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Modifications to the process for the synthesis of new 1,2,4-oxadiazole analogues and the short review on synthetic methodologies of 1,2,4-oxadiazoles

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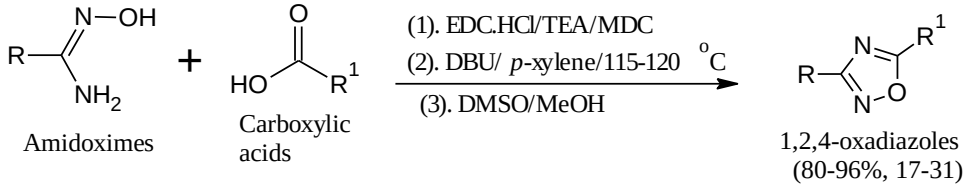
Abstract: **We herein represent the modifications of synthesis and easy isolation of new 1,2,4-oxadiazoles from the corresponding amidoximes were treated with the carboxylic acids followed by the cyclodehydration in *p*-xylene in the presence of 0.1 equivalent of 1,8-Diazabicyclo[5.4.0] undec-7-one (DBU) afforded in 80-96% yield. All the final compounds were isolated followed by purification with Dimethyl sulphoxide (DMSO) and Methanol (MeOH) and the review to the synthetic methodologies. This robust purification protocol and modified process is applicable for the bulk production in the pharmaceutical industry.**



Keywords: **Amidoximes, Carboxylic acids, cyclodehydration. 1,2,4-oxadiazoles and DBU.**

I. INTRODUCTION

Heterocyclics are the most important constituent among the drug and bioactive molecules. 1,2,4-Oxadiazoles is a versatile building block in ongoing drug discovery research and development.1,2,4-Oxadiazoles have been described as bioisosteres of esters and amides[1] and used as dipeptide mimetics[2] in a structurally divergent pharmacologically important molecules and also found in a number of biologically active molecules such as muscarinic agonists[3], serotoninergic (5-HT_3) antagonists [4], benzodiazepine receptor agonists[5] and dopamine ligands.[6] Enhanced hydrolytic[7] and metabolic stability of the oxadiazole ring well proved in the literature which makes this skeleton an important heterocyclic structural motif to the pharmaceutical industry, synthetic organic and medicinal chemistry. Currently, the drugs (which are available) in the market exist the 1,2,4-oxadiazoles as their structural heterocyclic motif (Table 1) and mention along with the potential biological functions. Phidianidine A and Phidianidine B were isolated from aeolid opisthobranch phidiana militaris[8] and these two were identified as naturally occuring 1,2,4-oxadiazoles.

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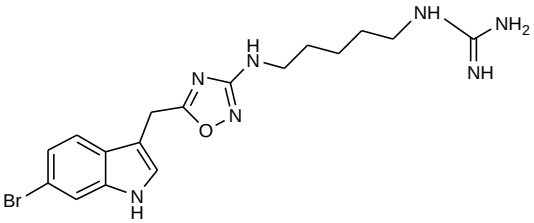
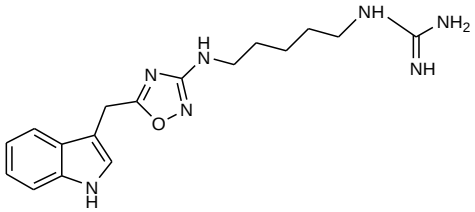
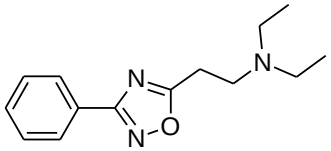
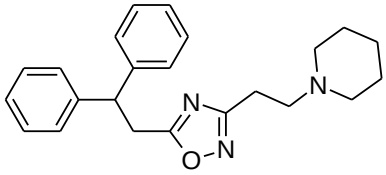
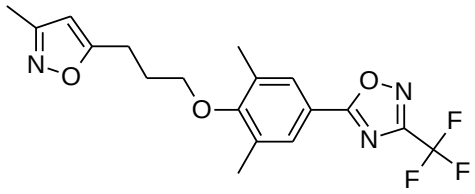
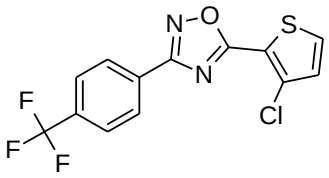
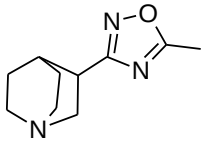


Phidianidine A



Phidianidine B

Table 1: Drugs with 1,2,4-oxadiazole as their structural motif.

Entry	Drug Molecule	Target diseases	Therapeutic functions
1.	 N,N-diethyl-2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethanamine [Oxolamine]	Cough & Cold	Cough suppressant. Antitussive. Generic Name: Perebron.[9]
2.	 1-(2-(5-(2,2-diphenylethyl)-1,2,4-oxadiazol-3-yl)ethyl)piperidine [Prenoxadiazine]	Cough & Cold	Cough suppressant. Antitussive. Generic Name: Libexin.[10]
3.	 3-(4-(3-(3-methylisoxazol-5-yl)propoxy)-3,5-dimethylphenyl)- 5-(trifluoromethyl)-1,2,4-oxadiazole [Pleconaril]	Asthma exacerbations Picornavirus respiratory infections	Antiviral Generic Name: Picovir.[11, 12]
4.	 5-(3-chlorothiophen-2-yl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole	Human Breast Cancer T47D cells	Anticancer activity.[13]
5.	 3-(5-methyl-1,2,4-oxadiazol-3-yl)quinuclidine	Neurological disorder	Alzheimer's Disease.[14]

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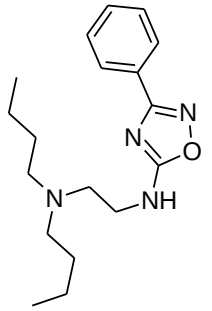
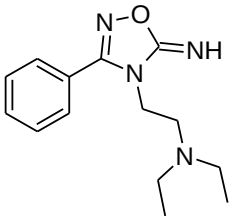
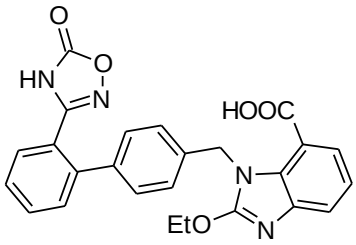
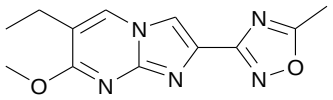
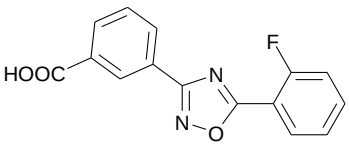
6.	 N-(2-(dibutylamino)ethyl)-3-phenyl-2,4-oxadiazol-5-amine [Butalamine]	Hypertension Heart failure	Vasodilators.[15] Generic Name: Adrevil (Zyma) Surheme (Merck KGaA)
7.	 N,N-diethyl-2-(5-imino-3-phenyl-1,2,4-oxadiazol-4(5H)-yl)ethanamine [Imolamine]	Hypertension Heart failure	Vasodilators.[16] Generic Name: Irrigor (Merck KGaA).
8.	 1 -[[2'-(4,5-dihydro-5-oxo-4H-1,2,4 oxadiaZol-3-yl)biphenyl-4-yl]methyl]-2-ethoxy-1H benz imidaZole-7-carboxylic Acid	High blood pressure	Angiotension II receptor Antagonist.[17] Generic Name: Azilsartan
9.	 6-ethyl-7-methoxy-2-(5-methyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyrimidine	Sedative and Muscle relaxant	Anxiolytic and nonbenzodiazepine drug Generic Name: Fasiplon.[18]
10.	 3-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)benzoic acid	Non-sense mutations or Genetic disorders	Muscular dystrophy Generic Name: Ataluren.[19]

Due to the multifarious nature of 1,2,4-oxadiazole's biological activities and functions, we were interested to review and modify the existing process to have the protocol for the easy isolation and purification for the scale-up in the academic and pharmaceutical industry without isolating any intermediates and column chromatography for the synthesis of 1,2,4-oxadiazoles.

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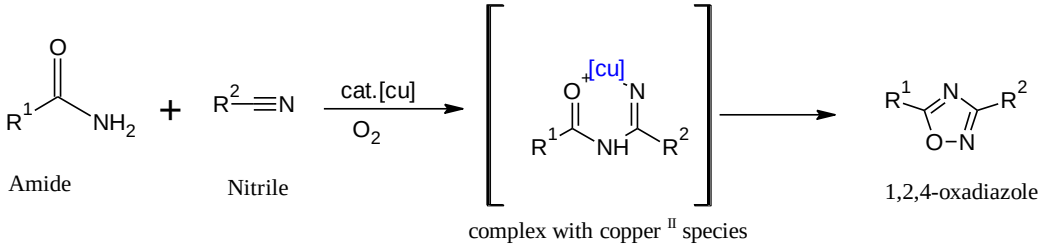
II. REVIEW THE SYNTHESIS OF CONJUGATED 1,2,4-OXADIAZOLES:

The synthesis of conjugated 1,2,4-oxadiazoles were approached by several methodologies. The important methodology is from nitriles.

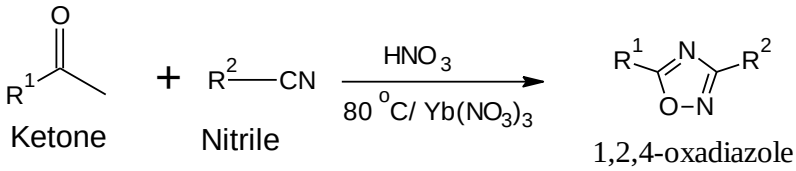
II. 1. Synthesis from nitriles:

Sung you hong and coworkers[20]described the synthesis of 1,2,4-oxadiazole from nitriles with amides in the presence of copper and molecular oxygen. The nucleophilic addition of the amide to the nitrile activated by a Lewis acidic copper ^{II} species and it forms complex through co-ordination with the amide and nitrile (Scheme I).



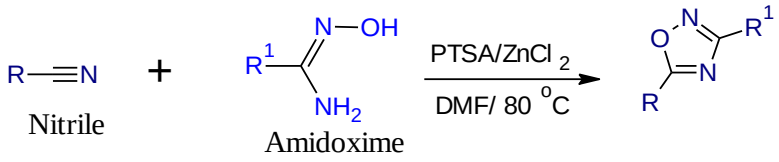
Scheme I.

Vale and coworkers[21] have reported the 1,2,4-oxadiazoles synthesized from the nitriles reacted with ketones in the presence of catalytic amount of yterbium nitrate(III) and nitric acid at 80 ^{o}C afforded the desired product in the range of 55-87% yield with structurally different electronic groups, existing in the ketones and nitriles (Scheme II).



Scheme II.

John kallikat et al[22] reported the nitriles when treated with the amidoximes in the presence of mixture of catalyst PTSA/$ZnCl_2$ in DMF at 80 ^{o}C afforded the corresponding 1,2,4-oxadiazoles in good yields (Scheme III) and isolated by column chromatography.



Scheme III.

II. 2. MECHANISTIC PATHWAY OF 1,2,4-OXADIAZOLE FORMATION FROM AMIDOXIMES:

The general synthetic route to the synthesis of amidoximes from the nitriles were obtained when the nitriles treated with hydroxylamine hydrochloride in a protic or aprotic solvent in the presence of base afforded the corresponding amidoximes. The amidoximes when treated with carbonyl derivatives like aldehydes, carboxylic acid esters, esters and acid chlorides provided the corresponding N-O-acylamidoxime derivative which upon at elevated temperatures underwent cyclodehydration afforded the 1,2,4-oxadiazoles.

Initially the proton was abstracted by the base from the hydroxyl group of amidoxime provided the nitroxide anion of corresponding amidoxime derivative. This anion was added to the electron deficient carbon of carbonyl group and formed the N-O-acylamidoxime derivative followed by the elimination of leaving group which upon intramolecular cyclodehydration afforded the desired 1,2,4-oxadiazole (Scheme IV).

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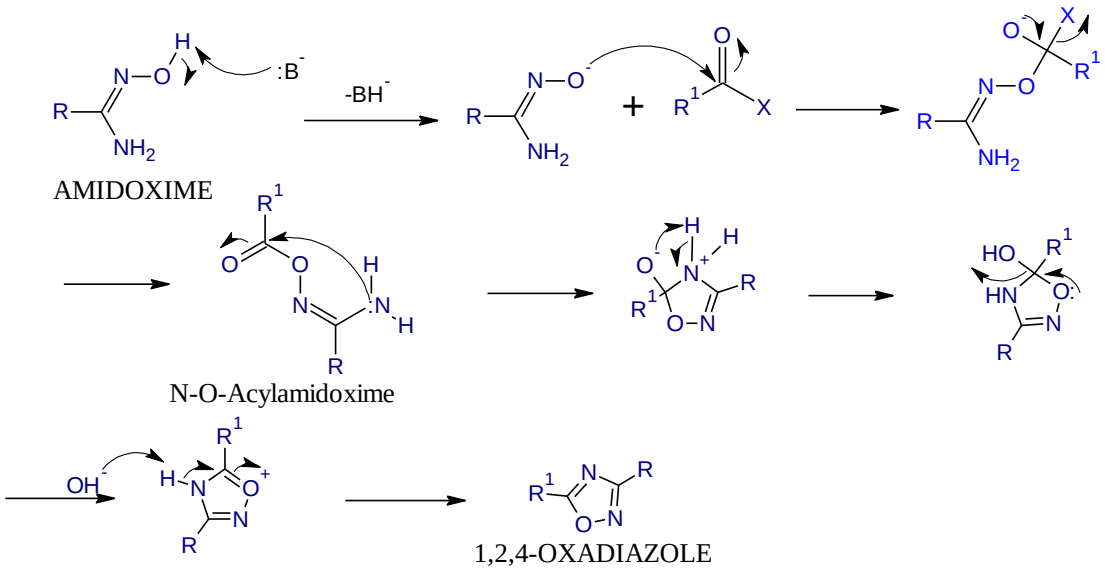
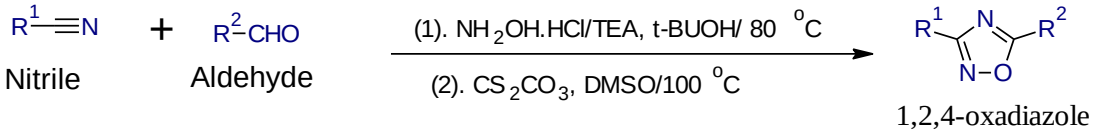


Scheme IV.

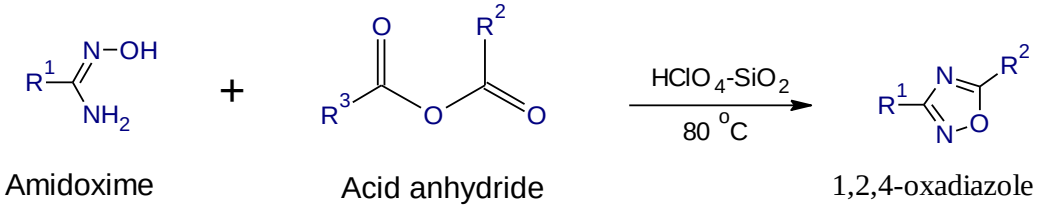
II. 2. 1. SYNTHESIS FROM AMIDOXIMES:

Wang and coworkers[23] have also been described the synthesis of 1,2,4-oxadiazole derivatives from the aldehydes reacted with amidoximes in DMSO and in the presence of cesium carbonate afforded the corresponding derivatives in 55-93% yield. But the side product formed in this reaction was the main disadvantage and considerably reduces the yield. The impurity formed in this reaction was removed by column purification (Scheme V).



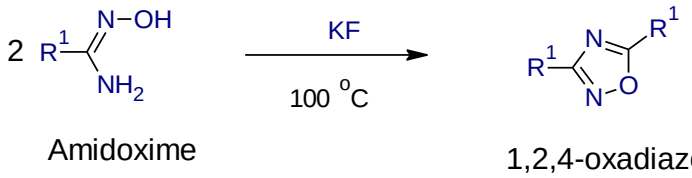
Scheme V.

Amidoximes were treated with acid anhydrides in the presence of silica-supported perchloric acid as a reusable catalyst under solvent free conditions at 80 °C provided the corresponding 1,2,4-oxadiazoles have been reported by tadikonda and coworkers[24] in 83-96% yield (Scheme VI).



Scheme VI.

Two identically substituted aryl groups at 3rd and 5th positions of 1,2,4-oxadiazoles synthesized from 2.0 equivalents of amidoximes in one-pot reaction in the presence of potassium fluoride as a catalyst and solid support under solvent free conditions (Scheme VII) have been described by Rostamizadeh and coworkers[25].



Scheme VII.

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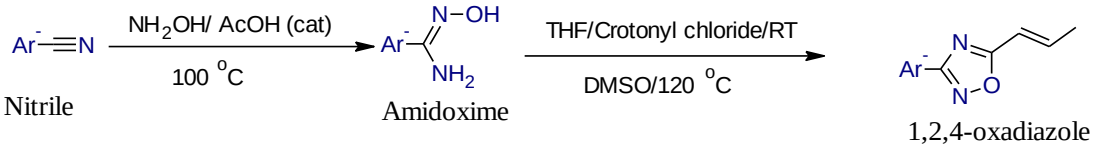
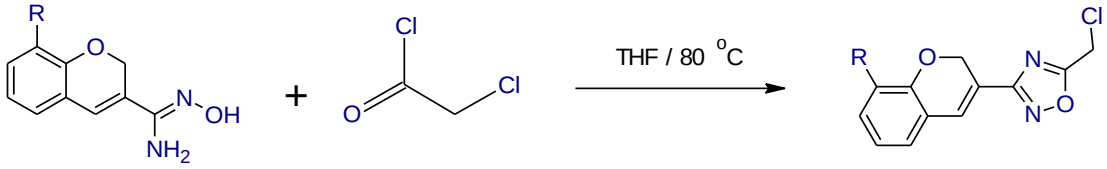
Amidoxime[26] were obtained from the aryl nitriles in the presence of acetic acid as a catalyst under solvent free conditions and it was treated with crotonyl chloride in THF at room temperature (Scheme VIII). To this reaction mixture was added DMSO and raised to 120 °C for 1 hour afforded 1,2,4-oxadiazoles.



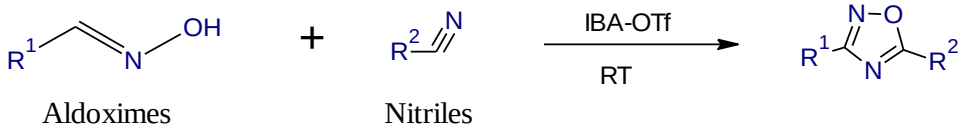
Scheme VIII.

Santhosh kumar et al[27]., have synthesized the 1,2,4-oxadiazole analogues by treated the amidoximes with acid chlorides in THF at 80 °C (Scheme IX).



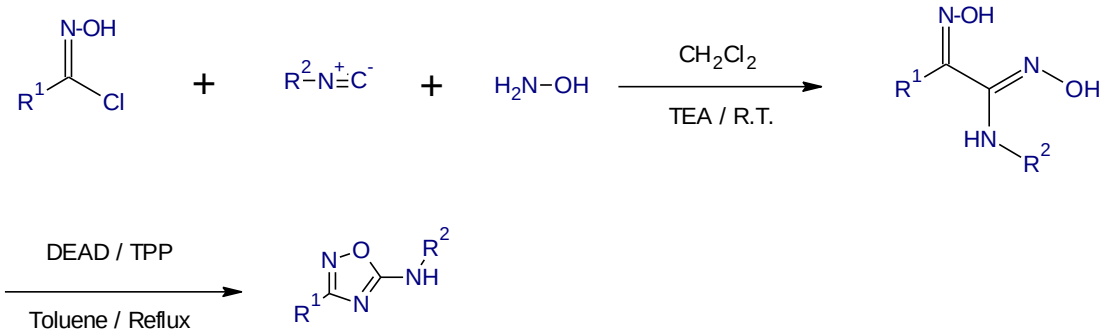
Scheme IX.

Aldoximes instead of amidoximes and the nitriles were mixed together in the presence of hypervalent Iodine (III) reagent (2-Iodosylbenzoic acid triflate) act as oxidants during the oxidative cycloaddition to form 1,2,4-oxadiazoles (Scheme X) have reported by Akira et al[28].



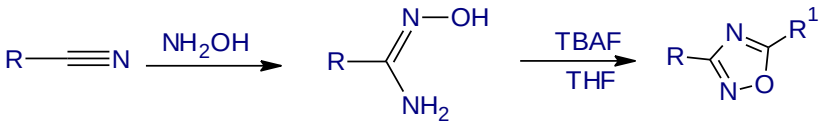
Scheme X.

Through multicomponent reaction of Z-chlorooximes, Isocyanides and hydroxyl amine in MDC in the presence of trimethylamine at room temperature afforded the corresponding aminodioximes via [3+1] cycloaddition which upon cyclization in the presence of TPP/DEAD called Mitsunobu-Beckmann rearrangement[29] afforded the corresponding 1,2,4-oxadiazole-5-amines (Scheme XI).



Scheme XI.

Cyclodehydration is achieved in the presence of tetra-N-butylammonium fluoride (TBAF, Scheme XII) afforded the corresponding product in high yields[30] in THF.



Scheme XII.

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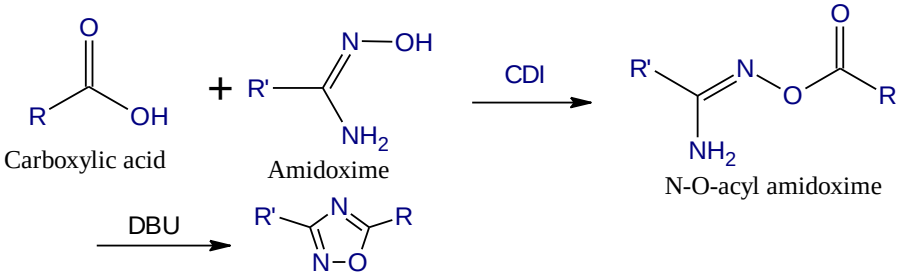
Carboxylic acids were activated by CDI (1,1-carbonyldiimidazole) and insitu, the activated carboxylic acid reacted with amidoxime formed N-O-acyl amidoxime derivative which underwent cyclodehydration (Scheme XIII) in the presence of DBU in acetonitrile afforded the corresponding 1,2,4-oxadiazoles[31].



Scheme XIII.

Moreover, Hemming K et al[32] and Mahazar farooqui et al[33] have been reviewed the synthetic methodologies of 1,2,4-oxadiazoles were upto 2007 and 2010 respectively. We incremented recently the review process until 2018 and identified the following drawbacks which is not applicable in the pharmaceutical industry to scale up for the bulk production of 1,2,4-oxadiazoles.

The drawbacks are

(1). The use of acid chlorides which are synthesized from the corresponding carboxylic acids by the use of $SOCl_2$ or $(COCl)_2$ which involves the evolution of SO_2 and HCl gases and these gases were serious concern to the environment.

(2). Pyridine as a solvent for the cyclization of N-O-acyl amidoximes and the disposal of the effluent causes severe environmental issues.

(3). Oxidative cyloaddition of oximes to the nitriles involves the preparation of IBA-OTf as oxidants which consumes more duration and preserving the reagents for prolonged time cause its own stability issues.

(4). Chlorinated solvents like 1,2-dichlorobenzene causes severe allergic and has carcinogenic property. Hence the use of chlorinated solvents in the process should be substituted with other less harmful solvents.

(5). Use of TPP/DEAD (mitsunobu reaction) in the coupling of nitriles with chlorooximes and hydroxylamine hydrochloride affords the TPPO as a by product and the removal of TPPO is main concern in the pharmaceutical industry.

(6). The use of heavy metals like palladium, copper, zinc and manganese generating more sludges and the disposal causes severe environmental problems. The isolation of the desired compounds from the sludges also consumes more duration and costlier in procuring those heavy metals and treatment in the ETP.

(7). The stability of CDI is the main concern and the preparation of the CDI coupling reagent for the amidoximes with carboxylic acids also one of the factor which influences duration and cost of the process.

(8). Several literatures have been applied to the synthesis of 1,2,4-oxadiazole analogues under microwave conditions. Commercially the use of microwave condition for the bulk production is limited or not the viable process.

(9). Amidoximes coupled with the carboxylic acids in the presence of DCC/Pyridine, DIC/DMF, HBTU/Polymer supported PS-BEMP or PS-PPh_3 and TBTU/DMF. These methodologies have setback regarding the use of pyridine, costlier preparation of polymer supported resins with BEMP or PPh_3 and TBTU.

(10). Preparation of iminoesters to couple with chlorooximes requires more duration and it has been a additional step which influences overhead cost to the process. And also the use of molecular sieves is major setback for the synthesis of 1,2,4-oxadiazole analogues.

Due to the above synthetic problems and concerns, we were interested to develop the convergent and modified synthetic methodology for the synthesis of 1,2,4-oxadiazoles and reduce the effluent waste without the use of heavy metals. Simplify the purification protocols and easy isolation of 1,2,4-oxadiazole analogues.

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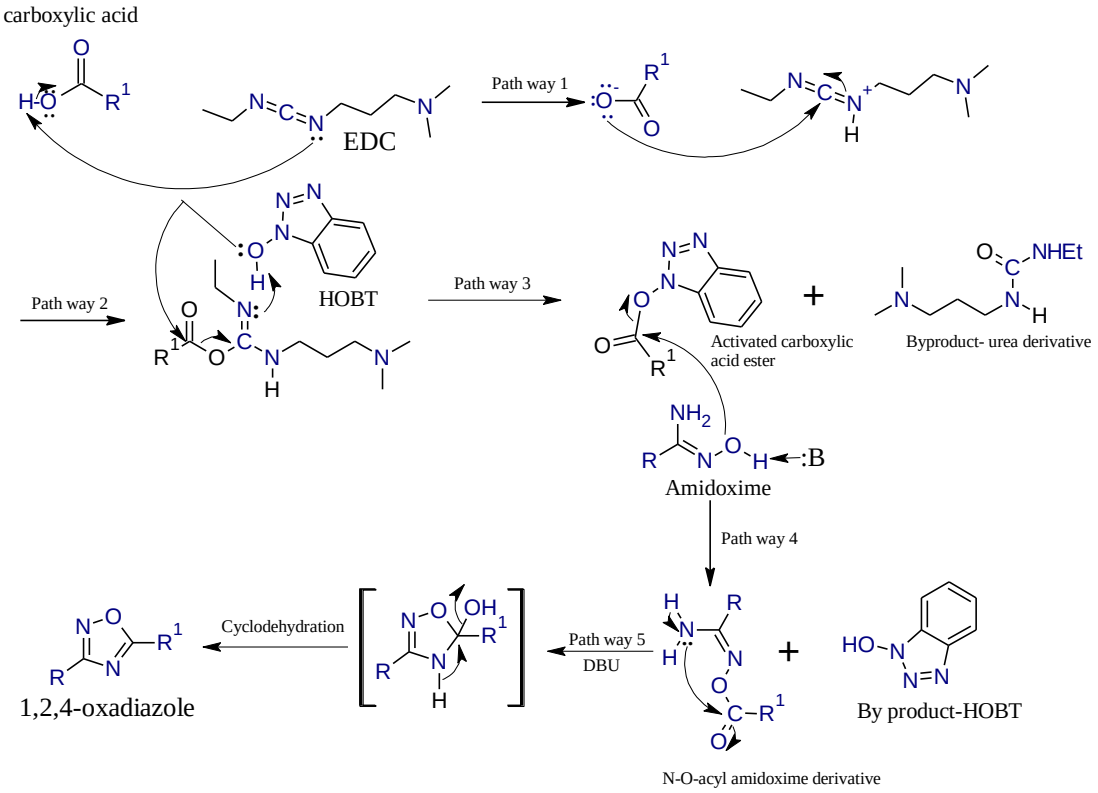
III. RESULTS AND DISCUSSION

We initially attempted to synthesize 1,2,4-oxadiazoles in the presence of TBAF followed by CDI in THF, provided the poor yields with unreacted starting materials. 1.0 equivalent of TBAF is not sufficient to complete the cyclization of (N-O)-acyl amidoximes (Scheme XIV) and the reaction was monitored by TLC for every 30 minutes. CDI's stability also the main concern as the coupling reaction is also not completely underwent in our hands. Then we tried with the coupling reagent EDC.HCl and were obtained the corresponding products in good yields (entry 17-31, Table I). The carboxylic acids were activated by HOBT to form the activated carboxylic acid ester which reacted with amidoxime to form the (N-O)-



Scheme XIV. Plausible mechanism of EDC.HCl and DBU cyclodehydration.

acyl amidoxime derivative, through intramolecular cyclodehydration the acyl amidoxime in the presence of DBU in p-xylene cyclized and affored the 1,2,4-oxadiaoles (Scheme XIV). Amidoximes were prepared from the nitriles (entry 1-4, Scheme XV) which reacted with the carboxylic acids (entry 10-16) in the presence of HOBT and EDC.HCl in MDC and the base triehylamine were used to neutralize the HCl then maintained the reaction for 1.5-2.0 hrs afforded the (N-O)-acyl amidoxime. Further, we were added the *p*-xylene and DBU to the acyl amidoxime (crude compound after the removal of volatiles) and subjected the reaction mixture to reflux at 115-120 ^{o}C for 3-4 hours (Scheme XV). As the procedure was mentioned by Lukin et al[50]., 3.0 equivalents of DBU were used to complete the cyclodehydration, but in contrast to the procedure, we considerably reduced to 0.1 equivalents which is more sufficient quantity to complete the cyclodehydration. In ^{13}C NMR, the carbon of 1,2,4-oxadiazole at 5th and 3rd position observed at 174-176 and 166-169 ppm respectively.

IV. EXPERIMENTAL SECTION

General: All the raw materials and Reagents were purchased from the available commercial sources and used without further purification. All the melting points taken from open capillary tube using optimelt (Automated melting point system, I-37) from SRS maker and are uncorrected. Alpha FTIR (I-38) from Bruker used to record all IR of the compounds. NMR of all the intermediates were recorded from 300 MHZ, Bruker and NMR of all the final 1,2,4-oxadiazole analogues were recorded from 400 MHZ, Bruker. ^{1}H and ^{13}C NMR are referenced to the residual. Solvent signals in $CDCl_3$, DMSO-d_6 and CD_3OD are 7.26, 2.50 and 3.31 ppm in ^{1}H NMR. 77.16, 39.52 and 49.00 ppm in ^{13}C NMR.

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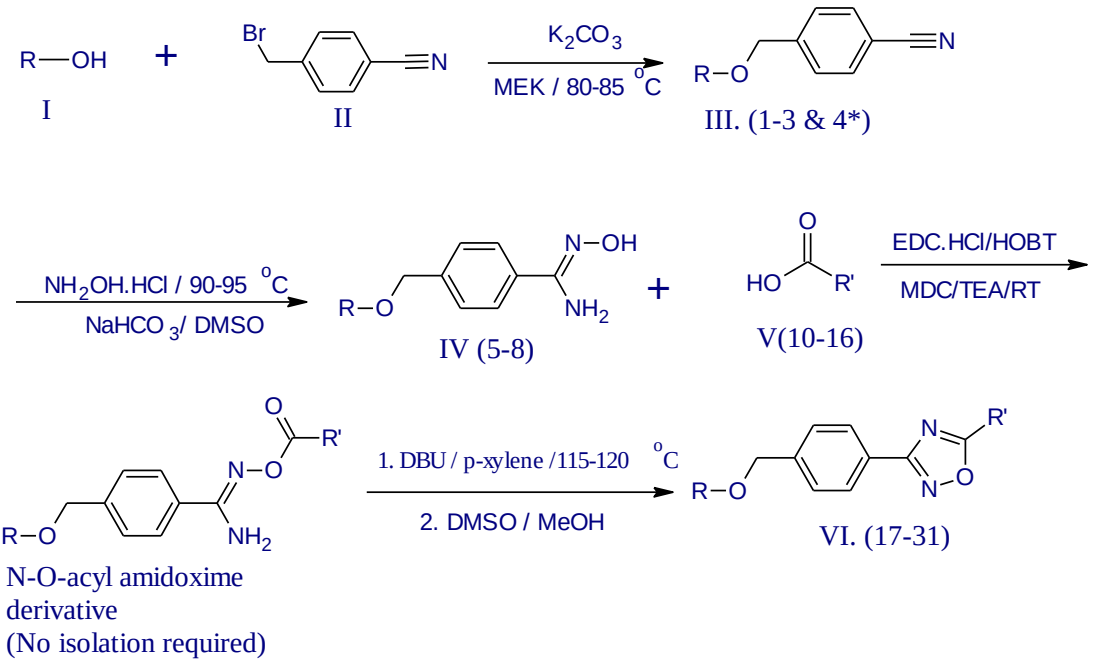
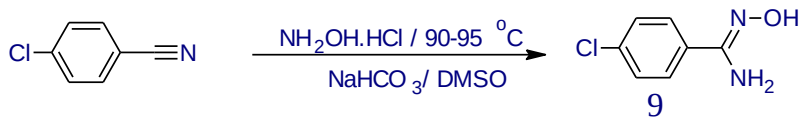
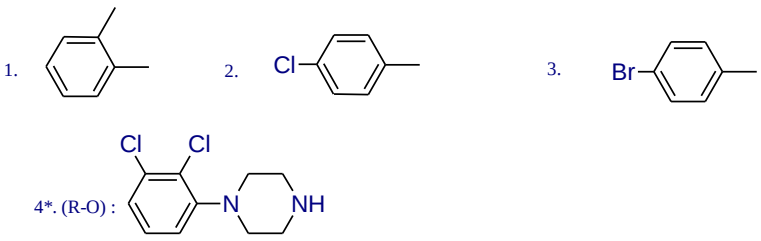
Scheme XV (A):



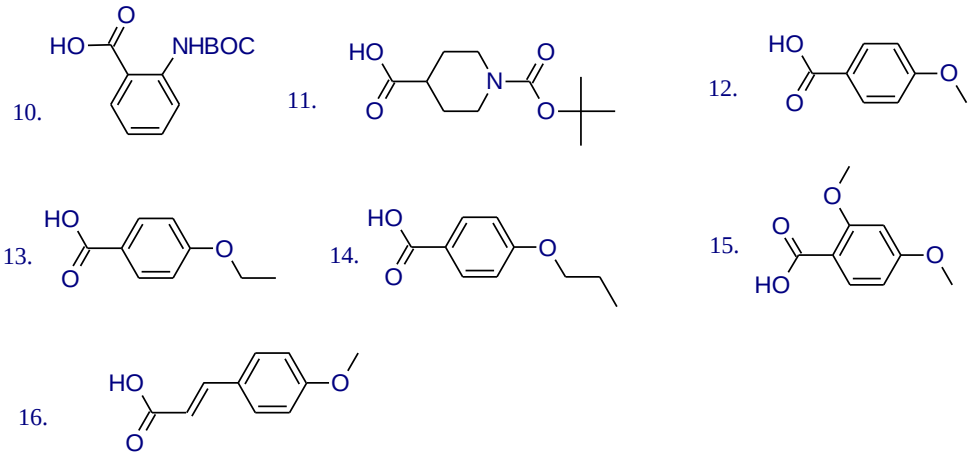
Scheme XV (B):



R=



R'=



Scheme XV. Synthetic route to prepare the new 1,2,4-oxadiazoles.

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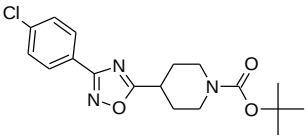
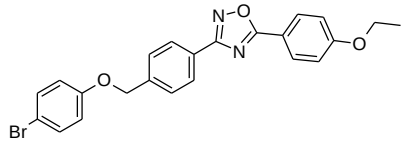
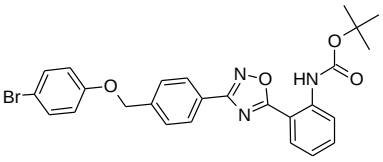
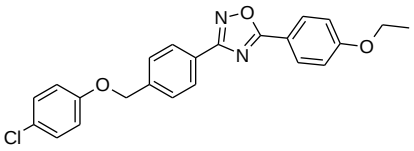
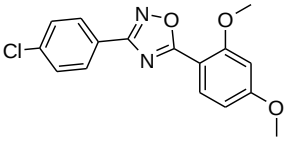
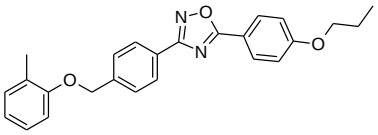
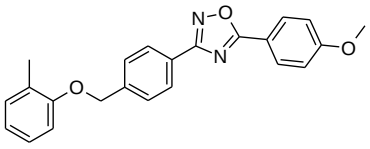
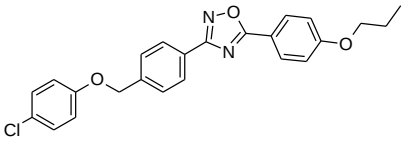
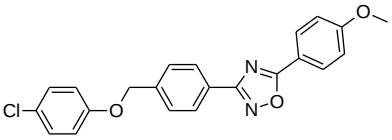
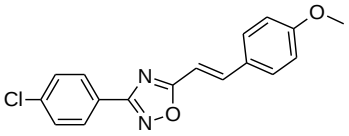
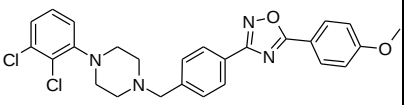
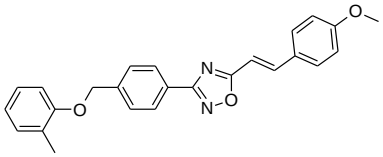
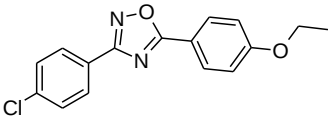
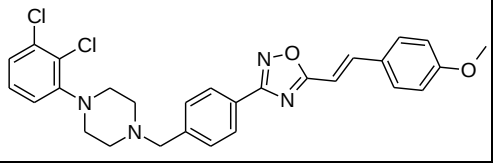
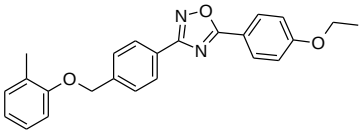
Table 2: Synthesis of New 1,2,4-oxadiazoles by modified convergent process.

Entry & Yield	structure	Entry & Yield	Structure
17 & 85%		25 & 96%	
18 & 80%		26 & 93%	
19 & 95%		27 & 92.5%	
20 & 86%		28 & 94.7%	
21 & 90%		29 & 88%	
22 & 84%		30 & 89.6%	
23 & 87%		31 & 90%	
24 & 88%			

General procedure (Scheme XV):

For the entries from 1-4*: To the stirred solution of I (1-4*, 1.0 eq) and was added II (1.2 eq) in MEK (5-6 Vol) and treated with K_2CO_3 (2.0 eq), then stirred the reaction mixture at 80-85^oC for a period of 3-4 hours. Completion of the reaction was monitored by TLC and IR. Brought the reaction mixture to 25-30^oC, then added potable water (5.0 Vol) and stirred for 30 minutes. Separated the layers and the organic layer was dried over Na_2SO_4, then the volatiles are evaporated to dryness to get the title compound. All the compounds without purification was taken for the next step for the conversion of amidoxime.

For the entries from 5-9:

To the stirred solution of sodium bicarbonate (8.0 eq) in DMSO (10 Vol) was added hydroxyl amine hydrochloride (4.0 eq) and the reaction mixture was stirred for 25-30 minutes at 25-30 ^{o}C. Then it was heated to 60-65^{o}C for a period of 1.0 hour. After 1.0 hour, nitrile (III, 1.0 eq) was added at 60-65^{o}C and further heated at 90-95^{o}C for another 5-6 hours. Completion of the reaction was monitored by TLC and IR. Brought the reaction mixture temperature at 25-30 ^{o}C and was poured into cold potable water (750 ml). Stirred the quenched reaction mixture for 25-30 minutes and it was filtered, washed with potable water (500 ml). Then it was dried at 75-80^{o}C for 12-15 hours.

Preparation of entry 15 from 2,4-hydroxy benzoic acid: 2,4-dihydroxy benzoic acid (91, 0.025 Kg, 0.162 mol) and K_2CO_3 (0.179 Kg, 1.3 mol) were mixed in a 1.0 L four necked round bottom flask fitted with reflux condenser in MEK (250 ml). The reaction mass was stirred under room temperature for 10 minutes. Then to this stirred reaction mixture was added $(CH_3)_2SO_4$ (0.092 Kg, 0.73 mol) in one portion. Stirred the reaction mixture and reflux at 80-85^{o}C for 10-12 hours. Confirmed the product formation by TLC and IR. The reaction mixture was brought into the room temperature and quenched with the potable water (500 ml). Separated the layers and the top layer (organic layer) was dried over anhydrous sodium sulphate (0.075 Kg) and evaported to dryness to get the desired methyl-2,4-dimethoxy benzoate (crude).Yield: 0.030 Kg, 94.30%. To this crude compound (0.030 Kg, 0.15 mol), NaOH (0.013 Kg, 0.30 mol) in a 500 ml four necked round bottom flask fitted with reflux condenser in Methanol (300 ml). Stirred the reaction mixture and reflux at 60-65^{o}C for 5-6 hours. Confirmed the product formation by TLC and IR.. Methanol was distilled completely from the reacton miixture at reduced pressure. To the residue was added potable water (100 ml) and acidified the reaction mass to the P^H 2-3 using conc. HCl (20 ml). Solid was precipitated and filtered then washed with potable water (200 ml). Dired the isolated product at 70-75^{o}C for 12-15 hours. Yield: 0.026 Kg, 93.35%.

Preparation of entry 16: To the stirred solution of malonic acid (0.076 Kg, 0.73 mol) in pyridine was added 4-Methoxy benzaldehyde (0.050 Kg, 0.37 mol) and piperidine (6.0 ml). This reaction mixture was stirred at 80-85^{o}C for a period of 1.0 hour. After 1.0 hour, the reaction mixture was further refluxed at 109-115 ^{o}C for 3.0 hours. The completion of the reaction was confirmed by TLC and IR. The reaction mixture was cooled to 10-15 ^{o}C. It was poured into 2.0 litre cold water. Acidified the reaction mass by concentrated HCl (150 ml) and the solid was precipitated. It was filtered and washed with water (1000 ml). The solid was dried at 75-80 ^{o}C for 12-15 hours. Yield: 0.055 Kg, 84.04%.

Preparation of entry from 10-14: Recently Selvaraj et al[34,35] have been described the synthesis for entry 10 and for the entry 12, 13 & 14. we prepared the entry 11 as the procedure mentioned for the entry 10.

For the entries from 17-31 (1,2,4-oxadiazole analogues, Table 2):

Amidoxime (entry 5-9, 1.0 eq) and acid (entry 10-16, 1.2 eq) mixed together in MDC (10 Vol). To this reaction mixture was added TEA (2.5 eq) and HOBT (0.2 eq), then stirred the reaction mixture for 10-15 minutes at 25-30^{o}C. Added EDC.HCl (1.2 eq) and further the reaction mixture was stirred for 1.5-2.0 hours. Completion of the reaction was monitored by TLC and IR. Added potable water (2×5.0 Vol) and stirred for 25-30 minutes. Separated the layers and the MDC was evaporated to dryness to get the crude compound (N-O-acyl amidoxime derivative) as a residue. To this crude compound was added p-xylene (5-6 Vol) and DBU (0.1 eq). Then the reaction mixture was reflux at 115-120^{o}C for 3-4 hours. As monitored the completion by TLC and IR, the reaction volatiles are evaporated to dryness and p-xylene was recovered for recycle.

To this residue was added DMSO (1.5-2.0 Vol) and methanol (0.5 Vol). Cooled the reaction mass and stirred at 0-10 ^{o}C for 1.5-2.0 hours. Filtered the solid and washed with chilled methanol (0.2 Vol) and dried at 75-80^{o}C for 12-15 hours. The complete process details were described in the process flow chart **(Figure I)**.

4-[(4-chlorophenoxy)methyl]benzonitrile(1): White crystalline solid. Melting point: 90-92.8^{o}C. Yield:94.50%. IR(neat,cm^{-1}): 2352.70, 1579.60, 1489.31, 1459.51, 1412.96, 1380.34, 1308.06, 1279.41, 1233.27, 1164.69, 1088.87, 1035.14, 858.42, 810.27. ^{1}HNMR(300 MHZ,$CDCl_3$): δ_H 7.70 (d, Ar-2H, *J*=8.1 Hz), 7.55 (d, Ar-2H, *J*= 7.8 Hz), 7.26 (d, Ar-2H, *J*= 8.7 Hz), 6.89 (d, Ar-2H, *J*= 8.7 Hz), 5.11 (s, 2H,OCH_2). ^{13}CNMR(75 MHZ,$CDCl_3$): δ_C 156.75, 142.05, 132.47, 129.54, 127.55, 126.41, 118.66, 116.08, 111.85, 69.15.

4-[(4-bromophenoxy)methyl]benzonitrile(2): Pale brown solid. Yield: 93.68%.

Melting point:101-107.5°C. IR(neat, cm^{-1}): 2222.93, 1574.92, 1486.12, 1411.82, 1377.58, 1278.88, 1226.88, 1170.65, 1042.47, 845.06, 813.67. ^{1}HNMR (300 MHZ,$CDCl_3$): δ_H 7.67 (dd, Ar-2H, *J*=8.1 Hz), 7.53 (dd, Ar-2H, *J*=8.1 Hz), 7.43-7.38 (m, Ar-2H), 6.86-6.82 (m, Ar-2H), 5.11 (s, 2H, OCH_2).^{13}CNMR (75 MHZ,$CDCl_3$): δ_C 157.26, 142.00, 132.60, 132.48, 127.55, 118.40, 116.60, 113.73, 112.20, 69.09.

4-{[4-(2, 3-dichlorophenyl)piperazin-1-yl]methyl}benzonitrile (4*): Off-white crystalline powder. Yield: 95.82%. Melting point: 110-115°C. IR (neat, cm^{-1}): 3070.78, 2939.61, 2814.24, 2756.37, 2225.93, 1604.83, 1575.89, 1504.53, 1446.66, 1417.73, 1367.58, 1346.36, 1305.85, 1228.70, 1134.18, 1039.67, 1010.73, 954.80, 831.35.

^{1}HNMR (300 MHZ,$CDCl_3$): δ_H 7.62 (d, Ar-2H, *J*=8.1 Hz), 7.49 (d, Ar-2H, *J*=8.1 Hz), 7.15 (dd, Ar-2H, *J*=4.8 & 2.7 Hz), 6.96 (dd, Ar-1H, *J*=4.5 & 2.7 Hz), 3.63 (s, $\underline{CH_2}$), 2.980 (s, 4H), 2.53 (s, 4H). ^{13}CNMR (75 MHZ,$CDCl_3$): δ_C 151.16, 144.07, 134.06, 132.18, 129.58, 127.53, 127.47, 124.66, 118.61, 111.00, 62.44, 53.30, 51.27.

4-[(4-chlorophenoxy)methyl]-N-hydroxy benzene carboximidamide(5):

White solid. Melting point: 142-144.5°C. Yield: 95.91%. IR(neat, cm^{-1}): 3454.25, 3361.39, 2892.82, 2857.44, 1643.48, 1592.07, 1578.16, 1521.61, 1487.14, 1453.22, 1409.81, 1381.50, 1286.94, 1227.61, 1165.08, 1092.79, 1038.55, 1007.00, 922.97, 819.42. ^{1}HNMR(300 MHZ,CD_3OD): δ_H 7.66 (d, Ar-2H, *J*=7.8 Hz), 7.47 (d, Ar-2H, *J*=8.1 Hz), 7.25 (d, Ar-2H, *J*=8.7 Hz), 6.97 (d, Ar-2H, *J*=8.7 Hz), 5.92 (s, OH), 5.10 (s, 2H, OCH_2), 3.32 (s, 2H, NH_2).^{13}CNMR (75 MHZ,CD_3OD): δ_C 157.34, 153.97, 138.72, 132.30, 128.97, 127.19, 126.10, 125.45, 116.09, 69.36.

N'-hydroxy-4-[(2-methylphenoxy)methyl]benzene carboximidamide(6):

Off-white solid. Melting point: 141-145.3°C. Yield: 96.43%. IR (neat, cm^{-1}): 3478.84,

3383.85, 1656.57,1580.48, 1232.39, 1186.40, 1115.15, 1009.25, 931.86, 873.37,

752.35. ^{1}HNMR(300 MHZ, DMSO-d_6): δ_H 7.68 (d, Ar-2H, *J*=8.1 Hz), 7.45 (d, Ar-2H,

J=8.4 Hz), 7.15 (d, Ar-2H, *J*=7.5 Hz), 6.98 (d, Ar-2H, *J*=8.1 Hz), 6.85 (d, Ar-2H,

J=7.5 Hz), 9.67 (s, OH), 5.82 (s, 2H, NH_2), 5.13 (s, 2H), 2.20 (s, 3H).

^{13}CNMR (75 MHZ, DMSO-d_6): δ_C 156.18, 150.54, 138.11, 132.67, 130.45, 126.88,

125.89, 125.46, 120.38, 111.67, 68.64, 16.10.

4-[(4-bromophenoxy)methyl]-N-hydroxy benzene carboximidamide(7): Off-white solid. Melting point: 148-151.8°C. Yield: 87.36%. IR (neat, cm^{-1}):3456.69, 3363.87, 2893.30, 2857.02, 1645.74, 1588.70, 1577.27, 1488.00, 1458.22, 1383.14, 1232.87, 1169.42, 1039.863, 1005.82, 926.54, 819.28. ^{1}HNMR (300 MHZ, $CDCl_3$ with drop of DMSO): δ_H 7.82 (d, Ar-2H, *J*=8.1 Hz), 7.61 (d, Ar-2H, *J*=8.1 Hz), 7.43 (d, Ar-2H, *J*=8.1 Hz), 6.78 (d, Ar-2H, *J*=8.7 Hz), 9.80 (s, OH), 4.99 (s, 2H), 4.93 (s, 2H, NH_2). ^{13}CNMR (75 MHZ,$CDCl_3$ with drop of DMSO): δ_C 157.62, 151.86, 137.91, 132.75, 132.24, 127.33, 125.98, 116.68, 113.13, 69.68.

4-{[4-(2,3-dichlorophenyl)piperazin-1-yl]methyl}benzenecarboximidamide(8):

Off-white crystalline powder. Melting point: 162-167.5°C. Yield: 98.65%.

IR(neat, cm^{-1}): 3423.76, 3331.18, 2972.40, 2939.61, 2823.88, 2769.87,1641.48,

1577.82, 1518.03, 1446.66, 1417.73, 1373.36, 1246.06, 1128.39, 1043.52, 1001.09,

954.80, 925.86, 833.28, 790.84, 729.12. ^{1}HNMR (300 MHZ, DMSO-d_6):

δ_H 7.65 (d, Ar-2H, *J*=7.8 Hz), 7.32 (d, Ar-2H, *J*=7.8 Hz), 7.30-7.26 (dd, Ar-4H, *J*=4.2

& 2.1 Hz), 7.15-7.11 (dd, Ar-1H, *J*=3.9 & 3.6 Hz), 6.85 (d, Ar-2H, *J*=7.5 Hz), 9.61 (s,

OH), 5.79 (s, 2H, NH_2), 3.550 (s, 2H), 2.98 (s, 4H), 2.53 (s, 4H).

^{13}CNMR(75 MHZ, DMSO-d_6): δ_C 151.14, 150.72, 138.73, 132.57, 132.14, 128.65,

128.39, 126.00, 125.25, 124.31, 119.54, 61.63, 52.57, 50.91.

4-Chloro-N'-hydroxy benzene carboximidamide (9):

White crystalline powder. Melting point: 133-134.1^{o}C. Yield: 97%.

IR(neat,cm^{-1}): 3465.19, 3340.63, 1653.17, 1584.56, 1494.05, 1374.42, 1085.06, 1013.19, 917.65, 835.99, 818.41.^{1}HNMR (300 MHZ, DMSO-d_6): δ_H 7.684 (d, Ar-2H, *J*=8.7 Hz), 7.45 (d, Ar-2H, *J*=8.7 Hz), 9.80 (brS, OH), 5.95 (brS, 2H).

^{13}CNMR (75 MHZ, DMSO-d_6): δ_C 150.08, 133.52, 131.84, 128.15, 127.22, 127.15.

1-(tert-butoxycarbonyl)piperideine-4-carboxylic acid (11): White solid powder. Melting point: 140-145^{o}C. Yield: 88.5%. IR (neat, cm^{-1}): 3153.02, 2963.77, 1731.26, 1654.70, 1472.51, 1429.30, 1366.67, 1279.62, 1239.60, 1154.62, 1130.07, 1079.13, 1031.83, 944.54, 921.89. ^{1}HNMR (300 MHZ, DMSO-d_6): δ_H 3.82 (d, 2H, *J*=12.3 Hz), 2.80 (brs, 2H), 2.399-2.363 (m, 1H), 1.77 (d, 2H, *J*= 11.4 Hz), 5.27 (s, 9H).

^{13}CNMR(75 MHZ,DMSO-d_6): δ_C 175.60, 153.84, 78.63, 42.63, 28.00, 27.67.

Methyl-2,4-dimethoxy benzoate: IR(neat,cm^{-1}): 2949.50, 2840.07, 1719.91, 1696.85, 1604.89, 1574.39, 1504.50, 1459.90, 1244.47, 1209.22, 1185.60, 1135.85, 1084.82, 1024.55, 97.75, 832.51. ^{1}HNMR (300 MHZ,$CDCl_3$): δ_H 7.84 (dd, Ar-1H, *J*=6.9 & 2.1 Hz), 6.47 (dd, Ar-2H, *J*=6.9 & 2.4 Hz), 3.87 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3).

^{13}CNMR(75 MHZ,$CDCl_3$): δ_C 166.08, 164.24, 161.30, 133.83, 112.17, 104.51, 98.89, 55.93, 55.44, 51.66. **Entry 15:** Off -white solid powder. Melting Point: 108-110^{0}C. IR(neat,cm^{-1}): 1664.84, 1609.20, 1571.04, 1507.36, 1456.64, 1408.35, 1317.23, 1281.50, 1206.26, 1161.35, 1098.12, 1031.65, 923.54, 818.68.^{1}HNMR (300 MHZ, DMSO-d_6): δ_H 7.70 (d, Ar-1H, *J*= 8.7 Hz), 6.57 (d, Ar-2H), 3.80 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3).^{13}CNMR (75 MHZ, DMSO-d_6): δ_C 166.32, 163.69, 160.59, 133.28, 112.34, 105.12, 98.74, 55.70, 55.45.

4-methoxycinnamic acid (16): White solid. Melting point: 169-175^{o}C. IR(neat, cm^{-1}): 2842.55, 1675.09, 1622.87, 1596.61, 1511.58, 1313.10, 1254.64, 1216.91, 1191.35, 1172.12, 1114.82, 1028.07, 935.19, 823.06. ^{1}HNMR (300 MHZ,$CDCl_3$+CD_3OD): δ_H 11.40 (Ar-2H), 10.20 (Ar-2H), 11.55 (d, 1H, *J*=15.6 Hz), 10.82 (d, 1H, *J*=15.6 Hz),7.75(s, 3H, OCH_3).^{13}CNMR(75 MHZ,$CDCl_3$+CD_3OD): δ_C 173.68, 165.31, 149.12, 133.71, 130.98, 119.40, 118.21, 59.22.

tert-butyl-4-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carboxylate (Entry 17, Table 2): Crystalline powder solid. Melting point: 104-106.5^{o}C. IR(neat, cm^{-1}): 3298.49, 2925.32, 1735.81, 1596.98, 1535.73, 1438.12, 1410.17, 1366.98, 1302.33, 1261.73, 1157.48, 1046.05, 838.80, 751.42.^{1}H NMR (400 MHz, DMSO-d_6): 8.0 (d, 2H, *J*=8.4 Hz), 7.63 (d, 2H, *J*=8.8 Hz), 3.94 (d, 2H, *J*=12.8 Hz), 2.98 (s, 2H), 2.50 (t, 2H, *J*=1.6 Hz), 2.07 (dd, 2H, *J*=13.2 & 2.8 Hz), 1.719-1.619 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 182.54, 167.13, 154.31, 136.71, 129.89, 129.25, 125.56, 79.30, 42.98, 33.81, 29.12, 28.52.

tert-butyl {2-[3-(4-(4-bromophenoxy)methyl)phenyl)-1,2,4-oxadiazol-5yl]phenyl}

carbamate (Entry 18, Table 2): White solid. Melting point: 161.5-163.9^{o}C. IR(neat, cm^{-1}):2926.16, 1732.15, 1599.07, 1541.33, 1486.50, 1419.59, 1364.61, 1304.95, 1239.75, 1165.29, 1066.85, 1043.84, 829.80, 749.46.^{1}H NMR (400 MHz, DMSO-d_6): 10.32 (s, 1H, NH), 8.12 (dd, 4H, *J*=8.4 Hz), 7.69 (d, 3H, *J*=8.4 Hz), 7.48 (d, 2H, *J*=8.8 Hz), 7.29 (t, 1H, *J*=8.0 Hz), 7.03 (d, 2H, *J*=8.8 Hz), 5.23 (s, 2H), 1.49 (s, 9H).

^{13}C NMR (100 MHz, DMSO-d_6): 174.71, 167.34, 158.39, 141.22, 135.44, 133.58, 132.68, 131.52, 129.81, 128.82, 127.59, 126.67, 125.74, 124.81, 123.54, 117.67, 116.79, 115.85, 112.83, 110.44, 80.68, 69.40, 28.33.

3-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-1,2,4-oxadiazole (Entry 19, Table 2): Light brown crystalline solid. Melting point: 152-154.6^{o}C. IR (neat, cm^{-1}) 2925.23, 1590.42, 1491.77, 1406.45, 1359.94, 1331.88, 1281.37, 1244.87, 1213.17, 1176.80, 1132.61, 1087.65, 1132.61, 1026.35, 833.52. ^{1}H NMR (400 MHz, DMSO-d_6): 8.07 (dd, 2H, *J*=8.8 & 1.6 Hz), 7.66 (d, 2H, *J*=8.4Hz), 6.78 (ddd, 2H, *J*=8.8 & 2.0 Hz), 3.97 (s, 3H), 3.90 (s, 3H). ^{13}CNMR (100 MHz, DMSO-d_6): 175.65, 167.03, 165.21, 160.51, 136.58, 133.20, 129.87, 129.32, 125.86, 107.21, 105.35, 99.51, 56.71, 56.29.

5-(4-methoxyphenyl)-3-{4-[(2-methylphenoxy)methyl]phenyl}-1,2,4-oxadiazole (Entry 20, Table 2): Pale brown solid. Melting point: 114-116.3^{o}C. IR (neat, cm^{-1}) 2923.65, 2856.15, 1614.11, 1564.39, 1540.82, 1503.36, 1477.46, 1461.16, 1441.13, 1421.27, 1362.14, 1279.40, 1256.91, 1177.49, 1124.96, 1074.31, 1059.85, 1024.16, 840.57, 821.65. ^{1}H NMR (400 MHz, DMSO-d_6): 8.12 (d, 4H, *J*= 8.12 Hz), 7.68 (d, 2H, *J*= 4.8 Hz), 7.19 (d, 4H, *J*= 7.19 Hz), 7.02 (d, 1H, *J*= 6.0 Hz), 6.87 (d, 1H, *J*= 6.8 Hz), 5.23 (s, 2H), 3.89 (s, 3H), 2.25 (s, 3H). ^{13}CNMR (100 MHz, DMSO-d_6): 175.75, 168.40, 163.61, 156.63, 141.61, 130.99, 130.41, 128.24, 127.70, 127.40, 126.45, 126.67, 121.02, 116.17, 115.47, 112.22, 69.03, 56.10, 16.56.

3-{4-[(4-chlorophenoxy)methyl]phenyl}-5-(4-methoxyphenyl)-1,2,4-oxadiazole (Entry 21, Table 2): White crystalline solid. Melting point: 140.5-143.2^{o}C.

IR (neat, cm^{-1}) 2925.74, 1612.08, 1593.95, 1538.86, 1504.07, 1467.27, 1441.34, 1420.52, 1356.96, 1320.82, 1268.00, 1240.87, 1188.19, 1136.58, 1026.12, 868.44.

^{1}H NMR (400 MHz, DMSO-d$_6$): 8.13 (ddd, 4H, *J*= 8.4, 6.8 & 2.8 Hz), 7.66 (d, 2H, *J*=8.4 Hz), 7.35 (dd, 2H, *J*= 8.8 & 2.0 Hz), 7.21 (d, 2H, *J*=9.2 Hz), 7.07 (d, 2H, *J*=8.8 & 2.0 Hz), 5.22 (s, 2H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d$_6$): 175.89, 168.75, 163.71, 157.50, 140.84, 130.46, 129.78, 128.69, 127.73, 126.24, 125.08, 117.11, 116.15, 115.51, 69.66, 56.47.

3-(4-{[4-(2,3-dichlorophenyl)-1-piperazinyl]methyl}phenyl)-5-(4-methoxyphenyl)-1,2,4-oxadiazole (Entry 22, Table 2):

Pale brown solid. Melting point: 171.7-173.9^{o}C.

IR (neat, cm^{-1}) 2825.49, 1613.51, 1535.83, 1502.85, 1450.52, 1419.86, 1362.78, 1307.38, 1253.25, 1177.61, 1132.04, 1024.01, 960.00, 834.38, 781.69, 759.82.

^{1}H NMR (400 MHz, DMSO-d$_6$): 8.15 (dd, 4H, *J*=8.8 & 8.0 Hz), 7.50 (d, 2H, *J*=8.0 Hz), 7.14 (dd, 2H, *J*=8.0 & 3.2 Hz), 7.04 (d, 2H, *J*=8.8 Hz), 6.97 (dd, 1H, *J*= 3.2 Hz), 3.91 (s, 3H), 3.66 (s, 2H), 3.08 (s, 4H), 2.68 (s, 4H).

^{13}C NMR (100 MHz, DMSO-d$_6$): 175.59, 168.74, 163.19, 151.33, 141.51, 134.04, 130.11, 129.60, 127.53, 127.46, 126.05, 124.57, 118.65, 116.91, 114.53, 62.81, 55.56, 53.32, 51.35.

3-(4-chlorophenyl)-5-(4-ethoxyphenyl)-1,2,4-oxadiazole (Entry 23, Table 2):

Almost white powder solid. Melting point:139-142.5^{o}C. IR (neat, cm^{-1}) 2982.77, 2928.06, 1610.48, 1563.41, 1501.21, 1472.87, 1405.83, 1359.46, 1308.20, 1259.03, 1169.87, 1117.20, 1089.23, 1042.34, 1011.80, 965.49, 844.17.

^{1}H NMR (400 MHz, DMSO-d$_6$): 8.10 (dd, 4H, *J*=8.8 & 1.6 Hz), 7.67 (d, 2H, *J*=8.0Hz), 7.18 (d, 2H, *J*=8.4 Hz), 4.16 (q, 2H, *J*=6.8 Hz), 1.37 (t, 3H, *J*=7.2 Hz).

^{13}C NMR (100 MHz, DMSO-d$_6$): 175.98, 167.88, 166.15, 163.00, 136.77, 130.49, 129.92, 129.36, 125.64, 115.87, 64.22, 14.93.

3-{4-[(2-methylphenoxy)methyl]phenyl}-5-(4-ethoxyphenyl)-1,2,4-oxadiazole

(Entry 24, Table 2): Off-white crystalline solid. Melting point: 126-128.3^{o}C.

IR (neat,cm^{-1}): 2980.43, 2924.93, 1609.51, 1590.36, 1536.77, 1500.02, 1470.47, 1417.40, 1395.30, 1362.91, 1306.15, 1255.69, 1169.26, 1119.56, 1043.54, 967.41, 922.59, 833.33, 761.52. ^{1}H NMR (400 MHz, DMSO-d$_6$): 8.17 (t, 4H, *J*=7.2 Hz), 7.73 (d, 2H, *J*=8.0 Hz), 7.24 (d, 4H, *J*=8.0 Hz), 7.07 (d, 1H, *J*=8.0 Hz), 6.92 (t, 1H, *J*=7.2 Hz), 5.28 (s, 2H), 4.22 (q, 2H, *J*=6.8 Hz), 1.43 (t, 3H, *J*=6.8 Hz). ^{13}C NMR (100 MHz, DMSO-d$_6$):175.78, 168.39, 162.92, 156.61, 141.63, 131.01, 130.45, 128.28, 127.72, 127.43, 126.45, 126.04, 121.04, 115.97, 115.87, 112.23, 69.01, 64.20, 16.60, 14.94.

3-{4-[(4-bromophenoxy)methyl]phenyl}-5-(4-ethoxyphenyl)-1,2,4-oxadiazole (Entry 25, Table 2): White crystalline solid. Melting point: 130-132.5^{o}C.

IR (neat, cm^{-1}) 2925.54, 2852.56, 1610.56, 1592.86, 1538.56, 1503.42, 1487.85, 1450.99, 1417.32, 1397.56, 1353.10, 1320.21, 1252.52, 1134.99, 1171.73, 1072.72, 1114.62, 1072.72, 1040.86, 1019.41, 919.67, 828.82.

^{1}H NMR (400 MHz, DMSO-d$_6$): 8.11 (t, 4H, *J*=8.8Hz), 7.65 (d, 2H, *J*=8.0Hz), 7.47 (d, 2H, *J*=9.2Hz), 7.18 (d, 2H, *J*=9.2Hz), 7.02 (d, 2H, *J*=9.2Hz), 5.21 (s, 2H), 4.16 (q, 2H, *J*=6.8Hz), 1.37 (t, 3H, *J*=6.8Hz).^{13}C NMR (100 MHz, DMSO-d$_6$): 175.98, 169.83, 162.91, 157.72, 140.84, 132.67, 130.46, 128.68, 127.72, 126.13, 125.26, 117.65, 115.86, 112.93, 69.38, 64.20, 14.94.

3-{4-[(4-chlorophenoxy)methyl]phenyl}-5-(4-ethoxyphenyl)-1,2,4-oxadiazole (Entry 26, Table 2): Pale brown solid. Melting point: 128-130.3^{o}C.

IR (neat, cm^{-1}) 2925.74, 2852.07, 1611.62, 1595.30, 1540.12, 1503.67, 1475.66, 1452.60, 1418.31, 1398.78, 1370.68, 1354.26, 1320.24, 1304.13, 1252.21, 1172.58, 1135.89, 1114.81, 1089.76, 1042.22, 918.93, 827.67, 804.45. ^{1}H NMR (400 MHz, DMSO-d$_6$): 8.11 (t, 4H, *J*=8.4Hz), 7.65 (d, 2H, *J*=8.4Hz), 7.35 (d, 2H, *J*=8.8Hz), 7.18 (d, 2H, *J*=8.8Hz), 7.07 (d, 2H, *J*=8.8Hz), 5.22 (s, 2H), 4.16 (q, 2H, *J*=6.8Hz), 1.37 (t, 3H, *J*=6.8Hz).

^{13}C NMR (100 MHz, DMSO-d_6): 175.81, 168.34, 162.93, 157.47, 140.87, 130.45, 129.78, 128.68, 127.72, 126.25, 125.07, 117.10, 115.96, 115.85, 69.45, 64.21, 14.94.

3-{4-[(2-methylphenoxy)methyl]phenyl}-5-(4-propyloxyphenyl)-1,2,4-oxadiazole

(Entry 27, Table 2): Off-white crystalline solid. Melting point: 101.5-102.6^{o}C.

IR (neat, cm^{-1}) 2924.39, 2878.82, 1612.99, 1565.42, 1542.04, 1503.66, 1468.65, 1424.80, 1363.68, 1310.57, 1262.58, 1177.00, 1123.70, 1072.90, 1045.25, 1012.79, 922.91, 836.45.^{1}H NMR (400 MHz, DMSO-d_6): 8.11 (t, 4H, *J*=7.2 Hz), 7.67 (d, 2H, *J*=8.0 Hz), 7.16 (dd, 4H, *J*=8.0 Hz), 7.01 (d, 1H, *J*=8.4 Hz), 6.86 (t, 1H, *J*=7.2 Hz), 5.22 (s, 2H), 4.06 (t, 2H, *J*=6.4 Hz), 2.24 (s, 3H), 1.819-1.732 (m, 2H), 1.00 (t, 3H, *J*=7.6 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): 175.78, 168.38, 163.08, 156.61, 141.62, 131.01, 130.44, 128.28, 127.71, 127.43, 126.44, 126.05, 121.04, 115.96, 115.88, 112.22, 69.93, 69.00, 22.34, 16.60, 10.78.

3-{4-[(4-chlorophenoxy)methyl]phenyl}-5-(4-propyloxyphenyl)-1,2,4-oxadiazole

(Entry 28, Table 2): White crystalline solid .Melting point:129.3-130.9^{o}C.

IR (neat, cm^{-1}) 2925.47, 2877.51, 1611.76, 1564.70, 1538.49, 1504.30, 1491.89, 1467.44, 1422.61, 1377.63, 1305.16, 1253.74, 1182.10, 1092.09, 1012.98, 868.41, 824.31, 758.58. ^{1}H NMR (400 MHz, DMSO-d_6): 8.11 (dd, 4H, *J*=7.2 & 1.6 Hz), 7.65 (d, 2H, *J*=8.0 Hz), 7.35 (dd, 2H, *J*=6.8 & 2.0 Hz), 7.19 (d, 2H, *J*=8.8 Hz), 7.098-7.047 (m, 2H), 5.22 (s,2H), 4.06 (t, 2H, *J*=6.4 Hz), 1.825-1.738 (m, 2H), 1.00 (t, 3H, *J*=7.2 Hz).

^{13}CNMR (100 MHz, DMSO-d_6): 175.80, 168.35, 163.10, 157.49, 140.87, 130.44, 129.78, 128.67, 127.72, 126.27, 125.08, 117.11, 115.98, 115.89, 69.95, 69.46, 22.35, 10.78.

3-(4-chlorophenyl)-5-[(E)-2-(4-methoxyphenyl)ethenyl]-1,2,4-oxadiazole

(Entry 29, Table 2): Pale brown solid. Melting point: 158.5-160.2^{o}C.

IR(neat, cm^{-1}) 2921.53, 1638.87, 1602.55, 1578.00, 1540.37, 1508.07, 1467.90, 1425.23, 1406.47, 1359.97, 1309.80, 1293.14, 1250.50, 1172.43, 1114.42, 1088.87, 1034.32, 1013.57, 972.10, 860.66, 754.15. ^{1}H NMR (400 MHz, DMSO-d_6): 8.06 (d, 2H, *J*=8.8 Hz), 7.91 (d, 1H, *J*=16.4 Hz), 7.83 (d, 2H, *J*=8.8 Hz), 7.16 (d, 2H, *J*=8.4 Hz), 7.29 (d, 1H, *J*=16.4 Hz), 7.04 (d, 2H, *J*=8.8 Hz), 3.83 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6): 176.49, 167.61, 161.87, 143.41, 136.69, 130.80, 129.91, 129.28, 127.34, 125.76, 114.98, 107.85, 55.88.

3-{4-[(2-methylphenoxy)methyl]phenyl}-5-[(E)-2-(4-methoxyphenyl)ethenyl]-1,2,4-oxadiazole (Entry 30, Table 2):

White crystalline solid. Melting point: 124-125.8^{o}C. IR (neat, cm^{-1}) 2922.16, 2841.70, 1632.08, 1602.97, 1578.42, 1538.16, 1509.38, 1494.32, 1354.61, 1257.93, 1171.63, 1120.74, 1039,18, 1023.15, 860.35, 818.46. ^{1}H NMR (400 MHz, DMSO-d_6): 8.08 (d, 2H, *J*=8.0 Hz), 7.90 (d, 1H, *J*=16.4 Hz), 7.82 (d, 2H, *J*=8.8 Hz), 7.67 (d, 2H, *J*=8.0 Hz), 7.30 (d, 1H, *J*=16.4 Hz), 7.16 (dd, 2H, *J*=8.0 & 4.8 Hz), 7.02 (t, 3H, *J*=8.8 Hz), 6.86 (t, 1H, *J*=7.6 Hz), 5.23 (s, 2H), 3.83 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 176.24, 168.21, 161.82, 156.63, 143.16, 141.56, 131.01, 130.75, 128.27, 127.64, 127.42, 127.39, 126.44, 126.17, 121.03, 114.98, 112.24, 108.01, 69.03, 55.88, 16.61.

3-(4-{[4-(2,3-dichlorophenyl)-1-piperazinyl]methyl}phenyl)-5-[(E)-2-(4-methoxy phenyl)ethenyl]-1,2,4-oxadiazole (Entry 31, Table 2):

Brown solid. Melting point: 163.1-167.5 ^{o}C. IR (neat, cm^{-1}) 2931.06, 2824.74, 1640.39, 1604.44, 1578.76, 1540.20, 1508.99, 1450.05, 1359.26, 1247.84, 1231.85, 1176.26, 1130.24, 1028.60, 960.53, 861.81. ^{1}H NMR (400 MHz, DMSO-d_6): 8.01 (d, 2H, *J*=8.0 Hz), 7.77 (d, 1H, *J*=16.4 Hz), 7.50 (d, 2H, *J*=8.8 Hz), 7.43 (d, 2H, *J*=8.0 Hz), 7.07 (d, 2H, *J*=6.0 Hz), 6.89 (t, 4H, *J*=7.2 & 15.4 Hz), 3.79 (s, 3H), 3.58 (s, 2H), 3.01 (s, 4H), 2.60 (s, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): 174.55, 167.48, 160.56, 150.27, 141.32, 140.46, 132.99, 128.59, 128.56, 127.87, 126.48, 126.40, 126.17, 124.91, 123.52, 117.59, 113.51, 106.74, 61.74, 54.42, 52.26, 50.28.

V. CONCLUSION

This robust and modified process described without use of heavy metals in any of the stages involved. Recovery of p-xylene and significantly diminished equivalents of DBU certainly help to reduce the cost of operation and this process is viable for the commercialization in the pharmaceutical industry. We have synthesized all the new 1,2,4-oxadiazole

analogues by the application of this process and purely isolated them without any impurities like N.N'-substitued urea and N-O-acyl amidoxime. The review also helpful for the academics for further research activities.

Conflicts of interest

There are no conflicts to declare.

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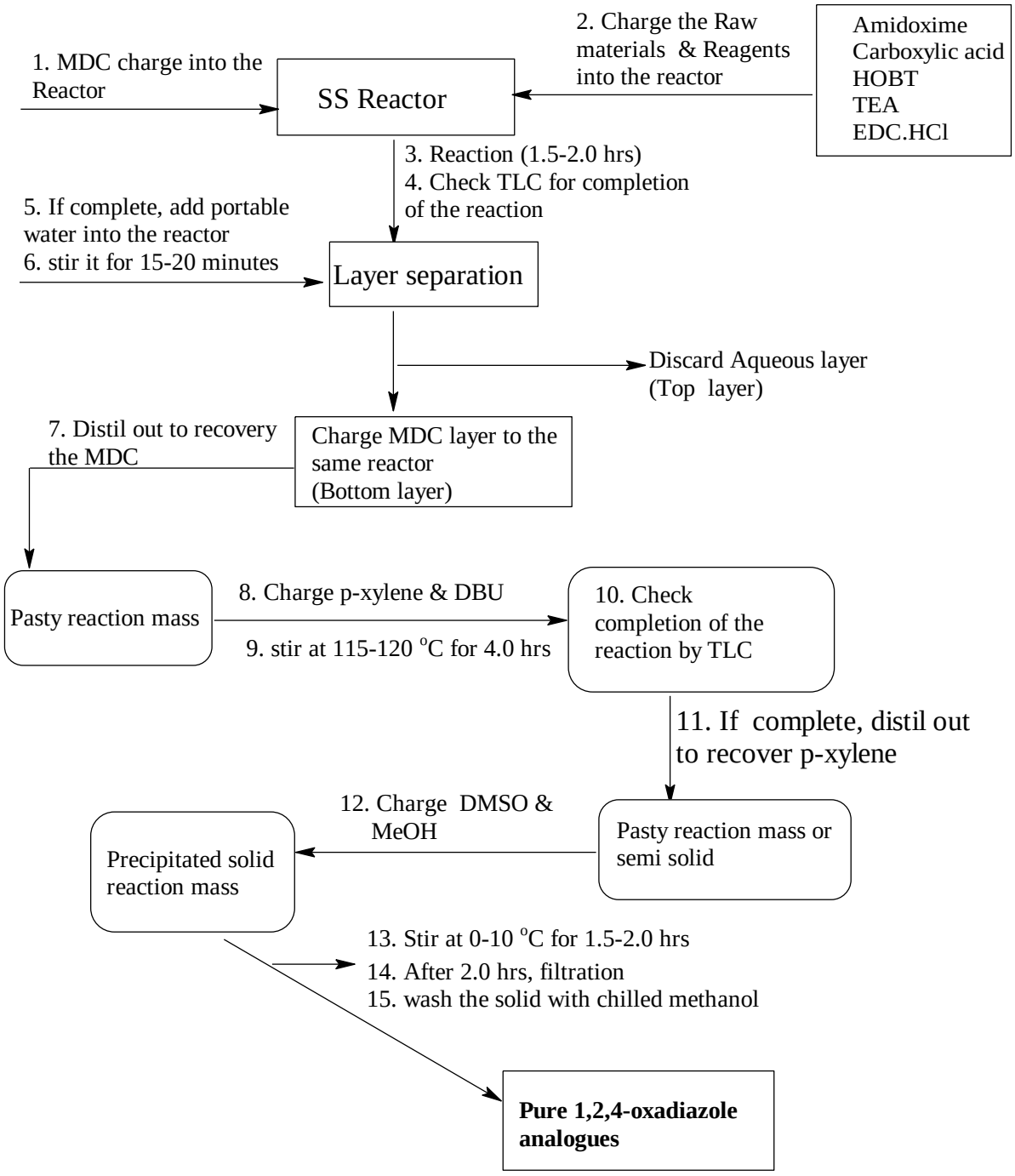

Figure I. Process flow chart for the commercialization of 1,2,4-oxadiazoles.

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