region of (N–H str.) and (C=O str.), 1246 (C–O str.) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz,): δ = 9.51 (1H, s, H-5″), 8.86 (2H, d, $J = 5.2$ Hz, H-2′, H-6′), 8.02–8.07 (4H, m, H-2‴″, H-6‴″-H & H-2‴, H-6‴), 7.94 (2H, d, $J = 5.6$ Hz, H-3′, H-5′), 7.58–7.60 (4H, m, H-3‴″, H-5‴″ & H-3‴, H-5‴), 7.43–7.46 (1H, t, H-4‴); ^{13}C NMR (DMSO-d_6, 100 MHz,): δ = 162.2 (C, C-5), 160.6 (C, C-2), 151.5 (CH, C-2′, C-6′), 150.0 (C, C-3″), 139.0 (C, C-4′), 134.4 (C, C-4‴″), 132.4 (CH, C-5″), 131.0 (CH, C-2‴″, C-6‴″), 130.8 (C, C-1‴), 130.7 (C, C-1‴″), 130.2 (CH, C-3‴″, C-5‴″), 128.8 (CH, C-3‴, C-5‴), 128.2 (CH, C-4‴), 120.6 (CH, C-3′, C-5′), 119.5 (CH, C-2‴, C-6‴), 106.1 (C, C-4″); MS (ESI) m/z: 400.08 $(M + 1)^+$, 402.08 $(M + 2)^+$ in the ratio showing typical chlorine isotope profile (3:1); Anal. Calcd. for $C_{22}H_{14}ClN_5O$: C, 66.15; H, 3.51; N, 17.54. Found: C, 66.10; H, 3.50; N, 17.50.

2-[3″-(4‴″-Bromophenyl)-1″-phenyl-pyrazol-4″-yl]-5-(pyridin-4′-yl)-1,3,4-oxadiazole (**4f**) Yield 90.2 %; mp 203–204 cm^{-1}; $R_f = 0.37$ [ethylacetate: hexane (1:1)]; IR (KBr) υ_{max}: transparent in the region of (N–H str.) and (C=O str.), 1246 (C–O str.) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz,): δ = 8.86 (2H, d, $J = 5.4$ Hz, H-2′, H-6′), 8.70 (1H, s, H-5″), 7.82–7.89 (6H, m, H-2‴″, H-6‴″ & H-Ph‴), 7.65 (2H, d, $J = 5.2$ Hz, H-3′, H-5′), 7.41–7.57 (3H, m, H-3‴″, 5‴″ & H-4‴); ^{13}C NMR (DMSO-d_6, 100 MHz,): δ = 161.6 (C, C-5), 160.0 (C, C-2), 151.0 (CH, C-2′, C-6′), 150.7 (C, C-3″), 138.2 (C, C-4′), 133.7 (CH, C-3‴″, C-5‴″), 132.0 (CH, C-5″), 131.6 (C, C-1‴″), 130.8 (C, C-1‴), 130.6 (CH, C-2‴″, C-6‴″), 128.5 (CH, C-3‴, C-5‴), 127.6 (CH, C-4‴), 124.6 (C, C-4‴″), 120.2 (CH, C-3′, C-5′), 119.3 (CH, C-2‴, C-6‴), 105.8 (C, C-4″); MS (ESI) m/z: 444.03 $(M + 1)^+$, 446.03 $(M + 2)^+$ in the ratio showing typical bromine isotope profile (1:1); Anal. Calcd. for $C_{22}H_{14}BrN_5O$: C, 59.59; H, 3.16; N, 15.80. Found: C, 59.57; H, 3.14; N, 15.78.

2-[3″-(4‴″-Methylphenyl)-1″-phenyl-pyrazol-4″-yl]-5-(pyridin-4′-yl)-1,3,4-oxadiazole (**4g**) Yield 92 %; mp 185–186 °C; $R_f = 0.25$ [ethylacetate: hexane (1:1)]; IR (KBr) υ_{max}: transparent in the region of (N–H str.) and

(C=O str.), 1253 (C–O str.) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz,): δ = 8.81 (2H, d, *J* = 5.6 Hz, H-2′, H-6′), 8.72 (1H, s, H-5″), 7.79–7.88 (6H, m, H-3′, H-5′, H-2‴, H-6‴ & H-2‴, H-6‴), 7.39–7.56 (3H, m, H-3‴, H-4‴, H-5‴), 7.33 (2H, d, *J* = 7.6 Hz, H-3‴, H-5‴), 2.47 (3H, s, 4‴-C**H**$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz,): δ = 161.6 (C, C-5), 160.3 (C, C-2), 150.9 (CH, C-2′, C-6′), 150.8 (C, C-3″), 138.6 (C, C-4′), 138.5 (C, C-4‴), 131.6 (CH, C-5″), 130.5 (CH, C-2‴, C-6‴), 129.6 (C, C-1‴), 128.8 (C, C-1‴), 128.6 (CH, C-3‴, C-5‴), 128.5 (CH, C-3‴, C-5‴), 127.5 (CH, C-4‴), 120.0 (CH, C-3′, C-5′), 118.9 (CH, C-2‴, C-6‴), 105.4 (C, C-4″), 20.9 (C, CH_3); MS (ESI) m/z: 380.14 $(M + 1)^+$; Anal. Calcd. for $C_{23}H_{17}N_5O$: C, 72.80; H, 4.48; N, 18.46. Found: C, 72.78; H, 4.46; N, 18.45.

Biological activity

DNA photocleavage study

DNA photocleavage experiment was performed by taking 10 µl solution containing *p*BR322 DNA in TE (*Tris* 10 mM, EDTA 0.01 mM, pH 8.0) buffer in the presence of 40 µg of synthesized compounds (Sharma *et al.,* 2014). The sample solution held in caps of polyethylene microcentrifuge tubes were placed directly on the surface of a transilluminator (8000 mW/cm) at 360 nm and were irradiated for 30 min at room temperature. After irradiation, samples were further incubated at 37 °C for 1 h. Irradiated samples were mixed with 6X loading dye containing 0.25 % bromophenol blue and 30 % glycerol. The samples were then analyzed by electrophoresis on a 0.8 % agarose horizontal slab gel in *Tris*–acetate EDTA buffer (40 mM *Tris*, 20 mM acetic acid, 1 mM EDTA, pH: 8.0). Untreated plasmid DNA was maintained as a control in each run of gel electrophoresis which was carried out at 5 V/cm for 2.0 h. Gel was stained with ethidium bromide (1 µg/mL) and photographed under UV light. To account the effect of synthesized compounds on DNA, the band intensities were analyzed using the GelQuant.NET software provided by biochemlabsolutions.com.

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