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Synthesis of Some New 2-(2-Isopropyl-5-Methyl Phenoxymethyl)-5-Aryl-1,3,4-Oxadiazoles

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ABSTRACT

In the present investigation, some new 1,3,4-oxadiazole derivatives have been prepared starting from readily available thymol. The reaction of thymol with ethylbromoacetate afforded the ethyl ester (1). Treatment of the latter with hydrazine hydrate yielded the corresponding hydrazide (2).

2,5-Disubstituted-1,3,4- oxadiazole (3a-h) were obtained by the reaction of the hydrazide with substituted benzoic acid in the presence of phosphorous oxychloride.

The structure of the new synthesized compounds were confirmed by spectral and physical means.

تحضير عدد من مركبات 2-(2-ايزوبروبيل-5-مثيل فينوكسي مثيل)-5-أريل-4,3,1-أوكسادايازول الجديدة

الملخص

في هذا البحث تم تحضير عدد من المشتقات الجديدة لمركبات 4,3,1 – أوكسادايازول باستخدام مادة الثايمول. إن تفاعل الثايمول مع بروموخلات الأثيل يعطي الأستر الأثيلي (1)، والذي عند مفاعلته مع الهيدرازين المائي يؤدي الى إعطاء الهيدرازيد المقابل (2).

اما مشتقات1، 3، 4- أوكسادايازول (3a-h) فقد حضرت من خلال تفاعل الهيدرازيد مع معوضات مختلفة لحامض البنزويك بوجود أوكسي كلوريد الفسفور. وقد تم إثبات الصيغ التركيبية للمركبات المحضرة بالطرائق الطيفية والفيزياوية .

INTRODUCTION

Derivatives of 1, 3, 4-oxadiazole constitute an important family of heterocyclic compounds . Since many of them have a wide variety of uses ,in particular as biologically active compounds in medicine as antitussive agents (Korbonits et al., 1989), antiinflammatory (Nargund et al., 1994; Omar et al., 1996), antifungus (Kidwai and Bhushan, 1999), antimicrobial (Matsumoto et al., 1998; Sahin et al., 2002), antibacterial (Maslat et al., 2002), anticancer (Mansour et al., 2003), antimutagenicity

(Maslat et al., 2004) and finally as antidepressant (Hennies et al., 2005). Furthermore, these compounds have an application in other fields such as agriculture as antimildew (Khanum et al., 2004) or in industry as polymers (Yang et al., 2003; Yang et al., 2003).

2,5-Disubstituted-1,3,4-oxadiazoles have synthesized in different methods,but the most popular one is based on the thermal or acid catalysed cyclization of 1, 2-diacylhydrazines (Katritzky and Reas, 1984). Ring closure usually proceeded in the presence of hot phosphorous oxychloride (Lee et al., 2001; Krayushkin et al., 2002).

Encouraged by these observations, it was considered worthwhile to synthesize the title compounds.

EXPERIMENTAL

Melting points were measured on Electrothermal (9300) melting point apparatus and are uncorrected. IR spectra were recorded in KBr disc using a Bruker, FT-IR, Spectrophotometer tensor 27. UV spectra were performed on Shimazu UV-Visible Spectrophotometer UV-1650 PC using methanol as a solvent.

Synthesis of ethyl (2-isopropyl-5-methyl phenoxy)acetate (1): (Husain et al.,1979):

To a solution of thymol (0.05mole, 7.5gm) and ethylbromoacetate (0.05 mole, 8.4 gm) in (30 ml) of dry acetone, anhydrous potassium carbonate (0.05 mole, 6.9 gm) was added. The reaction mixture was refluxed for (18 hours). After cooling, the solution was filtered, then the solvent was evaporated under vacuum. The product was separated as a yellow liquid in (95٪) yield, b.p.(240°C), IR 1760 cm^{-1}(C=O), 1166 cm^{-1} (C-O-C); UV (254nm).

Synthesis of 2-isopropyl-5-methylphenoxy acetic acid hydrazide (2): (Husain et al., 1979)

A mixture of compound (1) (0.01mole, 2.36gm) and hydrazine hydrate (0.02mole, 1gm) in (30 ml)of absolute ethanol was refluxed for (3 hours). After cooling, the solvent was evaporated under vacuum and the solid was collected, washed thoroughly with cold water and dried; yield (72٪), m.p. (97-98°C). IR 3319 cm^{-1} (NH), 1672 cm^{-1} (C=O), 1171 cm^{-1}(C-O-C); UV (268 nm).

Synthesis of 2-(2-isopropyl-5-methylphenoxymethyl)-5-aryl-1, 3, 4-oxadiazoles (3a-h): (Dutta et al.,1986)

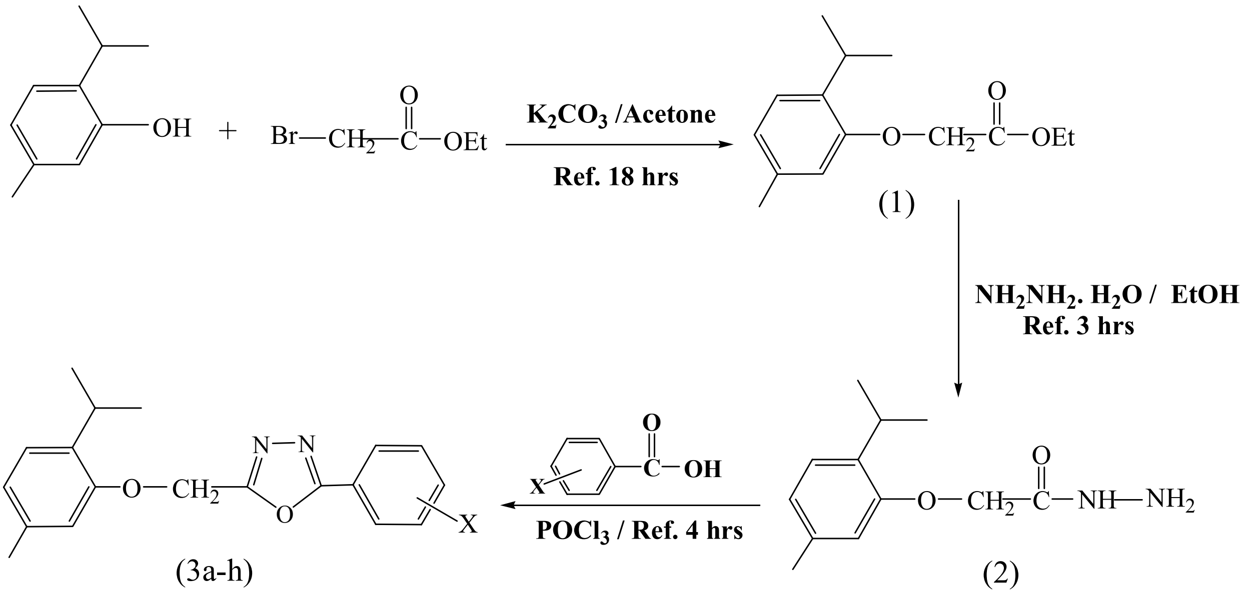
A mixture of compound (2) (0.001mole), different substituted benzoic acid (0.001mole) and (0.7 ml) of phosphorous oxychloride was refluxed for (4hours). After cooling, the reaction mixture was poured into ice-water and made basic by adding saturated solution of sodium bicarbonate. The precipitate was collected by filteration, washed with cold water and recrystallized from ethanol-water. If the product doesn't precipitate directly in water ,it will be extracted in benzene (3x30ml), the benzene layer is separated, dried with magnesium sulfate, filtered and evaporated under vacuum. The precipitate was collected and recrystallized from ethanol-water. Physical and spectral data for these compounds are recorded in Table (1) .

Table 1: Physical and Spectral data for compounds (3a-h).

Compd. No.	**X**	**Molecular Formula**	**M.P (°C)**	**Yield (%)**	**UV (MeOH) λmax (nm)**	**IR (KBr) υ (cm^{-1})**	
						C=N	**C-O-C**
3a	H	$C_{19}H_{20}N_2O_2$	115-118	83	307	1612	1250
3b	2-NO_2	$C_{19}H_{19}N_3O_4$	236-239	84	306	1611	1247
3c	3-NO_2	$C_{19}H_{19}N_3O_4$	118-119	87	307	1616	1252
3d	4-NO_2	$C_{19}H_{19}N_3O_4$	217-219	70	307	1591	1244
3e	3,5-di-NO2	$C_{19}H_{18}N_4O_6$	174-175	86	300	1627	1246
3f	3-Cl	$C_{19}H_{19}\ C_lN_2O_2$	149-150	81	299	1611	1247
3g	4-Cl	$C_{19}H_{19}\ C_lN_2O_2$	135-138	83	299	1616	1250
3h	2,4-di-Cl	$C_{19}H_{18}C_{l\ 2}N_2O_2$	124-127	80	298	1604	1248

RESULTS AND DISCUSSION

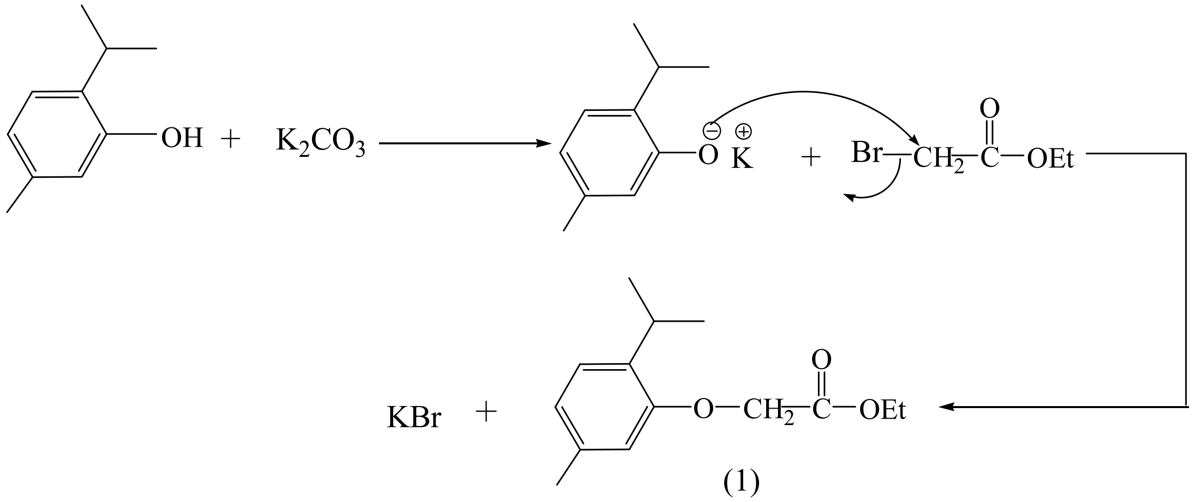
In this work, the synthesis of the titled compounds was carried out in three steps as shown in Scheme (1).



X= H, 2-NO_2 ,3-NO_2 , 4-NO_2, 3,5-di-NO_2 ,3-Cl , 4-Cl , 2,4-di-Cl

Scheme (1)

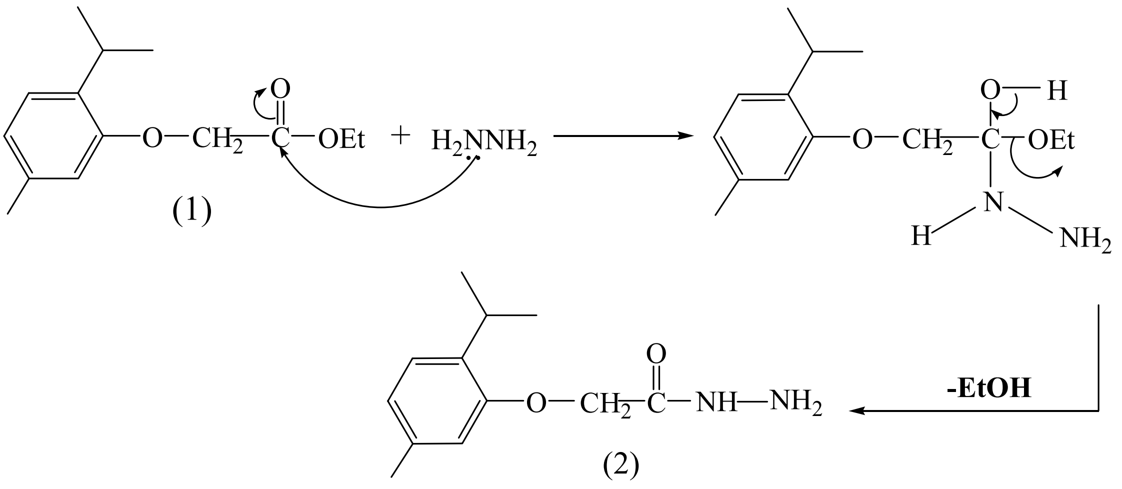
First of all nucleophilic substitution reaction take place between thymol and ethylbromoacetate in the basic medium (Schmid, 1996) to produce the corresponding ethyl ester (1) as shown in Scheme (2).



Scheme (2)

Spectral data gave a big support for the formation of this compound. The IR spectrum showed characteristic absorption bands in the region (1760 cm^{-1}) for (C=O) function and (1166 cm^{-1}) for (C-O-C) function. The presence of the (C-O-C) absorption band and the absence of the phenolic hydroxyl group absorption band indicate clearly the formation of the alkaryl ether linkage which inturne indicate the formation of the new ethyl ester. The UV spectrum for this compound gave λ max at (254nm).

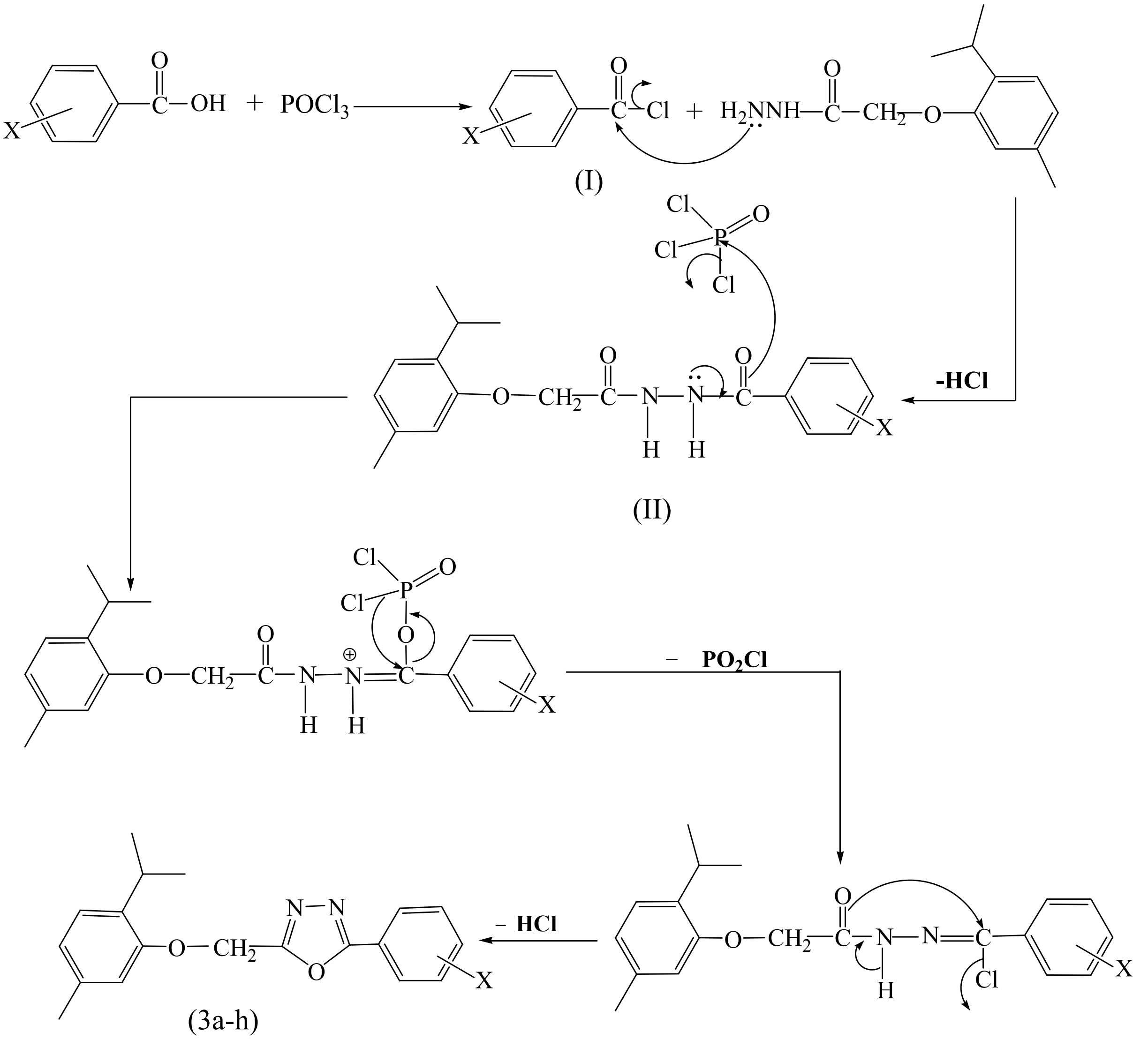
The second step involve the synthesis of the acid hydrazide through the reaction between hydrazine and the ethyl ester (1). The reaction proceed by nucleophilic substitution of hydrazine to the ethyl ester carbonyl group (McMurry, 2004), to give the corresponding hydrazide (2), which can be illustrated in Scheme (3).



Scheme (3)

The spectral data of this compound is found to be in a good agreement with the proposed structure. The IR spectrum showed significant absorption bands which indicate the formation of the hydrazide especially at (3319cm^{-1}) for (NH) function, (1672cm^{-1}) for (C=O) function and (1171cm^{-1}) for (C-O-C) function .We can see clearly from this spectrum that there is a depression in the absorption frequency for (C=O) function that attributed to the resonance effect between this group and the (NH) group. The UV spectrum gave λ max at (268nm) and here again the increasing of λ max is caused by the resonance effect (Parikh, 1974).

The final step involve the formation of oxadiazoles (3a-h) through the reaction between the hydrazide (2) and different substituted benzoic acid in the presence of phosphorous oxychloride which act as a chlorinating and dehydrating agent respectively as shown in the following suggested mechanism (Scheme 4).



X= H, 2-NO$_2$,3-NO$_2$, 4-NO$_2$, 3,5-di-NO$_2$,3-Cl , 4-Cl , 2,4-di-Cl

Scheme (4)

According to the scheme, the intermediate Aroyl acyl hydrazine (II) will be formed through the reaction of acid chloride (I) with hydrazide (2). The reaction proceed through an ordinary nucleophilic substitution of the electron pair of N-2 atom of the hydrazide to the acid chloride carbonyl group.

Finally, cyclodehydration process of the intermediate (II) will take place by it's reaction with phosphorous oxychloride (Abdullah and Waldron, 2004) to give the oxadiazoles (3a-h).

The structural assignment of these compounds is based on their spectral data.The IR spectra showed two significant absorption bands in the region (1591-1627 cm^{-1}) for (C=N) function and (1244-1252 cm^{-1}) for (C-O-C) function .We can see that the new cyclic (C-O-C) absorption band presence at higher frequency compared with acyclic (C-O-C) absorption band of the alkaryl ether linkage due to the ring strain (Alpert,1970) of the new synthesized ring system, furthermore the absence of both of (C=O) and (N-H) absorption bands of the parent compound (2) indicate clearly the formation of the oxadiazole ring system. Finally, the UV spectra for these compounds gave λ max at higher wave length at (298-307 nm) compared with the hydrazide (2), which attributed to the conjugation in the new synthesized system.

REFERENCES

Abdullah, Z. and Waldron, N., 2004. Synthesis and Fluorescence Studies of 5-Chlorothia zolo [5,4-d] Pyrimidine, Malysian Journal of Chemistry, 6(1), pp.114-117.

Alpert, N.L., Keiser, W.E. and Szymanski, H.A., 1970. IR Theory and Practice of Infrared Spectroscopy, Plenum Press, 380 p.

Dutta, M.M., Goswami, B.N. and Kataky, J.C.S., 1986. Studies on Biologically Active Heterocycles. Part I. Synthesis and Antifungal Activity of Some New Aroyl Hydrazones and 2,5-Disubstituted 1,3,4-Oxadiazoles, J. Heterocyclic Chem., 23, pp.793-795.

Hennies, H.H., Sundermann, C., Buschmann, H. and Sundermann, B., 2005. 2-Pyrrolidine 2-yl-[1,3,4] –oxadiazole Compounds and their uses as Anti-depressants, U.S.Pat., 20050187260.

Husain, M.I., Shukla, M.K. and Agrawal, S.K., 1979. Search for Potent Anthelmintics – Part VII. Hydrazone Derived from 4- Substituted-7-Coumarinyl Oxyacetic Acid Hydrazide, J. Indian Chem . Soc., LVI, pp.306-307.

Katritzky, A.R. and Rees, C.W., 1984. Comprehensive Heterocyclic Chemistry, Pergamon Prees,Vol.6, 1171 p.

Khanum, S.A., Shashikath, S., Sudha, B.S., Deepak, S.A. and Shetty, H.S., 2004. Synthesis and Antimildew Activity of 5-(2-Aroyl) Aryloxymethyl-2-Phenyl-1,3,4-Oxadiaz-oles against Downy mildew of Pearl millet ,Pest Management Science, 60(11), pp.1119-1124.

Kidwai, M. and Bhushan, K.R., 1999. A Novel Synthetic Method for Fungicidal Organo-Merecurials ,Chem.Papers, 53(2), pp.114-117.

Korbonits, D., Minker, E., Vargai, Z., Heja, G., Kovacs, G., Gottsegen, A., Antus, S., Virag, S., Bolehovszky, A., Marton, J., Mormarosi nee Kellner, K., Debereczeni, L., Tardos, L., Kormoczy, P., Gergely, V. and Horvath, G., 1989. Oxadiazole-Alkyl-Purine Derivatives useful as Antitussive agents, US. pat., 4840949.

Krayushkin, M.M., Stoyanovich, F.M., Zolotarskaya, O.Yu., Chernoburova, E.I., Makhova, N.N., Yarovenko, V.N., Zavarzin, I.V., Martynkin, A.Yu. and Uzhinov, B.M., 2002. Photochromic Dihetarylethenes.12*, Synthesis of 5-Alkyl-2-(1,3,4-Oxadiazole-2-yl) Thiophenes and Their Photochromic Derivatives, Chemistry of Heterocyclic Compounds, 38(2), pp.165-176.

Lee, D.W., Kwon, K., Jin, J., Park, Y., Kim, Y. and Hwang, I., 2001. Luminescence Properties of Structurally Modified PPVs:PPV Derivatives Bearing 2-(4-tert-Butylphe-nyl)-5-phenyl-1,3,4-Oxadiazole Pendants, Chem.Mater.,13, pp.565-574.

Mansour, A.K., Eid, M.M. and Khalil, N.S., 2003. Synthesis and Reaction of Some New Heterocyclic Carbohydrazides and Related Compounds as Potential Anticancer Agents, Molecules, 8, pp.744-755.

Maslat, A.O., Abussaud, M., Tashtoush, H. and Al-Talib, M., 2002. Synthesis, Antibacterial, Antifungal and Genotoxic Activity of Bis-1,3,4-Oxadiazole Derivatives, Pol.J. Pharmacol., 54, pp.55-59.

Maslat, A., Khalil, A., Fares, A., Tashtoush, H. and El-Talib, M., 2004. A Notable Antimutagenicity of Tow Nonmutagenic Novel Oxadiazoles in Salmonella Mutagenicity Assay, Drug and Chemical Toxicology , 27(2), pp.157-167.

Matsumoto, K.Y., Yasuda, Y., Tanimoto, T., Matsumoto, K., Yoshida, T. and Shoji, J., 1998. Isolation and Characterezation of Thioxamycine, J. Antibiotics, 42,pp.1465-1469.

McMurry, J., 2004. Organic Chemistry, Thomson Learning, Inc., 1176 p.

Nargund, L.V., Reddy, G.R. and Hariprasad, V., 1994. Antiinflammatory Activity of Substituted 1,3,4-Oxadiazoles , J.Pharm. Sci., 83(2), pp.246-248.

Omar, F.A., Mahfouz, N.M. and Rahman, M.A., 1996. Design, Synthesis and Antiinflammatory Activity of Some 1,3,4-Oxadiazole Derivatives, Eur. J. Med. Chem, 31, pp.819-825.

Parikh, V.M., 1974. Absorption Spectroscopy of Organic Molecules, Addison–Wesley Publishing Company, 325 p.

Sahin, G., Palaska, E., Ekizoglu, M. and Ozalp, M., 2002. Synthesis and Antimicrobial Activity of Some 1,3,4-Oxadiazole Derivatives , Farmaco, 57(7), pp.539-542.

Schmid, G.H., 1990. Organic Chemistry, Mosby-year book , Inc., 1208 p.

Yang, N.C., Chang, S. and Suh, D.H., 2003. Synthesis and Optically Acid-Sensory Properties of Novel Polyoxadiazole Derivatives, Polymer, 44, pp.2143-2148.

Yang, N.C., Park, Y.H. and Suh, D.H., 2003. Synthesis and Properties of New Ultraviolet-Blue-Emissive Fluorene-Based Aromatic Polyoxadiazoles with Confinement Moieties, Journal of Polymer Science, 41, pp.674-683.