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ARTICLE

Synthesis and Antiproliferative efficiency of novel bis(imidazol-1-yl)vinyl-1,2,4-oxadiazoles

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A new approach for the synthesis of novel bis(imidazol-1-yl) vinyl 1,2,4-oxadiazoles has been developed. The method operates in a single step giving the products in good to excellent yields. Antiproliferative efficiency of the synthesized compounds was tested against HCT116 (Colon cancer) and A549 (Lung cancer) cell lines. Among them, the compounds **3m** (IC_{50}, 9.7 µM) and **3h** (IC_{50}, 20.3 µM) were found to be the best antiproliferative agents.

Introduction

Oxadiazoles are the important class of heterocycles exhibiting wide range of application as drugs in pharmaceuticals.[1,2] Oxadiazoles are important bioisosters for esters and amides and have been reported to have various muscarinic agonists,[3] benzodiazepine receptor partial agonists,[4] dopamine transporters,[5] antirhinovirals,[6] a growth hormone secretagogue,[7] and 5-HT agonists,[8] as well as an urea bioisostere in β3-adrenergic receptor agonists. Among oxadiazoles, 1,2,4-oxadiazole derivatives have gained significant importance in medicinal chemistry, namely prenoxdiazole, oxolamine, proxazole and butalamine (Figure. 1).[9]

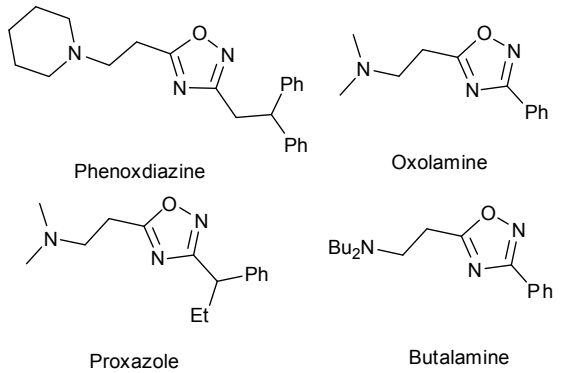

Fig. 1: Bioactive oxadiazoles

1,2,4-Oxadiazoles are most commonly synthesized from amidoximes and carboxylic acid derivatives in two steps. O-Acylation of amidoxime by an activated carboxylic acid followed by cyclodehydration in two steps.[9] Activated carboxylic acid derivative used for the *o*-acylation step includes esters,[10,11] acid chlorides,[12] and anhydrides.[13] The use of carbodiimides such as EDC,[9] and DCC[10] for *in situ* activation of carboxylic acids were reported. The use of PTSA-$ZnCl_2$[14] provides a milder alternative for the synthesis of 3,5,-disubstituted 1,2,4-oxadiazoles from amidoximes and organic nitriles.[15] Microwave assisted organic synthesis of 1,2,4-oxadiazoles involving one-pot three component reaction between organic nitriles, hydroxylamine and aldehydes heating at 150 °C.[16] Synthesis of 1,2,4-oxadiazole was carried out in one-pot palladium mediated coupling of amidoxime with aryl iodides under one atmosphere carbon monoxide.[17] All these approaches generally require long reaction time, and drastic conditions. This prompted us to study the feasibility of synthesizing 1,2,4-oxadiazoles from amidoximes with CDI (*N,N'*-Carbonyldiimidazole).

Results and discussions

In continuation of our efforts in the development of novel synthetic methodologies,[18-25] herein we report a method to access new classes of novel oxadiazoles containing the unprecedented bis(imidazol)vinyl-1,2,4-oxadiazoles. The present protocol involves the synthesis of new class of 1,2,4-oxadiazoles namely, bis(imidazol)vinyl-1,2,4-oxadiazoles for the first time.

Initially, we investigated the reaction involving the condensation of amidoxime with 3,3,3-trifluropropionoic acid in MDC using CDI (1.0 equiv) as an additive at room temperature, which leads to the formation of the intermediate *o*-acyl amidoxime **1a** in 74% yield. The reaction of amidoxime with trifluropropionic acid, in the presence of CDI (1.0 eq) in MDC at reflux condition offers an unexpected product **3a** in 20 % yield (Table 1, entry 2). Encouraged by this initial result, the reaction was screened with

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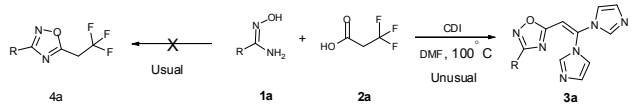
Table 1. Reaction optimization for **3a**



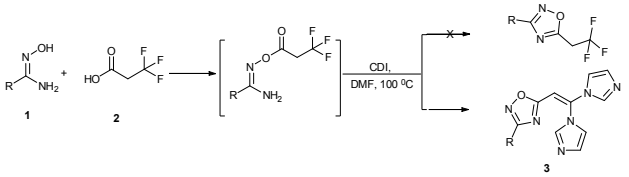
Entry	Solvent	Reagents	Equivalence	T (^{o}C)	Time (hr)	Yield (%)
1	MDC	CDI	1.0	rt	24 h	-
2	MDC	CDI	1.0	Reflux	24 h	20
3	THF	CDI	1.0	Reflux	24 h	26
4	CH3CN	CDI	1.0	Reflux	24 h	36
5	EtOAc	CDI	1.0	Reflux	24 h	-
6	Toluene	CDI	1.0	Reflux	24 h	32
7	DMF	CDI	1.0	Reflux	12h	43
8	DMF	CDI	1.5	Reflux	4 h	60
9	DMF	CDI	2.0	Reflux	4h	70
10	DMF	CDI	2.5	Reflux	4 h	68
11	DMF	CDI	2.0	100 ^{o}C	6 h	76
12	DMF	CDI	2.0	90 ^{o}C	8 h	72
13	DMF	CDI	2.0	80 ^{o}C	12 h	65
14	MDC	DCC	2.0	Reflux	24 h	-
15	MDC	EDC	2.0	Reflux	12 h	-
16	DMF	T3P	2.0	110 ^{o}C	12 h	-

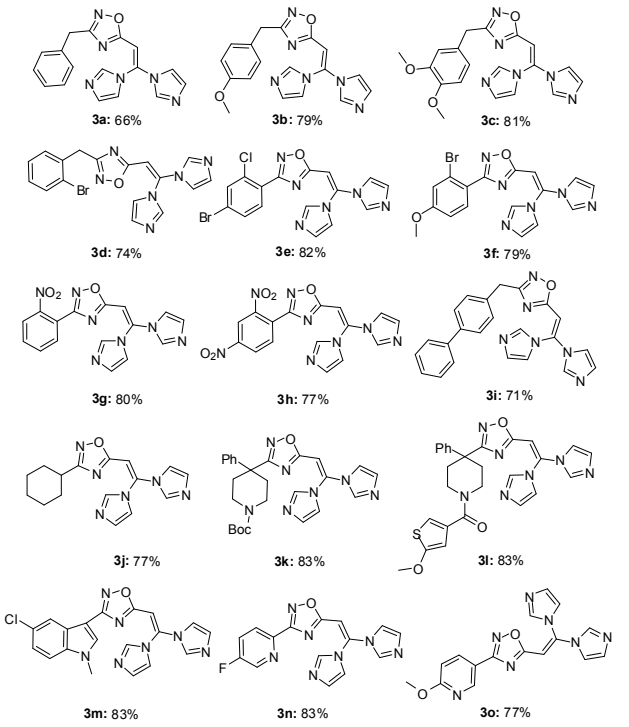
[a]All reaction were carried out using amidoximes (1.0 mmol), acid (1.1 mmol),[b] solvent (5 mL), yield obtained after column chromatography. MDC-Methylene di chloride, CDI-*N,N'*-Carbonyldiimidazole, DCC- *N,N'*-Dicyclohexylcarbodi -imide, T3P- Propylphosphonic anhydride.

various solvents like MDC, THF, CH_3CN, EtOAc, DMF and toluene among which DMF was found to be the best choice (entries, 2-7).The effect of the amount of CDI on the yield of the product was examined. Yield of the product increased with the increase in the loading of CDI (Table 1, entries 7-9), and the best result (76%) was obtained at 2 eq (Table 1, entry 8). However, no significant increase in the yield of product was found on further increase in the loading of CDI beyond 2 equivalents. Later, the effect of temperature on the reaction was also examined and it was found to proceed efficiently at 100 ^{o}C (Table 1, entry 11). Negative effect on the yield of **3a** was observed on lowering the temperature to 90 ^{o}C and 80 ^{o}C (Table 1, entry 12 and 13). Pleasingly, the reaction performed on a large scale underwent smooth conversion to afford the compound **3** in good yield. At last, the effect of the other coupling reagents such as DCC, T3P and EDC at reflux condition was tried and were failed to form bis(imidazol)vinyl-1,2,4-oxadiazoles.

With the optimized reaction conditions in hand, substrate scope of the reaction was successfully established with various electronic demands on amidoximes **1a** and was as shown in scheme 1. Trifluropropionic acid efficiently reacted with various amidoximes bearing electron-donating as well as electron-withdrawing substituent's to afford the corresponding products under the optimized reaction conditions **3(a–o)**. Amidoximes with various

Scheme 1. Synthesis of bis(imidazol-1-yl) vinyl 1,2,4-oxadiazoles





functionalities in phenyl group including –OMe, –$(OMe)_2$ 3(**b-c**) and halogens such as –Br, dihalo **3**(**d-f**) successfully formed the products in good yields. Strong electron-withdrawing group like –(NO_2) in the phenyl ring also successfully produced the product (**3g** and **3h**). Biphenyl amidoxime also reacted well **3i**. The reactivity's of aliphatic amidoximes such as cyclohexyl amidoximes were also evaluated **3j**. Importantly, various substituted heterocyclic amidoximes like

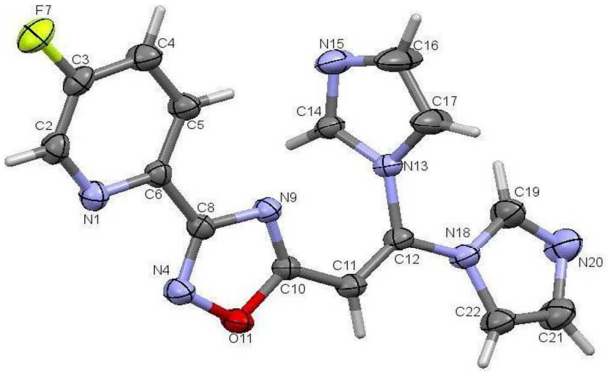
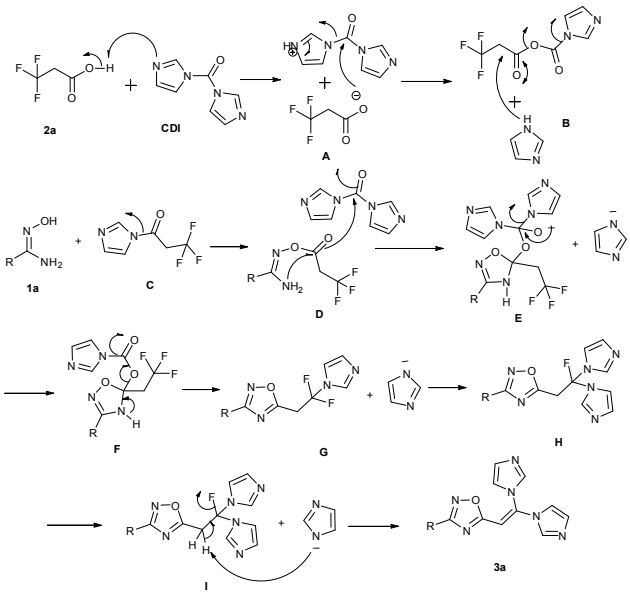


Fig. 2 ORTEP crystal structure of **3n**.



Scheme 2 Probable mechanism for the formation of imidzo bis(imidazol)vinyl-1,2,4-oxadiazoles

piperidine, indole and pyridine also underwent the title reaction under equally mild conditions 3**(k-o)**. The structure of **3n** was also confirmed by single X-ray crystallographyic study (fig. 2).

A plausible reaction mechanism for the CDI catalyzed coupling reaction is presented in Scheme 2. It is assumed that, the reaction starts with abstraction of proton from trifluropropionic acid compound followed by the substitution of protonated CDI by carboxylate anion **A** led to intermediate **B**. The amide hydroxyl group attacks the central carbonyl group of CDI which them undergoes CDI catalyzed intramolecular condensation forming tetrahedral intermediate **E**. The free imidazole group participate in a substitution reaction, which leads to the formation of the desired bis(imidazol)vinyl-1,2,4-oxadiazole **3a**.[26]

Antiproliferative activity on HCT116 and A549 cell lines

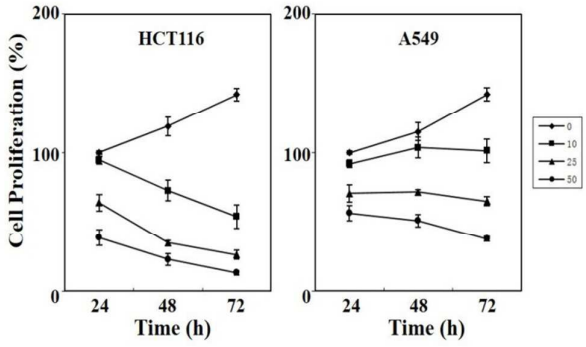


Figure 3. 3m suppresses proliferation of HCT116 and A549 cells in time and dose dependent manner.

The antiproliferative effect of all the newly synthesized **3(a-o)** derivatives was tested against HCT116 cells using MTT assay. Among these, compounds **3m** and **3h** found to be most potent antiproliferative agents with the IC_{50} value of 9.7 µM and 20.3 µM respectively. Further, Compounds **3(a-g), 3(i-l)**, and **3(n-o)** were found to be inactive up to 50 µM and the IC_{50} values of remaining compounds of the series ranges between 36 µM to 50 µM. Later, the effect of compound **3m** against HCT116 and A549 was tested at indicated dose and time points. Compound **3m** exhibited a substantial decrease of viable cells in both the cell lines in time and dose dependent manner (Figure 3). Further, the effect of our lead compound on normal cells (Vero) was carried out. However, compound **3m** did not induce a considerable cytotoxic activity against Vero (Monkey kidney epithelial) cells up to 72 h at 50 µM. Reconfirmation of antiproliferative efficacy of compound **3m** was done using SRB assay and the results displayed the similar cytotoxicity profile. Paclitaxel was used as the positive control for antiproliferative assay and the IC_{50} values against HCT116 and A549 were found to be 0.0051 µM and 0.0045 µM respectively.

Compound 3m interferes with cell cycle in HCT116 cells.

The hallmark event in apoptosis is activation of DNases which degrade genomic DNA into small DNA oligomers thereby leading to the formation of hypo diploid cells.[27] The cells with lesser DNA content are detected as sub-G1 population using propidium iodide staining. We evaluated the effect of compound **3m** on the cell cycle of HCT116 using flow cytometry. The results clearly demonstrated the significant increase in sub-G1 cell population and decline in the G1/G0 cells in the time dependent manner as compared to control cells (Fig. 4).

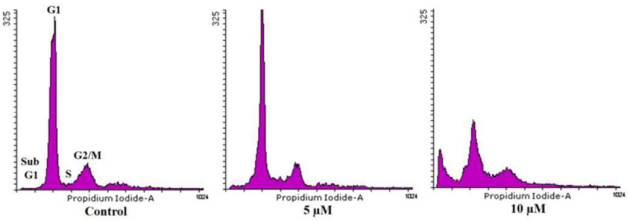


Figure 4. Flow cytrometric analysis indicates that 3m interferes with cell cycle and substantially declines G1 cell population and arrest cell Sub G1 phase.

Conclusion

In conclusion, we have developed an efficient method for synthesis of 1,2,4-oxadiazoles from amidoximes and trifluropropionic acid. Moreover it is to be noted that this heterocyclic system has not been so far reported and the proposed synthetic strategy allows the introduction of vinyl imidazols to oxadiazoles. The protocol involves CDI mediated *o*-acylation of amidoximes followed by cyclodehydration and di-substitution to afford bis(imidazol-1-yl) vinyl 1,2,4-oxadiazoles in one-pot operation with excellent yield. Interestingly, these new class of

1,2,4-oxadiazoles were able to inhibit the cell growth of HCT116 and A549 cell lines effectively. The Compounds **3m** and **3h** were found to be the most potent antiproliferative agents with the IC_{50} value of 9.7 μM and 20.3 μM.

Experimental section

3-benzyl-5-(2,2-di(*1H*-imidazol-1-yl)vinyl)-1,2,4-oxadiazole (3a). White solid; yield: (66%); MP 116-118 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.11−7.37 (m, 11H), 7.41 (d, *J* = 13.6 Hz, 1H), 7.84 (s, 1H), 8.04 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.6, 97.0, 118.7, 120.4, 127.3, 127.4, 128.0,128.5, 128.9, 129.0, 129.3, 130.4, 131.3, 135.8, 135.9, 136.6, 137.3, 139.3, 169.8, 171.9; HRMS-(ESI-TOF): m/z calcd for $C_{17}H_{14}N_6O$ $[M + H]^+$ 319.3327. Found: 319.3362

5-(2,2-di(*1H*-imidazol-1-yl)vinyl)-3-(4-methoxybenzyl)-1,2,4-oxadiazole (3b). White solid; yield: (79%); MP 154−156 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.72 (s, 3H), 3.94 (s, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 7.14−7.19 (m, 4H), 7.26 (s, 1H), 7.40 (s, 1H), 7.44 (s, 1H), 7.86 (s, 1H), 8.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.7, 55.5, 97.1, 114.3, 118.7, 120.4, 127.8, 130.4, 131.3, 136.6, 137.3, 139.3, 158.6, 170.1, 171.8; HRMS-(ESI-TOF): m/z calcd for $C_{18}H_{16}N_6O_2$ $[M + H]^+$ 349.3586. Found: 349.3571

5-(2,2-di(*1H*-imidazol-1-yl)vinyl)-3-(3,4-dimethoxybenzyl)-1,2,4-oxadiazole (3c). White solid; yield: (81%); MP 142−144 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.73 (d, *J* = 6.8 Hz, 6H), 3.93 (s, 2H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 17.6 Hz, 2H), 7.27 (s, 1H), 7.45 (d, *J* = 16.8 Hz, 2H), 7.87 (s, 1H), 8.10 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.1, 56.0, 97.1, 112.3, 113.2, 118.7, 120.4, 121.4, 128.2, 130.3, 131.2, 128.2, 130.3, 131.2, 136.5, 137.3, 139.4, 148.2, 149.1, 170.0, 171.8; HRMS-(ESI-TOF): m/z calcd for $C_{19}H_{18}N_6O_2$ $[M + H]^+$ 379.3846. Found: 379.3816

3-(2-bromobenzyl)-5-(2,2-di(*1H*-imidazol-1-yl)vinyl)-1,2,4-oxadiazole (3d). White solid; yield: (74%): MP 156−158 °C;^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.13 (s, 1H), 6.97–7.01 (m, 2H), 7.07−7.11 (m, 1H), 7.17–7.23 (m, 4H), 7.53 (d, *J*= 8.4Hz, 1H), 7.60 (s, 1H), 7.70 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 32.5, 95.8, 117.7, 119.0, 124.5, 127.6, 128.9, 131.1, 132.1, 132.9, 134.6, 136.1, 136.3, 138.1, 169.0, 170.6; HRMS-(ESI-TOF): m/z calcd for $C_{17}H_{13}BrN_6O$ $[M + H]^+$ 398.2287. Found: 398.2227

3-(4-bromo-2-chlorophenyl)-5-(2,2-di(*1H*-imidazol-1-yl)vinyl)-1,2,4-oxadiazole (3e). White solid; yield: (82%); MP 140−142 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.18 (d, *J* = 14.0 Hz, 2H), 7.38 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.66−7.73 (m, 2H), 7.89−7.93 (m, 2H), 8.11 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 96.40, 96.43, 118.81, 118.84, 120.3, 120.4, 124.8, 125.6, 130.5, 131.3, 131.4, 133.2, 133.67, 133.69, 133.71, 137.2, 137.4, 139.4, 166.4, 172.0; HRMS-(ESI-TOF): m/z calcd for $C_{16}H_{10}BrClN_6O$ $[M + H]^+$ 418.6472. Found: 418.6408

3-(2-bromo-4-methoxyphenyl)-5-(2,2-di(*1H*-imidazol-1-yl)vinyl)-1,2,4-oxadiazole (3f). White solid; yield: (79%); MP 147-149 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.84 (s, 3H), 7.14 (s, 1H), 7.18−7.20 (m, 1H), 7.23 (s, 1H), 7.33 (s, 1H), 7.44 (s, 1H), 7.49 (s, 1H), 7.69 (d, *J* = 1.6 Hz, 1H), 7.86−7.89 (m, 1H), 7.95 (s, 1H), 8.12 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 56.1, 96.5, 96.6, 111.6, 117.2, 118.7, 118.8, 119.2, 120.4, 128.3, 130.4, 131.4, 135.5, 137.2, 137.3, 139.4, 158.9, 167.6, 171.8; HRMS-(ESI-TOF): m/z calcd for $C_{17}H_{13}BrN_6O_2$ $[M + H]^+$ 414.2281. Found: 414.2261

5-(2,2-di(*1H*-imidazol-1-yl)vinyl)-3-(2-nitrophenyl)-1,2,4-oxadiazole (3g). Pale yellow solid; yield: (80%); MP 130−132 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.16 (d, *J* = 8.8 Hz, 2H), 7.37 (s, 1H), 7.43−7.46 (m, 2H), 7.80−7.88 (m, 4H), 8.06−8.08 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 96.3, 118.8, 120.1, 120.45, 120.48, 125.0, 126.1, 130.4, 131.4, 131.49, 133.2, 133.9, 137.4, 139.2, 148.9, 165.9, 172.5; HRMS-(ESI-TOF): m/z calcd for $C_{16}H_{11}N_7O_3$ $[M + H]^+$ 350.3036. Found: 350.3022

5-(2,2-di(*1H*-imidazol-1-yl)vinyl)-3-(2,4-dinitrophenyl)-1,2,4-oxadiazole (3h). Yellow solid; yield: (77%); MP 160-162 °C;^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.14 (d, J= 7.2 Hz, 1H), 7.41−7.43 (m, 2H), 7.85–7.93 (m, 2H), 8.00 (s, 1H), 8.11–8.16 (m, 1H), 8.37 (s, 1H), 8.39 (d, *J* = 8.0 Hz, 1H) 8.54 (d, *J*= 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 96.40, 96.43, 118.81, 118.84, 120.38, 120.4, 124.8, 125.6, 130.5, 131.3, 131.4, 133.2, 133.67, 133.69, 133.7, 137.2, 137.41, 137.44, 139.4, 166.4, 172.0; HRMS-(ESI-TOF): m/z calcd for $C_{16}H_{10}N_8O_5$ $[M + H]^+$ 395.3012. Found: 395.3011

3- ([1, 1-biphenyl]-4-ylmethyl)-5-(2,2-di(*1H*-imidazol-1-yl)vinyl)-1,2,4-oxadiazole (3i). White solid; yield: (71%); MP 110−112 °C;^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.04 (s, 2H), 6.65 (s, 1H), 7.03 (d, *J* = 12.0 Hz, 2H), 7.21 (s, 1H), 7.28 (d, *J* = 12.8 Hz, 1H), 7.32−7.34 (m, 3H), 7.41−7.43 (m, 2H), 7.52−7.56 (m, 4H), 7.63 (s, 1H), 7.77 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.8, 95.9, 96.0, 117.8, 119.1, 127.0, 127.3, 127.4, 128.7, 129.4, 131.1, 132.1, 133.9, 136.0, 136.3, 140.2, 140.6, 169.9, 170.5; HRMS-(ESI-TOF): m/z calcd for $C_{23}H_{18}N_6O$ $[M + H]^+$ 395.4286. Found: 395.4232

3-(cyclohexyl)-5-(2,2-di(*1H*-imidazol-1-yl)vinyl)-1,2,4-oxadiazole (3j). Grey solid; yield: (77%); MP 138−140 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.23−1.31 (m, 2H), 1.39−1.48 (m, 2H), 1.66−1.69 (m, 2H), 1.75−1.79 (m, 2H), 1.90−1.93 (m, 2H), 2.66−2.73 (m, 1H), 6.58 (s, 1H), 7.02 (s, 1H), 7.05 (s, 1H), 7.21 (s, 1H), 7.27 (s, 1H), 7.67 (s, 1H), 7.79 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.4, 25.5, 27.8, 29.3, 30.2, 35.4, 96.3, 117.8, 119.0, 130.8, 131.8, 135.6, 136.3, 138.3, 162.4, 169.9, 174.4; HRMS-(ESI-TOF): m/z calcd for $C_{17}H_{20}N_6O$ $[M + H]^+$ 311.3535. Found: 311.3561

***Tert*-butyl 4-(5-(2,2-di(*1H*-imidazol-1-yl)vinyl)-1,2,4-oxadiazol-3-yl)-4-phenylpiperidine-1-carboxylate (3k).** White solid; yield: (83%); MP 158-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.38 (s, 9H), 1.98−1.91 (s, 2H) 2.43−2.39 (m, 2H), 3.04−2.90 (m, 2H), 3.79−3.76 (m, 2H), 7.12 (s, 1H), 7.21 (s, 1H), 7.41−7.24 (m, 6H), 7.89 (s, 1H), 8.06 (s,

1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0, 33.7, 41.7, 78.7, 96.3, 118.3, 119.8, 125.9, 126.9, 186.6, 129.9, 130.8, 136.3, 136.9, 138.9, 143.6, 153.9, 171.7, 172.9, ; HRMS-(ESI-TOF): m/z calcd for $C_{26}H_{29}N_7O_3$ $[M + H]^+$ 488.5536. Found: 488.5578

(4-(5-(2,2-di(*1H*-imidazol-1-yl)vinyl)-1,2,4-oxadiazol-3-yl)-4-phenylpiperidin-1-yl)(5-methoxythiophen-3-yl)methanone (3l). Pale brown solid; yield: (83%); MP 116–118 °C;^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01 (t, *J*= 10.5 Hz, 1H), 2.18 (d, *J*= 13.0 Hz, 1H), 2.48 (d, *J*= 13.0 Hz, 1H), 2.59 (d, *J* = 13.0 Hz, 1H), 3.00 (t, *J* = 12.0 Hz, 1H), 3.10 (t, *J* = 12.0 Hz, 1H), 3.52 (d, *J* = 10.8 Hz, 1H), 3.73 (s, 3H), 4.34 (d, *J* = 12.5 Hz, 1H), 6.18 (s, 1H), 6.49 (s, 1H), 6.89 (s, 1H), 6.98 (s, 1H), 7.14–7.27 (m, 6H), 7.56 (s, 1H), 7.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 33.7, 34.9, 39.1, 42.5, 44.4, 57.9, 96.1, 97.6, 117.9, 119.2, 125.4, 126.2, 127.5, 128.7, 129.0, 131.3, 132.5, 136.5, 138.4, 142.9, 155.2, 164.3, 170.9, 174.1; HRMS-(ESI-TOF): m/z calcd for $C_{23}H_{18}N_6O$ $[M + H]^+$ 528.5975. Found: 528.5960

3-(6-chloro-1-methyl-*1H*-indol-3-yl)-5-(2,2-di(*1H*-imidazol-1-yl)vinyl)-1,2,4-oxadiazole (3m). Pale brown solid; yield: (83%); MP 218-220 °C;^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.71 (s, 3H), 7.01, 7.00 (dd, *J* = 12, 5.6 Hz, 1H), 7.12 (d, *J* = 14.0 Hz, 2H), 7.16 (d, *J* = 3.2 Hz, 1H), 7.34 (s, 1H), 7.39–7.40 (m, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.83 (s, 1H), 8.04 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 33.5, 97.1, 101.5, 111.22, 111.25, 118.750, 118.759, 120.51, 120.56, 121.7, 122.5, 123.8, 127.9, 130.4, 131.3, 133.2, 133.23, 136.6, 137.31, 137.35, 138.0, 164.9, 171.0; HRMS-(ESI-TOF): m/z calcd for $C_{19}H_{14}ClN_7O$ $[M + H]^+$ 392.8138. Found: 392.8141

5-(2,2-di(*1H*-imidazol-1-yl)vinyl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (3n). Pale brown solid; yield: (83%): MP 202–204 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.20 (d, *J* = 10.8 Hz, 2H), 7.36 (s, 1H), 7.44–7.47 (m. 2H), 7.90–7.91 (m. 3H), 8.12 (s, 1H), 8.73 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 96.6, 118.8, 120.4, 124.9, 125.1, 130.5, 131.3, 137.4, 139.5, 142.4, 159.2, 161.8, 167.3, 172.7; HRMS-(ESI-TOF): m/z calcd for $C_{15}H_{10}FN_7O$ $[M + H]^+$ 324.2846. Found: 324.2895

5-(2,2-di(*1H*-imidazol-1-yl)vinyl)-3-(6-methoxypyridin-3-yl)1,2,4-oxadiazole (3o). White solid; yield: (77%): MP 212-214 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.92 (s, 3H), 6.65 (s, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 14.4 Hz, 2H), 7.19 (s, 1H), 7.28 (s, 1H), 7.76 (s, 1H), 7.08 (d, *J* = 14.4 Hz, 2H), 7.19 (s,1H), 7.28 (s, 1H), 7.67 (s, 1H), 7.80 (s, 1H), 8.02, 8.02 (dd, *J* = 10.8, 6.8 Hz, 1H), 8.68 (d, *J* = 2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 111.2, 115.6, 117.7, 119.0, 125.4, 131.1, 132.1, 136.3, 136.4, 137.0, 138.3, 146.9 151.9, 165.9, 166.8, 170.6; HRMS-(ESI-TOF): m/z calcd for $C_{16}H_{13}N_7O_2$ $[M + H]^+$ 336.3201. Found: 336.3252

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Graphical abstract

Synthesis and Antiproliferative efficiency of novel bis(imidazol-1-yl)vinyl-1,2,4-oxadiazoles

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A new class of bis(imidazol)vinyl-1,2,4-oxadiazoles were synthesised and their anti proliferative efficiency was tested against HCT116 and A549 cancer cell lines.