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Metal-Free Tandem Approach to Structurally Diverse *N*-Heterocycles: Synthesis of 1,2,4-Oxadiazoles and Pyrimidinones

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A metal-free one-pot approach to the diversity oriented synthesis of *N*-heterocycles, 1,2,4-oxadiazoles and 2,6 disubstituted pyrimidin-4-ones is described via carboxamidation of amidines with aryl carboxylic acids and aryl propargylic acids. The reactions occur at room temperature forming N-acylamidines which undergo tandem nucleophilic addition / deamination / intramolecular cyclisation to give the corresponding heterocyclic compounds in good to excellent yields. This one pot approach has led to the successful synthesis of drug lead molecule, ataluren, (3-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl) benzoic acid in two steps.

Introduction

Nitrogen-containing heterocycles are ubiquitous in many natural and synthetic bioactive molecules.[1] Within drug discovery and development, the 1,2,4-oxadiazole ring system is a privileged scaffold and oxadiazole rings form an essential part of the pharmacophore in several drugs and drug lead molecules[2,3] across a variety of disease areas including diabetes, obesity, inflammation, cancer and infection.[4] A number of compounds containing either 1,2,4 or 1,3,4-oxadiazole moieties are in different stages of clinical trials, such as ataluren for the treatment of cystic fibrosis,[5] zibotentan as an anticancer agent[6] and raltegravir, a recently marketed antiretroviral drug for the treatment of HIV infection.[7]

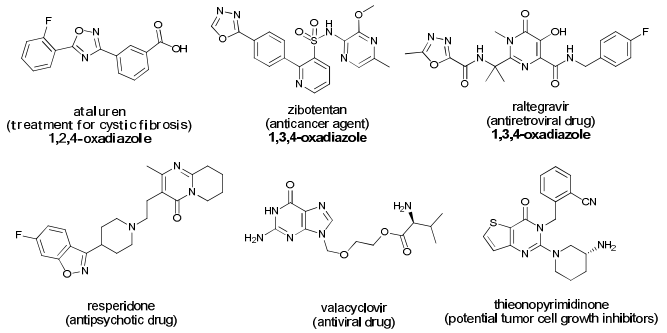

Figure 1 Structures of drugs/ bioactive molecules containing oxadiazoles and pyrimidinones.

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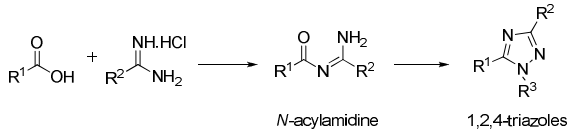
Additionally, oxadiazoles are often used as important bioisosteric replacements for amides and ester functionalities[8] for improved physical and biological properties by making them resistant to enzyme-catalyzed hydrolysis.[9] Pyrimidinones are also of wide occurrence and display significant biological activities.[10] Recently, some new pyrimidinone-amides,[11] thienopyrimidinones and their derivatives have been synthesized as antimalarial, anti-inflammatory, antimicrobial and anti-HIV agents (Figure 1).[12]

In recent years, transition metal-catalyzed tandem reactions have emerged as a useful tool for the syntheses of heterocyclic compounds.[13] However, due to the high cost, sensitivity to moisture and toxic nature of many of these metal catalysts, there has been a recent surge in reports of eco-friendly organic transformations[14] with readily available and cost-effective reagents. Plethora of methods have been reported for the synthesis of 1,2,4-oxadiazoles. Most of them involve condensation of amidoximes or its precursor nitriles with activated acid derivatives like esters, acid chlorides, anhydrides, orthoesters followed by cyclodehydration[15] but none has been reported through direct condensation of amidines and carboxylic acids. Recently, Staben and co-workers[16] have reported rapid synthesis of 1,2,4-triazoles through direct condensation with the intermediate formation of *N*-acylamidine (Scheme 1).

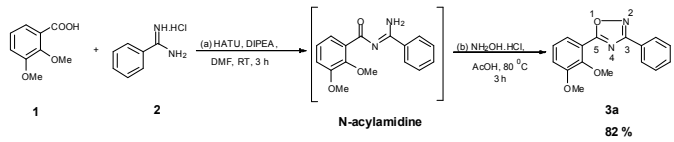


Scheme 1 Synthesis of 1,2,4- triazoles.

The use of *N*-acylamidines in heterocyclic synthesis is not very well documented, we therefore, envisioned if these could be explored and effectively exploited in the synthesis of diverse heterocyclic molecules. In continuation of our work on heterocyclic molecules,[17] we report in this communication, an innovative synthesis of 1,2,4-oxadiazoles and 2,6-disubstituted pyrimidin-4-ones using *N*-acylamidines as a common synthon which undergoes tandem nucleophilic addition / deamination and subsequent cyclisation to give different heterocyclic compounds in good to excellent yields.

Results and discussion

The study was commenced with a pilot reaction between 2,3-dimethoxy benzoic acid **1** and benzamidine hydrochloride **2** at room temperature using HATU as coupling reagent and DIPEA as base in DMF. *N*-acylamidine (confirmed by ^{1}H, ^{13}C-NMR and HRMS Spectra) was formed in > 95% in 3h. Subsequent, acid catalysed tandem reaction of acylamidine with hydroxylamine hydrochloride in acetic acid at 80 ^{0}C for 3h gave 1,2,4-oxadiazole **3a** in 82% yield (Scheme 2).



Scheme 2 Synthesis of 1,2,4-oxadiazoles.

The structure of **3a** was confirmed by complete assignments of all the ^{1}H and ^{13}C signals with the help of different 1D (^{1}H, ^{13}C, DEPT) and 2D NMR experiments (COSY, HSQC, HMBC and NOESY). HMBC correlation of H-6´´ with quaternary carbon C-5 (at δ 174.8 ppm) and HMBC correlation of H-2´,6´ with quaternary carbon C-3 (at δ 168.7 ppm) clearly indicated that 2,3-dimethoxy phenyl group is attached at C-5 position of 1,2,4-oxadiazole ring, while phenyl group is attached at C-3 position (Figure 2).

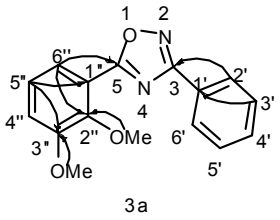


Figure 2 Significant HMBC correlations of oxadiazole **3a**.

In addition to spectral characterisation, single crystal X-ray analysis[18] of **3a** also showed the structure as 3-(phenyl)-5-(2,3-dimethoxyphenyl)-1,2,4-oxadiazole shown in the ORTEP diagram (Figure 3).

Having established the structure of **3a**, we tried to perform the reaction in one pot that is, without the isolation of the intermediate *N*-acylamidine and to our pleasant surprise the reaction was complete in 6 h with the isolated yield 82% of **3a**

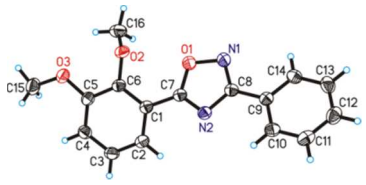
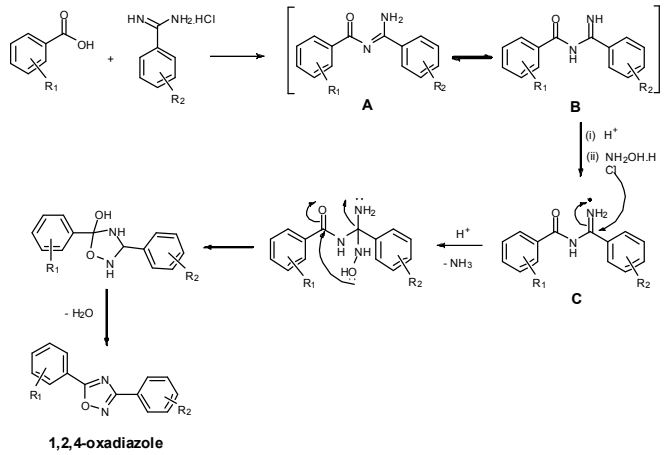


Figure 3 ORTEP diagram drawn with 30% ellipsoid probability for non-H atoms of one of the two independent molecules of compound 3a determined at 293 K.

We have postulated a plausible mechanism for its formation (Scheme 3). *N*-acylamidines are known to exist in tautomeric forms A and B with the amide tautomer B being preferred over *N*-acylimine tautomer A.[19] Under acidic reaction conditions, protonation of B results in the formation of iminium cation C which undergoes nucleophilic attack by hydroxylamine hydrochloride followed by tandem deamination and cyclisation. Subsequent removal of water molecule results in the formation of 1,2,4-oxadiazole.



Scheme 3 A plausible mechanism for the formation of 3,5-substituted 1,2,4-oxadiazoles.

Next, to establish an effective and generalized protocol, we focussed on the scope and optimization of the reaction in one pot, initially by screening the suitability of the coupling agent. The reaction was performed using different coupling agents and it was found that a variety of reagents worked well, however HATU was found to be the most suitable giving a neat reaction, complete conversion to N- acylamidine and good to excellent yields of 1,2,4-oxadiazoles. Among the bases used, the reaction was found to be neat in DIPEA and completed in 6h (entry 8, Table 1). Compatibility of the reaction with other alternative bases such as sodium or potassium carbonate or cesium carbonate was found to be less, reaction times were substantially increased and product isolated in moderate yields. DMF was found to be the solvent of choice., among the investigated solvents like DMSO, MeOH and dioxane. Only DMSO was found to be comparable with DMF (entry 9, Table 1).

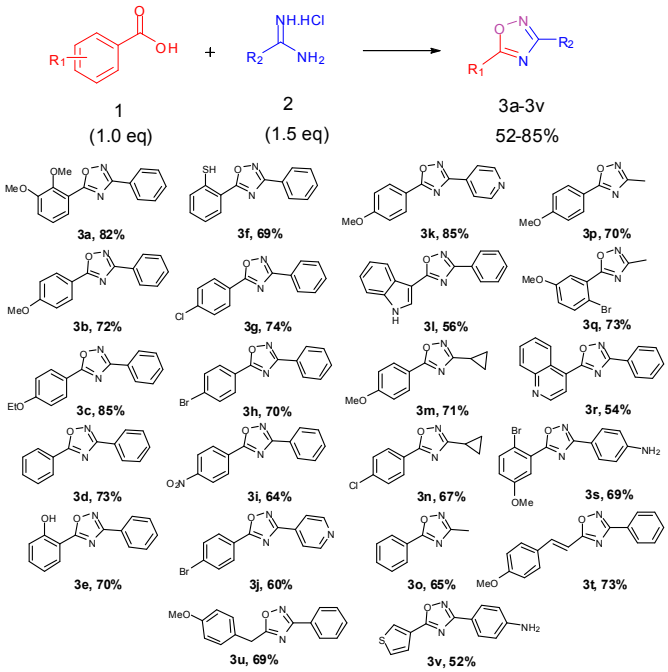
Table 1 Coupling reagent and base study for the synthesis of 1,2,4-oxadiazoles.[a, b, c]

Entry	Coupling reagent	Base	Solvent	Time (h)[b]	(Yeild %)[c] 3a
1.	DCC	DIPEA	DMF	10	10
2.	DCC/HOBt	DIPEA	DMF	12	40
3.	EDC	DIPEA	DMF	6	0
4.	EDC/HOBt	DIPEA	DMF	12	46
5.	HATU	K_2CO_3	DMF	8	56
6.	HATU	Na_2CO_3	DMF	9	54
7.	HATU	$NaHCO_3$	DMF	9	40
8.	**HATU**	**DIPEA**	**DMF**	**6**	**82**
9.	HATU	DIPEA	DMSO	7	74
10.	HATU/HOBt	DIPEA	DMF	7	70
11.	HATU	Cs_2CO_3	DMF	7	52
12.	HBTU	DIPEA	DMF	7	69

[a] Reaction conditions: substrate acid (1 mmol), amidine (1.5 mmol), coupling reagent (1.1 mmol), base (3 mmol), solvent (2 mL). [b] Time related to oxadiazole formation. [c] Isolated yield.

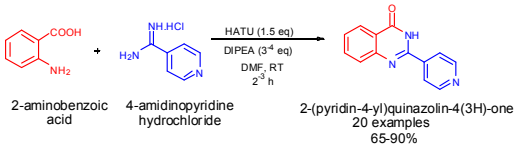
With defined reaction conditions in hand, exploration of substrates using different aryl as well as alkyl amidines and carboxylic acids was carried out to study the generality scope of the reaction. Both aryl and alkyl amidines were found to be equally reactive forming 1,2,4-oxadiazoles **3a-v** in 52-85% yields. Aromatic acids with either electron donating or withdrawing substituents formed the products with equal ease whereas, with heteroaromatic acids, yields were comparatively decreased and ranged between 52-56% (**3l, 3r & 3v**, Table 2).

Table 2 Substrate scope of the reaction in one pot.[a]



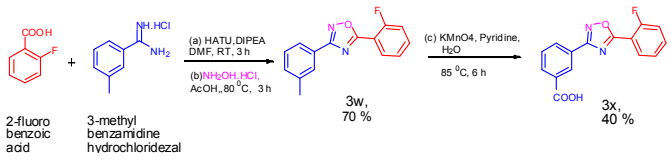
[a] isolated yield

The only exception to the above reaction was 2-aminobenzoic acid (anthranilic acid), which used as acid substrate did not form 1,2,4-oxadiazole, instead, the product obtained was characterised as 2-aryl-quinazolin-4(3H)-one. Though several methods are reported in literature for the synthesis of quinazolinones,[20] it is worthy to note that none has been reported through direct reaction of amidines with 2-aminobenzoic acids. The reaction is fast with differently substituted 2-amino benzoic acids and aromatic as well as aliphatic amidines and 2-aryl quinazolin-4-(3H)-ones were isolated in excellent yield (Scheme 4).



Scheme 4 Synthesis of 2-(pyridin-4-yl)quinazolin-4(3H)-one from 2-amino benzoic acid and 4-amidinopyridine hydrochloride.

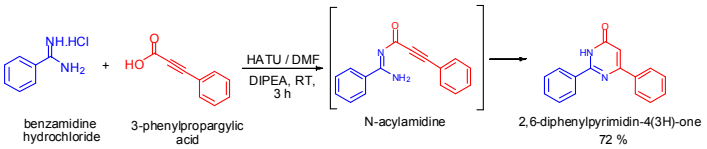
Our method has been validated by the synthesis of ataluren (3-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl) benzoic acid, Figure 1), an oral investigational drug currently under confirmatory phase 3 clinical trials for the treatment of cystic fibrosis.[20] The compound was successfully synthesised using our one pot approach. Under the optimised conditions, reaction of commercially available 3-methyl benzamidine with 2-fluoro benzoic acid resulted in the formation of the desired 5-(2-fluoro phenyl)-3-m-tolyl-1,2,4-oxadiazole **3w** as white solid in 70% yield. Subsequent oxidation of the methyl group with aq. potassium permanganate in pyridine furnished ataluren **3x** in 40% yield (Scheme 5). It was characterised by spectral analysis, 1H, 13C Mass and HRMS (see supporting information) and had physical characteristics identical to the compound reported in the literature.[21]



Scheme 5 Synthesis of Ataluren.

Our method results in the synthesis of ataluren in 2 steps from the commercially available amidine and acid. It is a vast improvement over the reported methods which generally require 4 to 5 steps.[22]

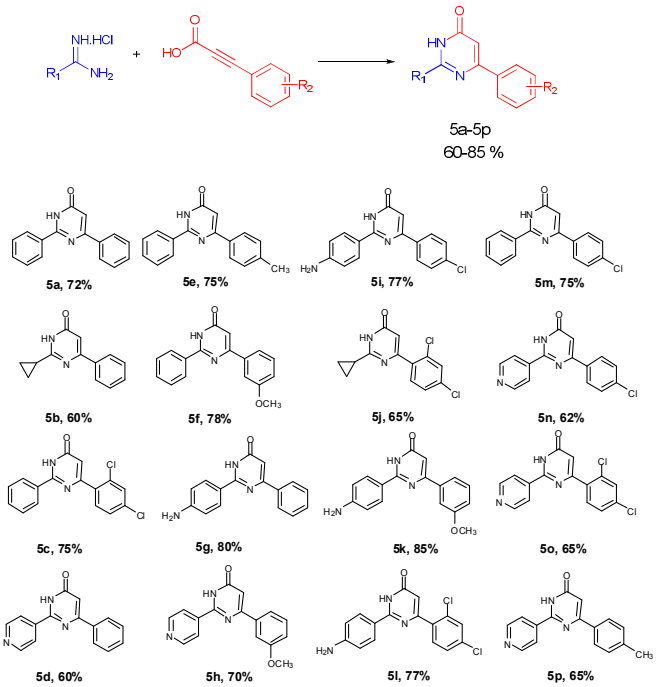
The scope of the reaction was extended further, by exploring the reactivity of amidines with aryl propargylic acids. Benzamidine reacted smoothly with 3-phenylpropargylic acid under the optimised conditions, resulting in one pot synthesis of 2,6-diphenyl pyrimidin-4(3H)-one. The reaction was complete in 3h and the pyrimidinone obtained as crystalline solid in 72% yield (Scheme 6).



Scheme 6 Synthesis of 2,6-diphenylpyrimidin-4(3H)-one from 3-phenyl-propargylic acid and benzamidine hydrochloride.

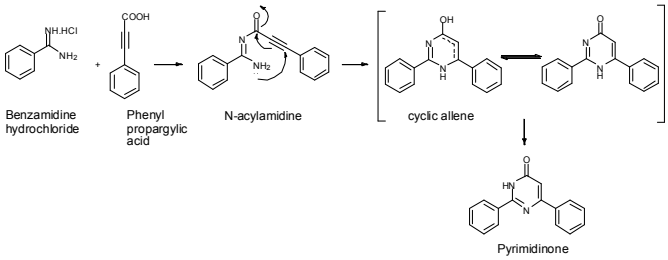
The generality of the reaction was demonstrated with the facile synthesis of substituted pyrimidinone derivatives with different propargylic acids and amidines (Table 3).

Table 3 Generality of pyrimidinones formation[a,b]



[a] Reaction conditions: substrate propargylic acid (1 mmol), amidine (1.5 mmol), HATU (1.1 mmol), DIPEA (3 mmol), DMF (2 mL). [b] Isolated yield.

Mechanistically, the formation of pyrimidinones can be represented as shown in Scheme 7. The reaction follows the same route of formation of *N*-acylamidine followed by intramolecular cyclisation via nucleophilic attack to triple bond forming cyclic allene which undergoes rearrangement to give pyrimidinones.



Scheme 7 Proposed mechanism for the formation of pyrimidin-4-ones.

Conclusions

In summary, *N*-acylamidines have been used as a common synthon for the synthesis of two different heterocyclic compounds 1,2,4-oxadiazoles and 2,6-disubstituted pyrimidinones in one pot reaction using metal-free single catalyst system. The simplicity of the starting materials, wide-substrate scope, high functional group compatibility and excellent yields are the advantages of this method. We believe that this experimentally simple approach can be a useful addition to reported methods for the synthesis of these heterocyles and this has been validated by the successful synthesis of drug lead molecule, ataluren (3-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl) benzoic acid.

Experimental section

General Information. ^{1}H NMR spectra were recorded on a 300 MHz and 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6 (all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, or the internal DMSO signal at 2.50 ppm as standard). ^{13}C NMR spectra were recorded on 75 MHz and 100 MHz spectrometer in $CDCl_3$ or DMSO-d_6 (all signals are reported in ppm with the internal chloroform signal at 77.16 ppm, or the internal DMSO signal at 39.52 ppm as standard). Chemical shifts δ are given in ppm relative to the residual signals of tetramethylsilane in $CDCl_3$ or deuterated solvent $CDCl_3$/ DMSO-d_6 for ^{1}H and ^{13}C NMR. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), multiplet (m). IR spectra were recorded using a FTIR spectrophotometer. X-ray data was collected at room temperature using a CCD diffractometer with graphite monochromated MoKα radiation (λ = 0.71073) with ω-scan method. The purity and characterization of these compounds were further established using HR/EI Mass spectroscopy. Melting points are uncorrected and were determined on a capillary melting point apparatus. All reagents and solvents were purchased from commercial sources and used without purification.

General procedure for the synthesis of 1,2,4-oxadiazole derivatives 3a-3v

Representative method for the synthesis of 3a: To a mixture of 2,3-dimethoxy benzoic acid **1** (1.0 mmol), benzamidine hydrochloride **2** (1.5 mmol) and HATU (1.1 mmol) in an RB flask, was added DMF (3 mL) and DIPEA (3mmol). The reaction mixture was stirred at room temperature and progress of the reaction was monitored by TLC. After 3h, reactants **1** and **2** were totally consumed. The product formed was isolated and characterised by spectral analysis as ***N*-(amino (phenyl)methylene)-2,3-dimethoxybenzamide (N-acyl amidine)**; colourless liquid; 96% yield; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.47 (s, 1H), 7.98-7.96 (m, 2H), 7.83 (dd, J_1 = 6.2 Hz, J_2 = 1.6 Hz, 1H), 7.64-7.60 (m, 1H), 7.55-7.51 (m, 2H), 7.27 (t, J = 8.0 Hz, 1H), 6.19 (dd, J_1 = 6.5 Hz, J_2 = 1.6 Hz, 1H), 4.02 (s, 3H), 3.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 164.8, 162.7, 152.5, 147.4. 133.6, 132.9, 128.9, 127.5, 125.9, 125.1, 123.6, 116.8, 62.1, 56.2; IR (Neat): 3318, 1737, 1679, 1479, 1240, 1082, 759 cm^{-1}; HRMS (ESI) Calcd. for $C_{16}H_{16}N_2O_3$ $[M+H]^+$ 285.1239 Found 285.1247. Subjecting the acylamidine to reaction with hydroxylamine hydrochloride (1.5 mmol) in acetic acid (10 mmol) at 80 ^{0}C, the reaction was complete in 3.5 h. It was cooled and extracted with EtOAc (3 x 15 mL). The combined organic phase was washed with saturated $NaHCO_3$ (1 x 20 mL), dried over anhy.Na_2SO_4 and the solvent evaporated under reduced pressure. The crude

residue was purified by column chromatography (EtOAc/hexane) to afford pure compound, **5-(2,3-dimethoxyphenyl)-3-phenyl-1,2,4-oxadiazole, (3a):** white solid; 82% yield; m.p. 126-128 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.21-8.17 (m, 2H), 7.70 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H) 7.51-7.47 (m, 3H), 7.22 (t, J = 8.0 Hz, 1H), 7.14 (dd, J_1 = 8.0 Hz, J_2 = 1.2Hz, 1H), 4.03 (s, 3H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.8, 168.57, 154.0, 131.2, 129.0, 127.7 127.3, 124.7, 122.5, 119.4, 116.5, 61.8, 56.3; IR (KBr): 1608, 1551, 1480, 1363, 1265, 1216, 765 cm^{-1}; HRMS (ESI) Calcd. for $C_{16}H_{14}N_2O_3$ $[M+H]^+$ 283.1083 Found 283.1092.

Compound **3a** was also synthesised in one pot (82% yield) under the same reaction conditions and without the isolation of intermediate N- acylamidine. Rest of the compounds **3b-3v** were prepared following the one pot method.

5**-(4-Methoxyphenyl)-3-phenyl-1,2,4-oxadiazole (3b):** white solid; 72% yield; m.p. 106-108 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.25 (d, J = 7. 3Hz, 2H), 8.15 (d, J = 8.5 Hz, 2H) 7.65-7.55 (m, 3H), 7.05 (d, J = 8.6 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.4, 168.6, 161.9, 132.6, 129.1, 129.0, 128.1, 124.4, 119.4, 114.2, 55.3; IR (KBr): 1609, 1465, 1365, 1256, 1031, 736 cm^{-1}; HRMS (ESI) Calcd. for $C_{15}H_{12}N_2O_2$ $[M+H]^+$ 253.0977 Found 253.0966.

5-(4-Ethoxyphenyl)-3-phenyl-1,2,4-oxadiazole (3c): white solid; 85% yield; m.p. 116-118 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.18 (d, J = 8.5 Hz, 4H), 7.53 (d, J = 1.9 Hz, 3H), 7.06 (d, J = 8.6 Hz, 2H), 4.18 (q, J = 6.9 Hz, 2H), 1.50 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.6, 168.8, 162.6, 131.0, 130.0, 128.8, 127.5, 127.2, 116.7, 114.9, 63.8, 14.6; IR (KBr): 1607, 1465, 1360, 1224, 1034, 769 cm^{-1}; HRMS (ESI) Calcd. for $C_{16}H_{14}N_2O_2$ $[M+H]^+$ 267.1134, Found 267.1141.

3,5-Diphenyl-1,2,4-oxadiazole (3d): white solid; 73% yield; m.p. 106-108 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.26-8.20 (m, 4H), 7.64-7.55 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.7, 169.0, 132.7, 131.2, 129.0, 128.8; 128.1, 127.5, 127.0, 124.3; IR (KBr): 1617, 1439, 1364, 684 cm^{-1}; HRMS (ESI) Calcd. for $C_{14}H_{10}N_2O$ $[M+H]^+$ 223.0871 Found 223.0876.

2-(3-Phenyl-1,2,4-oxadiazole-5-yl) phenol (3e): white solid; 70% yield; m.p. 158-160 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.55 (s, OH, 1H), 8.16 (d, J = 5.6 Hz, 2H), 8.04 (d, J = 7.3 Hz, 1H), 7.57 (d, J = 6.4 Hz, 4H), 7.19 (d, J = 8.3Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.3, 167.0, 158.1, 135.2, 131.6, 129.0, 128.8, 127.8, 127.5, 125.8, 120.1, 117.8, 108.1; IR (KBr): 3134, 1620,1369, 1244, 1147, 749 cm^{-1}; HRMS (ESI) Calcd. for $C_{14}H_{10}N_2O$ $[M+H]^+$ 239.0821 Found 239.0836.

2-(3-Phenyl-1,2,4-oxadiazole-5-yl) benzenethiol (3f): white solid; 69% yield; m.p. 116-118 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.27-8.23 (m, 4H), 7.94 (d, J = 8.0 Hz, 1H), 7.55-7.50 (m, 3H), 7.43 (t, J = 7.2 Hz, 1H), 7.09; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.9, 168.7, 138.2, 132.8, 131.3, 130.5, 128.9, 127.7, 126.8, 126.7, 126.4, 121.8; IR (KBr): 3442, 1602, 1447, 1360, 1154, 1035, 728 cm^{-1}; HRMS (ESI) Calcd. for $C_{14}H_{10}N_2OS$ $[M+H]^+$ 255.0592 Found 255.0598.

5-(4-Chlorophenyl)-3-phenyl-1,2,4-oxadiazole (3g): white solid; 74% yield; m.p. 118-120 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.17-8.15 (m, 4H), 7.54-7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 179.5, 166.9, 136.6, 134.8, 132.5, 131.3, 128.9, 127.3, 127.0; IR (KBr): 1595, 1465, 1355, 1082, 744 cm^{-1}; HRMS (ESI) Calcd. for $C_{14}H_9ClN_2O$ $[M+H]^+$ 257.0482 Found. 257.0496.

5-(4-Bromophenyl)-3-phenyl-1,2,4-oxadiazole (3h): white solid; 70% yield; m.p. 114-116 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.20-8.17 (m, 2H), 8.12 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.55-7.53 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.0, 169.0, 132.5, 131.3, 129.5, 128.8, 127.7, 127.5, 126.7, 123.2; IR (KBr): 1627, 1365, 1220, 771 cm^{-1}; HRMS (ESI) Calcd. for $C_{14}H_9BrN_2O$ $[M+H]^+$ 300.9977 Found 300.9991.

5-(4-Nitrophenyl)-3-phenyl-1,2,4-oxadiazole (3i): white solid; 64% yield; m.p. 164-166 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.42 (s, 4H), 8.19-8.16 (m, 2H), 7.56-7.51 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.6, 173.3, 154.1, 135.5, 133.3, 133.1, 132.8, 131.4, 130.1, 128.2; IR (KBr): 1525, 1339, 1103, 853, 725 cm^{-1}; HRMS (ESI) Calcd. for $C_{14}H_9N_2O_3$ $[M+H]^+$ 268.0722 Found 268.0738.

5-(4-Bromophenyl)-3-(pyridine-4-yl)-1,2,4-oxadiazole (3j): white solid; 60% yield; m.p. 132-134 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.84 (s, 2H), 8.12-8.04 (m, 4H), 7.76-7.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.6, 167.5, 150.7, 134.1, 132.6, 129.5, 128.2, 122.6, 121.3; IR (KBr): 1602, 1472, 1364, 1071, 688 cm^{-1}; HRMS (ESI) Calcd. for $C_{13}H_8BrN_3O$ $[M+H]^+$ 301.9929 Found 301.9934 .

5-(4-Methoxyphenyl)-3-(pyridin-4-yl)-1,2,4-oxadiazole (3k): white solid; 62% yield; m.p. 122-124 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.82 (d, J = 3.6 Hz, 2H), 8.19 (d, J = 8.7 Hz, 2H), 8.05 (d, J = 5.4 Hz, 2H), 7.09 (d, J = 8.7 Hz, 2H) 3.9 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 176.3, 167.2, 163.4, 150.6, 134.6, 130.1, 121.3, 116.3, 114.6, 55.5; IR (KBr): 1616, 1503, 1375, 1310, 1266, 1179, 1022, 838, 759 cm^{-1}; HRMS (ESI) Calcd. for $C_{14}H_{11}N_3O_2$ $[M+H]^+$ 254.0930 Found 254.0941.

5-(1H-indol-3-yl)-3-phenyl-1,2,4-oxadiazole (3l): white solid; 56% yield; m.p. 170-172 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.85 (s, 1H, NH), 8.46-8.43 (m, 1H), 8.26-8.23 (m, 2H), 8.15 (d, J = 2.8 Hz, 1H) , 7.55-7.50 (m, 4H), 7.41-7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.9, 168.1, 136.4, 131.0, 129.6, 129.4, 128.8., 127.4, 127.1, 124.7, 123.3, 122.0, 120.8, 112.0, 101.4; IR (KBr): 1606, 1443, 1343, 1252, 1185, 1129, 691 HRMS (ESI) Calcd. for $C_{16}H_{11}N_3O$ $[M+H]^+$ 262.0980 Found 262.0995.

3-Cyclopropyl-5-(4-methoxyphenyl)-1,2,4-oxadiazole (3m): white solid; 71% yield; m.p. 112-114 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.05 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 2.16-2.11 (m, 1H), 1.13-1.07 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.9, 172.8, 162.9, 129.8, 117.0, 114.3, 55.4, 7.6, 6.9; IR (KBr): 1617, 1382, 1259, 1176, 1028 cm^{-1}; HRMS (ESI) Calcd. for $C_{12}H_{11}N_2O_2$ $[M+H]^+$ 217.0977 Found 217.0986

5-(4-Chlorophenyl)- 3-cyclopropyl-1,2,4-oxadiazole (3n): colourless liquid; 67% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.05 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 2.20-2.12 (m, 1H). 1.3(d, *J* = 8.1 Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.2, 173.1, 138.9, 129.3, 122.8, 7.7, 6.8; IR (Neat): 1620, 1407, 760, 684 cm^{-1}; HRMS (ESI) Calcd. for $C_{11}H_9ClN_2O$ $[M+H]^+$ 221.0482 Found 221.0498.

3-Methyl-5-phenyl-1,2,4-oxadiazole (3o): colourless liquid; 65% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.15 (d, *J* = 6.7 Hz, 2H), 7.63-7.52 (m, 3H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.4, 167.7, 132.6, 129.0, 128.0, 124.2, 11.6; IR (Neat): 1638, 1403, 720 cm^{-1}; HRMS (ESI) Calcd. for $C_9H_8N_2O$ $[M+H]^+$ 161.0715 Found 161.0732 .

5-(4-Methoxyphenyl)-3-methyl-1,2,4-oxadiazole (3p): white solid; 70% yield; m.p. 120-122 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.08 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 1H), 3.89 (s, 3H), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.2, 167.5, 163.0, 129.8, 116.7, 114.4, 55.4, 11.6; IR (KBr): 1606, 1255, 1028, 836 cm^{-1}; HRMS (ESI) Calcd. for $C_{10}H_{10}N_2O_2$ $[M+H]^+$ 191.0821 Found 191.0823.

5-(2-Bromo-5-methoxyphenyl)-3-methyl-1,2,4-oxadiazole (3q): white solid; 73% yield; m.p. 80-82 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.65 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 2.8 Hz, 1H), 7.00-6.96 (m, 1H), 3.87 (s, 3H), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.5, 167.5, 158.8, 135.5, 126.1, 119.9, 116.4, 112.2, 55.7, 11.7; IR (KBr): 1638, 1465, 1332, 1223, 769 cm^{-1}; HRMS (ESI) Calcd. for $C_{10}H_9BrN_2O_2$ $[M+H]^+$ 268.9926 Found 269.9937.

3-Phenyl-5-(quinolin-4-yl)-1,2,4-oxadiazole (3r): white solid; 54% yield; m.p. 186-188 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.26-9.14 (m, 2H), 8.29-8.24 (m, 4H), 7.91-7.78 (m, 2H), 7.60-7.58 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.0, 169.2, 149.7, 149.2, 139.2, 131.6, 130.3, 129.0, 128.8, 128.5, 128.2, 128.1, 127.6, 126.4, 125.7, 124.0, 121.9, 114.0; IR (KBr): 1447, 1352, 1259, 1077, 766 cm^{-1}; HRMS (ESI) Calcd. for $C_{17}H_{11}N_3O$ $[M+H]^+$ 274.0980 Found 274.0992.

4-(5-(2-Bromo-5-methoxyphenyl)-1,2,4-oxadiazol-3-yl) aniline (3s): white solid; 69% yield; m.p. 176-178 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.51 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 2.9 Hz, 3H), 6.89 (dd, J_1 = 5.8 Hz, J_2 = 2.9 Hz, 2H), 6.21 (d, NH_2, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.9, 162.0, 141.0, 137.4, 120.8, 117.7, 112.5, 58.7; IR (KBr): 1637, 1459, 1222, 768 cm^{-1}; HRMS (ESI) Calcd. for $C_{15}H_{12}BrN_3O_2$ $[M+H]^+$ 346.0191 Found 346.0198.

(E)-5-(4-Methoxystyryl)-3-phenyl-1,2,4-oxadiazole (3t): white solid; 73% yield; m.p. 156-158 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.16-8.14 (m, 2H), 7.89 (d, *J* = 16.3 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.53 (d, *J* = 4.9 Hz, 3H), 6.99-6.92 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.6, 168.6, 161.5, 142.3, 131.1, 129.6, 128.8, 127.4, 127.1, 127.0, 114.5, 107.7, 55.4; IR (KBr): 1599, 1450, 1362, 1247, 1176, 1026, 963, 820 cm^{-1}; HRMS (ESI) Calcd. for $C_{17}H_{14}N_2O_2$ $[M+H]^+$ 279.1134 Found 279.1145.

5-(4-Methoxybenzyl)-3-phenyl-1,2,4-oxadiazole (3u): white solid; 69% yield; m.p. 128-130 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.07 (d, *J*= 6.9 Hz, 2H), 7.50-7.44 (m, 3H), 7.30 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.22 (s, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ =178.3, 168.4, 159.0, 131.1, 130.0, 128.8, 127.4, 126.8, 125.5, 114.3, 55.3, 32.2; IR (KBr): 1620, 1440, 1320, 1230, 1080, 740 cm^{-1}; HRMS (ESI) Calcd. for $C_{16}H_{14}N_2O_2$ $[M+H]^+$ 267.1134 Found 267.1167.

4-(5-(Thiophen-3-yl)-1,2,4-oxadiazol-3-yl)aniline (3v): white solid; 52% yield; m.p. 168-170 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.27 (s, 1H), 7.98 (d, *J* = 7.0 Hz, 2H), 7.76 (s, 1H), 7.48 (s, 1H), 6.78 (d, *J* = 7.1 Hz, 2H), 3.98 (s, br, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.4, 168.7, 149.2, 139.2, 129.8, 129.0, 127.2, 126.7, 126.1, 116.6, 114.7, 114.0; IR (KBr): cm^{-1}; HRMS (ESI) Calcd. for $C_{12}H_9N_3OS$ $[M+H]^+$ 244.0545 Found 244.0556.

5-(2-fluorophenyl)-3-m-tolyl-1,2,4-oxadiazole (3w): white solid; 70% yield; m.p. 93 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.27-8.23 (m, 1H), 8.03-8.00 (m, 2H), 7.76-7.60 (m, 1H), 7.44-7.31 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.6, 168.8, 162.0, 159.4, 138.6, 134.5, 134.4, 132.0, 130.9, 128.7, 128.1, 126.6, 124.7, 124.6, 117.2, 117.0, 112.9, 112.8 (Additional peaks are due to splitting with o-Fluoro group); IR (KBr): 1622, 1463, 1216, 759 cm^{-1}; HRMS (ESI) Calcd. for $C_{15}H_{11}FN_2O$ $[M+H]^+$ 255.0934 Found 255.0914.

3-(5-(2-fluorophenyl)-1,2,4-oxadiazole-3-yl) benzoic acid (ataluren, 3x) : Compound **3w** (1 mmol) was magnetically stirred in a mixture of pyridine (3 ml) and water (1 ml) at 85 ^{0}C. Potassium permangnate (3 mmol) was added over a period of 30min. and the reaction mixture was heated for another 6 h. On completion of the reaction as checked by TLC, the solution was cooled to room temperature and neutralised with 10N HCl to pH 4-5. It was then extracted with ethyl acetate and washed with water. The organic layer was dried over anhyd. Na_2SO_4 and concentrated at reduced pressure to give crude compound which was purified by coloumn chromatography (MeOH/ $CHCl_3$). Pure compound **3w** was obtained as white solid; 40% yield; m.p. 240-242 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 13.36 (s, 1H), 8.64-8.63 (m, 1H), 8.34 (td, J_1 = 7.7 Hz, J_2 = 1.2 Hz 1H), 8.29 (dt, J_1 = 7.6 Hz, J_2 = 1.7 Hz, 1H), 8.19 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H) , 7.84-7.79 (m, 1H), 7.78 (t, *J* = 7.76, 1H), 7.59-7.54 (m, 1H), 7.52 (dt, J_1 = 7.7 Hz, J_2 = 1.0 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.2, 167.9, 167.0, 161.7, 159.2, 136.3, 136.2, 132.7, 132.3, 131.5, 131.4, 130.3, 128.2, 126.8, 126.0, 117.9, 117.7, 112.2, 112.1 (Additional peaks are due to splitting with o-fluoro group); IR (KBr): 3415, 1692, 1619, 1406, 1215, 760 cm^{-1}; HRMS (ESI) Calcd. for $C_{15}H_9FN_2O_3$ $[M+H]^+$ 285.0675 Found 285.0653.

General procedure for the synthesis of pyrimidinone derivatives 5a-5p

To a stirred mixture of phenylpropargylic acid (1 mmol), benzamidine hydrochloride (1.5 mmol) and HATU (1.1 mmol) in DMF (3ml), DIPEA (3 mmol) was added and the reaction mixture was stirred at rt for 3h. After completion of the reaction as indicated by TLC, cold water (15 mL) was added to the reaction mixture and allowed to stand for 2h. The solid precipitated was filtered and crystallized from methanol or ethyl acetate to afford pure compounds.

2,6-Diphenylpyrimidin-4(3H)-one (5a) as yellow solid; 72% yield; m.p. □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 12.10 (s, 1H), 8.33 (d, *J* = 6.3 Hz, 2H), 8.19 (d, *J* = 6.0 Hz, 2H), 7.63 (s, 3H), 7.50 (d, *J* = 6.2 Hz, 3H), 7.04 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 172.6, 161.3, 140.8, 134.6, 133.1, 132.5, 130.6, 129.5, 129.2, 128.3, 127.8, 125.7; IR (KBr): 3440, 3021, 1639, 764 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_{12}N_2O$, $[M+H]^+$ 249.1028 Found 249.1024.

2-Cyclopropyl-6-phenylpyrimidin-4(3H)-one (5b): white solid; 60% yield; m.p. □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 11.38 (s, 1H), 8.19 (d, *J* = 7.0 Hz, 2H), 7.49-7.37 (m, 3H), 6.79 (s, 1H), 1.92-1.88 (m, 1H), 1.17-1.14 (m, 4H); ^{13}C NMR (DMSO-d_6, 75MHz): δ = 171.6, 168.9, 139.9, 134.3, 131.4, 129.3, 128.5, 121.9, 10.58, 9.0; IR (KBr): 3437, 3019, 1643, 1215, 757 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{12}N_2O$ $[M+H]^+$ 213.1028, Found 213.1042.

6-(2,4-Dichlorophenyl)-2-phenylpyrimidin-4(3H)-one (5c): yellow solid; 75% yield; m.p. □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 12.36 (s, 1H), 9.12 (d, *J* = 8.6 Hz, 1H), 8.25 (d, *J* = 7.0 Hz, 2H), 7.82 (d, *J* = 2.0 Hz, 1H), 7.73-7.64 (m, 4H), 7.26 (s, 1H); ^{13}C NMR (DMSO-d_6, 75MHz): δ = 172.3, 163.3, 142.5, 136.0, 135.4, 134.4, 133.6, 131.1, 129.5, 128.6, 128.3, 128.1, 117.6; IR (KBr): 3439, 3019, 1641, 1210, 753 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{12}N_2O$, $[M+H]^+$ 213.1028 Found 213.1042.

6-Phenyl-2-(pyridin-4-yl)pyrimidin-4(3H)-one (5d): green solid; 60% yield; m.p. □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 12.29 (s, 1H), 8.85 (d, *J* = 5.8 Hz, 2H), 8.35 (d, *J* = 6.1 Hz, 2H), 8.07 (d, *J* = 5.9 Hz, 2H), 7.52-7.47 (m, 3H), 7.16 (s, 1H); ^{13}C NMR (MeOD + $CDCl_3$, 75 MHz): δ = 174.2, 159.8, 151.3, 141.4, 137.9, 135.4, 134.1, 132.2, 131.5, 130.1, 122.6; IR (KBr): 3438, 3021, 1639, 1216, 764 cm^{-1}; HRMS (ESI) Calcd for $C_{15}H_{11}N_3O$ $[M+H]^+$ 250.0980 Found 250.0980.

2-Phenyl-6-p-tolylpyrimidin-4(3H)-one (5e): yellow solid; 75% yield; m.p. □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 12.11 (s, 1H), 8.23-8.16 (m, 4H), 7.65-7.58 (m, 3H), 7.33 (d, *J* = 7.5 Hz, 2H), 7.01 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 172.0, 160.3, 139.7, 132.1, 131.1, 129.5, 129.0, 128.0, 127.9, 127.3, 126.9, 125.3, 21.28; IR (KBr): 3445, 3027,2966, 1645 cm^{-1}; HRMS (ESI) Calcd for $C_{17}H_{12}N_2O$ $[M+H]^+$ 263.1184 Found 263.1151.

6-(3-Methoxyphenyl)-2-phenylpyrimidin-4(3H)-one (5f): yellow solid; 78% yield; m.p. □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.70 (s, 1H), 8.63 (d, *J* = 1.7 Hz, 1H), 8.24-8.21 (m, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 1H), 6.78 (s, 1H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.12 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 172.2, 160.7, 157.0, 139.9, 136.5, 133.9, 132.9, 129.5, 129.0, 128.4, 127.7, 124.0, 113.2, 111.4, 56.9; IR (KBr); 3442, 3018, 1612, 1216, 755 cm-^{1}; HRMS (ESI) Calcd for $C_{17}H_{14}N_2O_3$ $[M+H]^+$ 279.1133 Found 279.1134.

2-(4-Aminophenyl)-6-phenylpyrimidin-4(3H)-one (5g): yellow solid; 80% yield; m.p. □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 11.76 (s, 1H), 8.29 (d, *J* = 7.2 Hz, 2H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.50-7.45 (m, 2H), 7.41 (d, *J* = 7.3 Hz, 1H), 6.81 (s, 1H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.17 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 172.8, 161.2, 153.7, 141.0, 135.1, 131.9, 129.9, 129.8, 129.1, 121.9, 114.3, 114.0; IR (KBr): 3420, 3354, 3019, 1641, 755 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_{13}N_3O$ $[M+H]^+$ 264.1137 Found 264.1173.

6-(3-Methoxyphenyl)-2-(pyridin-4-yl)pyrimidin-4(3H)-one (5h): green solid; 70% yield; m.p. □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 12.30 (s,1H), 8.90 (d, *J* = 6.0 Hz, 2H), 8.71 (d, *J* = 1.8 Hz, 1H), 8.39 (m, 1H), 8.06 (d, *J* = 6.0 Hz, 3H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.17 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 171.9, 159.2, 157.5, 139.5, 136.8, 135.6, 134.3, 128.6, 126.4, 121.0, 113.2, 111.5, 57.0; IR (KBr): 3441, 3017, 1612, 1215, 760 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_{13}N_3O_2$, $[M+H]^+$ 280.1088 Found 280.1078.

2-(4-Aminophenyl)-6-(4-chlorophenyl)pyrimidin-4(3H)-one (5i): yellow solid; 77% yield; m.p. □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 11.77 (s, 1H), 8.31 (d, *J* = 7.8 Hz, 2H), 7.89 (d, *J* = 7.7 Hz, 2H), 7.52 (d, *J* = 7.7 Hz, 2H), 6.78 (s, 1H), 6.69 (d, *J* = 7.7 Hz, 2H), 6.18 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 172.6, 161.7, 154.0, 142.0, 134.4, 133.8, 133.4, 130.0, 129.1, 119.5, 114.2, 113.7; IR (KBr): 3442, 3430, 3019, 1635, 756 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_{12}ClN_3O$ $[M+H]^+$ 298.0747 Found 298.0754.

2-Cyclopropyl-6-(2,4-dichlorophenyl)pyrimidin-4(3H)-one (5j): white solid; 65% yield; m.p. □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.53 (s, 1H), 8.82 (d, *J* = 8.6 Hz, 1H), 7.71(d, *J* = 2.1 Hz, 1H), 7.55-7.52 (m, 1H), 6.94 (s, 1H), 1.91-1.88 (m, 1H), 1.17-1.15 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 172.0, 142.2, 135.4, 134.6, 133.9, 131.2, 129.5, 128.1, 114.4, 11.3, 10.0; IR (KBr): 3436, 3019, 1648, 1216, 755 cm^{-1} HRMS (ESI) Calcd for $C_{13}H_{10}Cl_2N_2O$ $[M+H]^+$ 281.0248 Found 281.0245.

2-(4-Aminophenyl)-6-(3-methoxyphenyl)pyrimidin-4(3H) one (5k): yellow solid; 85% yield; m.p. □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 11.75 (s,1H), 8.66 (d, *J* = 1.8 Hz, 1H), 8.28-8.25 (m, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 1H), 6.78 (s,1H), 6.72 (d, *J* = 8.6 Hz, 3H), 6.17 (s, 2H), 3.95 (s, 3H), ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 172.5, 160.9, 156.3, 153.7, 140.6, 135.9, 133.1, 129.7, 119.7, 114.4, 113.1, 111.3, 56.87; IR (KBr): 3439, 3018, 1660, 1217, 760 cm^{-1}; HRMS (ESI) Calcd for $C_{17}H_{15}N_3O_2$, $[M+H]^+$ 294.1242 Found 294.1240.

2-(4-Aminophenyl)-6-(2,4-dichlorophenyl)pyrimidin-4(3H)-one (5l): yellow solid; 77% yield; m.p. □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 11.92 (s, 1H), 9.10 (d, *J* = 8.6 Hz, 1H), 7.91 (d, *J* =8.6 Hz, 2H), 7.72 (d, *J* =2.1 Hz, 1H), 7.58-7.56 (m, 1H), 6.98 (s, 1H), 6.69 (d, *J* = 8.7 Hz, 2H), 6.28 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 172.7, 163.0, 154.2, 143.1, 135.2, 134.2, 133.9, 131.6, 130.4, 129.4, 128.0, 126.2, 120.4, 113.9; IR (KBr): 3440, 3439, 3023, 1638, 1216, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_{11}Cl_2N_3O$ $[M+H]^+$ 232.0357 Found 232.0354.

6-(4-Chlorophenyl)-2-phenylpyrimidin-4(3H)-one (5m): yellow solid; 75% yield; m.p. □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 12.17 (s, 1H), 8.36 (d, *J* = 8.0 Hz, 2H), 8.19 (d, *J* = 7.4Hz, 2H), 7.67-7.55 (m, 5H), 7.04 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 172.4, 161.7, 141.2, 135.1, 134.0,

133.2, 129.5, 129.3, 128.3, 128.1, 127.9, 124.1; IR (KBr): 3439, 3027, 1642, 1215, 759 cm-1; HRMS (ESI) Calcd for $C_{16}H_{11}ClN_2O$ $[M+H]^+$ 283.0638 Found 283.0630.

6-(4-Chlorophenyl)-2-(pyridin-4-yl)pyrimidin-4(3H)-one (5n): green solid; 62% yield; mp □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.17 (s, 1H), 8.67-8.65 (m, 2H), 8.17 (d, *J* = 6.4 Hz, 2H), 8.01 (s, 1H), 7.92-7.90 (m, 2H), 7.37 (d, *J* = 6.6 Hz, 2H), 6.96 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 172.1, 160.0, 150.8, 140.7, 135.8, 135.5, 134.2, 133.1, 129.2, 126.5, 121.2; IR (KBr): 3440, 3018, 1639, 1216, 764, cm^{-1}; HRMS (ESI) Calcd for $C_{15}H_{10}ClN_3O$ $[M+H]^+$ 284.0590 Found 284.0586.

6-(2,4-Dichlorophenyl)-2-(pyridin-4-yl)pyrimidin-4(3H)-one (5o): green solid; 65% yield; m.p. □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 12.56 (s, 1H), 9.10 (d, *J* = 8.7 Hz, 1H), 8.93 (d, *J* = 5.7 Hz, 2H), 8.13 (d, *J* = 5.9 Hz, 2H), 7.86 (d, *J* = 2.1 Hz, 1H), 7.70-7.66 (m, 1H), 7.37 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 172.0, 162.0, 151.1, 142.1, 136.3, 135.9, 135.2, 134.6, 130.8, 129.8, 128.4, 121.6, 119.6; IR (KBr): 3435, 3020, 1639, 1215, 756, cm-1; HRMS (ESI) Calcd for $C_{15}H_9Cl_2N_3O$, $[M+H]^+$ 318.0201 Found 318.0199.

2-(Pyridin-4-yl)-6-p-tolylpyrimidin-4(3H)-one (5p): green solid; 65% yield; m.p. □ 250 ^{0}C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.29 (s, 1H), 8.84 (d, *J* = 5.8Hz, 2H), 8.24 (d, *J* = 8 Hz, 2H), 8.06 (d, *J* = 5.8 Hz, 2H), 7.34(d, *J* = 8 Hz, 2H), 7.12 (s, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.1, 158.0, 148.8, 138.8, 133.8, 133.5, 132.2, 131.2, 127.2, 124.5, 119.3; IR (KBr): 3438, 3018, 1639, 1215, 764, cm-1; HRMS (ESI) Calcd for $C_{16}H_{13}N_3O$ $[M+H]^+$ 264.1137 Found 264.1135.

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Electronic Supporting Information (ESI) Available: Copies of the ^{1}H NMR and ^{13}C NMR spectra for all the compounds. CCDC No: 951425. See DOI: 10.1039/b000000x/

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18 **X-Ray Data Collection and Structure Refinement Details**: A good quality single crystal of size 0.50 x 0.41 x 0.21 mm, was selected under a polarizing microscope and was mounted on a glass fiber for data collection. Single crystal X-ray data for compound **3a** were collected on the Rigaku Kappa 3 circle diffractometer equipped with the AFC12 goniometer and enhanced sensitivity (HG) Saturn724+ CCD detector in the 4x4 bin mode using the monochromated Mo-Kα radiation generated from the microfocus sealed tube MicroMax-003 X-ray generator, equipped with specially designed confocal multilayer optics. Data collection was performed using ω-scans of 0.5^{o} steps at 293(2) K. Cell determination, data collection and data reduction was performed using the Rigaku CrystalClear-SM Expert 2.1 b24[a] software. Structure solution and refinement were performed by using SHELX-97.[b] Refinement of coordinates and anisotropic thermal parameters of non-hydrogen atoms were carried out by the full-matrix least-squares method. The hydrogen atoms attached to carbon atoms were generated with idealized geometries and isotropically refined using a riding model. (*a*) Crystal Clear 2.1, Rigaku Corporation, Tokyo, Japan. (*b*) G. M. Sheldrick, Acta Crystallogr. Sect. A, 2008, **64**, 112–122.

Crystal data of 3a: $C_{16}H_{14}N_2O_3$, M = 282.29, Monoclinc, $P2_1/c$, a = 16.558(5) Å, b = 11.363(4) Å, c = 17.351(4) Å, β = 119.49(2)°, V = 2841.6(15) Å^3, Z = 8, D_c = 1.320 g cm^{-3}, μ (Mo-Kα) = 0.093mm^{-1}, F(000) = 1184, rectangular block, colourless, 21437 reflections measured (R_{int} = 0.0364), 5152 unique, wR_2 = 0.1663 for all data, conventional $R1$ = 0.0479 for 4160 Fo > 4σ(Fo) and 0.0663 for all 5152 data, S = 1.131 for all data and 383 parameters. CCDC (deposit No: 951425) contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U. K; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk.

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Metal-Free Tandem Approach to Structurally Diverse *N*-Heterocycles: Synthesis of 1,2,4-Oxadiazoles and Pyrimidinones

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N-heterocycles, namely 1,2,4-oxadiazoles and 2,6 disubstituted pyrimidin-4-ones have been synthesised in one pot via carboxamidation of amidines with aryl carboxylic acids and aryl propargylic acids under metal-free conditions.