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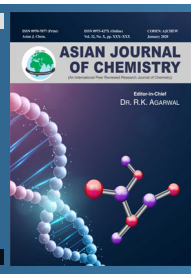

Synthesis, Antioxidant Activity and DFT Study of Some Novel *N*-Methylated Indole Incorporating Isoxazole Moieties

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A novel series of indolyl isoxazole derivatives were synthesized and the structure of the products is confirmed on the basis of IR, ^{1}H NMR, MS and analytical data. The synthesized compounds were evaluated for their antioxidant and anticancer activities. The results revealed clearly those compounds **4b** and **4d** exhibited better radical scavenging ability. The optimized structural parameters of all compounds was carried out at the B3LYP/6-311++G (d, p) level of DFT basis set implemented in Gaussian 09 program package. Theoretical calculation of the title compounds were carried out using density functional theory method (DFT).

Keywords: Acetyl indoles, Isoxazoles, Antioxidant activity, DFT.

INTRODUCTION

The life style related changes in the present day (sedentary life style, wrong dietary practices, stress, smoking/alcohol consumption/drug abuse) may cause overage of reactive oxygen species and free radicals. A number of natural antioxidants not only reduce oxidative stress, but also provides considerable protection against several degenerative nerve diseases and thus antioxidants play an important role in medical attendance. The implementation and development of new and more efficient synthetic or natural antioxidants are of great significance [1,2]. In addition, such compounds have also been used for the treatment and prevention of stroke or coronary heart disease. In last few decades, a search for better antioxidants led to the synthesis and isolation of different organic molecules which showed more effective antioxidant activity in comparison with standard antioxidants, such as β-carotene, vitamin C, butylated hydroxyanisole (BHA), lutein and vitamin A [3-5].

Indole derivatives are common motifs in natural products as well as drugs. Isoxazoles are aromatic five-membered heterocycles containing adjacent nitrogen and oxygen atoms [6,7]. These heterocyclic compounds are useful synthetic building blocks in medicinal and organic chemistry [8]. Indolyl isoxazole ring systems are found in a variety of naturally occurring compounds and medicinally important molecules. They are useful as pharmaceuticals, since many antioxidant and anticancer drugs are isoxazolyl derivatives.

As a result, researchers are on a continuous search to design and produce better heterocyclic compounds and also in order to enhance its biological property, we combine indole and isoxazole moieties in a single molecular framework to obtain a new class of highly potent bioactive compounds [9-12]. Hence, the present investigation aims to the synthesis and antioxidant activity of indolyl isoxazole derivatives. Computational methods predict relatively accurate molecular structure and molecular vibrations of indolyl isoxazole molecules applying the density functional theory (DFT) methods to derive information about electronic effects and evaluate the interaction between these molecules responsible for biological activity [13,14].

EXPERIMENTAL

All the reagents and solvents used were of AR grade which were purchased from Sigma-Aldrich and Merck Specialties Pvt. Ltd. NMR spectra was recorded on recorded on Bruker Avance III, 400 MHz NMR spectrometer (400 MHz for ^{1}H and 400 MHz for ^{13}C NMR spectra) and mass spectra on Waters UPLC-TQD mass spectrometer (ESI-MS). Nicolet 400D FTIR

spectrometer was used for FTIR spectra. Melting points were determined using Digital Program Rate melting point apparatus and are uncorrected. Elemental analysis was carried out at Central Drug Research Institute, Lucknow, India.

Synthesis of 5-phenyl-3-(1-methylindol-3-yl)isoxazole (IVa-h): The reaction of actyl indole with an aromatic aldehyde in the presence of NaOH afforded 3-aryl-1-(1-methylindole-3-yl)-2-propen-1-one. A mixture of 3-aryl-1-(1-methylindole-3-yl)-2-propen-1-one (0.01 mol), hydroxylamine hydrochloride (0.01 mol) in the presence of sodium acetate and exactly 50 mL of ethanol with glacial acetic acid was added and refluxed for 8-10 h. The mixture was then poured into ice water. The product obtained was filtered, dried and recrystallized from rectified spirit (**Scheme-I**).

Antioxidant activity: Evaluation of antioxidant activity of the synthesized compound was measured using, 1,1-diphenyl-2-picryl hydrazyl radical (DPPH). The samples were made up with methanol to different concentrations (50, 100, 250, 500 and 750 μM). Each sample (2 mL) was allowed to react with 2 mL of DPPH, an stable free radical, for 30 min in dark at room temperature. The deep purple colour of DPPH solution turns yellow in the presence of antioxidants. The disappearance of this radical is measured at 517 nm in a methanolic solution. Butylated hydroxyanisole (BHA) was used as a reference compound. From the absorbance values, the percentage inhibition was calculated as follows:

$$\text{Inhibition (\%)} = \frac{\text{Control absorbance} - \text{Sample absorbance}}{\text{Control absorbance}} \times 100$$

Spectral data

5-Phenyl-3-(1-methylindol-3-yl)isoxazole (4a): Greenish yellow solid; yield 63 %; m.w.: 550.6, m.p.: 144-148 ºC; IR (KBr, ν_{max}, cm^{-1}): 3020 (C-H), 1697 (C=N), 1468(C=C), 1287, 1218, 1126, (C-N). ^{1}H NMR (DMSO-d_6): δ 7.22-7.51 (m, 4H, ArH), 7.22-7.51 (m, 5H, ArH), 3.63 (s, 3H, N-CH_3), 5.42 (s, 1H, isoxazole ring proton), 6.83 (s, 1H, indolyl proton), *m/z*: 274.11 (100.0 %), 275.11 (19.5 %), 276.12 (1.8 %). Elemental analysis of $C_{18}H_{14}N_2O$ calcd. (found) %: C, 78.81 (78.79); H, 5.14 (5.19); N, 10.21 (10.29).

5-(2-Chlorophenyl)-3-(1-methylindol-3-yl)isoxazole (4b): Greenish yellow solid; yield 61 %; m.w.: 308.07, m.p.: 126-129 ºC; IR (KBr, ν_{max}, cm^{-1}): 3017 (C-H), 1721 (C=N), 1498 (C=C), 1086 (C-N). ^{1}H NMR (DMSO-d_6): δ 7.21-7.56 (m, 4H, ArH), 7.33 (d, 1H, ArH), 7.20 (m, 2H, ArH), 7.16 (m, 2H, ArH), 7.33 (d, 1H, ArH), 3.61 (s, 3H, N-CH_3), 5.51 (s, 1H, CH),6.83 (s, 1H, CH). *m/z*: 308.07 (100.0 %), 310.07 (32.0 %), 309.07 (19.5 %), 311.07 (6.2 %), 310.08 (1.8 %). Elemental analysis of $C_{18}H_{13}N_2OCl$ calcd. (found) %: C, 70.02 (7.11); H, 4.24 (4.28); N, 9.07 (9.11%.

5-(4-Chlorophenyl)-3-(1-methylindol-3-yl)isoxazole (4c): Greenish yellow solid; yield 60 %; m.w.: 308.07. m.p.: 123-127 ºC;IR (KBr, ν_{max}, cm^{-1}): 3019 (C-H), 1716 (C=N), 1521 (C=C), 1075 (C-N). ^{1}H NMR (DMSO-d_6): δ 7.25-7.58 (m, 4H, ArH), 7.33-7.42 (m, 4H, ArH), 3.60 (s, 3H, N-CH_3), 5.53 (s, 1H, CH), 6.84 (s, 1H, CH). *m/z*: 308.07 (100.0 %), 310.07 (32.0 %), 309.07 (19.5 %), 311.07 (6.2 %), 310.08 (1.8 %). Elemental analysis of $C_{18}H_{13}N_2OCl$ calcd. (found) %: C, 70.02 (7.14); H, 4.24 (4.21); N, 9.07 (9.17).

5-(2-Methylphenyl)-3-(1-methylindol-3-yl)isoxazole (4d): Greenish yellow solid; yield 57 %; m.w.: 288.13, m.p.: 135-138 ºC; IR (KBr, ν_{max}, cm^{-1}): 3059 (C-H), 1564 (C=N), 1522 (C=C), 1074 (C-N). ^{1}H NMR (DMSO-d_6): δ 7.20-7.51 (m, 4H, ArH), 7.12 (d, 1H, ArH), 7.10 (m, 2H, ArH), 7.13 (m, 2H, ArH), 7.36 (d, 1H, ArH), 3.61 (s, 3H, N-CH_3), 5.55 (s, 1H, CH), 2.35 (s, 3H, CH_3), 6.82 (s, 1H, CH). *m/z*: 288.13 (100.0 %), 289.13 (20.5 %), 290.13 (2.0 %). Elemental analysis of $C_{19}H_{16}N_2O$ calcd. (found) %: C, 79.14 (79.25); H, 5.59 (5.62); N, 9.72 (9.69).

5-(4-Methylphenyl)-3-(1-methylindol-3-yl)isoxazole (4e): Greenish yellow solid; yield 53 %; m.w.: 288.13, m.p.: 133-136 ºC. IR (KBr, ν_{max}, cm^{-1}): 3071 (C-H), 1569 (C=N), 1612 (C=C), 1079 (C-N). ^{1}H NMR (DMSO-d_6): δ 7.22-7.53 (m, 4H, ArH), 7.12-7.39 (m, 4H, ArH), 3.63 (s, 3H, N-CH_3), 5.67 (s, 1H, CH), 2.36 (s, 3H, CH_3), 6.85 (s, 1H, CH). *m/z*: 288.13 (100.0 %), 289.13 (20.5 %), 290.13 (2.0 %). Elemental analysis of $C_{19}H_{16}N_2O$ calcd. (found) %: C, 79.14 (79.21); H, 5.59 (5.57); N, 9.72 (9.73).

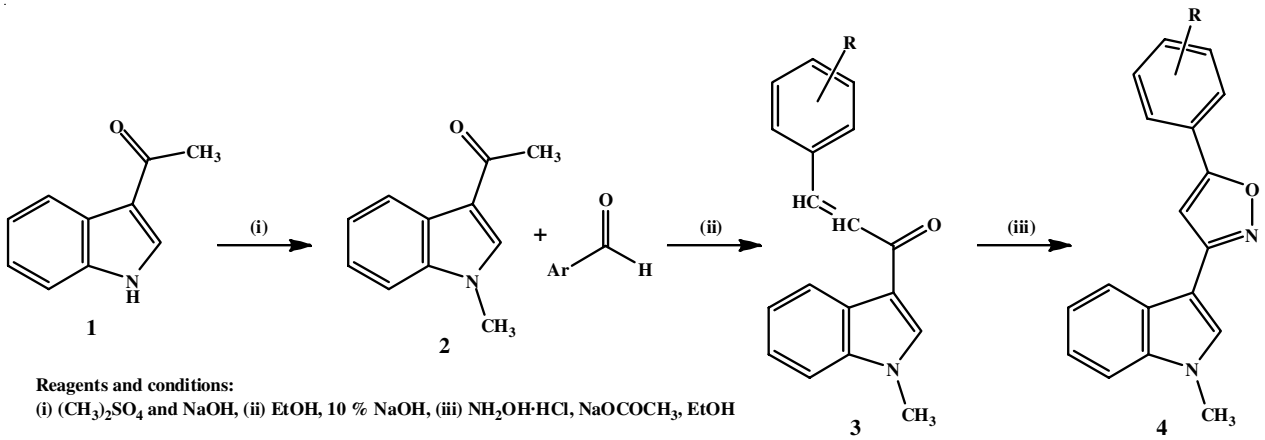
5-(2-Methoxyphenyl)-3-(1-methylindol-3-yl)isoxazole (4f): Greenish yellow solid; yield 47 %, m.w.: 304.12, m.p.: 178-179 ºC; IR (KBr, ν_{max}, cm^{-1}): 3069 (C-H), 1679 (C=N), 1612 (C=C), 1074 (C-N). ^{1}H NMR (DMSO-d_6): δ 7.23-7.49 (m, 4H, ArH), 6.83(d, 1H, ArH), 7.11 (m, 2H, ArH), 6.88 (m, 2H, ArH), 7.37 (d, 1H, ArH), 3.60 (s, 3H, N-CH_3), 5.42 (s, 1H, CH),3.72 (s, 3H, OCH_3), 6.80 (s, 1H, CH). *m/z*: 304.12 (100.0 %), 305.12 (20.5 %), 306.13 (2.0 %). Elemental analysis of $C_{19}H_{16}N_2O_2$ calcd. (found) %: C, 74.98 (74.87);H, 5.30 (5.38); N, 9.20 (9.33).

5-(4-Methoxyphenyl)-3-(1-methylindol-3-yl)isoxazole (4g): Greenish yellow solid; yield 53 %; m.w.: 304.12, mp.: 175-178 ºC; IR (KBr, ν_{max}, cm^{-1}): 3019 (C-H), 1716 (C=N), 1555 (C=C), 1248,1287 (C-N). ^{1}H NMR (DMSO-d_6): δ 7.23-7.49 (m, 4H, ArH), 6.83-7.39 (m, 4H, ArH), 3.60(s, 3H, N-CH_3), 5.42 (s, 1H, CH), 3.73(s, 3H, OCH_3), 6.82(s,1H,CH). *m/z*: 304.12 (100.0 %), 305.12 (20.5 %), 306.13 (2.0 %). Elemental analysis of $C_{19}H_{16}N_2O_2$ calcd. (found) %: C, 74.98 (74.97); H, 5.30 (5.31); N, 9.20 (9.31).

5-(2-Hydroxyphenyl)-3-(1-methylindol-3-yl)isoxazole (4h): Greenish yellow solid; yield 55 %; m.w.: 290.11, m.p.: 163-165 ºC; IR (KBr, ν_{max}, cm^{-1}): 3447(OH), 3024 (C-H), 1659 (C=N), 1540 (C=C), 1250, 1227 (C-N). ^{1}H NMR (DMSO-d_6): δ 7.21-7.41(m, 4H, ArH), 6.79-7.31 (m, 4H, ArH), 3.63 (s, 3H, N-CH_3), 5.48 (s, 1H, CH), 5.03 (s, 1H, Ar-OH), 6.88 (s, 1H, CH). *m/z*: 290.11 (100.0 %), 291.11 (19.5 %), 292.11 (1.8 %). Elemental analysis of $C_{18}H_{14}N_2O_2$ calcd. (found) %: C, 74.47 (74.48); H, 4.86 (4.79); N, 9.65 (9.64).

RESULTS AND DISCUSSION

As seen in **Scheme-I**, the reaction of starting material, 3-acetyl indole (**1**) with dimethyl sulphate in the presence of various bases is a classical method to form *N*-methylated indole derivatives. Methylation with dimethyl sulphate has been found to be a practical method to develop *N*-methylated indole analogues in good yields and purity. Therefore, development of efficient synthetic methods for the synthesis of target compounds using 3-acetyl-1-methyl indole. Next, 3-acetyl-1-methyl (**2**) indole treated with commercially available aromatic aldehydes, afforded



Scheme-I: Synthetic route of some novel *N*-methylated indole containing isoxazole moieties

3-aryl-1-(1-methylindole-3-yl)-2-propen-1-one (**3**). A mixture of 3-aryl-1-(1-methylindole-3-yl)-2-propen-1-one (0.01 mol), hydroxylamine hydrochloride (0.01 mol) in the presence of sodium acetate and exactly 50 mL of ethanol with glacial acetic acid was added and refluxed for 8-10 h to afford the target compound (**4**). This reaction pathway shows that the nucleophilc attack of hydroxylamine hydrochloride at the β-carbon of α,β-unsaturated carbonyl system leads ultimately to isoxazole. The homogeneity of compounds was monitored by purified by column chromatography (silica gel 60, 150 mesh) using chloroform as the eluent to obtain pure colourless crystals of compounds.

Antioxidant activity: Indolyl isoxazole derivatives were investigated for their free radical scavenging activities using DPPH assay. The antioxidant activity of synthesized compounds were also determined with measuring the IC_{50} (μM) values in Table-1. The data revealed that the indolyl isoxazole hybrids showed potent DPPH radical scavenging activity, comparable to that of standard butylated hydroxyanisole. Compounds **4c** and **4f** which exhibited good radical scavenging activity and their IC_{50} values were found to be 92 and 78 μM, respectively because compound having substitution with electron withdrawing groups enhanced antioxidant activity against DPPH free radicals. Moreover, compounds **4d** and **4g** showed moderate scavenging activity with IC_{50} values 157 and 130 μM (Table-1).

Geometric optimization (molecular analysis): The optimized structural parameters of all compounds was carried out at the B3LYP/6-311++G (d, p) level of DFT basis set implemented in Gaussian 09 program package. The optimized structure of compound (**4a**) with numbering of the atoms is depicted in Fig. 1 and the important geometrical parameters are listed in Table-2. The atomic orbital components of HOMO and LUMO distribution pattern of indolyl derivatives **4a** are shown in Fig. 2.

TABLE-1
DPPH RADICAL SCAVENGING ACTIVITY OF 5-PHENYL-3-(1-METHYLINDOL-3-YL)ISOXAZOLE (**4a-h**)

Compounds	IC_{50} (μM)	Compounds	IC_{50} (μM)
4a	564	**4f**	78
4b	321	**4g**	130
4c	92	**4h**	188
4d	157	BHA	624
4e	307	–	–

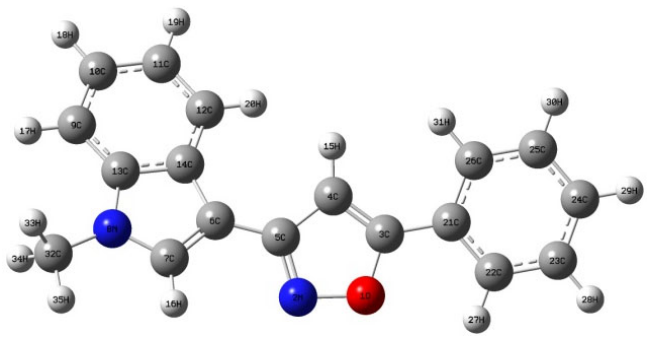


Fig. 1. Structure of 5-phenyl-3-(1-methylindol-3-yl)isoxazole (**4a**)

Frontier molecular orbitals of compound **4a** shows that the electrons are transferring from the indole moiety towards

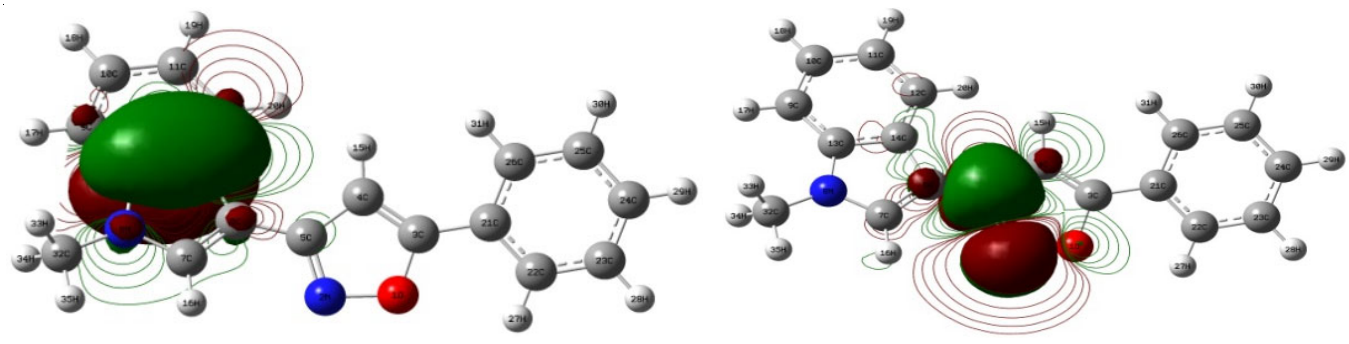


Fig. 2. HOMO and LUMO of 5-phenyl-3-(1-methylindol-3-yl)isoxazole (**4a**)

TABLE-2
OPTIMIZED GEOMETRICAL PARAMETERS OF 5-PHENYL-3-(1-METHYLINDOL-3-YL)ISOXAZOLE (**4a**)

Atom	Bond length (Å)	Atom	Bond angle (°)	Atom	Dihedral angle (°)
O1–N2	1.4576	O1–C3–C4	108.81	O1–C3–C21–C26	179.95
O1–C3	1.3837	C3–C4–H15	127.44	C4–C3–C21–C22	179.56
C3–C4	1.3709	C4–C5–H15	126.45	C7–C6–C5–C4	-157.56
C4–H15	1.0758	C4–C5–C6	128.28	C13–C14–C12–H20	-177.76
C4–C5	1.4336	C5–C6–C7	124.63	H19–C11–C10–C9	179.18
N2–C5	1.3405	C6–C7–H16	128.57	N2–C5–C4–H15	-178.12
C5–C6	1.4521	N8–C7–H16	121.21	H27–C22–C23–C24	-179.99
C6–C7	1.3834	C9–C13–C14	107.77	H16–C7–C6–C14	-179.59
C7–H16	1.0784	C13–C9–H17	121.51	N2–C5–C6–C14	-159.05
N8–C7	1.3838	C13–C9–C10	117.56	H18–C10–C11–C12	179.95
N8–C13	1.3942	C9–H17–C10	120.92	N8–C13–C14–C12	178.51
C13–C14	1.4276	C9–C10–H18	119.52	C9–C13–C14–C6	-179.87
C14–C12	1.4073	C10–C11–H18	119.49	C21–C22–C23–H28	-179.96
C12–H20	1.0842	C10–C11–H19	119.24	C32–N8–C7–C6	-179.34
C11–C12	1.3939	C10–C11–C12	121.23	C21–C26–C25–H30	-179.99
C11–H19	1.0852	C12–C14–H20	25.35	C13–N8–C32–H33	-60.18

isoxazole moiety due to HOMO-LUMO excitation. The comparison between frontier molecular orbitals of indolyl derivatives at the ground state, HOMO is delocalized over the indole ring whereas the LUMO is placed over the isoxazole ring. HOMO and LUMO energies of compounds **4a-h** along with their gaps and the reactivity indices of compounds (**4a-h**) were calculated and are listed in Table-3. Among all compounds, compound **4a** showed the lowest HOMO-LUMO energy gap, *i.e*. -0.2387 eV, while **4b** and **4c** showed the largest energy gap *i.e*. 0.2360 eV. In the Mulliken analysis, half the overlap population is assigned to each contributing orbital, giving the total population of each atomic orbital. Summing over all the atomic orbitals on a specific atom gives the gross atomic population. From the Mulliken population analysis, atomic charge values were obtained (Fig. 3).The Mulliken atomic charges of 5-phenyl-3-(1-methylindol-3-yl)isoxazole (**4a**) are presented in Table-3. The Mulliken atom charge is positive for all hydrogen atoms. Oxygen and nitrogen atoms possess negative charge and chlorine atoms carry positive charge.

The proton transfer of indolyl isoxazole compounds has been investigated here using reactivity indices. From Table-3, it is clear that among all the compounds, **4g** has the lowest

TABLE-3
MULLIKEN CHARGE DISTRIBUTION OF 5-PHENYL-3-(1-METHYLINDOL-3-YL)ISOXAZOLE (**4a**)

Atom	Mulliken atomic charge	Atom	Mulliken atomic charge
O1	-0.454	H16	0.187
N2	-0.185	H17	0.128
C3	0.234	H18	0.120
C4	-0.105	H19	0.118
C5	0.077	H20	0.129
C6	0.002	C21	0.076
C7	0.120	C22	-0.129
N8	-0.691	C23	-0.138
C9	-0.085	C24	-0.109
C10	-0.150	C25	-0.142
C11	-0.135	C26	-0.121
C12	-0.136	H27	0.170
C13	0.255	H28	0.133
C14	0.020	H29	0.131
H15	0.159	H30	0.131

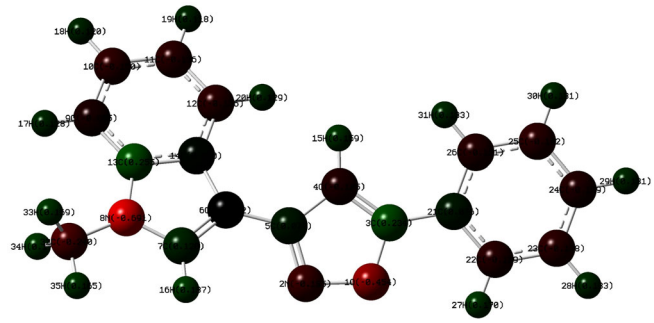


Fig. 3. Mulliken charge distribution of 5-phenyl-3-(1-methylindol-3-yl)-isoxazole (**4a**)

value of hardness (η), *i.e*. 0.1125eV, whereas **4d** has the highest value of hardness (0.2301 eV).Compound **4d** has the highest ionization potential (I) value (0.2958 eV) among the other compounds, while **4g** has the lowest chemical potential value (0.2336 eV). The results indicate that the compound **4a** has the lowest electron affinity (A) value -0.0009 eV, whereas compound **4b** has the highest value is 0.0055 eV. In addition, among the set of the synthesized compounds, compound **4b** has the highest electronegativity (χ) value (0.1236 eV) while compound **4d** has the lowest value (0.0656 eV). Compound **4c** (4.2371 eV) has the highest value of softness of the compound and the lowest value is 2.1723 eV for compound **4d** (Table-4).

Conclusion

In conclusion, a new series of 5-phenyl-3-(1-methylindol-3-yl)isoxazole derivatives were successfully synthesized by the reaction of 3-acetyl-1-methyl indole with different aromatic aldehydes. All the synthesized compounds were screened for their antioxidant activity. The compound with highest antioxidant activity was **4d**, whose IC_{50} value is found to be 78 μM. The optimized geometrical parameters calculated at B3LYP/6-31G (d,p) basis set. Compounds with lower HOMO-LUMO band gap has higher biological activities. The feasibilities of hydrogen bonding were explained by Mulliken charge analysis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

TABLE-4
ENERGIES OF HOMO-LUMO OF 5-PHENYL-3-(1-METHYLINDOL-3-YL)ISOXAZOLE (**4a-h**)

Parameters (a.u)	B3LYP/631G							
	4a	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**
HOMO	-0.2377	-0.2416	-0.2391	-0.2958	-0.2373	-0.2357	-0.2336	-0.2342
LUMO	0.0009	-0.0055	-0.0031	0.1644	0.0019	0.0045	0.0085	0.0074
HOMO-LUMO	-0.2387	0.2360	0.2360	-0.4603	-0.2392	-0.2402	-0.2421	-0.2416
I	0.2377	0.2416	0.2391	0.2958	0.2373	0.2357	0.2336	0.2342
A	-0.0009	0.0055	0.0031	-0.1644	-0.0019	-0.0045	-0.0085	-0.0074
χ	0.1183	0.1236	0.1211	0.0656	0.1176	0.1156	0.1210	0.1133
η	0.1193	0.1180	0.1180	0.2301	0.1196	0.1201	0.1125	0.1208
S	4.1893	4.2362	4.2371	2.1723	4.1795	4.1618	4.1295	4.1378

I-Ionisation potential; A-Electron affinity; χ-Electronegativity; η-Hardness; S-Softness

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