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Short communication

Synthesis of novel 1,2,4-oxadiazoles and analogues as potential anticancer agents

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ABSTRACT

A library of 3,5-disubstituted-1,2,4-oxadiazoles **7**–**9** and their bioisosters, 1,3,4-oxadiazole **14** and 1,3,4-thiadiazole **16**, were synthesized and evaluated *in vitro* for their anticancer potential against a panel of six human cancer cell lines. The key step in the synthesis of oxadiazoles **7**–**9** involve coupling of amidoxime **6** with an appropriate carboxylic acid followed by thermal cyclization. The bioisosteres, 1,3,4-oxadiazole **14** and 1,3,4-thiadiazole **16** were prepared from the reaction of a common precursor diacylhydrazine **13** with thionyl chloride and Lawesson's reagent, respectively. The anticancer studies on the synthesized compounds revealed that presence of a cyclopentyloxy or *n*-butyloxy on the C-3 aryl ring and piperdin-4-yl or trichloromethyl at the C-5 position of 1,2,4-oxadiazole is essential for good activity. In particular, 1,2,4-oxadiazole **7i** and analogue 1,3,4-thiadiazole **16** exhibited significant activity against DU145 (IC_{50}: 9.3 μM) and MDA-MB-231 (IC_{50}: 9.2 μM) cell lines, respectively.

1. Introduction

The oxadiazole is a five-membered nitrogen and oxygen containing heterocycle which has been commonly used as a privileged scaffold to produce various novel therapeutic molecules [1]. In particular, the 1,2,4-oxadiazoles mimic a hydrolysis-resistant ester or amide bioisostere and are significant in the design of novel therapeutics for a wide range of diseases [2–5]. Proxazole **1** (Fig. 1), a 1,2,4-oxadiazole derivative, is currently marketed as an analgesic, antiinflammatory, antitussive, antispasmodic and muscle relaxant drug [6]. 1,2,4-Oxadiazoles are earlier reported for selective inhibition of receptors such as 5-hydroxytry-ptamine1B/D(5-HT1B/D) [7, 8], 5-HT4 [9], muscarinic [10,11], histamine-H_3 [12], and benzodiazepines [13,14]. They also exhibit antiinflammatory [15] and anti-tumor [16–20] properties.

Cancer is a major cause of death around the world. WHO projected twelve million deaths by cancer with existing therapeutics by 2030. Out of the twenty seven types of characterized cancers, only lung, stomach, liver, colon and breast cancers are mainly implicated in cancer mortality. Taking into consideration the existing cancer therapies, chemotherapy has turned out to be one of the most significant treatments in cancer management [21]. The natural product based drugs, Paclitaxel and Docetaxel, are extensively used in the treatment of wide variety of cancers because of their efficacy [22]. However, they suffer from hematopoietic and neurologic toxicities [21]. The 16-membered cyclic macrolides, Epothilones, are a ray of hope for cancer patients with multidrug resistance because of their positive results in various clinical trials [23]. Microtubule-targeting combretastatin analogues are also of prime importance due to their simple structural features and efficacy in initial clinical studies [24]. In general, dose limiting side effects, toxicity to normal tissues of the body and drug resistance are the major challenges in development of novel small molecule chemotherapeutics. In the light of existing problems in cancer therapy, discovery of novel, efficient, safe and selective anticancer agents is a thrust area for medicinal chemists.

The 3,5-disubstituted-1,2,4-oxadiazoles are reported in literature for their anticancer potential [16–20]. Zhang et al. have investigated the anticancer and apoptosis inducing potential of a series of 3,5-diaryl-1,2,4-oxadiazoles [17]. The studies revealed that compound **2** was selectively potent against breast and colorectal cancer cell lines by arresting cell cycle in G_1 phase followed by inducing apoptosis. Their further explorations to ameliorate the activity led to the preparation of 5-furyl-1,2,4-oxadiazoles, out of which, the 1,2,4-oxadiazole **3** exhibited good in vivo efficacy in animal studies [19]. Recently, we have reported the synthesis and anticancer activity of 3,5-disubstituted-1,2,4-oxadiazoles, and our studies resulted in a potent and selective 1,2,4-oxadiazole **4** [20]. In our quest to develop potent and selective anticancer compounds, we explored this template for further studies. Herein, we report the synthesis of novel 3,5-disubstituted-1,2,4-oxadiazoles and their anticancer activity against various cancer cell lines.

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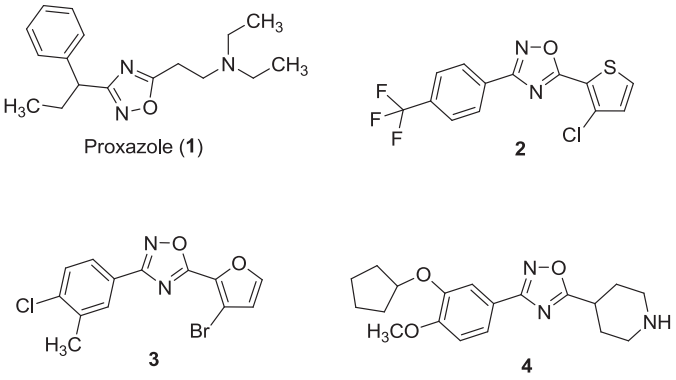


Fig. 1. Structures of some potent anticancer 1,2,4-oxadiazoles **1**–**4**.

2. Results and discussion

2.1. Chemistry

The synthesis of the target 1,2,4-oxadiazoles **7** was achieved starting from substituted benzonitriles **5** through the preparation of intermediate benzamidoximes **6** (Scheme 1). The benzonitriles **5** when reacted with hydroxylamine in ethanol under refluxing condition resulted in the formation of benzamidoximes **6** in good yields (73-85%). The reaction of **6** with carboxylic acids in presence of DCC produced *in situ O*-acylamidoximes, which upon thermal cyclization afforded 3,5-disubstituted 1,2,4-oxadiazoles **7a**–**n** in moderate yields (23–47%).

The *t*-Boc deprotection of 1,2,4-oxadiazole **7c**–**g** was carried out in presence of trifluoroacetic acid affording **8a**–**e** in very good yields (78–87%) (Scheme 2). Further, the synthesis of compounds **9a** and **9b** was achieved from the reaction of 4 (analogue of compounds **8**) with ethyl chloroformate and methanesulfonyl-chloride in presence of triethylamine respectively (Scheme 3).

The preparations of 1,2,4-oxadiazole **4**, 1,3,4-oxadiazole **14** and 1,3,4-thiadiazole **16** are illustrated in Scheme 4. The *N*-protection of methyl piperidine-4-carboxylate **10** afforded compound **11**, which was further reacted with hydrazine hydrate to yield *t*-butyl-4-(hydrazinecarbonyl)piperidine-1-carboxylate (**12**) [25]. Treatment of compound **12** with 3-cyclopentyloxy-4-methoxybenzoyl chloride in presence of triethylamine resulted in diacylhydrazine **13**, which is a common precursor for compounds **14** and **16**. The diacylhydrazine **13** when reacted with thionyl chloride undergoes intramolecular cyclization and *t*-Boc deprotection to afford 1,3,4-oxadiazole **14** in 27% yield [26]. The formation of thiadiazole **16** was accomplished by the reaction of **13** with Lawesson's reagent [27] followed by deprotection in presence of trifluoroacetic acid.

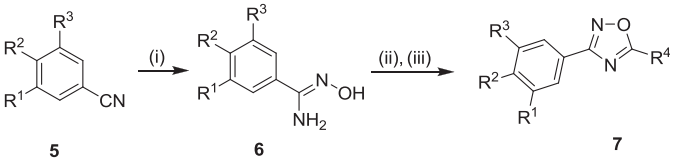
3. Anticancer activity

The synthesized library of 23 compounds was evaluated *in vitro* for their anticancer potential against a panel of six human cancer cell lines: prostate (PC3, DU145 and LnCaP), breast (MCF7 and MDA-MB-231), and pancreas (PaCa2). The screening results showed that all compounds decreased cell viability in colorimetric MTT assay with IC_{50} values ranging from 9 μM to greater than 1 mM (Tables 1 and 2).

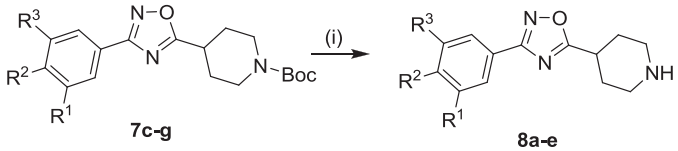
Incited by our initial result [20], we chose alkoxyaryl as the C-3 substituent of 1,2,4-oxadiazole. Compounds **7a** and **7b** with bulky cylcopentyloxy-4-methoxyphenyl at C-3 and lipophilic cycloalkyl at C-5 exhibited moderate anticancer activity against all cancer cell lines but were relatively more cytotoxic towards MCF7. Replacement of cyclohexyl group of **7a** with *N*-Boc-piperidin-4-yl at C-5 resulted in compound **7h**, which was found to be more cytotoxic towards MDA-MB-231 and PaCa2 with IC_{50} values of 38.3 μM and 23.3 μM, respectively. Replacement of *t*-Boc group on C-5 piperidine nitrogen of **7h** with carbethoxy and methylsulfonyl groups afforded **9a** and **9b**, respectively. With respect to **7h**, compound **9a** exhibited improved activity against DU145 (29.3 μM) and MCF7 (27 μM), while maintaining similar activity for MDA-MB-231 and PaCa2, whereas compound **9b** plunged the activity against all screened cell lines.

In order to evaluate the role of cyclopentyl group in **7h**, it was replaced with straight chain alkanes. This resulted in the preparation of compounds, **7c**, **7d** and **7e** with methoxy, ethoxy and *n*-butoxy substituents, respectively. Compound **7c** exhibited good activity towards PaCa2 with IC_{50} 32.5 μM and **7d** was selective towards prostate cell line PC3 (IC_{50}: 41 μM). The compound **7e** was moderately active against all assayed cell lines. The effect of *N*-deprotection of compounds **7c**, **7d** and **7e** on the activity was evaluated by the preparation of compounds **8a**, **8b** and **8c**. The *N*-deprotection in compound **8a** improved potency and selectivity towards LnCaP (38.8 μM) and MCF7 (27 μM). The *N*-deprotected compound 8c exhibited several fold improved activity against all cell lines when compared to *N*-protected compound **7e**, whereas **8b** looses activity upon deprotection. Interchanging the two alkoxy groups on C-3 aryl ring of **7h** resulted in its regioisomer **7f**, which exhibited identical activity against MDA-MB-231and PaCa2 but improved potency against breast cancer cell line MCF7 (IC_{50}: 38 μM) relative to the **7h**. Deprotection of piperidinyl *NH* of **7f** resulted in **8d**, which showed promising activity against all cell lines screened (IC_{50}: 11–42 μM). It is worth to note that piperidinyl **8d** demonstrated twenty six fold higher activity against PC3 (IC_{50}: 11.7 μM) when compared to parent **7f** (IC_{50}: 315.3 μM). In general, the 1,2,4-oxadiazoles with unsubstituted piperidinyl moiety exhibit better activity when compared with *N*-substituted piperidinyl substituent at C-5 position. In our curiosity to evaluate the effect of lipophilic halogens at C-5 position of 1,2,4-oxadiazole, we prepared trichloromethyl derivative **7i** which was found to be one of the most promising compounds in the series with very good activity against all cancer lines, especially DUP145 with IC_{50} 9.2 μM. Introduction of a chlorine atom in the 1,2,4-oxadiazole nucleus is also reported to be beneficial for the cytotoxicity [17].

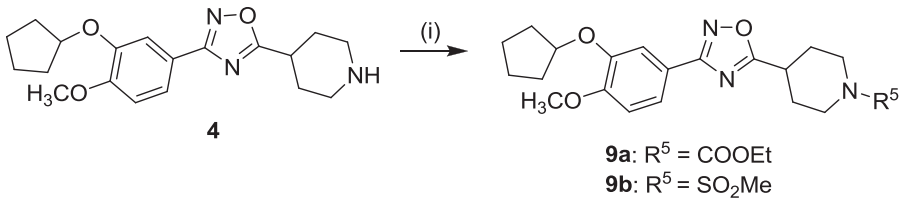
Having studied the importance of alkoxy groups on the C-3 aryl ring, we have prepared compound **7g** with additional methoxy group on C-3 aryl. Incorporation of this additional methoxy group in **7g** led to significant improvement in activity against all cancer



Scheme 1. Synthesis of oxadiazoles **7**: Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, Na_2CO_3, aqueous ethanol, reflux, 5 h; (ii) R^4COOH, DCC, DMF, 0–30 °C 3 h; (iii) heating 110 °C.



Scheme 2. Synthesis of oxadiazoles **8**: Reagents and conditions: (i) TFA, DCM, 25 °C, 3 h.



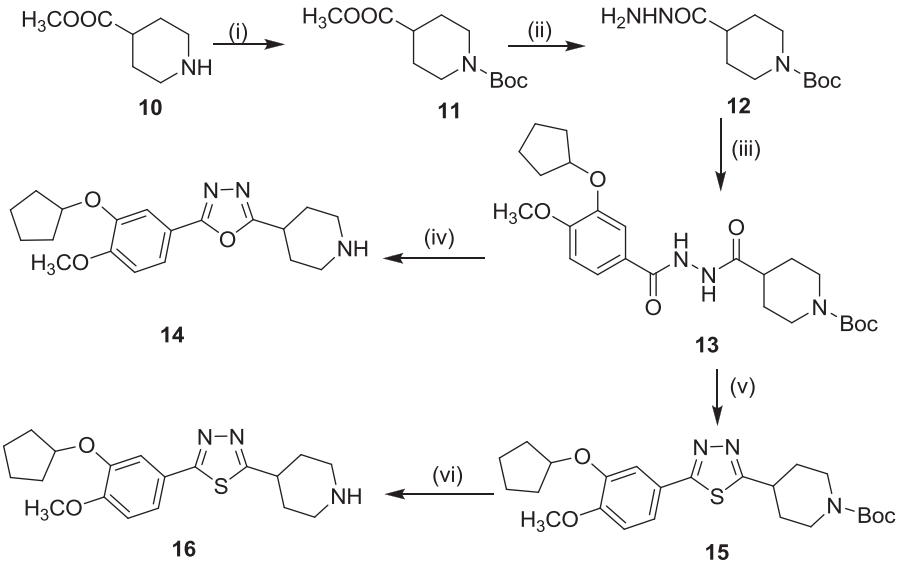
Scheme 3. Synthesis of oxadiazoles **9**: Reagents and conditions: (i) ethyl chloroformate or methanesulfonyl chloride, triethylamine, DCM, 0–25 °C, 8 h.

cell lines with noteworthy 10 fold improvement against MDA-MB-231 when compared with 3,4-dimethoxyphenyl at C-3 in **7c**. The compound **7g** exhibited three fold selectivity against MDA-MB-231 (IC_{50}: 13.6 μM), whereas **8e** with free *NH* and analogue of **7g**, exhibited a sharp drop in activity.

With reported importance of polyalkoxyaryl in discovery of anticancer agents [24], we prepared 3,5-diaryl 1,2,4-oxadiazoles **7j**–**n**. Compound **7j** with 4-methoxyphenyl at C-5 exhibited more than five fold selectivity towards MDA-MB-231, whereas other diaryl analogues **7k**–**n** exhibited poor activity. This finding reveals that flexible lipophilic piperidinyl moiety is critical for anticancer activity, whereas planar aryl substituents bearing polyalkoxy groups at C-3 are detrimental for activity. In order to investigate the role of central heterocycle 1,2,4-oxadiazole in **4**, two bioisosteres 1,3,4-oxadiazole **14** and 1,3,4-thiadiazole **16** were prepared. The compound **16** was found to be the most potent in the whole library displaying very good activity against all cell lines (IC_{50}: 9.2–19.6 μM). The 1,3,4-oxadiazole **14** showed more than three fold selectivity towards MDA-MB-231 (IC_{50}: 38.3 μM) when compared to other cell lines. The above findings unveil the scope for further development of this scaffold and to identify the molecular targets responsible for the observed activity of this new series of 3,5-disubstituted-1,2,4-oxadiazoles.

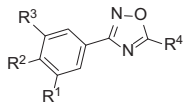
Multiple studies have identified that 3,5-disubstituted-1,2,4-oxadiazoles act as apoptosis-inducing agents, which inhibit cell growth selectively in tumor cells [17,19,28]. However, the exact molecular mechanism remains unclear. Tail-interacting protein 47 (Tip47) is the only molecular target discovered so far, which upon binding 3,5-disubstituted-1,2,4-oxadiazoles down regulates the levels of cyclin D1 causing apoptosis in T47D cells (human ductal breast epithelial tumor cell line) [17,28]. Tip47 is overexpressed in many tumors, and has been shown to protect mitochondrial membrane integrity, oxidative stress and taxol-induced cell death [29,30]. These studies suggest that Tip47 is a critical player in 3,5-disubstituted-1,2,4-oxadiazoles mediated apoptotic signaling pathway, however, it is likely that these compounds have additional molecular targets in cancer cells, which would explain their potency and selectivity towards certain cancer cells. Our future studies will be directed towards identification of these targets.

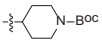
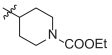
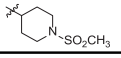
In summary, the SAR study shows that the 3,5-disubstituted 1,2,4-oxadiazoles, and their analogues decreased cell viability in various cancer cell lines with the overall IC_{50} values ranging from 9 μM to >1 mM. The compounds **7i**, **8c**, **8d** and **16** exhibited promising activity against all cancer cell lines. In particular, the 1,3,4-thiadiazole **16** emerged as the compound of primary interest with IC_{50} 9.2 μM against breast cancer cell line MDA-MB-231. The moderately active compound **7j** exhibited five-fold selectivity towards MDA-MB-231. The improved activity of compounds bearing lipophilic groups such as piperidinyl and trichloromethyl at the C-5 position of 1,2,4-oxadiazole may be due to their hydrogen bonding possibility with the biological targets. The presence of polyalkoxyaryl substituent is beneficial at C-3 position and detrimental at C-5 position of 1,2,4-oxadiazole. The bulky lipophilic cyclopentyloxy substituent at C-3 aryl ring is good for the cytotoxicity as well as selectivity of 1,2,4-oxadiazoles against various cancer cell lines. Further, studies on biological targets of oxadiazoles and related scaffolds are in progress.



Scheme 4. Synthesis of oxadiazole **14** and thiadiazole **16**: Reagents and conditions: (i) $(Boc)_2O$, $NaHCO_3$,THF, H_2O; (ii) NH_2NH_2, CH_3OH, reflux; (iii) 3-cyclopentyloxy-4-methoxybenzoyl chloride, Et_3N, DCM; (iv) $SOCl_2$, benzene, reflux; (v) Lawesson's reagent, xylene, reflux; (vi) TFA, DCM.

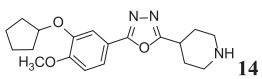
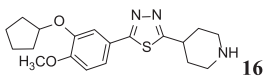
Table 1
In vitro cytotoxicity profile of oxadiazoles (**7**–**9**) against selected human cancer cell lines, IC_{50} (μM).[a]



Compound	R^1	R^2	R^3	R^4	PC3	DU145	LnCaP	MCF7	MDA-MB-231	PaCa2
7a	OC_5H_9	OCH_3	H		80.3	107.7	92.6	57.3	137.7	64.5
7b	OC_5H_9	OCH_3	H		194.3	105.7	137.5	62.3	87.5	99.2
7c	OCH_3	OCH_3	H		108.2	158.1	85.6	52.2	129	**32.5**
7d	OC_2H_5	OCH_3	H		**41**	155.6	96.1	93.8	116.1	91.1
7e	OC_4H_9	OCH_3	H		130	101.7	91	91	88	105.4
7f	OCH_3	OC_5H_9	H		315.3	98.6	106.5	**38**	**41**	**21.5**
7g	OCH_3	OCH_3	OCH_3		56.9	**48.4**	**48.2**	**43.6**	**13.6**	105.8
7h	OC_5H_9	OCH_3	H		107.6	120	121.8	60.27	**38.3**	**23.3**
7i	OC_5H_9	OCH_3	H	CCl_3	**15**	**9.3**	**17.8**	**47.4**	**16.1**	**14.5**
7j	OC_5H_9	OCH_3	H	4-$(OCH_3)C_6H_4$	408.4	414.1	843.1	>1000	77.7	420.4
7k	OC_5H_9	OCH_3	H	3,4-$(OCH_3)_2C_6H_3$	171.1	421.7	815.7	>1000	236.1	403.6
7l	OCH_3	OCH_3	OCH_3	4-$(OCH_3)C_6H_4$	213.8	100.1	327.2	>1000	768.1	**43.5**
7m	OCH_3	OCH_3	OCH_3	3,4-$(OCH_3)_2C_6H_3$	>1000	>1000	>1000	>1000	475.4	>1000
7n	OCH_3	OCH_3	OCH_3	3,4,5-$(OCH_3)_3C_6H_2$	698.2	575.9	406.8	>1000	261	>1000
8a	OCH_3	OCH_3	H		315.4	108.2	**38.8**	**27**	122.5	147
8b	OC_2H_5	OCH_3	H		165.5	167.4	154.3	173.2	183.7	112.5
8c	OC_4H_9	OCH_3	H		**35.8**	**17.04**	**32.5**	**15.7**	**23.8**	**18.5**
8d	OCH_3	OC_5H_9	H		**11.7**	**30**	**42.2**	**29**	**28.5**	**13**
8e	OCH_3	OCH_3	OCH_3		175.6	112.4	120.4	324.4	123.4	80.1
9a	OC_5H_9	OCH_3	H		80	**29.3**	58.7	**27**	**36.8**	**24**
9b	OC_5H_9	OCH_3	H		159	134.4	148.8	112.8	109	144.5

Bold values show IC_{50} less than 50 μM. OC_5H_9 = Cyclopentyloxy.
[a] Means of three independent determinations.

Table 2
In vitro cytotoxicity profiles of oxadiazole **14** and thiadiazole **16** against selected human cancer cell lines, IC_{50}(μM).[a]

Compound	PC3	DU145	LnCaP	MCF7	MDA-MB-231	PaCa2
 **14**	>1000	146.5	307.8	128.9	**38.3**	331.3
 **16**	**12.9**	**19.6**	**19.2**	**17.6**	**9.2**	**10.2**

Bold values show IC_{50} less than 40 μM.
[a] Means of three independent determinations.

4. Experimental

4.1. General

All the laboratory grade reagents were obtained commercially. Melting points were determined on EZ-Melt (Stanford Research Systems, USA) automated melting point apparatus and are uncorrected. The commercially unavailable arylnitriles **5** were prepared according to the literature procedures [31,32]. All the reactions were monitored by thin layer chromatography, which was performed on Merck pre-coated plates (silica gel 60 F254, 0.25 mm) and visualized by fluorescence quenching under UV light (254 nm). Column chromatography was performed using 200–400 mesh silica gel and a mixture of hexane and ethyl acetate for elution. ^{1}H NMR spectra were recorded on Bruker Avance II (400 MHz) and Bruker (200 MHz) NMR spectrometers. Mass spectra were obtained on a Hewlett-Packard HP GS/MS 5890/5972 mass spectrometer.

4.1.1. Synthesis of amidoximes **6**

To a mixture of appropriate benzonitrile **5** (10 mmol) and hydroxylamine hydrochloride (20 mmol) in ethanol (50 mL) was added dropwise an aqueous solution of sodium carbonate (20 mmol, 10 mL) while maintaining the temperature at 0 °C. The resulting mixture was allowed to reflux with stirring for 18 h. Ethanol was distilled off under reduced pressure and the remaining crude product was taken into water (50 mL). The pH (~2) of the solution was adjusted with 1 N HCl and the aqueous phase was washed with ethyl acetate (2 × 25 mL). On cooling (0 °C) and neutralization with sodium carbonate produced a white precipitate which was filtered, washed and air dried at 60 °C to afford pure amidoxime **6**.

4.1.2. General procedure for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles **7a–n**

A solution of appropriate carboxylic acid (0.8 mmol) in dry DMF (1 mL) was cooled to 0 °C and added dicyclohexylcarbodiimide (1.2 mmol) under nitrogen atmosphere and the reaction mixture stirred at same temperature for 0 °C for 1 h. The appropriate amidoxime **6** (0.8 mmol) was added to the mixture and stirred at 0 °C for 0.5 h, gradually brought up to 30 °C and continued stirring for another 3 h followed by heating at 110 °C for next 10 h. The reaction contents were cooled to 25 °C, poured into ice-cold water (25 mL), ethyl acetate (25 mL) was added and stirred for 10 min. The crystals of dicyclohexylurea thus obtained were filtered off. The separated aqueous phase was extracted with ethyl acetate (2 × 20 mL), washed with brine and dried over anhydrous sodium sulfate. After removal of ethyl acetate by distillation, the residue obtained was purified by flash column chromatography using ethyl acetate–hexane (0–25%) as eluent to afford pure 1,2,4-oxadiazole **7**.

*4.1.2.1. 5-Cyclohexyl-3-(3-cyclopentyloxy-4-methoxy-phenyl)-1,2,4-oxadiazole (**7a**).* Colorless gum. Yield: 45%. ^{1}H NMR ($CDCl_3$ 400 MHz): $\delta_H = 7.65$ (1H, d, $J = 8.36$, 1.91 Hz), 7.58 (1H, d, $J = 1.96$ Hz), 6.93 (1H, d, $J = 8.4$ Hz), 4.90–4.87 (1H, m), 3.90 (3H, s), 2.00–1.82 (11H, m), 1.75–1.58 (4H, m), 1.44–1.34 (4H, m). MS (ESI, m/z): 343.1 $(M + H)^+$.

*4.1.2.2. 5-Cyclopentyl-3-(3-cyclopentyloxy-4-methoxy-phenyl)-1,2,4-oxadiazole (**7b**).* Colorless gum. Yield: 47%. ^{1}H NMR ($CDCl_3$ 400 MHz): $\delta_H = 7.67$ (1H, d, $J = 8.36$, 1.91 Hz), 7.58 (1H, d, $J = 1.96$ Hz), 6.92 (1H, d, $J = 8.4$ Hz), 4.91–4.87 (1H, m), 3.92 (3H, s), 2.00–1.82 (11H, m), 1.77–1.30 (6H, m). MS (ESI, m/z): 329.1 $(M + H)^+$.

*4.1.2.3. t-Butyl 4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl) piperidin-1-carboxylate (**7c**).* Light cream solid. Yield: 37%, m.p. 93–94 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta_H = 7.68$ (1H, dd, $J = 8.40$, 1.96 Hz), 7.56 (1H, d, $J = 1.92$ Hz), 6.95 (1H, d, $J = 8.40$ Hz), 4.14–4.12 (2H, m), 3.97 (3H, s), 3.95 (3H, s), 3.19–3.13 (1H, m), 3.02–2.96 (2H, m), 2.13–2.09 (2H, m), 1.94–1.85 (2H, m), 1.48 (9H, s). MS (ESI, m/z): 332.1 $(M\text{-}C(CH_3)_3)^+$.

*4.1.2.4. t-Butyl 4-(3-(3-ethoxy-4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-carboxylate (**7d**).* Colorless gum. Yield: 36%. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta_H = 7.66$ (1H, dd, $J = 8.32$, 1.92 Hz), 7.56 (1H, d, $J = 1.92$ Hz), 6.95 (1H, d, $J = 8.44$ Hz), 4.21–4.11 (4H, m), 3.93 (3H, s), 3.18–3.13 (1H, m), 3.02–2.96 (2H, m), 2.12–2.10 (2H, m), 1.94–1.87 (2H, m), 1.52–1.47 (12H, m). MS (ESI, m/z): 404.2 $(M + H)^+$.

*4.1.2.5. t-Butyl 4-(3-(3-butoxy-4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-carboxylate (**7e**).* Light cream solid. Yield: 36%, m.p. 110–112 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta_H = 7.66$ (1H, dd, $J = 8.36$, 1.92 Hz), 7.56 (1H, d, $J = 1.92$ Hz), 6.94 (1H, d, $J = 8.44$ Hz), 4.13–4.08 (4H, m), 3.92 (3H, s), 3.17–3.13 (1H, m), 2.99–2.97 (2H, m), 2.13–2.09 (2H, m), 1.91–1.82 (4H, m), 1.54–1.49 (2H, m), 1.47 (9H, s), 1.00 (3H, t, $J = 7.36$ Hz). MS (ESI, m/z): 432.1 $(M + H)^+$.

*4.1.2.6. t-Butyl 4-(3-(4-cyclopentyloxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-carboxylate (**7f**).* Off white solid. Yield: 39%, m.p. 78–80 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta_H = 7.62$ (1H, dd, $J = 8.0$, 2.00 Hz), 7.54 (1H, d, $J = 2.00$ Hz), 6.92 (1H, d, $J = 8.0$ Hz), 4.85–4.78 (1H, m), 4.16–4.09 (2H, m), 3.91 (3H, s), 3.19–2.90 (3H, m), 2.12–1.73 (12H, m), 1.46 (9H, s). ^{13}C *NMR ($CDCl_3$, 100 MHz)* $\delta_C = 180.98$, *168.11*, 154.68, 150.34, 149.98, 120.75, 118.94, 114.06, 110.39, 80.43, 79.81, 79.59, 56.13, 42.01, 34.51, 32.85, 28.42, 24.14.

*4.1.2.7. t-Butyl 4-(3-(3,4,5-trimethoxyphenyl)-1,2,4-oxadiazol-5-yl) piperidine-1-carboxylate (**7g**).* Pale yellow gum. Yield: 42%. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta_H = 7.33$ (2H, s), 4.17–4.12 (2H, m), 3.95 (6H, s), 3.94 (3H, s), 3.77–3.66 (1H, m), 3.23–3.11 (1H, m), 3.04–2.96 (2H, m), 2.13–1.60 (3H, m), 1.49 (9H, s). MS (ESI, m/z): 442.5 $(M + Na)^+$.

*4.1.2.8. t-Butyl 4-(3-(3-cyclopentyloxy-4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-carboxylate (**7h**).* Light cream gum. Yield: 37%. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta_H = 7.63$ (1H, dd, $J = 8.00$, 2.00 Hz), 7.55 (1H, d, $J = 2.00$ Hz), 6.91 (1H, d, $J = 8.00$ Hz), 4.89–4.78 (1H, m), 4.16–4.09 (2H, m), 3.89 (3H, s), 3.08–2.87 (3H, m), 2.14–1.85 (9H, m), 1.65–1.62 (3H, m), 1.46 (9H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta_C = 180.93$, 168.10, 154.64, 152.50, 147.83, 120.68, 119.24, 113.19, 111.54, 80.52, 79.82, 56.02, 43.51, 34.51, 32.79, 29.16, 28.42, 24.10.

*4.1.2.9. 3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-(trichloromethyl)-1,2,4-oxadiazole (**7i**).* Light cream soild. Yield: 46%, m.p. 74–75 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta_H = 7.69$ (1H, dd, $J = 8.0$, 2.0 Hz), 7.56 (1H, d, $J = 2.0$ Hz), 7.94 (1H, d, $J = 8.0$ Hz), 4.92–4.89 (1H, m), 3.91 (3H, s), 2.03–1.80 (6H, m), 1.66–1.57 (2H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta_C = 174.04$, 168.99, 153.23, 147.97, 121.25, 117.75, 113.11, 111.56, 83.58, 80.68, 56.05, 32.80, 24.13. MS (ESI, m/z): 377.1 $(M + H)^+$.

*4.1.2.10. 3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-(4-methoxyphenyl)-1,2,4-oxadiazole (**7j**).* White solid. Yield: 40%, m.p. 74–75 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta_H = 8.09$ (2H, d, $J = 8.6$ Hz), 7.67 (1H, dd, $J = 8.4$, 1.4 Hz), 7.59 (1H, d, $J = 1.7$ Hz), 6.96 (2H, d, $J = 8.7$ Hz), 6.89 (1H, d, $J = 8.4$ Hz), 4.87–4.82 (1H, m), 3.84 (3H, s), 3.83 (3H, s), 1.99–1.73 (6H, m), 1.62–1.50 (2H, m). MS (ESI, m/z): 389.5 $(M + Na)^+$.

*4.1.2.11. 3-(3-Cyclopentyloxy-4-methoxyphenyl)-5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole (**7k**).* White solid. Yield: 36%, m.p. 125–126 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta_H = 7.85$ (1H, dd, $J = 8.4$, 2.0 Hz), 7.77 (1H, dd, $J = 8.4$, 2.0 Hz), 7.69 (2H, dd, $J = 7.8$, 1.9 Hz), 7.00 (2H, dd, $J = 10.5$, 8.5 Hz), 4.97–4.91 (1H, m), 4.03 (3H, s), 4.00 (3H, s), 3.93 (3H, s), 2.01–1.85 (6H, m), 1.68–1.60 (2H, m). MS (ESI, m/z): 419.5 $(M + Na)^+$.

*4.1.2.12. 5-(4-Methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-1,2,4-oxadiazole (**7l**).* Off white solid. Yield: 31%, m.p. 149–150 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta_H = 8.18$ (2H, d, $J = 8.9$ Hz), 7.41 (2H, d, $J = 10.1$ Hz), 7.05 (2H, d, $J = 8.9$ Hz), 3.98–3.88 (12H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta_C = 175.56$, 168.64, 163.21, 153.53, 140.45, 130.10, 129.25, 124.35, 122.36, 116.79, 114.50, 104.62, 60.97, 56.31, 55.53. MS (ESI, m/z): 365.4 $(M + Na)^+$.

*4.1.2.13. 5-(3,4-Dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-1,2,4-oxadiazole (**7m**).* White solid. Yield: 29%, m.p. 158–159 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta_H = 7.87$ (1H, dd, $J = 8.4$, 2.0 Hz), 7.70 (1H, d, $J = 1.9$ Hz), 7.43 (2H, s), 7.03 (1H, d, $J = 8.5$ Hz), 4.04 (3H, s), 4.00 (9H, s), 3.94 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta_C = 175.61$, 168.71, 153.55, 152.92, 149.30, 140.50, 122.29, 122.16, 116.80, 111.11, 110.50, 104.67, 60.97, 56.34, 56.22, 56.12. MS (ESI, m/z): 395.4 $(M + Na)^+$.

*4.1.2.14. 3,5-Bis(3,4,5-trimethoxyphenyl)-1,2,4-oxadiazole (**7n**).* White solid. Yield: 29%, m.p. 158–159 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta_H = 7.44$ (4H, d, $J = 7.44$ Hz), 4.02–3.98 (12H, m), 3.97 (3H, s), 3.94 (3H, s). MS (ESI, m/z): 425.4 $(M + Na)^+$

*4.1.3. General procedure for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles **8a–e***

A solution of appropriate oxadiazole 7 (0.4 mmol) in dry DCM (2 mL) was cooled to 0 °C and added trifluoroacetic acid (2 mL). The reaction mixture was then stirred at 25 °C for 6 h. After completion of the reaction, solvent was distilled off, basified with sodium bicarbonate and extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and distilled off on a rotary evaporator to afford 8 in excellent yield.

*4.1.3.1. 3-(3,4-Dimethoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (**8a**).* Off white solid. Yield: 84%, m.p. 190–192 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta_H = 9.70$ (1H, $s_{(br)}$), 7.66 (1H, dd, $J = 8.32$, 1.40 Hz), 7.54 (1H, d, $J = 1.48$ Hz), 6.98 (1H, d, $J = 8.4$ Hz), 3.95 (3H, s), 3.94 (3H, s), 3.50–3.36 (3H, m), 3.16–3.01 (2H, m), 2.42–2.39 (2H, m), 2.32–2.24 (2H, m). MS (ESI, m/z): 290.1 $(M + H)^+$.

*4.1.3.2. 3-(3-Ethoxy-4-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (**8b**).* Off white solid. Yield: 78%, m.p. 137–138 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta_H = 9.70$ (1H, $s_{(br)}$), 7.66 (1H, dd, $J = 8.36$, 1.88 Hz), 7.56 (1H, d, $J = 1.88$ Hz), 6.96 (1H, d, $J = 8.44$ Hz), 4.19 (2H, q, $J = 6.96$ Hz), 3.94 (3H, s), 3.52–3.47 (2H, m), 3.37–3.34 (1H, m), 3.21–3.14 (2H, m), 2.46–2.41 (2H, m), 2.36–2.30 (2H, m), 1.51 (3H, t, $J = 6.96$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta_C = 178.90$, 168.26, 151.94, 148.55, 120.86, 118.82, 111.26, 111.07, 64.49, 56.00, 42.26, 31.51, 25.66, 14.69. MS (ESI, m/z): 304.1 $(M + H)^+$.

*4.1.3.3. 3-(3-n-Butoxy-4-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (**8c**).* White solid. Yield: 86%, m.p. 130–131 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta_H = 9.70$ (1H, $s_{(br)}$), 7.66 (1H, dd, $J = 8.40$, 1.92 Hz), 7.55 (1H, d, $J = 1.88$ Hz), 6.95 (1H, d, $J = 8.44$ Hz), 4.10 (2H, t, $J = 6.76$ Hz), 3.92 (3H, s), 3.52–3.46 (2H, m), 3.36–3.34 (1H, m), 3.20–3.14 (2H, m), 2.46–2.41 (2H, m), 2.36–2.30 (2H, m), 1.90–1.83 (2H, m), 1.55–1.49 (2H, m), 1.00 (3H, t, $J = 7.4$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta_C = 178.87$, 168.28, 152.09, 148.83, 120.84, 118.80, 111.37, 111.21, 68.81, 56.02, 42.26, 31.52, 31.16, 25.63, 19.19, 13.86. MS (ESI, m/z): 332.1 $(M + H)^+$.

*4.1.3.4. 3-(4-Cyclopentyloxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (**8d**).* White solid. Yield: 83%, m.p. 110–112 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta_H = 7.62$ (1H, dd, $J = 8.00$, 2.00 Hz), 7.54 (1H, d, $J = 2.00$ Hz), 6.92 (1H, d, $J = 8.00$ Hz), 4.86–4.78 (1H, m), 3.91 (3H, s), 3.37–3.32 (6H, m), 2.94–2.81 (2H, m), 2.17–2.00 (2H, m), 1.97–1.62 (8H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta_C = 180.85$, 168.13, 150.36, 149.98, 120.77, 118.92, 114.07, 110.42, 80.44, 56.14, 44.72, 33.99, 32.85, 29.05, 24.14. MS (ESI, m/z): 344.1 $(M + H)^+$.

*4.1.3.5. 5-(Piperidin-4-yl)-3-(3,4,5-trimethoxyphenyl)-1,2,4-oxadiazole (**8e**).* White solid. Yield: 79%, m.p. 175–176 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta_H = 9.70$ (1H, $s_{(br)}$), 7.33 (2H, s), 3.96 (6H, s), 3.93 (3H, s), 3.55–3.13 (4H, m), 2.44–2.05 (5H, m). MS (ESI, m/z): 320.5 $(M + H)^+$.

*4.1.4. Synthesis of ethyl 4-(3-(3-cyclopentyloxy-4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (**9a**)*

A solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (**4**) (0.2 mmol) in dry dichloromethane (5 mL) was cooled to 0 °C and added triethylamine (0.25 mmol) followed by ethyl chloroformate (0.2 mmol) under nitrogen atmosphere, and the reaction mixture was stirred for 5 h at 30 °C. The reaction contents were poured into ice-cold water (5 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and distilled on a rotary evaporator. The residue so obtained was purified by flash column chromatography using ethyl acetate–hexane (0–50%) as eluent to afford pure 1,2,4-oxadiazole **9a**. White solid. Yield 78%, m.p. 55–56 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): 7.62 (1H, dd, $J = 8.0$, 2.0 Hz), 7.55 (1H, d, $J = 2.0$ Hz), 6.92 (1H, d, $J = 8.0$ Hz), 4.89–4.82 (1H, m), 4.20–4.09 (4H, m), 3.89 (3H, s), 3.22–2.94 (3H, m), 2.16–1.85 (10H, m), 1.62–1.58 (2H, m), 1.27 (3H, t, $J = 6$ Hz). MS (ESI, m/z): 416.1 $(M + H)^+$.

*4.1.5. Synthesis of 3-(3-cyclopentyloxy-4-methoxyphenyl)-5-(1-methylsulfonylpiperidin-4-yl)-1,2,4-oxadiazole (**9b**)*

The 1,2,4-oxadiazole **9b** was prepared according to the procedure described for **9a** except that methanesulfonyl chloride was used instead of ethyl chloroformate.

White solid. Yield 72%, m.p. 78–79 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta_H = 7.63$ (1H, dd, $J = 8.0$, 2.0 Hz), 7.55 (1H, d, $J = 2.0$ Hz), 6.92 (1H, d, $J = 8.0$ Hz), 4.90–4.82 (1H, m), 3.89 (3H, s), 3.79–3.71 (2H, m), 3.20–2.94 (3H, m), 2.81 (3H, s), 2.26–1.79 (10H, m), 1.62–1.58 (2H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta_C = 180.13$, 168.20, 152.62, 147.86, 120.73, 119.04, 113.20, 111.56, 80.60, 56.04, 44.87, 35.26, 33.48, 32.80, 28.77, 24.11. MS (ESI, m/z): 422.1 $(M + H)^+$.

*4.1.6. Synthesis of t-butyl 4-(2-(3-cyclopentyloxy-4-methoxybenzoyl) hydrazinecarbonyl)piperidine-1-carboxylate (**13**)*

To a cold (0 °C) solution of 3-cyclopentyloxy-4-methoxybenzoyl chloride [33] (4 mmol) in dry DMF (5 mL), the *t*-butyl 4-(hydrazinecarbonyl)-piperidine-1-carboxylate (**12**) [25] (4 mmol) was added followed by triethylamine (8 mmol). The reaction mixture was stirred for 5 h at 30 °C and poured into ice cold water, extracted with ethyl acetate (3 × 50 mL) and the combined organic phase was washed with brine solution and dried over anhydrous sodium sulfate. Ethyl acetate was distilled off and the residue thus obtained was purified by flash column chromatography using ethyl acetate as eluent to afford pure 13. White solid. Yield 62%, m.p. 178–179 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta_H = 9.22$ (1H, s), 9.08 (1H, s), 7.39–7.36 (2H, m), 6.83 (1H, d, $J = 8.92$ Hz), 4.81–4.76 (1H, m), 4.15–4.12 (2H, m), 3.87 (3H, s), 2.77–2.70 (2H, m), 2.48–2.42 (1H, m), 1.98–1.55

(12H, m), 1.45 (9H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta_C = 172.46$, 164.64, 154.56, 153.58, 147.67, 123.43, 120.40, 113.47, 110.93, 80.60, 79.67, 56.02, 42.77, 40.96, 32.73, 28.41, 28.33, 24.04. MS (ESI, *m*/*z*): 462.1 $(M + H)^+$.

4.1.7. Synthesis of 2-(3-cyclopentyloxy-4-methoxyphenyl)-5-(piperidin-4-yl)-1,3,4-oxadiazole (**14**)

To a suspension of diacylhydrazine 13 (0.5 mmol) in dry benzene (5 mL) was added freshly distilled thionyl chloride (1 mL). The mixture was refluxed until a homogeneous solution was formed. After completion of the reaction, the mixture was evaporated to dryness under reduced pressure and the crude residual solid obtained was percolated through a short bed of silica gel column using ethyl acetate-hexane (1:1) to afford pure 14. Light cream solid, Yield 38%, m.p. 138–139 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta_H = 9.37$ (1H, $s_{(br)}$), 7.56–7.53 (2H, m), 6.92 (1H, d, $J = 8.24$ Hz), 4.89–4.86 (1H, m), 3.91 (3H, s), 3.53–3.51 (1H, m), 3.40–3.35 (1H, m), 3.23–3.20 (1H, m), 2.86–2.84 (3H, m), 2.44–2.30 (3H, m), 2.05–1.82 (6H, m), 1.65–1.62 (2H, m). MS (ESI, *m*/*z*): 344.1 $(M + H)^+$.

4.1.8. Synthesis of t-butyl 4-(5-(3-(cyclopentyloxy)-4-methoxyphenyl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (**15**)

A suspension of diacylhydrazine 13 (0.5 mmol) and Lawesson's reagent (0.5 mmol) was refluxed in dry *p*-xylene (5 mL). Upon completion of the reaction, hot crude residue was loaded directly to chromatography column and eluted with ethyl acetate–hexane (0–50%) to isolate pure **15**.

White solid, Yield 58%, m.p. 104–105 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta_H = 7.62$ (1H, d, $J = 2.0$ Hz), 7.37 (1H, dd, $J = 8.32$, 2.04 Hz), 6.90 (1H, d, $J = 8.44$ Hz), 4.91–4.89 (1H, m), 4.22–4.19 (2H, m), 3.91 (3H, s), 3.36–3.33 (1H, m), 2.96–2.91 (2H, m), 2.17–2.14 (2H, m), 2.04–1.99 (2H, m), 1.93–1.77 (6H, m), 1.65–1.61 (2H, m), 1.48 (9H, s). MS (ESI, *m*/*z*): 460.1 $(M + H)^+$.

4.1.9. Synthesis of 2-(3-cyclopentyloxy-4-methoxyphenyl)-5-(piperidin-4-yl)-1,3,4-thiadiazole (**16**)

The compound **16** was prepared from **15** according to the general procedure described for **8a**–**e**. Off white solid. Yield 78%, m.p. 175–177 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta_H = 7.56$ (1H, d, $J = 1.48$ Hz), 7.34 (1H, dd, $J = 7.72$, 1.28 Hz), 6.92 (1H, d, 8.24 Hz), 4.89–4.86 (1H, m), 3.90 (3H, s), 3.60–3.58 (2H, m), 3.21–3.19 (2H, m), 2.82–2.79 (4H, m), 2.44–2.42 (1H, m), 2.33 (1H, $s_{(br)}$), 2.03–1.80 (6H, m), 1.65–1.62 (2H, m). MS (ESI, *m*/*z*): 360.1 $(M + H)^+$.

4.2. MTT assay

Six human cancer cell lines (LnCap, DU145, PC3, MCF7, MDA-MB-231, and PaCa2) were cultured in RPMI-1640 media supplemented with 10% heat inactivated fetal bovine serum and 1% penicillin/streptomycin. They were seeded in 96-well plates at a density of 4×10^3 cells per well for 12 h. Cells were incubated with various concentrations of the compounds ranging from 10 nM to 10 mM. After 48 h, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide) was added to the final concentration of 0.2 mg/mL and incubated for 30 min. The cells were washed twice with PBS and lysed in 100 μL dimethylsulfoxide, and the absorbance was measured at 570 nm using Tecan Spectrafluor Plus.

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