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KF-Al_2O_3 Catalyzed Domino One-Pot, Three-Component Synthesis of 3,5-Disubstituted-1,2,4-Oxadiazoles Under Microwave-Assisted Solvent Free Conditions and Their Biological Activity.

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Abstract
A simple and efficient one-pot approach for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles directly from corresponding aldehydes and amidoximes using recyclable KF-Al_2O_3 catalyst system under solvent free conditions have been developed. The 'domino' one-pot three component approach involves hydroxyamination of benzonitrile to amidoxim followed by 1,3-dipolar cycloaddition with aldehyde to generate 3,5-disubstituted-1,2,4-oxadiazoles. The method is operationally simple, regioselective, economical, and possesses excellent functional group compatibility to produce structurally assorted 1,2,4-oxadiazoles in good yields.

Keywords: *1,2,4-oxadiazoles, heterogeneous catalyst, microwave energy, bioactive molecules*

1 Introduction

3,5-Disubstituted-1,2,4-oxadiazoles have received substantial attention in the pharmaceutical manufacturing as heterocyclic amide and ester biosteres [1]. The oxadiazole nucleus is an extensively studied pharmacophoric scaffold that has turned out to be a core structural unit of various benzodiazepine receptor partial agonists [2], muscarinic agonists [3], a growth hormone secretatogue [4], a tyrosine kinase inhibitor [5], dopamine transporters [6] and antiinflammatory agents [7]. 1,2,4-oxadiazoles have also been employed as antitumor, tyrosine kinase inhibitors, serotoninergic (5-HT3) anti-inflammatory, coronary artery dilaters, anesthetic, monoamine oxidase inhibitors, muscle relaxant, anti-schistosomal, aldose reductase inhibi-tors [8] and histamine H3 antagonists agents [9]. Furthermore, derivatives containing 1,2,4-oxadiazole ring systems have revealed affinities for serotonin and norepinephrine transporters [10] and have been used as a urea bioisostere in *ß3* adrenergic receptor agonists[11].

Several methods have been reported in literature for the synthesis of 1,2,4-oxadiazoles [12]. The most general methods reported in recent times for the synthesis of 1,2,4-oxadiazoles are cyclization of O-acylamidoximes obtained from acylation of amidoximes by carboxylic acids or acid chlorides [13]. However, several drawbacks are associated with these methods. Toxic and reactive nature of acid chlorides makes them hard to store and handle, and only a few acid chlorides are readily available. Carboxylic acids on the other hand need a coupling reagent such as 1,1-carbonyldiimidazole (CDI), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), dicyclohexyl carbodiimide (DCC), O-(1H-benzotriazol-1-yl)- N,N,N^0,N^0-tetramethyluronium tetrafluoroborate (TBTU) or 1,2,3-benzotriazole-1-hydroxide (HOBt) etc. to react with amidoximes [14] and also the reaction time is relatively long. As a part of our continuing efforts to develop efficient methods for the preparation of widely used organic compounds from readily available building blocks [15], we herein report KF-Al_2O_3 catalyzed solvent free, domino, one-pot multicomponent approach for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles directly from benzonitrile and aldehydes via cycloaddition reaction between in situ generated amidoxime(from benzonitrile and hydroxylamine hydrochloride) and aldehydes under microwave irradiation.

In the recent years, multi-component reactions catalyzed by solid-support materials have

emerged as an efficient strategy to address the challenges of green synthesis. In particular, the use of potassium fluoride coated with alumina (KF-Al_2O_3) has become popular due to its inherent basic nature and characteristic properties such as enhanced reactivity, selectivity and a straight forward work-up procedure [16]. Using microwave irradiation as energy source along with heterogeneous catalyses makes the process more economic and ecofriendly. The application of microwave energy is an emerging technique for conducting synthetic reactions at highly accelerated rates. Actually microwaves have become popular among synthetic organic chemists to improve classical organic reactions and/or improving yields, as well as to promote new reactions [17].

2 Experimental

General procedure for the synthesis of1,2,4-oxadiazoles

A mixture of benzonitrile (103 mg, 100 mmol), hydroxylamine hydrochloride (208.47 mg, 3 mmol) and 5 mg KF-Al_2O_3 were taken into a 5 ml microwave vial. The vial was capped with a Teflon pressure cap and subjected to microwave irradiation for 8 min at 150^{o}C (300 watts). The microwave oven used was Scientific Microwave Synthesizer CATA - R I. After nearly complete conversion into an intermediate presumed to be the corresponding amidoxime, as indicated by TLC monitoring, the reaction mixture was cooled to room temperature, then an aldehyde (1.5 mmol) was added to the cooled reaction mixture. This mixture was again subjected to the above mentioned microwave irradiation. On completion of the reaction, followed by TLC examination, the mixture was cooled to room temperature, dissolved in ethyl acetate and filtered to separate the catalyst. The filtrate was concentrated under high vacuum and the crude 1,2,4-Oxadiazole derivatives were purified by column chromatography using petroleum ether-ethyl acetate (9:1). The products thus obtained are characterized by HRMS, NMR. The spectral data were found to be consistent with authentic samples.

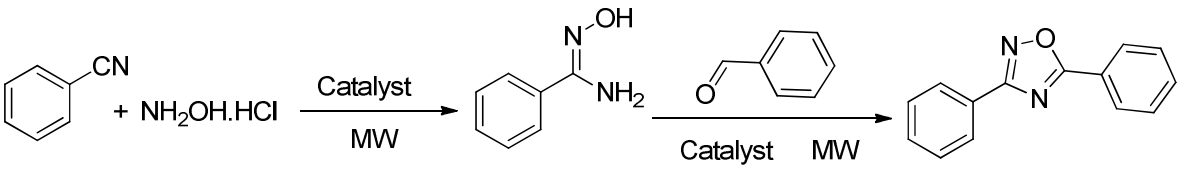
3. Results and Discussion:

In our initial studies synthesis of 3,5-disubstituted-1,2,4-oxadiazoles through the domino one pot condensation of benzonitrile, hydroxalamine hydrochloride and aldehyde was chosen as model reaction and several catalysts were screened for this reaction under solvent free conditions (scheme 1).

The results of these studies are summarized in Table 1, which clearly shows that in combination with microwave radiation all these catalysts could not accelerate the reaction to furnish the desired product in good yield. KF-Al_2O_3 (preparation given in experimental section) was found to be the most suitable catalyst among all the screened catalysts, which shows excellent catalytic activity without any byproduct formation. Using this catalyst under microwave irradiation and solvent free conditions, the model reaction mixture furnished 97% of the desired product within 8 min at the expense of catalytic amount of KF-Al_2O_3 (Scheme 2)

The optimum amount of the catalyst in this one-pot, three component reaction, was found to be 5 mg (Table 1, entry 10). By lowering the catalyst amount to 3 mg, the desired product was obtained in lower yield (Table 1, entry 11), while as increased catalyst amount above has no significant effect on reaction rate and isolated yield of product (Table 1, entries 6-9).

Scheme 1



Scheme 2

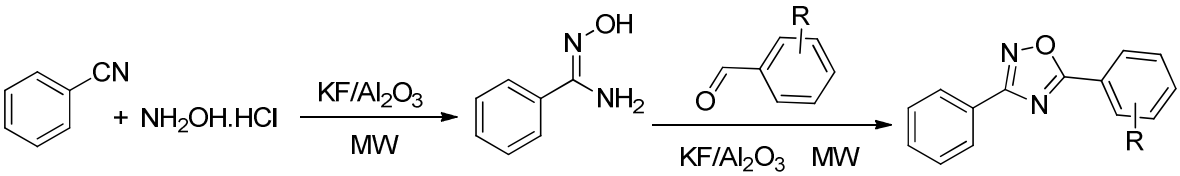
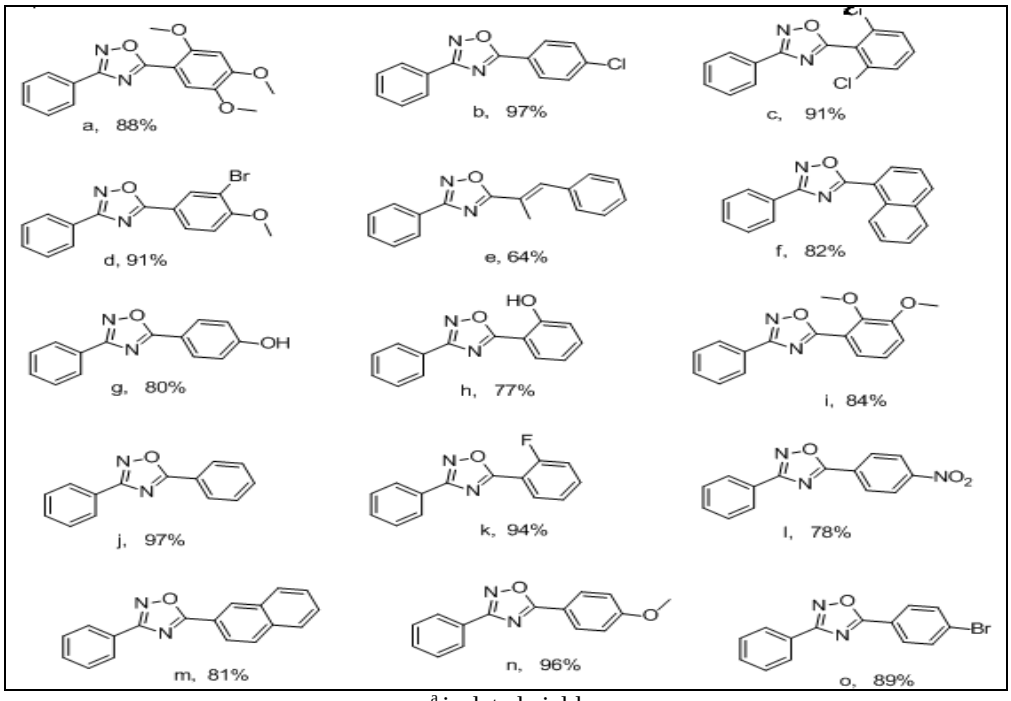


Table-1: Effect of different catalysts and conditions for the model reaction under solvent free environment

Entry	Catalyst	Catalyst Amount (mg)	Time	Yield[a] (%)
1.	K_2CO_3	15	10 min	55
2.	Na_2CO_3	15	10 min	55
3.	Al_2O_3 (neutral)	15	10 min	48
4.	Al_2O_3 (basic)	15	10 min	43
5.	Al_2O_3 (acidic)	15	10 min	88
6.	KF/Al_2O_3	15	10 min	97
7.	KF/Al_2O_3	15	8 min	97
8.	KF/Al_2O_3	15	5 min	61
9.	KF/Al_2O_3	10	8 min	97
10.	KF/Al_2O_3	5	8 min	97
11.	KF/Al_2O_3	3	8 min	84
12.	No catalyst	--	2h	Traces

[a] isolated yield,

After optimization of the reaction conditions, we studied the scope of this approach, particularly in regard to library construction. This methodology was evaluated for the synthesis of different 3,5-disubstituted-1,2,4-oxadiazoles from various structurally diverse aldehydes. KF-Al_2O_3 was found to catalyze the one pot synthesis of 3,5-disubstituted-1,2,4-oxadiazoles excellently and good to excellent yields of the desired products were obtained (Fig. 1). We investigated the reaction using several electron-donating and electron-withdrawing substituted benzaldehydes under optimized conditions. The reaction was found to be compatible with various functional groups such as electron donating groups like F, Cl, Br, OH, OMe and electron withdrawing group NO_2. All the reactions proceeded cleanly, to give the corresponding 3,5-disubstituted-1,2,4-oxadiazoles with no remarkable difference in their yields. No competitive nucleophilic methyl ether cleavage was observed in the substrate possessing an aryl-OMe group (Table 3, entries a, d, i and n). Napthaldehyde derivatives were found to produce the corresponding 3,5-disubstituted-1,2,4-oxadiazoles with good yields. 2-Napthaldehyde shows better reactivity and higher yield than 1-Napthaldehyde (Fig. 1, entries 9, 11).



[a] isolated yield

Fig.1: KF-Al_2O_3 catalyzed synthesis of 3,5-disubstituted-1,2,4-oxadiazoles[a]

4. Reusability of the catalyst

Recovery and reusability of KF-Al2O3 was studied for the model reaction. In this experiment the catalyst was separated by centrifuging the reaction mixture after diluting with ethylacetate. From this experiment it was proved that the catalyst can be reused several times without any appreciable loss in activity and generates the products with purities similar to those obtained in the first run. The catalyst reusability for 5 cycles is shown in Figure 1.

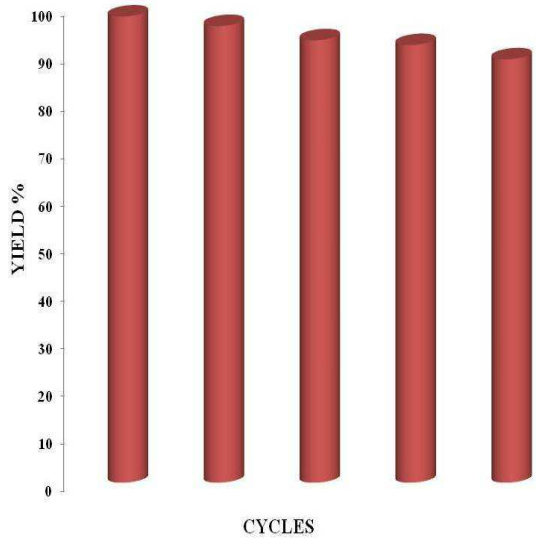


Figure 2. Recovery cycles of the catalyst

Anti-inflammatory activity:

*1. Selection of experimental animals:*Healthy Swiss albino rats were used for the experiments. 100 albino rats weighing 150-190g were used for the evaluation of anti-inflammatory activity.

2. Laboratory condition:

The rats were housed comfortably in a group of six in a single clean plastic cage with a metal frame lid on its tip. The animal house is maintained under normal controlled condition.

3. Food and water: Pelleted food and filtered tap water was made available ad libitum.

4. Bedding: In the present study, we have provided clean paddy husk bedding. Bedding was changed every alternate day to maintain proper hygienic condition.

5. Experimental procedure: Method: Carrageenin induced rat hind paw oedema method.

Principal: The inflammatory reaction is readily produced in rats in the form of paw oedema with the help of irritants of inflammogen. Carrageenin induced paw oedema is the most commonly used experimental method. Carragenin is sulphated polysaccharide obtained from seaweed (Rhodophyceae) causing the release of histamine, 5-HT, bradykinin and prostaglandins. It produces inflammation and oedema.

Requirements:

Animals: Swiss Albino rats (150-190g) 100 no.
Instrument: Plethysmograph

Inflammogen: Carrageenin 1% w/v solution in distilled water and injected 0.1mL in plantar region to induce foot oedema. Standard Drug: Ibuprofen aqueous suspension prepared with 0.2% w/v solution of CMC as suspending agent. Sample preparation: Sample was prepared as aqueous suspension prepared with 0.2% w/v solution of CMC as suspending agent.

Working Procedure:

Required number of albino rats of either sex was divided into required number of groups (each of six animals) and they were numbered individually. Animals were fasted for 24 h before administration of the drugs with water adlibitum. The animals were marked on their hind paw just beyond tibiotarsal junction to ensure constant dipping in the mercury column up to a fixed mark. The initial paw volume (both right and left) of each rat was noted by mercury displacement method using plethysmograph. Group I was marked as control which is administered with 0.1mL of 1% carrageenan solution. Group II received ibuprofen at a dose of 10.6mg/200g body weight along with the carrageenan, which was served as standard, while group III to last number received test samples along with the inflammogen. After drug treatment, 0.1mL of 1% w/v carrageenan solution was injected into plantar region of the left paw of the standard and test groups. The paw volume of both the legs of control and standard groups was measured with the help of plethysmograph for 30 min, 1 h, 2 h & 4 h after carrageenan administration. The percentage of inhibition of inflammation in the drug treated animals was recorded and calculated using the formula;

% inhibition volume = Wt –Wc/ Wt

Wherein; Wt: Mean oedema volume of control
Wc: Mean oedema volume of drug.

The Anti-inflammatory activity of some selected compounds (**d** to **i** of table 1) are given in table 3

below. It is evident from the table that some of these compounds like **d**, **e** and **f** are very active.

Table 3: Results of Anti-inflammatory activity

Compound	Standard Error Mean	% Inhibition	p-Value
d	0.02	64.21	<0.01
e	0.03	46.21	<0.05
f	0.06	50.33	<0.01
g	0.08	18.92	<0.01
h	0.13	12.66	Non-significant
i	0.13	22.30	Non-significant
j	0.04	16.30	Non-significant
Control	0.04	0.00	----------
Ibuprofen	0.04	91.60	<0.01

Analgesic activity:
1. Selection of experimental animals: Healthy Swiss albino mice were used for the experiments. Required numbers of albino rats weighing 20-25g were used for the evaluation of analgesic activity.

2. Laboratory condition: The mice were housed comfortably in a group of six in a single clean plastic cage with a metal frame lid on its tip. The animal house is maintained under normal controlled condition.
3. Food and water: Pelleted food and filtered tap water was made available ad libitum.

4. Bedding: In the present study, we have provided clean paddy husk bedding. Bedding was changed every alternate day to maintain proper hygienic condition.

5. Experimental procedure:
Method: Acetic acid induced writhing method was adopted for evaluation of analgesic activity.

Principal: Writhing is defined as a streatch, tension to one side, drawing up of a hind
leg, retraction of the abdomen so that the belly of mouse touches the floor. Any writhing is considered as positive response.

Requirements:
Animals: Swiss Albino mice (20-25g) required no.
Acetic acid: 1% w/v solution of acetic acid in distilled water.

Standard Drug: Aspirin dispersed in water (dose – 100mg/Kg).
Sample preparation: Synthesized compounds were prepared as an aqueous suspension using 0.2% CMC as suspending agent and administered orally.
Dose: 100 mg/Kg body weight.

Working Procedure: After 30mins of administration of the drug/s, writhing was induced by intra peritoneal injection of 1% acetic acid in volume of 0.1mL/10g body weight and the writhing episodes were recorded for 15mins. The percent protection against the writhing episodes were recorded and calculated by using formula;

% Protection = (1 – Wt/Wc) X 100
Where,
Wt = Mean of the writhing episodes in the test.
Wc = Mean of the writhing episodes in control.

The analgesic activity of some selected compounds (**d** to **i** of table 1) are given in table 4 below. Some of the prepared compounds like **d**, **e** and **h** show analgesic activity comparable to that of Aspirin. Compound **f** was observed to have analgesic activity higher than that of Aspirin.

Table 4: Results of analgesic activity

Compound	Writhing Episodes	Standard Error Mean	% Inhibition	p-Value
d	10.33	0.87	55.31	<0.01
e	16.00	1.11	51.26	<0.05
f	15.00	0.97	61.34	<0.01
g	17.66	1.17	18.23	Non-significant
h	15.33	1.06	55.48	<0.01
i	14.21	0.64	21.41	Non-significant
j	13.41	0.58	20.36	Non-significant
Control	21.66	0.55	----------	----------
Aspirin	8.66	1.05	60.00	<0.01

5. Conclusion

An expeditious, efficient, environment friendly, chemo-selective and simple protocol for the one-pot synthesis of 3,5-disubstituted-1,2,4-oxadiazoles is presented. Use of a catalytic amount of KF/Al_2O_3, short reaction time, no competitive side reactions

and simple experimental procedures contribute to the significant features of this method. The catalyst is efficient, inexpensive, shelf stable, heterogeneous and can be easily recovered from the reaction mixture via simple filtration and reused several times. The process is fast and the desired products are produced in good to excellent yield and can be easily separated and purified. This simple procedure allows a series of 1,2,4-oxadiazoles to be synthesized from inexpensive and commercially available starting materials. The synthesized compounds were found to have good analgesic and anti-analgesic activity.

Spectral data

3-Phenyl-5-(2,4,5-trimethoxyphenyl)-1,2,4-oxadiazole:- ^{1}H NMR (400MHz, $CDCl_3$, ppm): δ 7.6-7.5 (d, 2H), δ 7.50-7.45 (m, 3H), δ7.2 (s, 1H); δ6.6 (s, 1H); δ3.7 (s, 9H).
^{13}C NMR (100MHz, $CDCl_3$, ppm): δ 169.00, 163.58, 155.28, 154.60, 145.80, 132.65, 132.60, 131.40, 131.8, 128.40, 127.70, 120.00, 118.60, 102.70, 45.80, 44.35, 42.10

5-(4-Chlorophenyl)-3-phenyl-1,2,4-oxadiazole:- ^{1}H NMR (400MHz, $CDCl_3$, ppm): δ 7.5-7.35 (m, 6H), δ 7.30-7.25 (m, $3H_)$, δ7.1 (s, 1H); δ6.4 (s, 1H).
^{13}C NMR (100MHz, $CDCl_3$, ppm): δ 171.15, 165.18, 154.80, 153.10, 146.70, 133.60, 132.20, 130.10, 129.80, 128.10, 125.30, 118.50, 116.60, 110.10

5-(2,6-Dichlorophenyl)-3-phenyl-1,2,4-oxadiazole :- ^{1}H NMR (400MHz, $CDCl_3$, ppm): δ 7.55-7.45 (m, 5H), δ 7.35-7.25 (m, 3H), $_{δ}$7.0 (s, 1H); δ6.45 (s, 1H).
^{13}C NMR (100MHz, $CDCl_3$, ppm): δ 168.55, 163.16, 135.20, 135.10, 133.50, 132.60, 132.20, 131.70, 130.80, 129.60, 129.10, 127.50, 126.40, 120.10

5-(3-Bromo-4-methoxyphenyl)-3-phenyl-1,2,4-oxadiazole:- ^{1}H NMR (400MHz, $CDCl_3$, ppm): δ 7.60-7.50 (m, 3H), δ 7.35-7.25 (m, 4H), δ7.0 (s, 1H); δ6.45 (s, 1H); 3.68 (s, 3H);
^{13}C NMR (100MHz, $CDCl_3$, ppm): δ 173.40, 171.60, 162.20, 133.10, 132.40, 132.30, 132.10, 131.70, 131.40, 130.80, 130.10, 121.50, 120.30, 110.10, 53.60

3-Phenyl-5-(1-phenylprop-1-en-2-yl)-1,2,4-oxadiazole:- ^{1}H NMR (400MHz, $CDCl_3$, ppm): δ 7.60-7.50 (m, 6H), δ 7.35-7.25 (m, 4H), δ6.90 (s, 1H); 1.8 (s, 3H);
^{13}C NMR (100MHz, $CDCl_3$, ppm): δ 170.40, 168.30, 142.20, 136.20, 132.90, 132.70, 132.65, 132.55, 132.40, 132.20 , 132.00, 131.50, 131.30, 130.10,129.50, 115.20, 17.10

4-(3-Phenyl-1,2,4-oxadiazol-5-yl)phenol :- ^{1}H NMR (400MHz, $CDCl_3$, ppm): δ 7.80-7.40 (m, 5H), δ 7.35-7.25 (m, 4H), δ 4.30 (s, 1H).
^{13}C NMR (100MHz, $CDCl_3$, ppm): δ 172.30, 168.10, 165.30, 133.20, 132.15, 132.00, 131.25, 131.00, 130.40, 130.20, 129.10, 120.50, 114.80, 108.50

5-(Naphthalen-1-yl)-3-phenyl-1,2,4-oxadiazole :- ^{1}H NMR (400MHz, $CDCl_3$, ppm): δ 7.60-7.50 (m,6H), δ 7.35-7.25 (m, 7H).
^{13}C NMR (100MHz, $CDCl_3$, ppm): δ 171.40, 169.70, 139.50, 133.20, 132.65, 132.50, 132.25, 132.00, 131.40, 131.20, 130.60, 130.50, 130.10, 129.10, 128.40, 128.20, 128.00, 127.50

2-(3-Phenyl-1,2,4-oxadiazol-5-yl)phenol: ^{1}H NMR (400MHz, $CDCl_3$, ppm): δ 7.70-7.45 (m, 5H), δ 7.35-7.15 (m, 4H), δ 4.10 (s, 1H).
^{13}C NMR (100MHz, $CDCl_3$, ppm): δ 172.10, 168.40, 165.20, 133.60, 133.15, 132.40, 131.45, 131.00, 130.40, 130.00, 128.10, 118.50, 114.20, 111.50

5-(2,3-Dimethoxyphenyl)-3-phenyl-1,2,4-oxadiazole :- ^{1}H NMR (400MHz, $CDCl_3$, ppm): δ 7.6-7.5 (d, 2H), δ 7.50-7.45 (m, 3H), δ7.20-7.10 (m, 3H); 3.7 (s, 6H).
^{13}C NMR (100MHz, $CDCl_3$, ppm): δ 171.10, 163.40, 154.28, 154.60, 145.30, 132.60, 132.50, 131.40, 130.70, 128.20, 127.70, 120.20, 118.10, 102.70, 45.80, 44.35

3,5-Diphenyl-1,2,4-oxadiazole :- ^{1}H NMR (400MHz, $CDCl_3$, ppm): δ 7.6-7.5 (d, 4H), δ 7.50-7.45 (m, 6H).
^{13}C NMR (100MHz, $CDCl_3$, ppm): δ 171.40, 162.90, 134.80, 134.10, 133.30, 132.60, 132.10, 131.10, 130.30, 128.10, 127.40, 126.20, 125.40, 124.70

5-(2-Fluorophenyl)-3-phenyl-1,2,4-oxadiazole:- ^{1}H NMR (400MHz, $CDCl_3$, ppm): δ 7.5-7.30 (m, 4H), δ 7.30-7.20 (m, 5H).
^{13}C NMR (100MHz, $CDCl_3$, ppm): δ 170.50, 164.38, 154.18, 153.10, 145.70, 134.50, 132.40, 130.60, 129.90, 127.40, 124.20, 118.90, 115.40, 108.60

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References

[1] K. Luthman, S. Borg, U. Hacksell, Meth. Mol. Med. 23, 1-23 (1999).

[2] F. Watjen, R. Baker, M. Engelstof, R. Herbert, A. Macleod, A. Knight, K. Merchant, J. Moseley, J. Saunders, C. J. Swain, E. Wong, J. P. Springer, J. Med. Chem. 32, 2282-2291 (1989).

[3] B. S. Orlek, F. E. Blaney, F. Brown, M. S. G. Clark, M. S. Hadley, J. Hatcher, G. J. Riley, H. E. Rosenberg, H. J. Wadsworth, P. Wyman, J. Med. Chem. 34, 2726-2735 (1991).

[4] M. Ankersen, B. Peschke, B. S. Hansen, T. K. Hansen, Bi-oorg. Med. Chem. Lett. 7, 1293-1298 (1997).

[5] C. B. Vu, E. G. Corpuz, T. J. Merry, S. G. Pradeepan, C. Bartlett, R. S. Bohacek, M. C. Botfield, C. J. Eyermann, B. A. Lynch, l. A. MacNeil, M. K. Ram, M. R. Van Schraven-dijk, S. Violette, T. K. Sawyer, J. Med. Chem. 42, 4088-4098 (1999).

[6] F. l. Carrol, J. L. Gray, P. Abraham, M. A. Kuzemko, A. H. Lewin, J. W. Boja, M. Kuhar, J. Med. Chem. 36, 2886-2890 (1993).

[7] D. N. Nicolaides, K. C. Fylaktakidou, K. E. Litinas, D. Had-jipavlou-Litina, Eur. J. Med. Chem. 33, 715-724 (1998).

[8] J. C. Jochims in Comprehensive Heterocyclic Chemistry Il: A. R. Katritzky, C. W. Rees, E. V. F. Scriven, Eds. Pergamon Press London, Vol. 4, pp. 179(1966).

[9] J. C. Clitherow, P. Beswick, W. J. Irving, D. I. C. Scopes, J. C. Barnes, J. Clapham, J. D. Brown, D. J. Evans, A. G. Hayes, Bioorg. Med. Chem. Lett. 6, 833-838 (1996).

[10] F. l. Carrol, J. L. Gray, P. Abraham, M. A. Kuzemko, A. H. Lewin, J. W. Boja, M. Kuhar, J. Med. Chem. 36, 2886-2890 (1993).

[11] R. J. Mathvink, A. M. Barritta, M. R. Candelore, M. A. Cas-cieri, L. Deng, L. Tota, C. D. Strader, M. J. Wyvratt, M. H. Fisher, A. E. Weber, Bioorg. Med. Chem. Lett. 9, 1869-1874 (1999).

[12] a) K. D. Rice, J. M. Nuss, Bioorg. Med. Chem. Lett. 11, 753-755 (2001). b) N. Hebert, A. L. Hannah, S. C. Sutton, Tetrahedron Lett. 40, 8547-8550 (1999). c) N. M. M. Bezerra, De S. P. Oliveira, R. M. Srivastava, J. R. Da Silva, Il Farmaco, 60, 955-960 (2005). d) B. Kaboudin, F. Saadati, J. Heterocycl. Chem. 42, 699-701(2005). e) N. Tavoosi, M. Mahdavi, H. R. Bijanzadeh, Tetrahedron Lett. 47, 2965-2967 (2006).

[13] a) Y. Wang, R. L. Miller, D. R. Sauer, S. W. Djuric, Org. Lett. 7, 925–928 (2005). b) A. R. Gangloff, J. Litvak, E. J. Shelton, D. Sperandio, V. R. Wang, K. D. Rice, Tetrahedron Lett. 42, 1441–1443 (2001).

[14] a) R. F. P. Poulin, A. L.Tartar, B. P. De´prez, Tetrahedron Lett. 42, 1495–1498 (2001). b) F. Eloy, R. Lenaers, Chem. Rev. 62, 155–183 (1962).

[15] B. A. Dar, S. Singh, N. Pandey, A.P. Singh, P. Sharma, A. Lazar, M. Sharma, R. A. Vishwakarma, B. Singh Appl. Catal. A: Gen. 470, 232– 238 (2014). b) B. A. Dar, D. Vyas, V. Shrivastava, F. Saleem, A. Sharma, S. Sharma, P. R. Sharma, M. Sharma, B. Singh, Comptes Rendus Chimie, 17, 316–323 (2014). c) B.A. Dar, M. Mohsin, A. Basit, M. Farooqui, J. Saudi Chem. Soc. 17, 2, 177-180 (2013). d) B. A. Dar, A. Bhowmik, A. Sharma, P.R. Sharma, A. Lazar, A.P. Singh, M. Sharma, B. Singh, Appl. Clay Sci. 80, 351 (2013). e) B. A. Dar, N. A. Syed, M. A.Wagay, A. Hussain, N. Ahmad, K. A. Bhat, M. A. Khuroo, M. Sharma, B. Singh, Tetrahedron Lett. 54, 4880 (2013). f) B. A. Dar, A. K. Sahu, P. Patidar, P. R. Sharma, D. Vyas, S. Maity, M. Sharma, B. Singh, J. Ind. Eng. Chem. 19, 407 (**2013).** g) B. A. Dar, A. Chakraborty, P. R. Sharma, V. Shrivastava, A. Bhowmik, D. Vyas, B. Bhatti, M. Sharma, B. Singh, J. Ind. Eng. Chem. 19, 732 (2013). h) B. A. Dar, P. Bhatti, A. P. Singh, A. Lazar, P. R. Sharma, M. Sharma, B. Singh, Appl. Catal. A: Gen. 466, 60 (2013). i) B.A. Dar, A. Singh, A. Sahu, P. Patidar, A. Chakraborty, M. Sharma, B. Singh, Tetrahedron Lett. 53, 5497 (2012). j) B. A. Dar, M. Sharma, B. Singh, Bull. Chem. Reac. Eng. Catal. 7, 79 (2012).

[16] B. E. Blass, Tetrahedron, 58, 46, 9301-9320 (2002). B. A. Bunin, "The Combinatorial Index," Academic, New York, 1998. M. R. Rohman and B. Myrboh, Tetrahedron Lett. 51, 36, 4772-4775 (2010).

[17] a) V. Santagada, E. Perissutti, F. Fiorino, B. Vivenzio, G. Caliendo, Tetrahedron Lett. 42, 2397 (2001). b) V. Santagada, F. Fiorino, E. Perissutti, B. Severino, V. De Filippis, B. Vivenzio, G. Caliendo, Tetrahedron Lett. 42, 5171 (2001). c) S. Caddick, Tetrahedron 51, 10403 (1995). d) M. Larhed, A. Hallberg, Drug Discov. Today 6, 406 (2001).