Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 13, Issue 3, September 2018 , pp. (109-125)
ISSN: 1992-0849 (Print), 2616-6801 (Online)

# Green Chemistry Synthesis of Five-Membered Heterocylic Derivatives (1, 3, 4-oxadizoles) by Using Grinding Technique

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## Abstract

In this research we prepared about 28 derivatives of five-membered heterocyclic compounds (1,3,4-oxadizoles) in two lines , in the first line we used phenylhydrazide and in the second line we used 4-hydroxy phenylhydrazide as starting material for cyclization, By using eco–friendly efficient synthesis of oxadiazole derivatives through the reaction of aromatic hydrazide with different substituted aromatic aldehydes by grinding them in the presence of catalytical amounts of iodine.

**Keywords:** oxadiazole; green chemistry; aromatic hydrazide; grinding.

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Volume 13, Issue 3, September 2018 , pp. (109-125)
ISSN: 1992-0849 (Print), 2616-6801 (Online)

# تحضير مشتقات من الحلقات الخماسية غير المتجانسة (4,3,1 – اوكسادايازول) بطريقة كيمياء الخضراء من خلال استخدام تقنية الطحن

نهاد اسماعيل طه [1] ، ايهاب مالك رشيد رشيد[2]
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## الملخص

في هذا البحث قمنا بتحضير حوالي 28 مشتق لمركبات خماسية الحلقة غير المتجانسة (4،3،1- اوكسادايازول) بمسارين، في المسار الاول استخدمنا فنيل هيدرازايد وفي المسار الثاني استخدمنا 4- هيدروكسي فنيل هيدرازايد كمواد اولية لعملية الغلق الحلقي، وباستخدام طريقة صديقة للبيئة لتحضير مشتقات الاوكسادايازول من خلال تفاعل الهيدرازايد الاروماتي مع معوضات مختلفة من الالديهايدات الاروماتية من خلال طحنها معا بوجود جزيئة اليود كعامل مساعد.

**الكلمات الدالة:** اوكسادايازول، الكيمياء الخضراء، هيدرازايد اروماتي، طحن.

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## 1. Introduction

The importance of the 1, 3, 4-oxadiazoles ring is well established in different fields of sciences (industrial, agriculture and pharmaceutical chemistry) as show by the use of its derivatives in the treatment and solving problems in different cases. As an important class of five membered heterocycle 2, 5 – disubstituted-1, 3, 4 – oxadiazole proven abroad spectrum of biological activity due to the presence of toxophoric-N=C-O- linkage [1]. Considerable evidence has been accumulated to demonstrate the efficacy of 1, 3, 4 –oxadiazoles including its use in herbicide, fungicide, hypnotic sedatives [2] as well as its antibacterial [3], analgesic , antimalarial [4], anti-inflammatory [5], hypoglycemic [6], anticonvulsant [7], diuretic and antimitotic [8].

Synthesis of 2, 5 -disubstituted 1, 3, 4 -oxadiazoles by cyclodehydrogenation using different oxidizing reagents: for example using $POCl_3$ [9 – 10] for condensation of various alkyl hydrazides with substituted aromatic acids. Chloroamine T used as oxidizing agent in the cyclization of acyl hydrazide with different aldehydes [11], mercuric acetate also used as oxidizing agent for cyclization of substituted thiosemacarbazide [12]. Schiff bases of substituted thiosemacarbazide undergo oxidative cyclodehydrogenation by using ferric chloride or using iodine in the presence of sodium hydroxide [13]. Using microwave irradiation for 2, 5-disubstituted 1, 3, 4-oxadiazoles synthesis from hydrazide and substituted aromatic acids in the presence of thionyl chloride [14] or phosphorus oxychloride [15,16].

In this research we used simple, highly efficient and eco-friendly method without using solvent for preparation of 2, 5- disubstituted 1, 3, 4-oxadiazoles through the reaction between phenyl, (4-hydroxy phenyl), hydrazides with different substituted benzaldehydes in the presence iodine molecule as oxidizing agent by using grinding technique, also the starting material hydrazides were prepared by microwave irradiation as green chemistry [17] .

## 2. Methods and Instruments

Melting pionts were determined in open capillary tubes and are uncorrected by using Stuart Melting Point Apparatus. The IR spectra ($cm^{-1}$) were recorded on Schimadzu FT-IR-8400S by using KBr disc.$^1$HNMR spectra (DMSO-d6) were recorded on ultra shield 300MHz Bruker (2003) NMR spectrometer using TMS as internal standard in the university of Baghdad college of Ibn al-Haytham. Following up of the reactions and the purity of the

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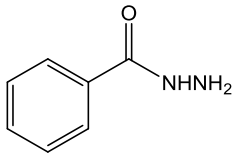
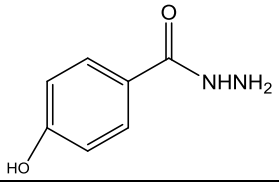
compounds have been done by using TLC-techniqe on aluminium plates percoated with silica gel in various solvent system using iodine vapours as detecting agent.

**2.1 Synthesis Of Aromatic Hydrazide by Using Microwave Irradiation[3]:**

(0.01mole) of ethyl benzoate / ethyl-4-hydroxy benzoate and (0.02 mole) of hydrazine hydrate where mixing in 50 ml beaker then (2 ml) of ethanol was added to the mixture. The becker placed into microwave oven for irradiation at different power for (2 min.) , and by cooling the reaction mixture in the ice bath until white crystal were precipitated, washed with water and recrystallized from ethanol. Yield (90-93)%, m.p. of phenyl hydrazide is (113-115)℃ and m.p. of 4 – hydroxy hydrazide is (265)℃ .

**Table 1:** Physical Data of Hydrazides.

| Compounds | Colour | m.p. $^{O}$C | Yield% | MWI/watt |
|---|---|---|---|---|
|  | White crystal | 113-115 | 93 | 136 |
|  | white | 265 | 90 | 152 |

**2.2 Synthesis of 2, 5-disubstutited –1, 3, 4 - Oxadizoles by Grinding Method(17):**

To ($0.25_{\times}10^{-3}$ mol) of aromatic hydrazide mixed with ($0.5_{\times}10^{-3}$ mol) of different substituted benzaldehyde, ( $0.05_{*}10^{-3}$mol ) of iodine was added to the mixture in the porcelain morter and was grinded with pestle for ( 8 minutes ). The reaction was follwed by thin layer chromatography (TLC- plates of silica gel using organic solvent as mobile phase), after completation of reaction a sodium thiosulphate (10% , 10 ml) solution was added to remove iodine present. The solid product was filtered and washed with water, recrystallised from ethanol to give pure product

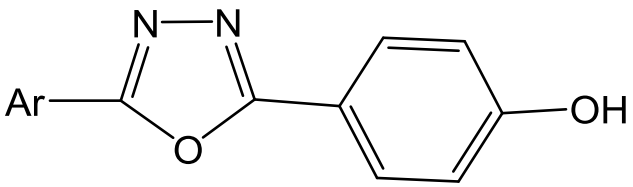


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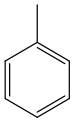
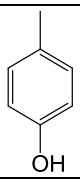
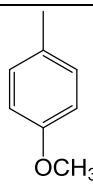
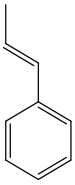
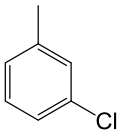
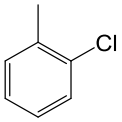
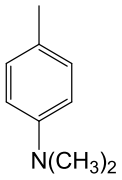
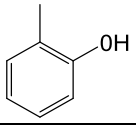
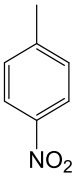
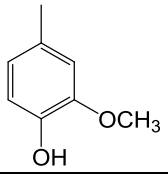
**Table 2:** Physical data of 2-( 4-hyroxy phenyl) -5- substituted phenyl 1,3,4- oxadiazole.

| Comp. NO. | Ar | Colour | m.p. $^{O}C$ | Yield % | M.Wt . |
|---|---|---|---|---|---|
| $E_1$ |  | white | 210-212 Lit (212)[18] | 84 | 238 |
| $E_2$ |  | Yellow | 348-349 Lit(350)[19] | 88 | 254 |
| $E_3$ |  | white | 275-277 Lit(279)[18] | 86 | 268 |
| $E_4$ |  | green | 240-242 Lit(242)[18] | 85 | 264 |
| $E_5$ |  | yellow | 202-204 | 82 | 273 |
| $E_6$ |  | yellow | 198-200 | 79 | 273 |
| $E_7$ |  | red | 165 | 82 | 281 |
| $E_8$ |  | white | 198-200 | 62 | 254 |
| $E_9$ |  | red | 226 Lit(258)[18] | 89 | 283 |
| $E_{10}$ |  | اصفرفاتح | 178-180 | 87 | 284 |

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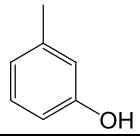
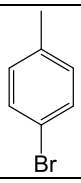
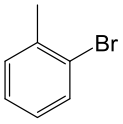
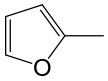
| Comp. NO. | Ar | Colour | m.p. $^{O}C$ | Yield % | M.Wt . |
|---|---|---|---|---|---|
| $E_{11}$ |  | white | 138-140 | 66 | 254 |
| $E_{12}$ |  | White-yellow | 159-161 | 74 | 317 |
| $E_{13}$ |  | White-yellow | 102-104 Lit(104)[20] | 77 | 317 |
| $E_{14}$ |  | Yellow-green | 172-174 | 67 | 228 |

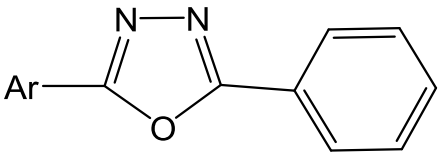
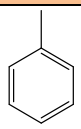
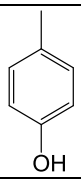
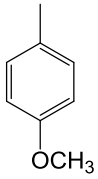
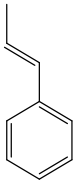


**Table 3:** Physical data of 2- phenyl -5- substituted phenyl 1,3,4- oxadiazole.

| Comp. NO. | Ar | Colour | m.p. $^{O}C$ | Yield% | M.Wt. |
|---|---|---|---|---|---|
| $E_{15}$ |  | white | 134-136 Lit(138)[19] | 83 | 222 |
| $E_{16}$ |  | white | 202-204 | 79 | 238 |
| $E_{17}$ |  | green | 220-222 Lit(221)[18] | 85 | 252 |
| $E_{18}$ |  | yellow | 178-180 | 78 | 248 |

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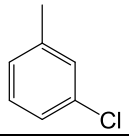
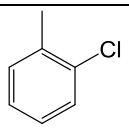
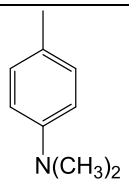
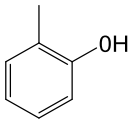
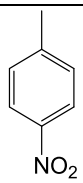
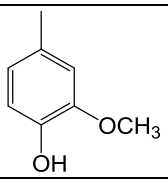
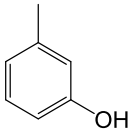
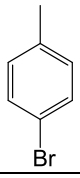
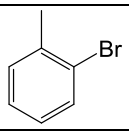
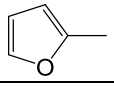
| Comp. NO. | Ar | Colour | m.p. $^{O}C$ | Yield% | M.Wt. |
|---|---|---|---|---|---|
| $E_{19}$ |  | White -yellow | 224-226 | 81 | 257 |
| $E_{20}$ |  | White -yellow | 220-222 | 80 | 257 |
| $E_{21}$ |  | red | 149-151 | 89 | 265 |
| $E_{22}$ |  | white | 185-187 | 59 | 238 |
| $E_{23}$ |  | Orange-red | 107-108 Lit(104-106)[20] | 74 | 267 |
| $E_{24}$ |  | Yellow-green | 211-214 | 81 | 268 |
| $E_{25}$ |  | white | 202-204 | 62 | 238 |
| $E_{26}$ |  | white | 169-171 | 78 | 301 |
| $E_{27}$ |  | white | 181-183 | 84 | 301 |
| $E_{28}$ |  | yellow | 101-102 Lit(99-100)[21] | 74 | 212 |

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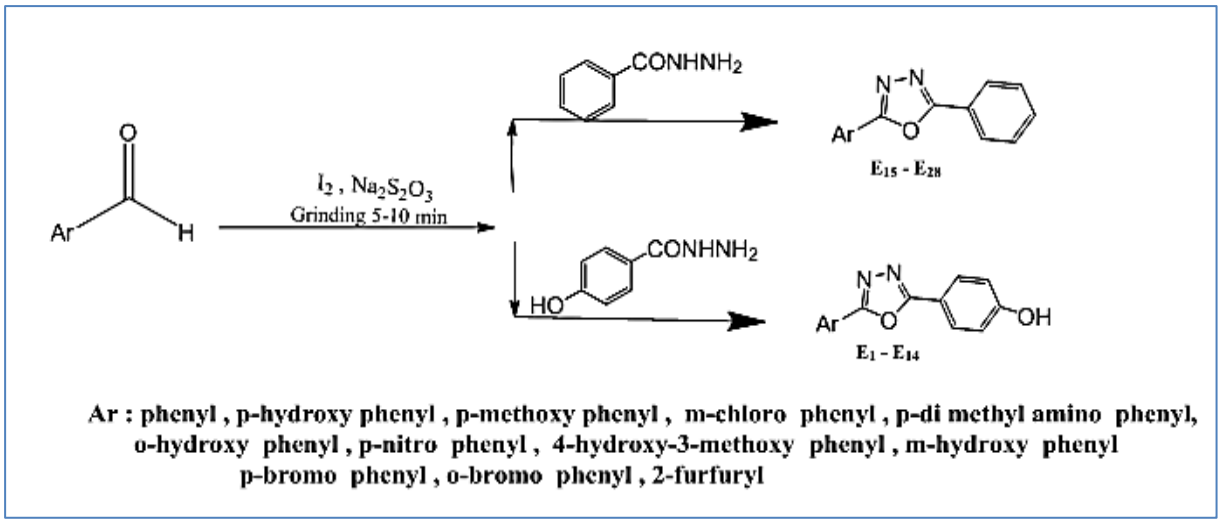
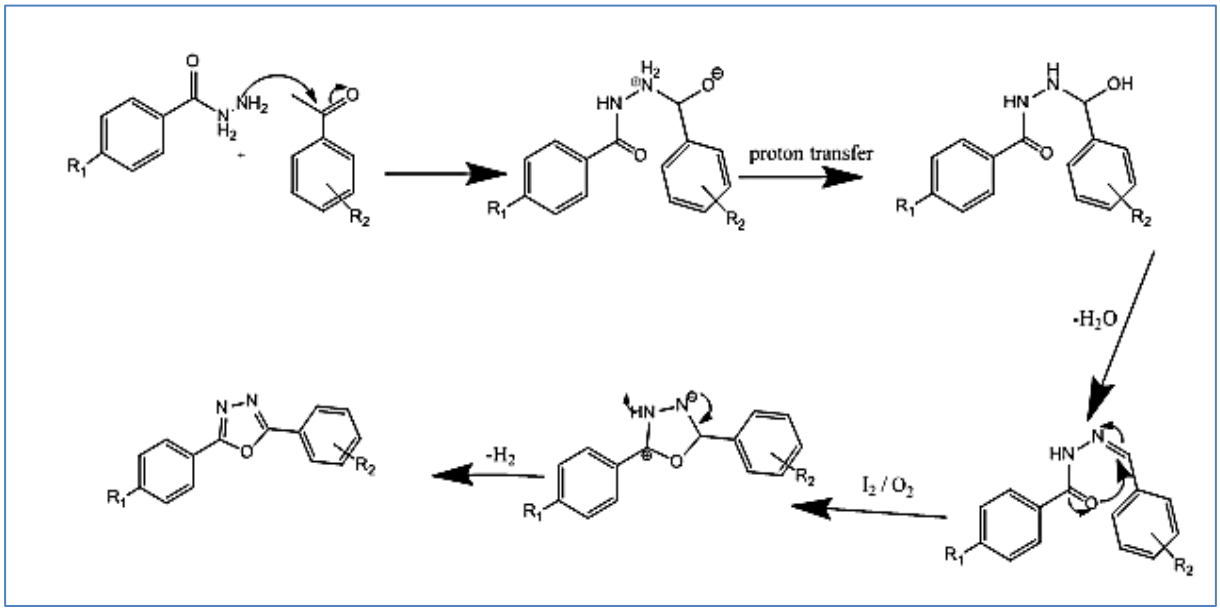



**Scheme 1:**Preparation of Oxadiazoles




**Scheme 2:** The Suggested Mechanism of Cyclization

## 3. Results and Discussion

In this paper, grinding technique which was used for synthesis of ($E_1$-$E_{28}$) is reported by the reaction of phenyl hydrazide, 4- hydroxyl phenyl hydrazide with different substituted benzaldehydes in the presence of molecular iodine. Then the mixture was treated with 10% sodium thiosulphate solution to yield 2, 5- disubstituted 1, 3, 4-oxadizoles. The synthetic procedure and reaction mechanism for preparation of title compounds is given in reaction scheme 1 and 2. The assigned structure of the synthesized compounds were confirmed and

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supported by $^1$HNMR and IR data as well as physical data. The IR spectra of compounds inducted the disappearance of carbonyl bands at (1690 – 1720)cm$^{-1}$ and primary amino band at ( 3200- 3300) cm$^{-1}$ and the appearance of band at ( 1650 -1670 ) cm$^{-1}$ due to (C=N) group in the oxadiazoles ring and at (1220 – 1260) cm$^{-1}$ due to (C-O-C) cyclic group in the oxadiazole ring, Table 4 shows IR data, Fig. 1 for $E_{23}$, Fig. 2 for $E_{15}$.

$^1$HNMR ($d_6$-DMSO) spectrum for compound $E_{15}$, $\delta$ (ppm): 7-8 (three proton adjacent to each other in the phenyl group, give complex signal). 8.3-8.7(two proton at the *ortho* position in the phenyl group, give singlet signal. Fig. 3 NMR spectrum for $E_{15}$.

$^1$HNMR ($d_6$-DMSO) spectrum for compound $E_{21}$, $\delta$ (ppm) showed a signal at $\delta$ (ppm): 2.9 (two methyl group substituted on the nitrogen atom, 6 H, give singlet). 6.6-6.7 (two protons), in the *4*- substituted benzene ring, at the *ortho* position, 2H ,give doublet). 7.4-7.5 (two proton in the *4*- substituted phenyl, at the meta position, 2H, give doublet). 7.8- 8.2 (five protons in the unsubstituted phenyl, 5H, give complex signal). Fig. 4 NMR spectrum for $E_{21}$.

$^1$HNMR ($d_6$-DMSO) spectrum for compound $E_{27}$, showed complex signal at (7.4- 7.6)ppm for four proton in the *4*-bromo phenyl, two proton closer to bromine atom appear at 7.4 ppm and two other protons closer to five membered ring appear at 7.6 ppm .The five protons at the unsubstituted phenyl appear at (7.7–8.3)ppm, in which two proton closer to the five membered ring appear at 8.3 ppm and three protons appear at (7.7-7.8) ppm. Fig. 5 NMR spectrum for $E_{27}$

$^1$HNMR ($d_6$-DMSO) spectrum for compound $E_{23}$, showed complex signal at (7.5 - 8)ppm for five protons , two protons closer to five membered ring appear at 8 ppm and three protons appear at (7.5–7.6) ppm. The four protons in the other *4*-nitro phenyl appear at (8.2-8.5)ppm, in which two protons closer to the nitro group appear at 8.5 ppm and the other two protons appear at 8.2ppm. Fig. 6 NMR spectrum for $E_{23}$.

**Table 4:** IR specta data for the synthesized compounds ( $E_1$- $E_{28}$).

| Comp NO. | $Ar_1$ | $Ar_2$ | IR(KBr)Cm$^{-1}$ | | | | Others |
|---|---|---|---|---|---|---|---|
| | | | C=N | C=C | C-O-C Asym | C-O-C sym | |
| $E_1$ | -$C_6H_5$ | 4-Ho-$C_6H_4$ | 1618 | 1549 | 1280 | 1173 | (OH) 3224 |
| $E_2$ | 4-HO-$C_6H_4$- | 4-Ho-$C_6H_4$ | 1650 | 1552 | 1263 | 1170 | (OH) 3414 |

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| Comp NO. | $Ar_1$ | $Ar_2$ | IR(KBr)$Cm^{-1}$ | | | | Others |
|---|---|---|---|---|---|---|---|
| | | | C=N | C=C | C-O-C Asym | C-O-C sym | |
| $E_3$ | 4-$CH_3O$-$C_6H_4$- | 4-Ho-$C_6H_4$ | 1602 | 1538 | 1251 | 1167 | (C-H) al 3000 (0H) 3274 |
| $E_4$ | -CH=CH-$C_6H_5$ | 4-Ho-$C_6H_4$ | 1656 | 1604 | 1280 | 1174 | (C-H) al 2990 |
| $E_5$ | 3-Cl-$C_6H_4$- | 4-Ho-$C_6H_4$ | 1647 | 1577 | 1263 | 1171 | (C-Cl) 774 |
| $E_6$ | 2-Cl-$C_6H_4$- | 4-Ho-$C_6H_4$ | 1647 | 1545 | 1249 | 1146 | (C-Cl) 764 |
| $E_7$ | 4-$(CH_3)_2N$-$C_6H_4$- | 4-Ho-$C_6H_4$ | 1603 | 1528 | 1232 | 1173 | C-N 1367 (C-H) al 2920 |
| $E_8$ | 2-HO-$C_6H_4$- | 4-Ho-$C_6H_4$ | 1656 | 1578 | 1238 | 1163 | (OH) 3335 |
| $E_9$ | 4-$NO_2$-$C_6H_4$- | 4-Ho-$C_6H_4$ | 1649 | 1552 | 1250 | 1149 | ($NO_2$) 1518-1334 |
| $E_{10}$ | 3-HO-4-$CH_3O$-$C_6H_3$ | 4-Ho-$C_6H_4$ | 1653 | 1577 | 1244 | 1152 | (OH) 3408 |
| $E_{11}$ | 3-HO-$C_6H_4$- | 4-Ho-$C_6H_4$ | 1654 | 1549 | 1249 | 1146 | (OH) 3321 |
| $E_{12}$ | 4-Br-$C_6H_4$- | 4-Ho-$C_6H_4$ | 1653 | 1562 | 1232 | 1163 | (C-Br) 622 |
| $E_{13}$ | 2-Br-$C_6H_4$- | 4-Ho-$C_6H_4$ | 1649 | 1538 | 1258 | 1167 | (C-Br) 581 |
| $E_{14}$ | Furan-2-yl | 4-Ho-$C_6H_4$ | 1656 | 1606 | 1280 | 1173 | — |
| $E_{15}$ | -$C_6H_5$ | $C_6H_5$- | 1642 | 1550 | 1286 | 1139 | —— |
| $E_{16}$ | 4-HO-$C_6H_4$- | $C_6H_5$- | 1654 | 1567 | 1282 | 1173 | (OH) 3200-3333 |
| $E_{17}$ | 4-$CH_3O$-$C_6H_4$- | $C_6H_5$- | 1605 | 1513 | 1260 | 1170 | (C-H) al 2850 |
| $E_{18}$ | -CH=CH-$C_6H_5$ | $C_6H_5$- | 1654 | 1578 | 1263 | 1167 | (C-H) al 3200 |
| $E_{19}$ | 3-Cl-$C_6H_4$- | $C_6H_5$- | 1647 | 1547 | 1285 | 1134 | (C-Cl) 692 |

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| Comp NO. | $Ar_1$ | $Ar_2$ | IR(KBr)$Cm^{-1}$ | | | | Others |
|---|---|---|---|---|---|---|---|
| | | | C=N | C=C | C-O-C Asym | C-O-C sym | |
| $E_{20}$ | 2-Cl-$C_6H_4$- | $C_6H_5$- | 1652 | 1549 | 1266 | 1170 | (C-Cl) 704 |
| $E_{21}$ | 4-$(CH_3)_2N$-$C_6H_4$- | $C_6H_5$- | 1654 | 1600 | 1281 | 1183 | (C-H) al 2900 (C-N) 1360 |
| $E_{22}$ | 2-HO-$C_6H_4$- | $C_6H_5$- | 1657 | 1577 | 1263 | 1164 | (OH) 3310-3400 |
| $E_{23}$ | 4-$NO_2$-$C_6H_4$- | $C_6H_5$- | 1649 | 1566 | 1298 | 1146 | ($NO_2$) 1520-1342 |
| $E_{24}$ | 3-HO-4-$CH_3O$-$C_6H_3$ | $C_6H_5$- | 1656 | 1567 | 1280 | 1167 | (C-H) al 2983 |
| $E_{25}$ | 3-HO-$C_6H_4$- | $C_6H_5$- | 1654 | 1559 | 1273 | 1173 | (OH) 3200-3300 |
| $E_{26}$ | 4-Br-$C_6H_4$- | $C_6H_5$- | 1653 | 1539 | 1282 | 1140 | (C-Br) 714 |
| $E_{27}$ | 2-Br-$C_6H_4$- | $C_6H_5$- | 1652 | 1546 | 1280 | 1166 | (C-Br) 587 |
| $E_{28}$ | Furan-2-yl | $C_6H_5$- | 1649 | 1578 | 1255 | 1134 | __ |

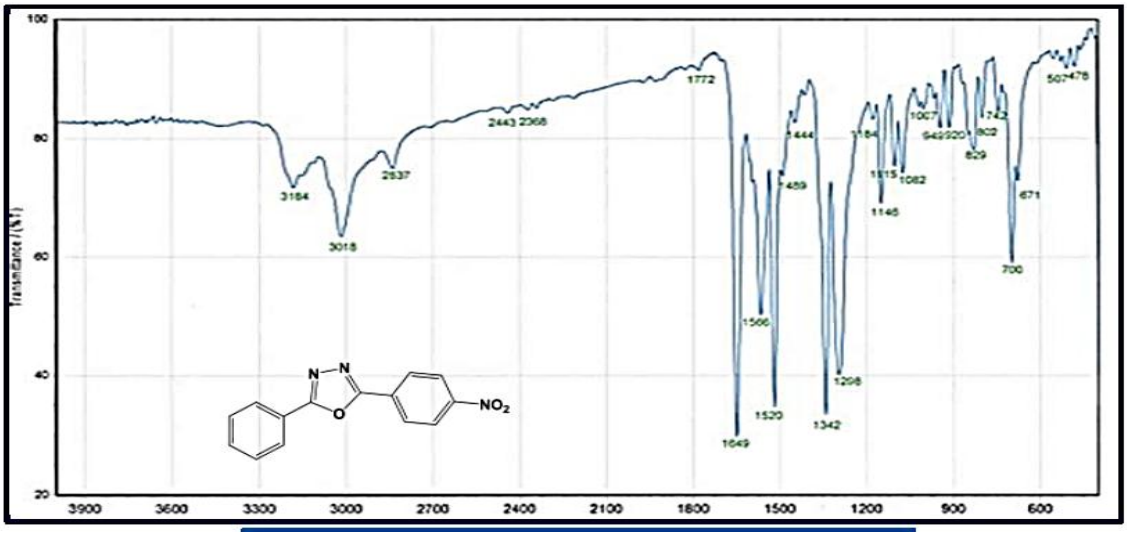


**Fig. 1:** IR spectrum of $E_{23.}$

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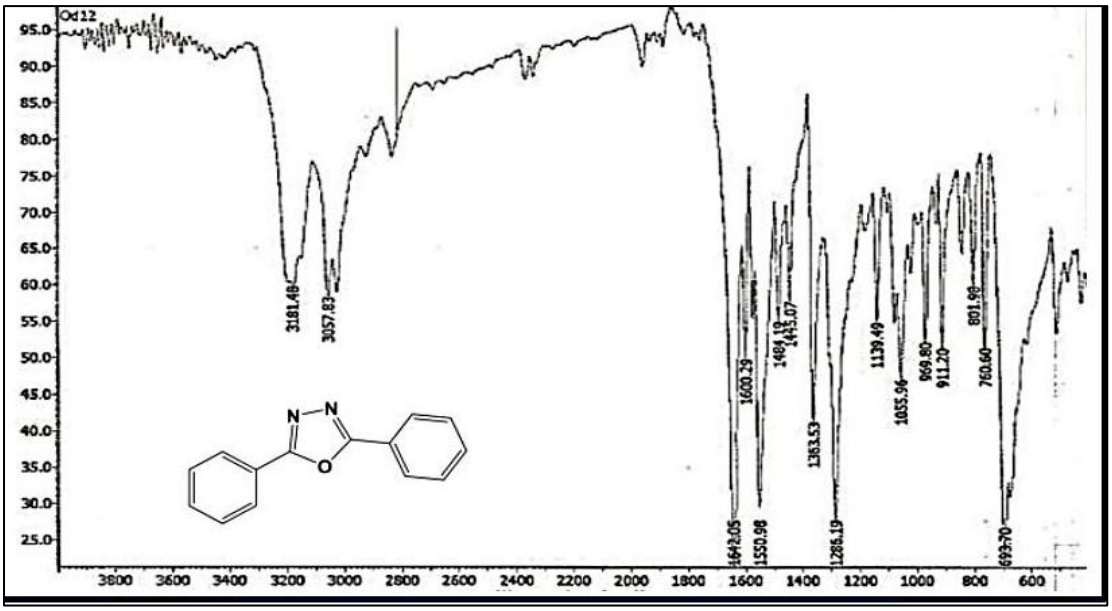


**Fig. 2:** IR spectrum of $E_{15.}$

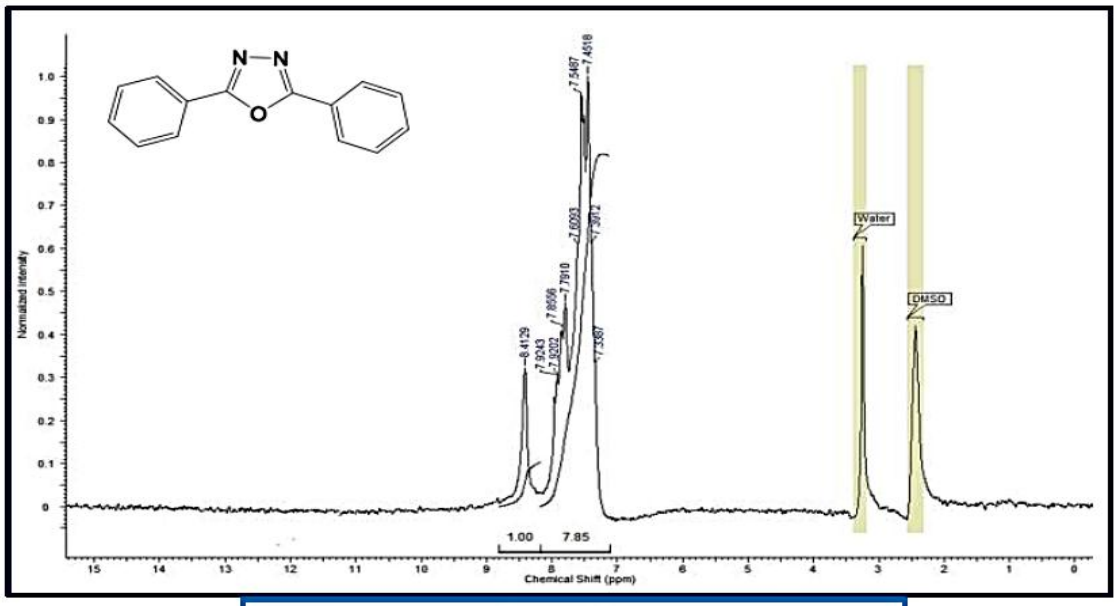


**Fig. 3:** NMR spectrum of $E_{15.}$

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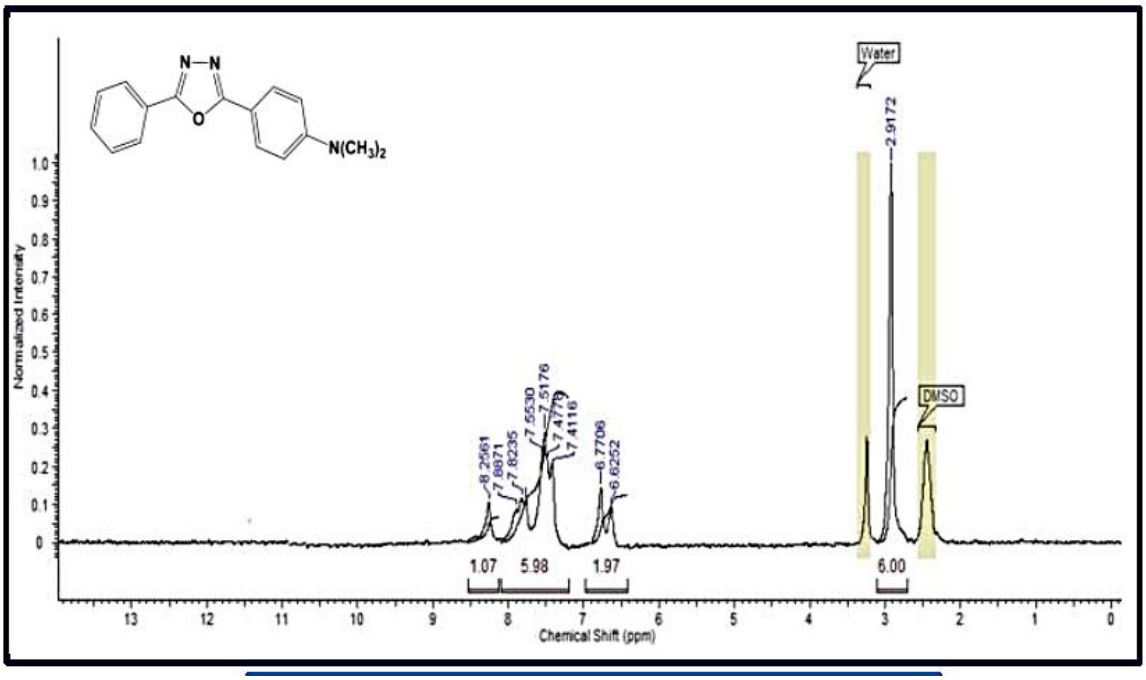


**Fig. 4:** NMR spectrum of $E_{21}$.

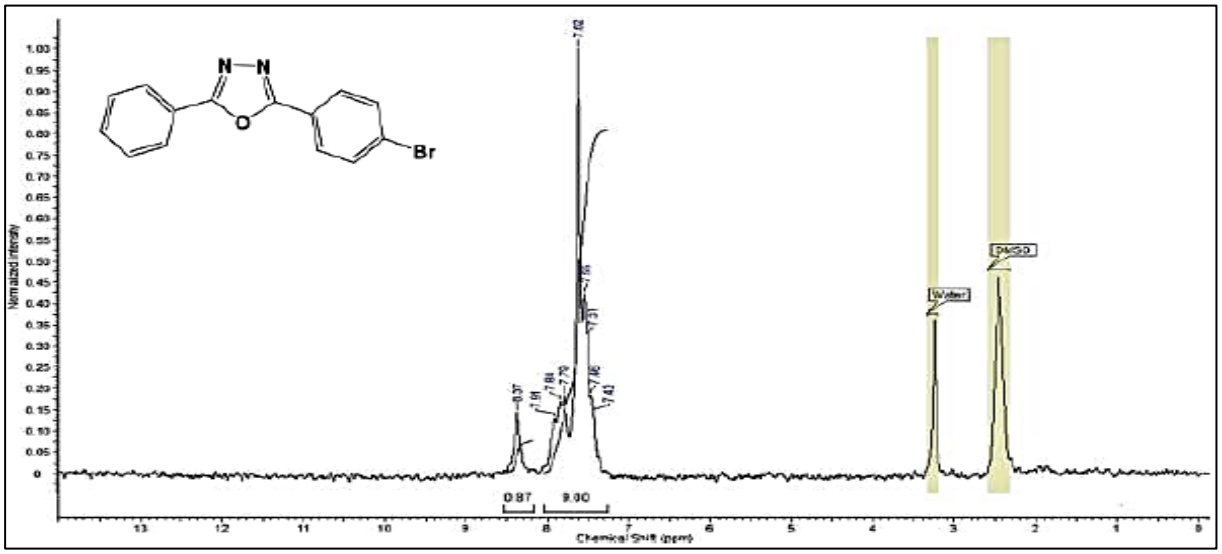


**Fig. 5:** NMR spectrum of $E_{27}$.

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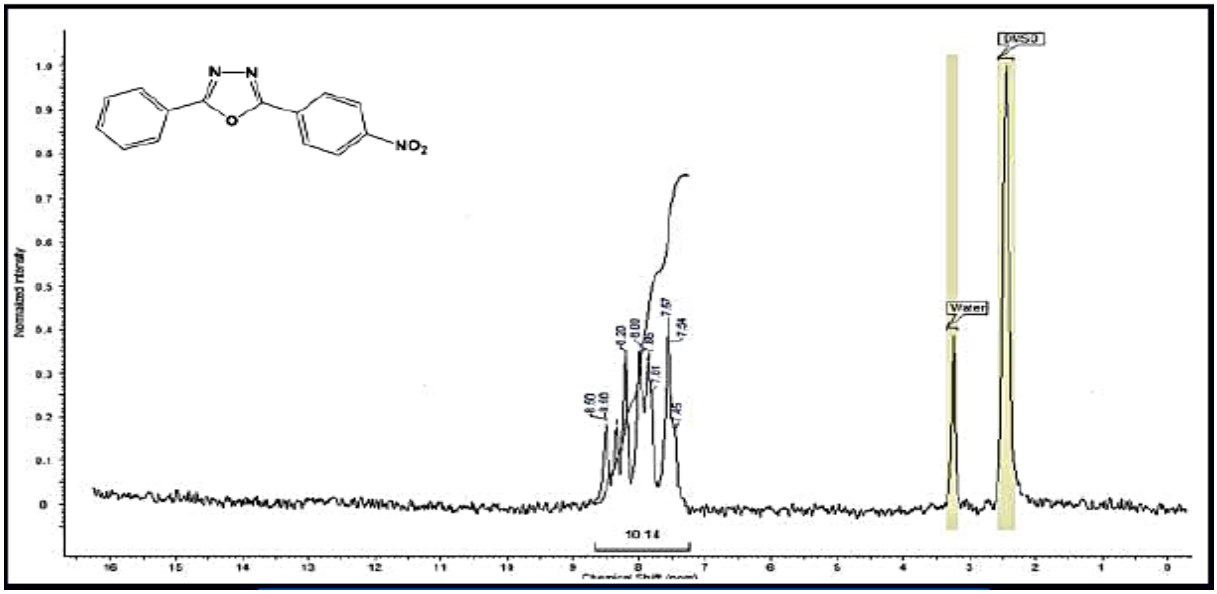


**Fig. 6:** NMR spectrum of $E_{23}$.

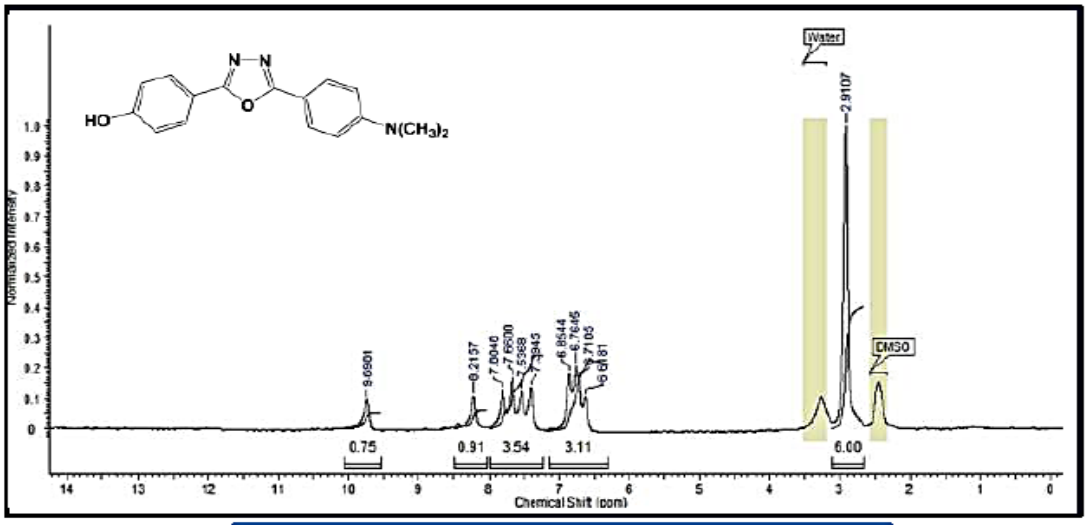


**Fig. 7:** NMR spectrum of $E_7$.

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