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Efficient synthetic routes to uncommon thiazole-tethered 1,2,4-oxadiazole derivatives

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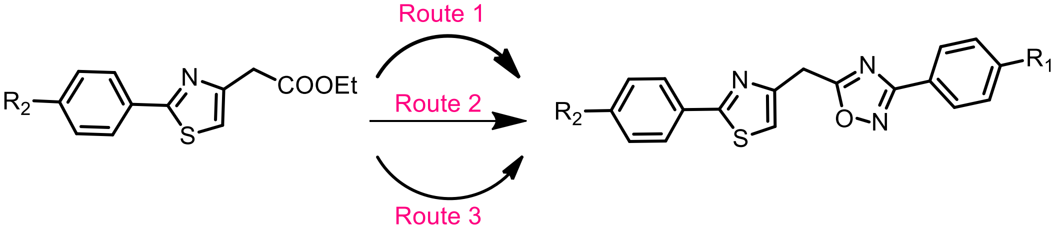
Abstract

Thiazole and 1,2,4-oxadiazole are influential scaffolds in drug discovery and development processes mainly due to the appreciable diversity in the biological actions of their derivatives. Herein, for the first time, we describe a mild and efficient method for the synthesis of thiazole-tethered 1,2,4-oxadiazole derivatives. A small focused library of uncommon 3-aryl-5-[(2-arylthiazol-4-yl)methyl]-1,2,4-oxadiazole derivatives have been efficiently synthesized by employing modified reaction conditions using DMAP and EDC·HCl. The title compounds were characterized by IR, NMR and mass spectroscopic analysis.



25 examples: efficient and rapid synthesis

Keywords: Thiazole, 1,2,4-Oxadiazole

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Introduction

1,2,4-Oxadiazole and its derivatives have developed into influential scaffolds in the field of chemical sciences due to the broad spectrum of biological actions of these compounds. The variability of the 1,2,4-oxadiazole core has been expressed in drug examples such as ataluren (Duchenne muscular dystrophy), fasiplon (nonbenzodiazepine anxiolytic drug), pleconaril (antiviral), butalamine (vasodilator), proxazole (gastrointestinal disorders), prenoxdiazine (cough suppressant) and oxolamine (anti-inflammatory). (Figure 1) The diverse pharmacological activities of 1,2,4-oxadiazole compounds have led many scientists to refine and develop new structural alternatives with the aim of affording compounds with efficient pharmacological actions.[1-22]

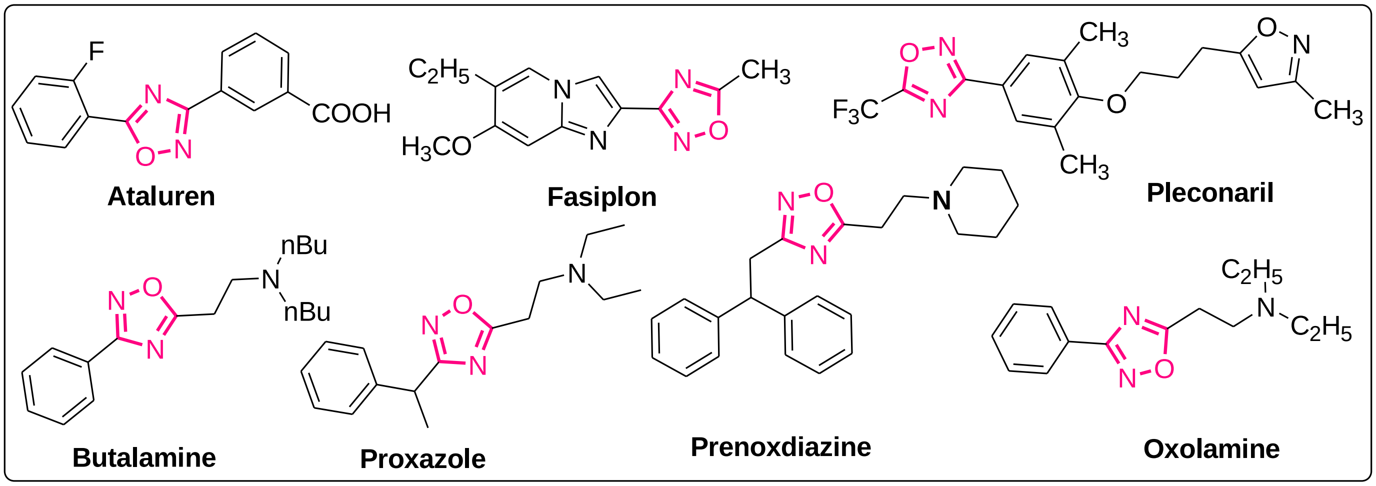


Figure 1. Commercially available drugs containing the 1,2,4-oxadiazole scaffold.

During the last two decades, synthetic researchers have focused on synthesising hybrid molecules by combining two or more structural domains with different biological functions. The activities of these hybrids have been increasingly studied and have resulted in a diverse range of pharmacological agents and potent drugs.[23,24] Hybridization of 1,2,4-oxadiazole with other pharmacophores may thus provide new candidates with interesting potencies.

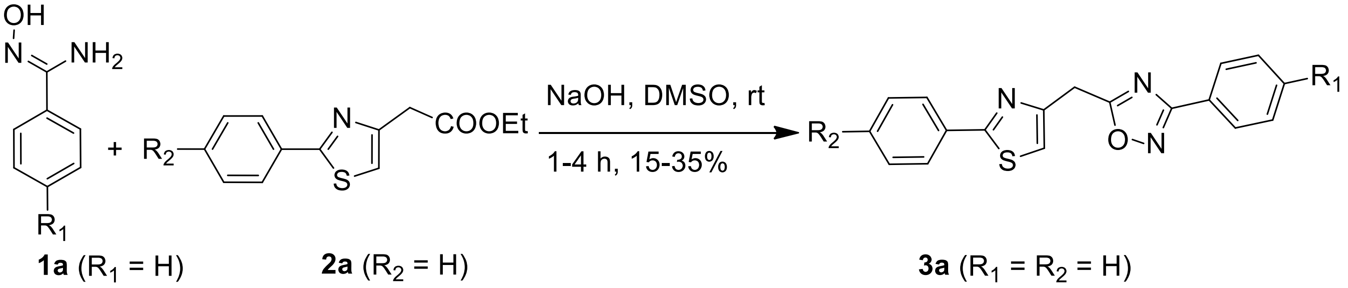
Thiazoles are 5-membered aromatic heterocyclic compounds which demonstrate significant biological activities. Divergent modification of the thiazole ring at various positions have resulted in the formation of various novel compounds with a broad spectrum of biological activities, *viz*., antimicrobial,[25-27] anti-inflammatory,[28–30] antiviral,[31-33] anti-tubercular,[34-37] CNS active agents[38,39] and compounds with anticancer activities.[40-43]

Thus, in our opinion, hybridization of the 1,2,4-oxadiazole and thiazole scaffolds would be interesting to potentially give promising lead compounds. A literature review has revealed that thiazole-appended 1,3,4-oxadiazoles have been synthesized and screened for pharmacological potential.[44-47] However, the synthesis of thiazole-tethered 1,2,4-oxadiazole derivatives and their biological activities have been not reported. This challenged us to synthesize 3-aryl-5-[(2-arylthiazol-4-yl)methyl]-1,2,4-oxadiazole derivatives, (**3a-y**) employing as key step the cyclocondensation reaction of *N*'-hydroxybenzimidamide and 2-(2-phenylthiazol-4-yl)acetic acid.\

Results and Discussion

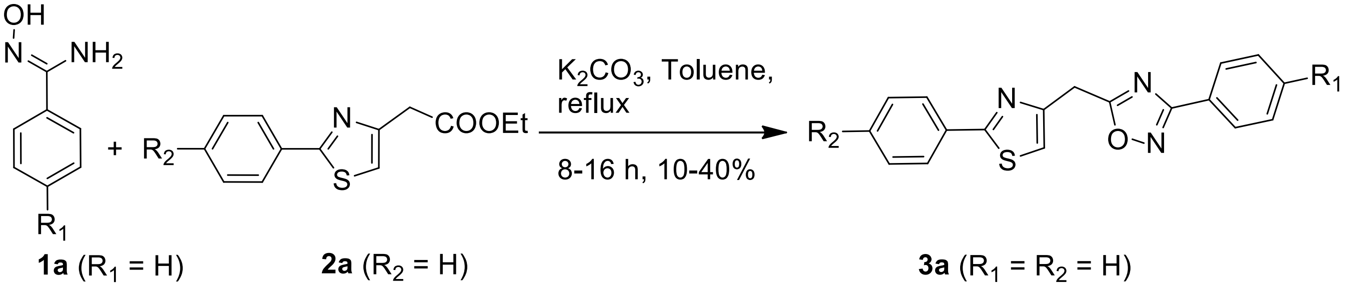
The synthetic strategies adopted for the synthesis of title compounds **3a**-**y** are depicted in Schemes 1-3. The starting compounds **2a-e** were synthesized as per the reported literature methods.[48] The cyclocondensation reaction of (*Z*)-*N*'-hydroxybenzimidamide **1a** and ethyl 2-(2-phenylthiazol-4-yl)acetate, **2a** was performed as a test reaction, as shown in Scheme 1 and 2. The progress of the reactions were monitored at different reaction conditions as shown under entries 1 and 2 in Table 1. The cyclocondensation of *N*'-hydroxybenzimidamide **1a** with ethyl 2-(2-arylthiazol-4-yl)acetate **2a** in alkaline DMSO, at room temperature using the route 1 reaction conditions gave 35% product formation in 2 hours. However, the yield of the product decreased with an increase in reaction time of 4 hours. In the second reaction route, the carboximidamide **1a**, ester **2a**, and K_2CO_3 were heated at reflux in toluene for 8 and 16 hours gave 1,2,4-oxadiazole **3a** in 10% and 20% yield, respectively. The same reaction was then performed at 130 °C in a sealed tube for 8 and 16 hours, improving the yield of the product up to 40% (Table 1). In our opinion, the yields of route 1 and route 2 were not satisfactory, and therefore the condensation reaction was modified as described in Scheme 3. To this end, ethyl 2-(2-phenylthiazol-4-yl)acetate **2a** was hydrolyzed by using aq. LiOH to afford 2-(2-phenylthiazol-4-yl)acetic acid **4a**. The subsequent reaction of acid **4a** with DMAP, EDC·HCl and *N*'-hydroxybenzimidamide (**2a)** was performed as shown by route 3 and gave 3-phenyl-5-[(2-phenylthiazol-4-yl)methyl]-1,2,4-oxadiazole **3a** in 66% yield. With these optimized reaction conditions in hand, derivatives **3b-3y** were synthesized by using route 3, the yields and physical characteristics thereof presented in Table 2.

Route 1



Scheme 1. Synthesis of 3-aryl-5-[(2-arylthiazol-4-yl)methyl]-1,2,4-oxadiazole by route 1.

Route 2



Scheme 2. Synthesis of 3-aryl-5-[(2-arylthiazol-4-yl)methyl]-1,2,4-oxadiazole by route 2.

Table 1. Reaction conditions and yields of 3-phenyl-5-[(2-phenylthiazol-4-yl)methyl]-1,2,4-oxadiazole (**3a)** derivatives at different reaction conditions

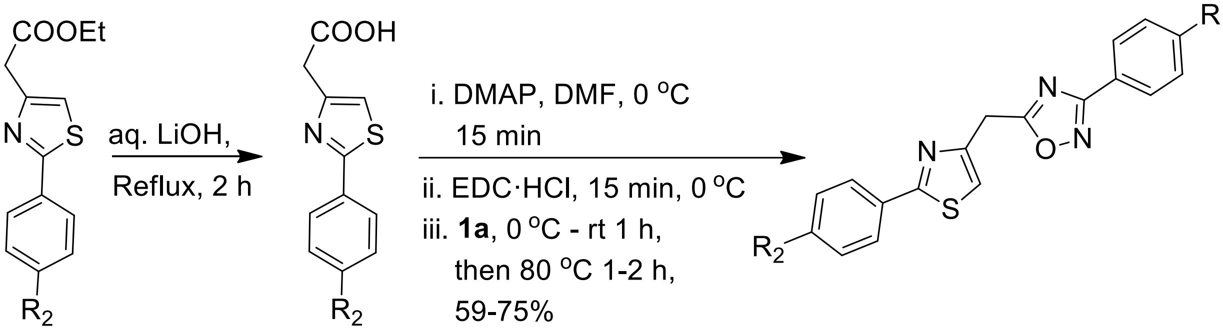
Entry	Reagents and solvents	Reaction Condition	Reaction Time (hrs)	Yields (%)
1	NaOH in DMSO	Room temperature	1	30
			2	35
			3	25
			4	15
2	K_2CO_3 in Toluene	Reflux	8	10
			16	20
		130 °C, sealed tube	8	25
			16	40
3	EDC·HCl, DMAP, DMF	0-80 °C	3	66

Table 2. Yields of 3-aryl-5-((2-arylthiazol-4-yl)methyl)-1,2,4-oxadiazole derivatives

Entry	Product **4**	R_1	R_2	Yield*	Melting Point °C
1	**3a**	H	H	67	78-80
2	**3b**	H	F	70	94-96
3	**3c**	H	Cl	68	102-104
4	**3d**	H	Br	70	118-120
5	**3e**	H	CH_3	72	86-88
6	**3f**	F	H	69	100-102
7	**3g**	F	F	73	114-116
8	**3h**	F	Cl	74	142-144
9	**3i**	F	Br	75	160-162
10	**3j**	F	CH_3	71	98-100
11	**3k**	Cl	H	65	111-112
12	**3l**	Cl	F	60	122-124
13	**3m**	Cl	Cl	64	112-114
14	**3n**	Cl	Br	68	114-116
15	**3o**	Cl	CH_3	66	122-124
16	**3p**	Br	H	68	112-114
17	**3q**	Br	F	69	120-122
18	**3r**	Br	Cl	70	138-140
19	**3s**	Br	Br	76	150-152
20	**3t**	Br	CH_3	73	138-140
21	**3u**	CH_3	H	69	96-98
22	**3v**	CH_3	F	68	120-122
23	**3w**	CH_3	Cl	65	108-110
24	**3x**	CH_3	Br	61	118-120
25	**3y**	CH_3	CH_3	59	100-112

[a] Yields are given for isolated products.

Route 3



2a (R_2 = H) **4a** (R_2 = H) **3a** ($R_1 = R_2$ = H)

Scheme 3. Synthesis of 3-aryl-5-[(2-arylthiazol-4-yl)methyl]-1,2,4-oxadiazole by route 3.

Conclusions

We have described a modified method for the synthesis of a new class of thiazole-tethered 1,2,4-oxadiazole derivatives. General and efficient methods for the synthesis of 3-aryl-5-[(2-arylthiazol-4-yl)methyl]-1,2,4-oxadiazole derivatives gave the desired products in moderate-to-good yields from simple and commercially-available reagents. The synthesized products are stable, easily isolable and readily characterized by spectral analysis. Further investigations to evaluate the pharmacological potential of the newly synthesized products are currently in progress in our laboratories and will be reported in due course.

Experimental Section

General. The progress of the reaction was monitored by thin layer chromatography (TLC) using TLC Merck 60 F-254 silica gel plates. Melting points were determined in capillary tubes in a silicon oil bath using a Universal melting point apparatus and are uncorrected. ^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra were recorded on Bruker spectrometer instruments. Chemical shifts are reported from the internal tetramethylsilane standard and are given in δ units. Column chromatography was performed on silica gel (100-200 mesh) supplied by Loba-Chemicals. The chemicals and solvents used were laboratory-grade and were purified as per literature methods. The starting compounds *N*'-hydroxybenzimidamide (**1a-d**) ethyl 2-(2-phenylthiazol-4-yl)acetate (**2a-e**) were synthesized by known literature methods.

Synthesis of *N*'-hydroxybenzimidamide (1a). To the stirred solution of benzonitrile (5.00 g, 48.5 mol) in ethanol (50 mL), hydroxyl amine hydrochloride (6.75 g, 97.1 mol) and sodium carbonate (10.29 g, 97.08 mol) in water (20 mL) were added and the resulting suspension was heated at reflux for 4 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under vacuum to remove excess ethanol. Water (50 mL) was then added to the reaction mixture and the mixture extracted with ethyl acetate (100 mL x 3). The combined organic layer was washed with water (50 mL) and brine (50 mL) and then dried over sodium sulphate. The organic layer was concentrated under reduced pressure giving a white solid (Yield 6.22 g, 94%). The crude product was used for further reaction without any purification.

Synthesis of ethyl 2-(2-phenylthiazol-4-yl)acetate (2a). Benzothioamide (680 mg, 5 mmol) and ethyl 4-chloro-3-oxobutanoate (823 mg, 5 mmol) in ethanol was refluxed for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction the solvent was distilled off by using a rotary evaporator, and the remaining residue was dissolved in water and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with 10% sodium bicarbonate solution (20 mL), dried over sodium sulphate and concentrated under vacuum to give a thick oil. The crude product was purified by column chromatography gave using 5% ethyl acetate in hexane as eluent to give compound **2a** in a 78% yield. The compounds **2b-e** were synthesized under similar experimental conditions.

Ethyl 2-(2-phenylthiazol-4-yl)acetate (2a).[47] ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.92–7.88 (m, 2H, Ar-C-2, C-6 H), 7.44-7.41 (m, 3H, Ar-C-3, C-4, C-5 H), 7.20 (s, 1H, Thiazole-C-5 H), 4.18 (q, *J* 7.2 Hz, 2H, O-C$\underline{H}_2$-CH_3), 3.87 (s, 2H, Thiazole-CH_2-Oxadiazole), 1.28 (t, *J* 7.2 Hz, 3H, O-CH_2-C$\underline{H}_3$). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 170.4 (C, C=O), 166.7 (C, Thiazole-C-2), 149.8 (C, Thiazole-C-4), 130.8 (C, Ar-C-1), 130.2 (CH, Ar-C-4), 129.0 (CH, Ar-C-2,C-6), 128.9 (CH, Ar-C-3, C-5), 116.0 (CH, Thiazole-C-5), 61.0 (CH_2, -OCH_2-), 37.1 (CH_2, Thiazole-CH_2-CO), 14.1 (CH_3, $H_3\underline{C}$-CH_2-O).

Ethyl 2-[2-(4-fluorophenyl)thiazol-4-yl]acetate (2b). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.92 (dd, *J* 8.6, 5.3 Hz, 2H, Ar-C-2, C-6 H), 7.18 (s, 1H, Thiazole-C-5 H), 7.11 (t, *J* 8.5 Hz, 2H, Ar-C-3, C-5), 4.20 (q, *J* 7.1 Hz, 2H, O-C$\underline{H}_2$-CH_3), 3.88 (s, 2H, Thiazole-CH_2-CO), 1.30 (t, *J* 7.1 Hz, 3H, O-CH_2-C$\underline{H}_3$). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 170.4 (C, C=O), 166.7 (C, Thiazole-C-2), 164.8 and 162.8 (C, Ar-C-4, $^1J_{C\text{-}F}$ 252 Hz), 149.9 (C, Thiazole-C-4), 130.0 and 129.9 (C, Ar-C-1, $^4J_{C\text{-}F}$ 2.52 Hz), 128.52 and 128.45 (CH, Ar-C-2, C-6, $^3J_{C\text{-}F}$ 8 Hz), 116.0 (CH, Thiazole-C-5), 116.1 and 115.9 (CH, Ar-C-3, C-5, $^2J_{C\text{-}F}$ 20 Hz), 61.10 (CH_2, -OCH_2-), 37.15 (CH_2, Thiazole-CH_2-CO), 14.21 (CH_3, $H_3\underline{C}$-CH_2-O).

Ethyl 2-[2-(4-chlorophenyl)thiazol-4-yl]acetate (2c). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.90 (d, *J* 8.6 Hz, 2H, Ar-C-2, C-6 H), 7.28 (d, *J* 8.6 Hz, 2H, Ar-C-3, C-5 H), 7.16 (s, 1H, Thiazole-C-5 H), 4.20 (q, *J* 7.1 Hz, 2H, O-C$\underline{H}_2$-CH_3), 3.86 (s, 2H, Thiazole-CH_2-CO), 1.30 (t, *J* 7.1 Hz, 3H, O-CH_2-C$\underline{H}_3$). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 170.3 (C, C=O), 168.0 (C, Thiazole-C2), 149.5 (C, Thiazole-C-4), 133.2 (C, Ar-C-1), 131.7 (C, Ar-C4), 129.3 (CH, Ar-C-3, C-5), 127.8 (CH, Ar-C-2, C-6), 116.0 (CH, Thiazole-C-5), 61.2 (CH_2, -OCH_2-), 37.3 (CH_2, Thiazole-CH_2-CO), 14.3 (CH_3, $H_3\underline{C}$-CH_2-O).

Ethyl 2-[2-(4-bromophenyl)thiazol-4-yl]acetate (2d). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.78 (d, *J* 8.6 Hz, 2H, Ar-C-2, C-6 H), 7.55 (d, *J* 8.6 Hz, 2H, Ar-C-3, C-5 H), 7.16 (s, 1H, Thiazole-C-5 H), 4.20 (q, *J* 7.2 Hz, 2H, O-C$\underline{H}_2$-CH_3), 3.85 (s, 2H, Thiazole-CH_2-CO), 1.30 (t, *J* 7.1 Hz, 3H, O-CH_2-C$\underline{H}_3$). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 171.0 (C, C=O), 168.2 (C, Thiazole-C2), 149.5 (C, Thiazole-C-4), 132.3 (C, Ar-C-1), 130.0 (CH, Ar-C-3, C-5), 128.7 (CH, Ar-C-2, C-6), 124.7 (C, Ar-C4), 116.1 (CH, Thiazole-C-5), 61.2 (CH_2, -OCH_2-), 37.3 (CH_2, Thiazole-CH_2-CO), 14.1 (CH_3, $H_3\underline{C}$-CH_2-O).

Ethyl 2-[2-(*p*-tolyl)thiazol-4-yl]acetate (2e). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.81 (d, *J* 8.2 Hz, 2H, Ar-C-2, C-6 H), 7.22 (d, *J* 7.9 Hz, 2H, Ar-C-3, C-5), 7.15 (s, 1H, Thiazole-C-5 H), 4.21 (q, *J* 7.1 Hz, 2H, O-C$\underline{H}_2$-CH_3), 3.88 (s, 2H, Thiazole-CH_2-CO), 2.38 (s, 3H, Ar-CH_3), 1.29 (t, *J* 7.1 Hz, 3H, O-CH_2-C$\underline{H}_3$). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 170.5 (C, C=O), 168.1 (C, Thiazole-C-2), 149.7 (C, Thiazole-C-4), 140.2 (C, Ar-C-4), 131.0 (C, Ar-C-1), 129.6 (CH, Ar-C-3, C-5), 126.5 (CH, Ar-C-2, C-6, 115.5 (CH, Thiazole-C-5), 61.1 (CH_2, -OCH_2-), 37.2 (CH_2, Thiazole-CH_2-CO), 21.4 (Ar-CH3), 14.2 (CH_3, $H_3\underline{C}$-CH_2-O).

Synthesis of 3-phenyl-5-[(2-phenylthiazol-4-yl)methyl]-1,2,4-oxadiazole (3a)

Route 1. To a stirred solution of *N*'-hydroxybenzimidamide (**1a**) (300 mg, 2.21 mmol) in DMSO, sodium hydroxide (115 mg, 2.87 mmol) was added. After stirring for 5 min, ethyl 2-(2-phenylthiazol-4-yl)acetate (**2a**) (710 mg, 2.87 mmol) was added and the reaction mixture was stirred for 1-4 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into water, and the resultant solid was separated by filtration on a Buchner funnel, air dried, and purified by column chromatography using 20% ethyl acetate in hexane as eluent to afford product **3a** (varying yields of 15-35%).

Route 2. The stirred suspension of *N'*-hydroxybenzimidamide (1**a**) (300 mg, 2.21 mmol), ethyl 2-(2-phenylthiazol-4-yl)acetate (**2a**) (710 mg, 2.87 mmol), and potassium carbonate (388 mg, 2.87 mmol) in toluene (10 mL) was heated at reflux for 16 h. The progress of the reaction was monitored by TLC. After 16 h excess toluene was evaporated under vacuum, after which water (30 mL) was added to the reaction mixture and it was extracted by ethyl acetate (20 mL x 3). The combined organic layer was dried over sodium sulphate and concentrated under vacuum to give a crude brown solid which was purified by column chromatography using 20% ethyl acetate in hexane as eluent, to ultimately afford **3a** in a 20% yield. In an alternative approach, the reaction mixture was heated at 130°C in a sealed tube for 16 hours, and after reaction workup and purification of the product by column chromatography gave compound **3a** in an improved yield of 40%.

Route 3. To the stirred solution of 2-(2-phenylthiazol-4-yl)acetic acid (**2a**) (1.65 g, 7.54 mol) in dry DMF, DMAP (1.84 g, 15.1 mol) was added after which the reaction mixture was stirred for 15 min. at 0 °C. EDC·HCl (0.33 g, 1.7 mol) was subsequently added to the reaction mixture and the reaction stirred at 0 °C for 15 min., followed by the addition of *N'*-hydroxybenzimidamide (**1a**) and further stirring for 1 h at room temperature. This was followed by heating to 80 °C under a nitrogen atmosphere for a further 2 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, water (40 mL) was added to the reaction mixture followed by extracting with ethyl acetate (30 mL x 3). The combined organic layers were dried over sodium sulphate and concentrated under a vacuum to afford a crude brown solid which was purified by column chromatography using 20% ethyl acetate in hexane as eluent to give compound **3a** in a yield of 66%. Compounds **3b-y** were synthesized using similar reaction conditions to give the desired products with yields described in Table 2.

3-Phenyl-5-[(2-phenylthiazol-4-yl)methyl]-1,2,4-oxadiazole (3a). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.10 (dd, *J* 7.9 and 1.7 Hz, 2H, Ar-C-2, C-6 H), 7.96–7.92 (m, 2H, Ar-C-2', C-6' H), 7.52–7.46 (m, 3H, Ar-C-3, C-4, C-5 H merged), 7.43 (dd, *J* 5.1 and 1.9 Hz, 3H, Ar-C-3', C-4', C-5' H merged), 7.27 (s, 1H, Thiazole-C-5 H), 4.56 (s, 2H, Thiazole-CH_2-Oxadiazole). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 176.7 (C, Thiazole-C-2), 168.7 (C, Oxadiazole-C-3), 168.6 (C, Oxadiazole-C-5), 148.9 (C, Thiazole-C-4), 133.3 (C, Ar-C-1), 131.2 (CH, Ar-C-4'), 130.3 (CH, Ar-C-4), 129.0 (CH, Ar-C-2' ,C-6'), 128.9 (CH, Ar-C-3' , C-5'), 127.5 (CH, Ar-C-3, C-5), 126.7 (C, Ar-C-1'), 126.6 (CH, Ar-C-2, C-6), 116.3 (CH,Thiazole-C-5), 29.5(CH_2, Thiazole-CH_2-Oxadiazole). HRMS calculated for $C_{18}H_{14}N_3OS$, *m/z*: 320.0858 $(M+H)^+$; found : 320.0858.

5-{[2-(4-Fluorophenyl)thiazol-4-yl]methyl}-3-phenyl-1,2,4-oxadiazole (3b). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.10 (dd, *J* 7.9 and 1.7 Hz, 2H, Ar-C-2, C-6 H), 7.92 (dd, *J* 8.9 and 5.3 Hz, 2H, Ar-C-2', C-6' H), 7.52– 7.46 (m, 3H, Ar-C-3, C-4, C-5_H merged), 7.26 (s, 1H, Thiazole-C-5 H), 7.12 (t, *J* 8.6 Hz, 2H, Ar-C-3', C-5' H), 4.54 (s, 2H, Thiazole-CH_2-Oxadiazole). ^{13}C NMR (126 MHz, $CDCl_3$) : δ_C 176.6 (C, Thiazole-C2), 168.6 (C, Oxadiazole-C-3), 167.4 (C, Oxadiazole-C-5), 165.0 and 163.0 (C, Ar-C-4', $^{1}J_{C\text{-}F}$ 252 Hz), 149.0 (C, Thiazole-C-4), 131.3 (CH, Ar-C-4), 129.69 and 129.66 (C, Ar-C-1', $^{4}J_{C\text{-}F}$ 3 Hz), 128.9 (CH, Ar-C-3,C-5), 128.58 and 128.51(CH, Ar-C-2', C-6', $^{3}J_{C\text{-}F}$ 8 Hz), 127.5 (CH, Ar-C-2,C-6), 126.7 (C, Ar-C-1), 116.3 (CH, Thiazole-C-5), 116.2 and 116.0 (CH, Ar-C-3', C-5', $^{2}J_{C\text{-}F}$ 20 Hz), 29.5 (CH_2,Thiazole-CH_2-Oxadiazole). HRMS calculated for $C_{18}H_{13}FN_3OS$, *m/z*: 338.0763 $(M+H)^+$; found : 338.0768

5-{[2-(4-Chlorophenyl)thiazol-4-yl]methyl}-3-phenyl-1,2,4-oxadiazole (3c). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.10 (dd, *J* 7.9 and 1.7 Hz, 2H, Ar-C-2, C-6 H), 7.87 (d, *J* 8.6 Hz, 2H, Ar-C-2', C-6' H), 7.53–7.45 (m, 3H, C-3, C-4, C-5), 7.40 (d, *J* 8.6 Hz, 2H, Ar-C-3', C-5' H), 7.29 (s, 1H, Thiazole-C-5 H), 4.55 (s, 2H, Thiazole-CH_2-Oxadiazole). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 176.5 (C, Thiazole-C2), 168.6 (C, Oxadiazole-C-3), 167.3 (C, Oxadiazole-C-5), 149.2 (C, Thiazole-C-4), 136.2 (C, Ar-C-1'), 131.8 (C, Ar-C4'), 131.3 (CH, Ar-C-4), 129.2 (CH, Ar-C-3', C-5'), 128.9 (CH, Ar-C-3, C-5), 127.8 (CH, Ar-C-2', C-6'), 127.5 (CH, Ar-C-2, C-6), 126.7 (C, Ar-C-1), 116.6 (CH, Thiazole-C-5), 29.4 (CH_2, Thiazole-CH_2-Oxadiazole). HRMS calculated for $C_{18}H_{13}FN_3OS$, *m/z*: 354.0468 $(M+H)^+$; found : 354.0469.

5-{[2-(4-Bromophenyl)thiazol-4-yl]methyl}-3-phenyl-1,2,4-oxadiazole (3d). ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 8.10 (dd, *J* 7.9 and 1.7 Hz, 2H, Ar-C-2, C-6 H), 7.81 (d, *J* 8.6 Hz, 2H, Ar-C-2', C-6' H), 7.56 (d, *J* 8.6 Hz, 2H, Ar-C-3', C-5' H), 7.52–7.46 (m, 3H, Ar-C-3, C-4, C-5), 7.30 (s, 1H, Thiazole-C-5 H), 4.55 (s, 2H, Thiazole-CH$_2$-Oxadiazole). ^{13}C NMR (126 MHz, CDCl$_3$): δ_C 176.6 (C, Thiazole-C2), 168.6 (C, Oxadiazole-C-3), 167.4 (C, Oxadiazole-C-5), 149.1 (C, Thiazole-C-4), 132.5 (C, Ar-C-1'), 131.3 (CH, Ar-C-4), 130.1 (CH, Ar-C-3', C-5'), 128.9 (CH, Ar-C-3, C-5), 128.6 (CH, Ar-C-2', C-6'), 128.5, 127.5 (CH, Ar-C-2, C-6), 126.7 (C, Ar-C-1), 124.8 (C, Ar-C'4), 116.3 (CH, Thiazole-C-5), 29.5 (CH$_2$, Thiazole-CH$_2$-Oxadiazole). HRMS calculated for C$_{18}$H$_{13}$BrN$_3$OS, *m/z*: 397.9963 (M+H)$^+$; found : 397.9975.

3-Phenyl-5-{[2-(*p*-tolyl)thiazol-4-yl]methyl}-1,2,4-oxadiazole (3e). ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 8.10 (dd, *J* 7.9 and 1.7 Hz, 2H, Ar-C-2, C-6 H), 7.82 (d, *J* 8.2 Hz, 2H, Ar-C-2', C-6' H), 7.53–7.45 (m, 3H, Ar-C-3, C-4, C-5), 7.23 (d, *J* 6.9 Hz, 3H, Ar-C-3', C-5', Thiazole-C-5 H merged), 4.55 (s, 2H, Thiazole-CH$_2$-Oxadiazole), 2.39 (s, 3H, Ar-CH$_3$). ^{13}C NMR (126 MHz, CDCl$_3$): δ_c 176.7(C, Thiazole-C-2), 168.9 (C,Oxadiazole-C-3), 168.6 (C, Oxadiazole-C-5), 148.7 (C, Thiazole-C-4), 140.5 (C, Ar-C-1'), 131.2 (CH, Ar-C-4), 130.7 (C, Ar-C-4'), 129.6 (CH, Ar-C-3', C-5') , 128.9 (CH, Ar-C-3, C-5) 127.5 (CH, Ar-C2,C6), 126.7 (C, Ar-C-1), 126.5 (CH, Ar-C-2', C-6'), 115.8 (CH, Thiazole-C-5), 29.5 (CH$_2$, Thiazole-CH$_2$-Oxadiazole), 21.4 (CH$_3$, Ar-CH$_3$). HRMS calculated for C$_{19}$H$_{16}$N$_3$OS, *m/z*: 334.1014 (M+H)$^+$; found : 334.1015.

3-(4-Fluorophenyl)-5-[(2-phenylthiazol-4-yl)methyl]-1,2,4-oxadiazole (3f). ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 8.10 (dd, *J* 8.9 and 5.4 Hz, 2H, Ar-C-2, C-6 H), 7.96–7.91 (m, 2H, Ar-C-2', C-6' H), 7.43 (m, 3H, Ar-C-3', C-4', C-5'), 7.27 (s, 1H, Thiazole-C-5 H), 7.16 (t, *J* 8.7 Hz, 2H, Ar-C-3, C-5 H), 4.55 (s, 2H, Thiazole-CH$_2$-Oxadiazole). ^{13}C NMR (126 MHz, CDCl$_3$): δ_C 176.8 (C, Thiazole-C2), 168.7 (C, Oxadiazole-C-3), 167.8 (C, Oxadiazole-C-5), 165.6 and 163.6 (C, Ar-C-4, $^{1}J_{C\text{-}F}$ 252 Hz), 148.9 (C, Thiazole-C-4), 133.3 (C, Ar-C-1), 130.3 (CH, Ar-C-2, C-6), 129.7 and 129.6 (C, Ar-C-2', C-6', $^{2}J_{C\text{-}F}$ 8 Hz), 129.0 (CH, Ar-C-3, C-5), 126.6, 123.0 and 123.0 (C, Ar-C-1', $^{4}J_{C\text{-}F}$ 2.52 Hz), 116.3 and 116.1 (C, Ar-C-3', C-5', $^{2}J_{C\text{-}F}$ 20 Hz), 115.9 (CH, Thiazole-C-5), 29.5 (CH$_2$, Thiazole-CH$_2$-Oxadiazole). HRMS calculated for C$_{18}$H$_{13}$FN$_3$OS, *m/z*: 338.0763 (M+H)$^+$; found : 338.0767.

3-(4-Fluorophenyl)-5-{[2-(4-fluorophenyl)thiazol-4-yl]methyl}-1,2,4-oxadiazole (3g). ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 8.10 (dd, *J* 8.9 and 5.4 Hz, 2H, Ar-C-2, C-6 H), 7.92 (dd, *J* 8.9 and 5.3 Hz, 2H, Ar-C-2', C-6' H), 7.26 (s, 1H, Thiazole-C-5 H), 7.16 (t, *J* 8.7 Hz, 2H, Ar-C-3, C-5 H), 7.12 (t, *J* 8.7 Hz, 2H, Ar-C-3', C-5' H), 4.53 (s, 2H, Thiazole-CH$_2$-Oxadiazole). ^{13}C NMR (126 MHz, CDCl$_3$): δ_C 176.7 (C, Thiazole-C-2), 167.8 (C, Oxadiazole-C-3), 167.5 (C, Oxadiazole-C-5), 165.6 and 163.6 (C, Ar-C-4', $^{1}J_{C\text{-}F}$ 252 Hz), 165.0 and 163.0 (C, Ar-C-4, $^{1}J_{C\text{-}F}$ 252Hz), 148.9 (C, Thiazole-C-4), 129.7 and 129.6 (CH, Ar-C-2', C-6', $^{3}J_{C\text{-}F}$ 8 Hz), 128.6 and 128.5(CH, Ar-C-2, C-6, $^{3}J_{C\text{-}F}$ 8Hz), 122.97 and 122.94 (C, Ar-C-1', C-1 $^{4}J_{C\text{-}F}$ 3 Hz, merged), 116.3 (CH, Thiazole-C-5) 116.2 and 116.0 (CH, Ar-C-3, C-5, C-3', C-5', $^{2}J_{C\text{-}F}$ 20Hz, merged), 29.4 (CH$_2$, Thiazole-CH$_2$-Oxadiazole). HRMS calculated for C$_{18}$H$_{12}$F$_2$N$_3$OS, *m/z*: 356.0669 (M+H)$^+$; found : 356.0681.

5-{[2-(4-Chlorophenyl)thiazol-4-yl]methyl}-3-(4-fluorophenyl)-1,2,4-oxadiazole (3h). ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 8.09 (dd, *J* 8.9 and 5.4 Hz, 2H, Ar-C-2, C-6 H), 7.87 (d, *J* 8.6 Hz, 2H, Ar-C-2', C-6' H), 7.40 (d, *J* 8.6 Hz, 2H, Ar-C-3', C-5' H), 7.28 (s, 1H, Thiazole-C-5 H), 7.16 (t, *J* 8.7 Hz, 2H, Ar-C-3, C-5 H), 4.53 (s, 2H, Thiazole-CH$_2$-Oxadiazole). ^{13}C NMR (126 MHz, CDCl$_3$): δ_c 176.6 (C, Thiazole-C-2), 167.8 (C, Oxadiazole-C-3), 167.3 (C, Oxadiazole-C-5), 165.6 and 163.6 (C, Ar-C-4, $^{1}J_{C\text{-}F}$ 252Hz), 149.1 (C, Thiazole-C-4), 136.3 (C, Ar-C-4'), 131.8 (C, Ar-C-1') , 129.7 and 129.6 (CH, Ar-C-2, C-6, $^{3}J_{C\text{-}F}$ 8 Hz), 129.2 (CH, Ar-C-3', C-5'), 127.8 (CH, Ar-C-2', C-6'), 122.9 and 122.9 (C, Ar-C-1, $^{4}J_{C\text{-}F}$ 3 Hz), 116.7 (CH, Thiazole-C-5), 116.2 and 116.0 (CH, Ar-C-3, C-5, $^{2}J_{C\text{-}F}$ 20 Hz), 29.4 (CH$_2$, Thiazole-CH$_2$-Oxadiazole). HRMS calculated for C$_{18}$H$_{12}$ClFN$_3$OS, *m/z*: 372.0374 (M+H)$^+$; found : 372.0375.

5-{[2-(4-Bromophenyl)thiazol-4-yl]methyl}-3-(4-fluorophenyl)-1,2,4-oxadiazole (3i). ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.09 (dd, *J* 8.9 and 5.4 Hz, 2H, Ar-C-2, C-6 H), 7.80 (d, *J* 8.6 Hz, 2H, Ar-C-2', C-6' H), 7.56 (d, *J* 8.6 Hz, 2H, Ar-C-3', C'5 H), 7.29 (s, 1H, Thiazole-C-5 H), 7.16 (t, *J* 8.7 Hz, 2H, Ar-C3, C5 H), 4.53 (s, 2H, Thiazole-CH$_2$-

Oxadiazole). ^{13}C NMR (126 MHz, CDCl$_3$): δ_c 176.6 (C, Thiazole-C-2), 167.8 (C, Oxadiazole-C-3), 167.4 (C, Oxadiazole-C-5), 165.6 and 163.6 (C, Ar-C-4, $^1J_{C\text{-}F}$ 252 Hz) , 149.1 (C, Thiazole-C-4), 132.2 (C, Ar-C-1'), 132.8 (CH, Ar-C-3', C-5'), 129.7 and 129.6 (CH, Ar-C-2, C-6, $^3J_{C\text{-}F}$ 8 Hz), 128.0 (CH, Ar-C-2', C- 6'), 124.6 (C, Ar-C-4'), 122.95 and 122.92 (C, Ar-C-1, $^4J_{C\text{-}F}$ 3 Hz), 116.7 (CH, Thiazole-C-5), 116.2 and 116.0 (CH, Ar-C-3, C-5 ,$^2J_{C\text{-}F}$ 22 Hz), 29.4 (CH$_2$, Thiazole-CH$_2$-Oxadiazole). HRMS calculated for $C_{18}H_{12}BrFN_3OS$, *m/z*: 415.9868 (M+H)$^+$; found : 415.9866.

3-(4-Fluorophenyl)-5-{[2-(*p*-tolyl)thiazol-4-yl]methyl}-1,2,4-oxadiazole (3j). ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 8.10 (dd, *J* 8.9 and 5.4 Hz, 2H, Ar-C-2, C-6 H), 7.82 (d, *J* 8.2 Hz, 2H, Ar-C-2', C-6' H), 7.23 (d, *J* 9.9 Hz, 3H, Ar-C-3', C-5', Thiazole-C-5 H), 7.16 (t, *J* 8.7 Hz, 2H, Ar-C-3, C-5 H), 4.53 (s, 2H, Thiazole-CH$_2$-Oxadiazole), 2.39 (s, 3H, Ar-CH$_3$). ^{13}C NMR (126 MHz, CDCl$_3$): δ_c 176.8 (C, Thiazole-C-2), 168.9 (C, Oxadiazole-C-3), 167.8 (C, Oxadiazole-C-5), 165.6 and 163.6 (C, Ar-C-4, $^1J_{C\text{-}F}$ 252 Hz), 148.7 (C, Thiazole-C-4), 140.6 (C, Ar-C-1'), 130.7 (C, Ar-C-4'), 129.7 and 129.6 (CH, Ar-C-2, C-6, $^3J_{C\text{-}F}$ 8 Hz), 129.6 (CH, Ar-C-3', C-5'), 126.5 (CH, Ar-C-2', C-6'), 123.0 and 122.9 (C, Ar-C-1, $^4J_{C\text{-}F}$ 3 Hz), 116.1 and 115.9 (CH, Ar-C-3,C-5,$^2J_{C\text{-}F}$ 22 Hz), 115.8 (CH, Thiazole-C-5), 29.5 (CH$_2$, Thiazole-CH$_2$-Oxadiazole) 21.4 (CH$_3$, Ar-CH$_3$). HRMS calculated for $C_{19}H_{15}FN_3OS$, *m/z*: 352.0920 (M+H)$^+$; found : 352.0921.

3-(4-Chlorophenyl)-5-[(2-phenylthiazol-4-yl)methyl]-1,2,4-oxadiazole (3k). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.04 (d, *J* 8.5 Hz, 2H, Ar-C2, C6 H), 7.94 (dd, *J* 6.5, 3.2 Hz, 2H, Ar-C'2, C'6 H), 7.46 (d, *J* 8.6 Hz, 2H, Ar-C3, C5 H), 7.43-7.47 (m, 3H, Ar-C'3, C'4, C'5 H merged), 4.55 (s, 2H, Thiazole-CH$_2$-Oxadiazole). ^{13}C NMR (126 MHz, CDCl$_3$): δ 176.9 (C, Thiazole-C-2), 168.7 (C, Oxadiazole-C-3), 167.8 (C, Oxadiazole-C-5), 148.8 (C, Thiazole-C-4), 137.4 (C, Ar-C-1') , 133.3 (C, Ar-C-4), 130.3 (CH, Ar-C-4'), 129.2 (CH, Ar-C-2', C-6'), 129.0 (CH, Ar-C-3, C-5), 128.8 (CH, Ar-C-3', C-5'), 126.6 (CH, Ar-C-2, C-6), 125.2 (C, Ar-C-1), 116.4 (CH, Thiazole-C-5), 29.5 (CH$_2$, Thiazole-CH$_2$-Oxadiazole). HRMS calculated for $C_{18}H_{13}FN_3OS$, *m/z*: 354.0468 (M+H)$^+$; found : 354.0469.

3-(4-Chlorophenyl)-5-{[2-(4-fluorophenyl)thiazol-4-yl]methyl}-1,2,4-oxadiazole (3l). ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 8.03 (d, *J* 8.2 Hz, 2H, Ar-C-2, C-6 H), 7.92 (dd, *J* 8.8 and 5.3 Hz, 2H, Ar-C-2', C-6' H), 7.45 (d, *J* 8.2 Hz, 2H, Ar-C-3, C-5 H), 7.26 (s, 1H, Thiazole-C-5 H), 7.12 (t, *J* 8.6 Hz, 2H, Ar-C-3', C-5' H), 4.53 (s, 2H, Thiazole-CH$_2$-Oxadiazole). ^{13}C NMR (126 MHz, CDCl$_3$): δ_c 176.8 (C, Thiazole-C-2), 167.8 (C, Oxadiazole-C-3), 167.5 (C, Oxadiazole-C-5), 165.0 and 163.0 (C, Ar-C-4' , $^1J_{C\text{-}F}$ 252 Hz), 148.8 (C, Thiazole-C-4), 137.4 (C, Ar-C-4), 129.65 and 129.62 (CH, Ar-C-1', $^4J_{C\text{-}F}$ 4 Hz), 129.2 (CH, Ar-C-3, C-5), 128.8 (CH, Ar-C-2, C-6), 128.6 and 128.5 (CH, Ar-C-2', C-6', $^3J_{C\text{-}F}$ 8 Hz), 125.2 (C, Ar-C-1), 116.4 (CH, Thiazole-C-5), 116.2 and 116.0 (CH, Ar-C-3', C-5', $^2J_{C\text{-}F}$ 22 Hz), 29.4 (CH$_2$, Thiazole-CH$_2$-Oxadiazole). HRMS calculated for $C_{18}H_{12}ClFN_3OS$, *m/z*: 372.0374 (M+H)$^+$; found : 372.0375.

3-(4-Chlorophenyl)-5-{[2-(4-chlorophenyl)thiazol-4-yl]methyl}-1,2,4-oxadiazole (3m). ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 8.03 (d, *J* 8.6 Hz, 2H, Ar-C-2, C-6 H), 7.87 (d, *J* 8.6 Hz, 2H, Ar-C-2', C-6' H), 7.45 (d, *J* 8.6 Hz, 2H, Ar-C-3, C-5 H), 7.40 (d, *J* 8.6 Hz, 2H, Ar-C-3', C-5' H), 7.29 (s, 1H, Thiazole-C-5 H), 4.54 (s, 2H, Thiazole-CH$_2$-Oxadiazole). ^{13}C NMR (126 MHz, CDCl$_3$): δ_c 176.8 (C, Thiazole-C-2), 167.8 (C, Oxadiazole-C-3), 167.3 (C, Oxadiazole-C-5), 149.0 (C, Thiazole-C-4), 137.4 (C, Ar-C-4), 136.3 (C, Ar-C-1'), 131.8 (C, Ar-C-4'), 129.2 (CH, Ar-C-3', C-5'), 129.2 (CH, Ar-C-3, C-5), 128.8 (CH, Ar-C-2', C-6'), 127.8 (CH, Ar-C-2, C-6), 125.2 (C, Ar-C-1), 116.7 (CH, Thiazole-C-5), 29.4 (CH$_2$, Thiazole-CH$_2$-Oxadiazole). HRMS calculated for $C_{18}H_{12}Cl_2N_3OS$, *m/z*: 388.0078 (M+H)$^+$; found : 388.0085.

5-{[2-(4-Bromophenyl)thiazol-4-yl]methyl}-3-(4-chlorophenyl)-1,2,4-oxadiazole (3n). ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 8.02 (d, J 8.2 Hz, 2H, Ar-C-2, C-6 H), 7.85 (d, *J* 8.6 Hz, 2H, Ar-C-2', C-6' H) 7.44 (d, *J* 8.2 Hz, 2H, Ar-C-3, C-5 H), 7.38 (d, *J* 8.6 Hz, 2H, Ar-C-3', C-5' H), 7.25 (s, 1H, Thiazole-C-5 H), 4.52 (s, 2H, Thiazole-CH$_2$-Oxadiazole). ^{13}C NMR (126 MHz, CDCl$_3$) δ 170.7 (C, Thiazole-C-2), 169.3 (C, Oxadiazole-C-3), 168.0 (C, Oxadiazole-C-5), 159.5 (C, Thiazole-C-4), 137.6 (C, Ar-C-4), 132.4 (CH, Ar-C-3', C-5'), 131.5 (C, Ar-C-1'), 129.3 (CH, Ar-C-3, C-5), 128.9 (CH, Ar-C-2', C-6'), 128.3 (CH, Ar-C-2, C-6), 125.9 (C, Ar-C-4'), 125.0 (C, Ar-C-1), 115.4 (CH, Thiazole-C-5), 17.8 (CH$_2$, Thiazole-CH$_2$-Oxadiazole). HRMS calculated for $C_{18}H_{12}BrClN_3OS$, *m/z*: 431.9573 (M+H)$^+$; found : 431.9578.

3-(4-Chlorophenyl)-5-{[2-(*p*-tolyl)thiazol-4-yl]methyl}-1,2,4-oxadiazole (3o). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.04 (d, *J* 8.6 Hz, 2H, Ar-C-2, C-6 H), 7.82 (d, *J* 8.1 Hz, 2H, Ar-C-2', C-6' H), 7.45 (d, *J* 8.6 Hz, 2H, Ar-C-3, C-5 H), 7.23 (d, *J* 9.2 Hz, 3H, Ar-C-3', C-5', thiazole-C-5 H merged), 4.53 (s, 2H, Thiazole-CH_2-Oxadiazole), 2.39 (s, 3H, Ar-CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ_c 176.9 (C, Thiazole-C-2), 168.9 (C, Oxadiazole-C-3), 167.8 (C, Oxadiazole-C-5), 148.6 (C, Thiazole-C-4), 140.6 (C, Ar-C-1'), 137.4 (C, Ar-C-4), 130.7 (C, Ar-C-4'), 129.7 (CH, Ar-C-3', C-5'), 129.2 (CH, Ar-C-3, C-5), 128.8 (CH, Ar-C-2, C-6), 126.5 (CH, Ar-C-2', C-6'), 125.3 (C, Ar-C-1), 115.9 (CH, Thiazole-C-5), 29.5 (CH_2, Thiazole-CH_2-Oxadiazole), 21.4 (CH_3, Ar-CH_3). HRMS calculated for $C_{19}H_{14}ClN_3OS$, *m/z*: 368.0624 $(M+H)^+$; found : 368.0628.

3-(4-Bromophenyl)-5-{[2-phenylthiazol-4-yl]methyl}-1,2,4-oxadiazole (3p). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.97 (d, *J* 8.6 Hz, 2H, Ar-C-2, C-6 H), 7.95–7.92 (m, 2H, Ar-C-2', C-6' H), 7.62 (d, *J* 8.6 Hz, 2H, Ar-C-3, C-5 H), 7.42-7.44 (m, 3H, Ar-C-3', C-5', C-4' H merged), 7.27 (s, 1H, Thiazole-C-5 H), 4.55 (s, 2H, Thiazole-CH_2-Oxadiazole). ^{13}C NMR (126 MHz, $CDCl_3$): δ_c 176.9 (C, Thiazole-C-2), 168.7 (C, Oxadiazole-C-5), 167.9 (C, Oxadiazole-C-3), 148.8 (C, Thiazole-C-4), 133.3 (C, Ar-C-1'), 132.1 (CH, Ar-C-3, C-5), 130.3 (CH, Ar-C-4'), 129.0 (CH, Ar-C-2, C-6), 129.0 (CH, Ar-C-2', C-6'), 126.6 (CH, Ar-C-3', C-5'), 125.8 (C, Ar-C-1), 125.7 (C, Ar-C-4), 116.4 (CH, Thiazole-C-5), 29.5 (CH_2, Thiazole-CH_2-Oxadiazole). HRMS calculated for $C_{18}H_{13}BrN_3OS$, *m/z*: 397.9963 $(M+H)^+$; found : 397.9975.

3-(4-Bromophenyl)-5-{[2-(4-fluorophenyl)thiazol-4-yl]methyl}-1,2,4-oxadiazole (3q). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.97 (d, *J* 8.6 Hz, 2H, Ar-C-2, C-6 H), 7.92 (dd, *J* 8.9 and 5.3 Hz, 2H, Ar-C-2', C-6' H), 7.62 (d, *J* 8.6 Hz, 2H, Ar-C-3, C-5 H), 7.26 (s, 1H, Thiazole-C-5 H), 7.12 (t, *J* 8.6 Hz, 2H, Ar-C-3', C-5' H), 4.53 (s, 2H, Thiazole-CH_2-Oxadiazole). ^{13}C NMR (126 MHz, $CDCl_3$): δ_c 176.8 (C, Thiazole-C-2), 167.9 (C, Oxadiazole-C-5), 167.5 (C, Oxadiazole-C-3), 165.0 and 163.0 (C, Ar-C-4', $^1J_{C-F}$ 250 Hz), 148.8 (C, Thiazole-C-4), 132.2 (CH, Ar-C-3, C-5), 129.7 and 129.6 (C, Ar-C-1', $^4J_{C-F}$ 4 Hz), 129.0 (CH, Ar-C-2, C-6), 128.6 and 128.5 (CH, Ar-C-2', C-6', $^3J_{C-F}$ 8 Hz), 125.8 (C, Ar-C-1), 125.7 (C, Ar-C-4), 116.4 and 116.2 (CH, Ar-C-3', C-5', $^2J_{C-F}$ 20 Hz), 116.0 (CH, Thiazole-C-5), 29.4 (CH_2, Thiazole-CH_2-Oxadiazole). HRMS calculated for $C_{18}H_{12}BrFN_3OS$, *m/z*: 415.9868 $(M+H)^+$; found : 415.9866.

3-(4-Bromophenyl)-5-{[2-(4-chlorophenyl)thiazol-4-yl]methyl}-1,2,4-oxadiazole (3r). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.96 (d, *J* 8.6 Hz, 2H, Ar-C-2, C-6 H), 7.87 (d, *J* 8.6 Hz, 2H, Ar-C-2', C-6' H), 7.62 (d, *J* 8.6 Hz, 2H, Ar-C-3, C-5 H), 7.41 (d, *J* 8.6 Hz, 2H, Ar-C-3', C-5' H), 7.29 (s, 1H, thiazole-C-5 H), 4.54 (s, 2H, Thiazole-CH_2-Oxadiazole). ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 176.8 (C, Thiazole-C-2), 167.9 (C, Oxadiazole-C-3), 167.3 (C, Oxadiazole-C-5), 145.0 (C, Thiazole-C-4), 136.3 (C, Ar-C-1'), 132.2 (CH, Ar-C-3, C-5), 131.8 (C, Ar-C-4'), 129.2 (CH, Ar-C-2', C-6'), 129.0 (CH, Ar-C-3', C-5'), 127.8 (CH, Ar-C-2, C-6), 125.8 (C, Ar-C-1), 125.6 (C, Ar-C-4), 116.7 (CH, Thiazole-C-5), 29.4 (CH_2, Thiazole-CH_2-Oxadiazole). HRMS calculated for $C_{18}H_{12}BrClN_3OS$, *m/z*: 431.9573 $(M+H)^+$; found : 431.9578.

3-(4-Bromophenyl)-5-{[2-(4-bromophenyl)thiazol-4-yl]methyl}-1,2,4-oxadiazole (3s). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.96 (d, *J* 8.5 Hz, 2H, Ar-C-2, C-6 H), 7.80 (d, *J* 8.5 Hz, 2H, Ar-C-2', C-6' H), 7.62 (d, *J* 8.5 Hz, 2H, Ar-C-3, C-5H), 7.56 (d, *J* 8.5 Hz, 2H, Ar-C-3', C-5' H), 7.29 (s, 1H, Thiazole-C-5 H), 4.54 (s, 2H, Thiazole-CH_2-Oxaiazole). ^{13}C NMR (126 MHz, $CDCl_3$): δ_c 176.8 (C, Thiazole-C-2), 167.9 (C, Oxadiazole-C-3), 167.4 (C, Oxadiazole-C-5), 149.0 (C, Thiazole-C-4), 132.2 (CH, Ar-C-3, C-5), 132.1 (CH, Ar-C-3', C-5'), 129.0 (CH, Ar-C-2', C-6'), 128.0 (CH, Ar-C-2, C-6), 125.8 (C, Ar-C-1), 125.6 (C, Ar-C-4), 124.6 (C, Ar-C-4'), 116.7 (CH, Thiazole-C-5), 29.4 (CH_2, Thiazole-CH_2-Oxadiazole). HRMS calculated for $C_{18}H_{12}Br_2N_3OS$, *m/z*: 475.9068 $(M+H)^+$; found : 475.9075.

3-(4-bromophenyl)-5-{[2-(p-tolyl)thiazol-4-yl]methyl}-1,2,4-oxadiazole (3t). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.97 (d, *J* 8.5 Hz, 2H, Ar-C-2, C-6 H), 7.82 (d, *J* 8.1 Hz, 2H, Ar-C-2', C-6' H), 7.61 (d, *J* 8.5 Hz, 2H, Ar-C-3, C-5 H), 7.23 (d, *J* 9.8 Hz, 3H, Ar-C-3', C-5', Thiazole-C-5 H, merged), 4.53 (s, 2H, Thiazole-CH_2-Oxadiazole), 2.39 (s, 3H, Ar-CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ_c 177.0 (C, Thiazole-C-2), 168.9 (C, Oxadiazole-C-3), 167.9 (C, Oxadiazole-C-5), 148.6 (C, Thiazole-C-4), 140.6 (C, Ar-C-4'), 132.1 (CH, Ar-C-3, C-5), 130.7 (C, Ar-C-1'), 129.7 (CH, Ar-C-2, C-6), 129.0 (CH, Ar-C-3', C-5'), 126.5 (CH, Ar-C-2', C-6'), 125.8 (C, Ar-C-1), 125.7 (C, Ar-C-4), 115.9 (CH, Thiazole-C-5), 29.5 (CH_2, Thiazole-CH_2-Oxadiazole), 21.4 (CH_3, Ar-CH_3). HRMS calculated for $C_{19}H_{15}BrN_3OS$, *m/z*: 412.0119 $(M+H)^+$; found: 412.0125.

5-[(2-Phenylthiazol-4-yl)methyl]-3-(*p*-tolyl)-1,2,4-oxadiazole (3u). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.98 (d, *J* 8.1 Hz, 2H, Ar-C-2, C-6 H), 7.94 (dd, *J* 6.5 and 3.1 Hz, 2H, Ar-C-2', C-6' H), 7.42-7.44 (m, 3H, Ar-C-3', C-5', C-4', H merged), 7.29 (s, 1H, Thiazole-C-5 H), 7.27 (d, *J* 4.1 Hz, 2H, Ar-C-3, C-5 H), 4.55 (s, 2H, Thiazole-CH_2-Oxadiazole), 2.41 (s, 3H, Ar-CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4 (C, Thiazole-C2), 168.6 (C, Oxadiazole-C-3), 168.6 (C, Oxadiazole-C-5), 149.0 (C, Thiazole-C-4), 141.6 (C, Ar-C-4), 133.3 (C, Ar-C-1'), 130.2 (C, Ar-C-4'), 129.6 (CH, Ar-C-2', C-6'), 129.0 (CH, Ar-C-3, C-5), 127.4 (CH, Ar-C-2, C-6), 126.6 (CH, Ar-C-3', C-5'), 123.9 (C, Ar-C-1), 116.3 (CH, Thiazole-C-5), 29.5 (CH_2, Thiazole-CH_2-Oxadiazole), 21.6 (CH_3, Ar-CH_3). HRMS calculated for $C_{19}H_{16}N_3OS$, *m/z*: 334.1014 $(M+H)^+$; found : 334.1015.

5-{[2-(4-Fluorophenyl)thiazol-4-yl]methyl}-3-(*p*-tolyl)-1,2,4-oxadiazole (3v). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.98 (d, *J* 8.2 Hz, 2H, Ar-C-2, C-6 H), 7.92 (dd, *J* 8.8 and 5.3 Hz, 2H, Ar-C-2', C-6' H), 7.28 (d, *J* 8.0 Hz, 2H, Ar-C-3, C-5 H), 7.26 (s, 1H, Thiazole-C-5 H), 7.12 (t, *J* 8.6 Hz, 2H, Ar-C-3', C-5' H), 4.53 (s, 2H, Thiazole-CH_2-Oxadiazole), 2.41 (s, 3H, Ar-CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ_c 176.4 (C, Thiazole-C2), 168.6 (C, Oxadiazole-C-3), 167.4 (C, Oxadiazole-C-5), 165.0 and 163.0 (C, Ar-C-4', $^1J_{C\text{-}F}$ 250 Hz), 149.1 (C, Thiazole-C-4), 141.6 (C, Ar-C-4), 129.7 and 129.7 (C, Ar-C-1', $^4J_{C\text{-}F}$ 4 Hz), 129.6 (CH, Ar-C-3, C-5), 128.6 and 128.5 (CH, Ar-C-2', C-6', $^3J_{C\text{-}F}$ 8 Hz), 127.4 (CH, Ar-C-2, C-6), 123.9 (C, Ar-C-1), 116.3 and 116.1 (CH, Ar-C-3', C-5', $^2J_{C\text{-}F}$ 20 Hz), 116.0 (CH, Thiazole-C-5), 29.5 (CH_2, Thiazole-CH_2-Oxadiazole), 21.6 (CH_3, Ar-CH_3). HRMS calculated for $C_{19}H_{15}FN_3OS$, *m/z*: 352.0920 $(M+H)^+$; found : 352.0921.

5-{[2-(4-Chlorophenyl)thiazol-4-yl]methyl}-3-(*p*-tolyl)-1,2,4-oxadiazole (3w). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.98 (d, *J* 8.2 Hz, 2H, Ar-C-2, C-6 H), 7.87 (d, *J* 8.6 Hz, 2H, Ar-C-2', C-6' H), 7.40 (d, *J* 8.6 Hz, 2H, Ar-C-3, C-5 H), 7.29 (d, *J* 8.6 Hz, 2H, Ar-C-3', C-5' H), 7.27 (s, 1H, Thiazole-C-5 H), 4.53 (s, 2H, Thiazole-CH_2-Oxadiazole), 2.41 (s, 3H, Ar-CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ_c 176.3 (C, Thiazole-C2), 168.6 (C, Oxadiazole-C-3), 167.2(C, Oxadiazole-C-5), 149.2 (C, Thiazole-C-4), 141.6 (C, Ar-C-4), 136.2 (C, Ar-C-1'), 131.8 (C, Ar-C-4'), 129.6 (CH, Ar-C-2', C-6'), 129.2 (CH, Ar-C-3, C-5), 127.8 (CH, Ar-C-3', C-5'), 127.4 (CH, Ar-C-2, C-6), 123.9 (C, Ar-C-1), 116.6 (CH, Thiazole-C-5), 29.4 (CH_2, Thiazole-CH_2-Oxadiazole), 21.6 (CH_3, Ar-CH_3). HRMS calculated for $C_{19}H_{14}ClN_3OS$, *m/z*: 368.0624 $(M+H)^+$; found : 368.0628.

5-{[2-(4-Bromophenyl)thiazol-4-yl]methyl}-3-(*p*-tolyl)-1,2,4-oxadiazole (3x). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.98 (d, *J* 8.2 Hz, 2H, Ar-C-2, C-6 H), 7.80 (d, *J* 8.5 Hz, 2H, Ar-C-2', C-6' H), 7.56 (d, *J* 8.5 Hz, 2H, Ar-C-3', C-5' H), 7.28 (d, *J* 8.4 Hz, 3H, Ar-C-3, C-5, Thiazole-C-5), 4.53 (s, 2H, Thiazole-CH_2-Oxadiazole), 2.41 (s, 3H, Ar-CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ_c 176.3 (C, Thiazole-C2), 168.6 (C, Oxadiazole-C-3), 167.3 (C, Oxadiazole-C-5), 149.3 (C, Thiazole-C-4), 141.6 (C, Ar-C-4), 132.2 (C, Ar-C-1'), 132.1 (CH, Ar-C-3, C-5), 129.6 (CH, Ar-C-2, C-6), 128.0 (CH, Ar-C-3', C-5'), 127.4 (CH, Ar-C-2', C-6'), 124.5 (C, Ar-C-1), 123.8 (C, Ar-C-4'), 116.7 (CH, Thiazole-C-5), 29.4 (CH_2, Thiazole-CH_2-Oxadiazole), 21.6 (CH_3, Ar-CH_3). HRMS calculated for $C_{19}H_{15}BrN_3OS$, *m/z*: 412.0119 $(M+H)^+$; found : 412.0126.

3-(*p*-Tolyl)-5-{[2-(*p*-tolyl)thiazol-4-yl]methyl}-1,2,4-oxadiazole (3y). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.98 (d, *J* 8.2 Hz, 2H, Ar-C-2, C-6 H), 7.82 (d, *J* 8.2 Hz, 2H, Ar-C-2', C-6' H), 7.28 (d, *J* 8.0 Hz, 2H, Ar-C-3', C-5' H), 7.23 (d, *J* 9.0 Hz, 3H, Ar-C-3, C-5, Thiazole-C-5 H), 4.53 (s, 2H, Thiazole-CH_2-Oxadiazole), 2.41 (s, 3H, Ar-CH_3), 2.39 (s, 3H, Ar-CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ_c 176.5 (C, Thiazole-C2), 168.8 (C, Oxadiazole-C-3), 168.6 (C, Oxadiazole-C-5), 148.8 (C, Thiazole-C-4), 141.5 (C, Ar-C-4), 140.5 (C, Ar-C-4'), 130.7 (C, Ar-C-1'), 129.6 (CH, Ar-C-3', C-5'), 129.6 (CH, Ar-C-3, C-5), 127.4 (CH, Ar-C-2', C-6'), 126.5 (CH, Ar-C-2, C-6), 123.9 (C, Ar-C-1), 115.8 (CH, Thiazole-C-5), 29.5 (CH_2, Thiazole-CH_2-Oxadiazole), 21.6 (CH_3, Ar-CH_3), 21.4 (CH_3, Ar-CH_3). HRMS calculated for $C_{20}H_{18}N_3OS$, *m/z*: 348.1171 $(M+H)^+$; found : 348.1175.

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Supplementary Material

^{1}H and ^{13}C NMR spectra of compounds **3a-y** are given in the Supplementary Material file associated with this manuscript.

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