Synthesis and *in vitro* antiproliferative activity of new adamantylthiazolyl-1,3,4-oxadiazoles

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Abstract

A new series of adamantanyl-1,3-thiazole and 1,3,4-oxadiazole derivatives (6a-l), bearing various aryl groups has been synthesized from adamantan-1-nitrile in four steps. All the compounds were evaluated, *in vitro*, for antiproliferative activity against a large panel of human tumor-derived cell lines. Compounds 6e exhibited activity against human splenic B-lymphoblastoid (WIL-2NS) and human acute B-lymphoblastic leukemia (CCRF-SB) cell lines with \( CC_{50} = 68 \) and 42 \( \mu \)M, respectively. Compound 6l showed activity against CCRF-SB cell lines with \( CC_{50} = 51 \) \( \mu \)M. All the other compounds were found inactive.

Key words: Adamantan-1-nitrile, antitumor activity, anti-HIV activity, thiazole, oxadiazoles.

Introduction

Amantadine hydrochloride 1 (1-adamantanamine hydrochloride, Symmetrel®) was the first adamantane derivative introduced in medicine as effective therapy\(^1\) against Asian A influenza virus. Among various substituents a growing interest in adamantyl derivatives is gaining prominence because of well known drugs like Rimantadine, Memantine, Adapalene, Adatanserin and others in clinical trials.\(^4\) The pronounced central nervous stimulant and cardiovascular effects of amantadine\(^6\) necessitated the search for newer more potent and less toxic agents for the control of pandemic influenza viruses. N-1-adamantyl-4-aminophthalamide 2 was endowed with anti-HIV-1 and -HIV-2 activities in CEM cell cultures.\(^6\) Potent anti-HIV-1 activity was recently observed for a series of (±)-2-(1-adamantyl-3-alkyl/aryl)thiazolidin-4-ones where these compounds behaved as
typical non-nucleoside reverse transcriptase inhibitors.\textsuperscript{7,8} Burstein \textit{et al.}\textsuperscript{9} developed adamantane derivatives, in which the adamantane moiety is chemically linked to a water soluble polyanionic matrix. These derivatives proved to be good inhibitors of replication in early stages of HIV-1. In addition, the activity of some adamantane derivatives has recently improved their use in clinical therapeutic efficacy of interferon/ribavirin combination against hepatitis C.\textsuperscript{10} Some other adamantyl derivatives have been used as anti-inflammatory,\textsuperscript{11-14} antimicrobial,\textsuperscript{15-17} antimalarial\textsuperscript{18} and antidepressant\textsuperscript{19} agents as well as inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1).\textsuperscript{20}

We have recently reported the synthesis and biological activities of various azoles.\textsuperscript{21-23} In the present study, we selected three pharmacophores \textit{i.e.} 1,3-thiazole, 1,3,4-oxadiazole and adamantyl precursors, to build up potent molecules possessing these three backbones, aiming to investigate their anticancer and antiviral activities.

**Results and Discussion**

Adamantan-1-nitrile was selected as starting material for the synthesis of target compounds. The nitrile was converted into thioamide 3 (52%), using \( \text{P}_4\text{S}_{10} \) followed by its treatment with ethyl bromopyruvate to afford 4 (80%). Hydrazinolysis of 4 gave the carbohydrazide-1,3-thiazole 5 in 75% yield. Heating 5 with substituted benzoic acids in the presence of polyphosphoric acid (PPA) furnished 1,3,4-oxadiazole derivatives 6a-l in 61-66% yield. The synthetic reactions are summarized in scheme 1.
Scheme 1. Synthesis of 2-(2-adamantyl-1,3-thiazol-4-yl)-5-aryl-1,3,4-oxadiazoles.

The synthesis of 3 was confirmed in the IR and NMR spectra. In the IR spectrum, the typical sharp absorptions at $\nu_{\text{max}}$ 3424 and 3323 cm\(^{-1}\) characteristic of the primary NH\(_2\) group were observed. The $^1$H-NMR spectrum exhibited two singlets at $\delta$ 7.95 and 7.10 attributed to the NH\(_2\) protons. In the $^{13}$C-NMR spectrum, the downfield signal at $\delta$ 218.9 was assigned to the thiocarbonyl carbon. Additional support for the formation of 3 was obtained by appearance of the molecular ion peak in the mass spectrum at m/z 195. The structures of compounds 4 and 5 were also established using IR and NMR spectroscopy and the molecular mass confirmed by MS. The IR spectra of 4 and 5 exhibited absorptions corresponding to the carbonyl groups at $\nu_{\text{max}}$ 1732 and 1663 cm\(^{-1}\), respectively. In the $^{13}$C-NMR spectra, the signals at $\delta$ 161.7 and 162.2 were attributed to the carbonyl carbon atoms in compound 4 and 5, respectively. In the $^1$H-NMR of compound 5, a broad singlet observed at $\delta$ 8.48 was assigned to the NH\(_2\) group. Additional support for formation of 4 and 5 were obtained by appearance of the molecular ion peaks in the mass spectra at m/z 291 and 277, respectively.

The structures of 6a-l were confirmed by the IR, NMR and mass spectra. The IR spectra were characterized by the C-O absorptions in the range $\nu_{\text{max}}$ 1262-1102 cm\(^{-1}\), an indicative for the 1,3,4-oxadiazole ring formation. In the $^1$H NMR spectra, four aromatic protons were appeared in the range of $\delta$ 7.33-8.33 ppm. The singlets in the range $\delta$ 7.88-8.12 were assigned to H-5 of the thiazole moiety. In the $^{13}$C-NMR spectra, the resonances in the region $\delta$ ~161.0 and $\delta$ ~163.0 were assigned to C-2 and C-5 of the oxadiazole ring, respectively. The carbons of the adamantane moiety were located at the region $\delta$ 28.5-43.1 ppm. Compound 6d was selected for further NMR study. From the gradient\(^{24}\) selected HMBC spectrum of 6d, H-5 of the thiazole ring at $\delta_{\text{H}}$ 8.09 showed a $^3J_{\text{C,H}}$
couplings with C-2 of the thiazole ring at $\delta_C$ 183.8 and C-2 of the oxadiazole ring at 160.9 ppm. Furthermore, a $^2J_{C,H}$ coupling of the same proton with C-4 of the thiazole ring at $\delta_C$ 139.2 ppm was also observed.

**In vitro antiproliferative activity**

Compounds 6a-l were tested, in vitro, against a large panel of human cell lines derived from hematological [CD4$^+$ human T-cells containing an integrated HTLV-1 genome (MT-4); CD4$^+$ human acute T-lymphoblastic leukemia (CCRF-CEM); human splenic B-lymphoblastoid cells (WIL-2NS); human acute B-lymphoblastic leukemia (CCRF-SB) and solid skin melanoma (SK-28); breast adenocarcinoma (MCF-7); lung squamous carcinoma (SK-MES-1); hepatocellular carcinoma (HepG-2); prostate carcinoma (DU-145)] or normal tissues [lung fibroblasts (MRC-5)]. For comparative purposes, we evaluated the cytotoxic activities of the compounds relative to Doxorubicin.

All compounds were inactive except 6e which showed activity against human splenic B-lymphoblastoid cells (WIL-2NS) and human acute B-lymphoblastic leukemia (CCRF-SB) cell lines with $CC_{50} = 68$ and 42 $\mu$M, respectively. Compound 6l exhibited activity against CCRF-SB cell lines with $CC_{50} = 51$ $\mu$M.

**Experimental Section**

**General Procedures.** Melting points are uncorrected and were measured on a Gallenkamp melting point apparatus (MP-D). The elemental analysis was performed on Leco CHNS-932 Elemental Analyzer, Leco Corporation (USA). NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer with TMS as an internal standard and on the 75 MHz ($^{13}$C) (scale in $\delta$). The multiplicities are expressed as s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, t = triplet and m = multiplet. Mass spectra were recorded on Agilent technologies 6890N gas chromatograph and an inert mass selective detector 5973 mass spectrometer. The $R_f$-values were determined employing pre-coated silica gel aluminium plates, Kieselgel 60 F$_{254}$ from Merck (Germany), using n-hexane: ethyl acetate (7:3) as an eluent unless otherwise mentioned. Column chromatography was carried out using silica gel 60 (0.063-0.200 mm) purchased form Merck. The IR spectra were recorded on FTS 3000 MX, Bio-Rad Merlin (Excalibur Model) spectrophotometer.

**2-Adamantanethioamide (3).** P$_4$S$_{10}$ (5.33 g, 12.00 mmol) was stirred at room temperature in EtOH (25 mL) for 2 h. Adamantane-1-nitrile (1.0 g, 6.20 mmol) was added to the above solution and the reaction mixture heated under reflux for 12 h. After completion of the reaction, the solution was concentrated in vacuo, diluted with water and extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic extracts were dried (Na$_2$SO$_4$), filtered and concentrated in vacuo and the yellow liquid was refrigerated. The resulting white crystals were filtered, dried and recrystallized from aq. EtOH to
give 3 (0.63 g, 52 %); mp 159-161 ºC; Rf: 0.54. IR (νmax, KBr, cm⁻¹): 3424, 3323, 2907, 2848, 1656, 1449, 1384, 1181. ¹H-NMR (CDCl₃): δ 1.79 (m, 6H, CH₂-4, CH₂-6, CH₂-10), 2.18 (m, 9H, CH₂-2, CH-3, CH-5, CH-7, CH₂-8, CH₂-9), 7.10 (bs, 1H, N-H), 7.95 (1H, bs, N-H). ¹³C-NMR (CDCl₃): δ 28.4, 36.2, 41.7, 45.6 (Cadamant); 218.9 (C=S). EI-MS (m/z, %): 195 (M⁺, 80), 135 (100), 121 (5), 107 (15), 93 (27), 60 (16). Anal. calcd. for C₁₁H₁₂N₅S: C, 67.64; H, 6.88; N, 15.11. Found: C, 67.54; H, 6.72; N, 15.03.

Ethyl 2-adamantyl-1,3-thiazole-4-carboxylate (4). A mixture of 2-adamantanethioamide (3) (0.29 g, 1.5 mmol) and ethyl bromopyruvate (0.29 g, 1.5 mmol) in EtOH (25 mL) were heated under reflux for 8 h. After cooling, the reaction mixture was concentrated in vacuo, diluted with water and extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated in vacuo to afford 3 as a yellow oil (0.35 g, 80 %), Rf: 0.73. IR (νmax, film, cm⁻¹): 3117, 2906, 2850, 1732, 1605, 1497, 1477, 1451, 1368, 1093. ¹H-NMR (CDCl₃): δ 1.40 (t, 3H, J = 7.2 Hz, OCH₂CH₃), 1.79 (m, 6H, CH₂-4, CH₂-6, CH₂-10), 2.18 (m, 9H, CH₂-2, CH-3, CH-5, CH-7, CH₂-8, CH₂-9), 4.41 (2H, q, J = 7.2 Hz, OCH₂CH₃), 8.05 (1H, s, H-12). ¹³C-NMR (CDCl₃): δ 121.8 (C=O); 182.1 (C=O); 125.9 (C5thiazole); 146.6 (C4thiazole); 161.7 (C=O); 182.3 (C²thiazole). EI-MS (m/z, %): 291 (M⁺, 90), 246 (100), 135 (45), 121 (3), 107 (9), 93 (15), 71 (50), 45 (10).

2-Adamantyl-1,3-thiazole-4-carboxylic acid (5). Hydrazine hydrate 80% (5.2 mmol) was added slowly to a stirred solution of ethyl 2-adamantyl-1,3-thiazole-4-carboxylate (4) (0.38 g, 1.3 mmol) in MeOH (5 mL) and the reaction mixture heated under reflux for 4 h. After cooling, the mixture was concentrated in vacuo, followed by addition of cold water. The precipitated solid was filtered, dried (Na₂SO₄) and recrystallized from aq. EtOH to give (5) (0.27 g, 75 %); mp 179-181 ºC; Rf 0.73 (petroleum ether : acetone; 2:3). IR (νmax, KBr, cm⁻¹): 3424, 3323, 3184, 1663, 1544, 1491. ¹H-NMR (CDCl₃): δ 1.79 (m, 6H, CH₂-4, CH₂-6, CH₂-10), 2.04 (m, 9H, CH₂-2, CH-3, CH-5, CH-7, CH₂-8, CH₂-9), 4.08 (bs, 2H, NH₂), 7.99 (s, 1H, H-12), 8.48 (bs, 1H, N-H). ¹³C-NMR (CDCl₃): δ 28.4, 36.4, 39.6, 41.7 (Cadamant); 61.2 (OCH₂CH₃); 147.9 (C²thiazole); 162.2 (C=O); 182.1 (C³thiazole). EI-MS (m/z, %): 277 (M⁺, 95), 246 (100), 219 (10), 179 (5), 135 (47), 121 (3), 107 (9), 93 (15). Anal. calcd. for C₁₄H₁₉N₃SO: C, 60.64; H, 6.88; N, 15.11. Found: C, 60.35; H, 6.66; N, 15.03.

General procedure for the synthesis of 2-(2-adamantyl-1,3-thiazol-4-yl)-5-aryl-1,3,4-oxadiazoles (6a-i)
A mixture of 5 (0.50 g, 1.8 mmol) and substituted benzoic acid (1.8 mmol) was heated at 100-120 ºC in presence of excess polyphosphoric acid (PPA) for 4 h. After cooling, the mixture was poured into crushed ice, and neutralized with 5% aq. NaHCO₃ solution. The precipitated solid was filtered and purified using column chromatography (petroleum ether : ethyl acetate; 9 : 1).

2-(2-Adamantyl-1,3-thiazol-4-yl)-5-(4-methylphenyl)-1,3,4-oxadiazole (6a). From 4-methylbenzoic acid (0.25 g). Yield: 0.45 g (66%); mp 187-189 ºC; Rf: 0.57. IR (νmax, KBr, cm⁻¹): 1600, 1497, 1261. ¹H-NMR (CDCl₃): δ 1.84 (m, 6H, CH₂-4, CH₂-6, CH₂-10), 2.17 (m, 9H, CH₂-2, CH-3, CH-5, CH-7, CH₂-8, CH₂-9), 2.46 (s, 3H, Ph-CH₃); 7.35 (d, 2H, J₂,₃ = J₅,₆ = 9.0 Hz, Ar-H-3, Ar-H-5); 8.07 (s, 1H, H⁵thiazole); 8.08 (d, 2H, Ar-H-2, Ar-H-6). ¹³C-NMR (CDCl₃): δ 21.7 (Ph-CH₃);
28.5, 36.4, 39.9, 43.1 (C$_{adamant}$); 120.7 (C$_5$$_{thiazole}$); 121.1, 127.1, 129.7 (C$_{arom}$); 139.5 (C$_4$$_{thiazole}$); 142.3 (C$_1$$_{arom}$); 160.6 (C$_{oxadiazole}$$_1$); 164.6 (C$_5$$_{oxadiazole}$); 183.5 (C$_2$$_{thiazole}$). El-MS (m/z; %): 377 (M$^+$, 100), 246 (10), 160 (33), 135 (15), 121 (10), 119 (25), 107 (3), 93 (7), 91 (27), 79 (15), 65 (10). Anal. calcd. for C$_{22}$H$_{33}$N$_5$SO: C, 69.90; H, 6.14; N, 11.10; S,8.49; Found: C, 69.95; H, 6.29; N, 10.81; S, 8.39.

2-(2-Adamantyl-1,3-thiazol-4-yl)-5-(3-methylphenyl)-1,3,4-oxadiazole (6b). From 3-methylbenzoic acid (0.25 g). Yield: 0.43 g (63%); mp 153-155 ºC; Rf: 0.55. IR (v$_{max}$, KBr, cm$^{-1}$): 1590, 1549, 1263. $^1$H-NMR (CDCl$_3$): $\delta$ 1.83 (m, 6H, CH$_2$-4, CH$_2$-6, CH$_2$-10); 2.17 (m, 9H, CH$_2$-2, CH-3, CH-5, CH-7, CH$_2$-8, CH$_2$-9); 2.47 (s, 3H, CH$_3$); 7.37 (d, 1H, J = 7.5 Hz, Ar-H-4); 7.43 (t, 1H, J$_{5,6}$ = 7.5 Hz, Ar-H-5); 7.98 (s, 1H, Ar-H-2); 8.02 (s, 1H, H$_3$$_{thiazole}$); 8.08 (d, 1H, Ar-H-6). $^{13}$C-NMR (CDCl$_3$): $\delta$ 22.3 (Ph-CH$_2$); 28.6, 36.5, 39.9, 43.1 (C$_{adamant}$); 120.8 (C$_5$$_{thiazole}$); 123.6, 124.3, 127.7, 128.9, 132.6 (C$_{arom}$); 139.5 (C$_4$$_{thiazole}$); 160.7 (C$_2$$_{oxadiazole}$); 164.5 (C$_5$$_{oxadiazole}$); 183.7 (C$_2$$_{thiazole}$). El-MS (m/z; %): 377 (M$^+$, 100), 246 (10), 160 (20), 135 (10), 119 (15), 121 (3), 107 (2), 93 (6), 91 (17), 79 (10), 65 (5).

2-(2-Adamantyl-1,3-thiazol-4-yl)-5-(2-chlorophenyl)-1,3,4-oxadiazole (6f). From 4-chlorobenzoic acid (0.16 g). Yield: 0.24 g (62%); mp 148-150 ºC; Rf: 0.47. IR (v$_{max}$, KBr, cm$^{-1}$): 1596, 1543, 1265, 1019. $^1$H-NMR (CDCl$_3$): $\delta$ 1.83 (m, 6H, CH$_2$-4, CH$_2$-6, CH$_2$-10); 2.16 (m, 9H, CH$_2$-2, CH-3, CH-5, CH-7, CH$_2$-8, CH$_2$-9); 7.52 (d, 2H, J$_{2,3}$ = J$_{5,6}$ = 8.7 Hz, Ar-H-2, Ar-H-6); 8.09 (s, 1H, H$_3$$_{thiazole}$); 8.13 (d, 2H, Ar-H-3, Ar-H-5). $^{13}$C-NMR (CDCl$_3$): $\delta$ 28.5, 36.4, 39.9, 43.1 (C$_{adamant}$); 121.1 (C$_5$$_{thiazole}$); 122.3, 128.4, 129.4 (C$_{arom}$); 134.9 (C$_4$$_{arom}$); 139.2 (C$_4$$_{thiazole}$); 160.9 (C$_2$$_{oxadiazole}$); 163.6 (C$_5$$_{oxadiazole}$); 183.8 (C$_2$$_{thiazole}$). El-MS (m/z; %): 399 (M$^+$+2, 33), 397 (M$^+$, 100), 246 (12), 217 (4), 182 (5), 180 (14), 141 (5), 139 (16), 135 (15), 121 (1), 113 (4), 111(12), 107 (2), 93 (12), 79 (15).

2-(2-Adamantyl-1,3-thiazol-4-yl)-5-(3-chlorophenyl)-1,3,4-oxadiazole (6e). From 3-chlorobenzoic acid (0.16 g). Yield: 0.24 g (61%); mp 165-168 ºC; Rf: 0.52. IR (v$_{max}$, KBr, cm$^{-1}$): 1576, 1547, 1262, 1086. $^1$H-NMR (CDCl$_3$): $\delta$ 1.83 (m, 6H, CH$_2$-4, CH$_2$-6, CH$_2$-10); 2.16 (m, 9H, CH$_2$-2, CH-3, CH-5, CH-7, CH$_2$-8, CH$_2$-9); 7.31-7.55 (m, 2H, Ar-H-4, Ar-H-5); 8.00-8.21 (m, 3H, Ar-H-2, Ar-H-6, H$_5$$_{thiazole}$). $^{13}$C-NMR (CDCl$_3$): $\delta$ 28.6, 36.2, 39.9, 43.0 (C$_{adamant}$); 121.3 (C$_5$$_{thiazole}$); 125.3, 125.4, 127.1, 130.4, 131.8, 135 (C$_{arom}$); (C$_3$$_{arom}$); 139.1 (C$_4$$_{thiazole}$); 160.5 (C$_2$$_{oxadiazole}$); 163.2, (C$_5$$_{oxadiazole}$); 183.8(C$_2$$_{thiazole}$). El-MS (m/z; %): 399 (M$^+$+2, 33), 397 (M$^+$, 100), 246 (10), 217 (2), 182 (2), 180 (7), 141 (5), 139 (16), 135 (15), 121 (1), 113 (4), 111(13), 107 (2), 93 (14), 79 (18).

2-(2-Adamantyl-1,3-thiazol-4-yl)-5-(2-chlorophenyl)-1,3,4-oxadiazole (6i). From 2-chlorobenzoic acid (0.16 g). Yield: 0.24 g (62%); mp 148-150 ºC; Rf: 0.50. IR (v$_{max}$, KBr, cm$^{-1}$):
1596, 1532, 1262, 1088. $^1$H-NMR (CDCl$_3$): $\delta$ 1.82 (m, 6H, CH$_2$-4, CH$_2$-6, CH$_2$-10); 2.16 (m, 9H, CH$_2$-2, CH-3, CH-5, CH-7, CH$_2$-8, CH$_2$-9); 7.44 (dt, 1H, $J_{4,5} = J_{3,4} = 7.7$ Hz, $J_{4,6} = 1.5$ Hz, Ar-H-4); 7.50 (m, 1H, Ar-H-5); 7.58 (dd, 1H, $J_{5,6} = 7.7$ Hz, $J_{5,7} = 1.5$ Hz, Ar-H-3); 8.09 (dd, 1H, $J_{5,6} = 7.5$ Hz, $J_{4,6} = 1.8$ Hz, H-6), 8.09 (s, 1H, H$_3$thiazole). $^{13}$C-NMR (CDCl$_3$): $\delta$ 28.5, 36.4, 39.9, 43.1 (C$_{adamant}$); 121.3 (C$_2$thiazole); 123.2, 127.1, 131.1, 131.5, 132.4 (C$_{arom}$); 133.3 (C$_1$arom); 139.3 (C$_4$thiazole); 161.2 (C$_2$oxadiazole); 162.7 C$_5$oxadiazole); 183.8 (C$_2$thiazole). El-MS (m/z; %): 399 (M+2, 33), 397 (M+, 100), 246 (14), 182 (3), 180 (10), 141 (5), 139 (16), 135 (15), 121 (1), 113 (3), 111(10), 107 (2), 93 (15), 79 (18).

2-(2-Adamantyl-1,3-thiazol-4-yl)-5-(4-bromophenyl)-1,3,4-oxadiazole (6f). From 4-bromobenzoic acid (0.20 g). Yield: 0.27 g (61%); mp 188-190 °C; Rf: 0.53. IR ($v_{max}$, KBr, cm$^{-1}$): 1593, 1474, 1102, 1075; $^1$H-NMR (CDCl$_3$): $\delta$ 1.83 (m, 6H, CH$_2$-4, CH$_2$-6, CH$_2$-10); 2.15 (m, 9H, CH$_2$-2, CH-3, CH-5, CH-7, CH$_2$-8, CH$_2$-9); 7.67 (d, 2H, $J_{2,3} = J_{5,6} = 8.6$ Hz, Ar-H-2, Ar-H-6); 8.04 (s, 1H, H$_3$thiazole); 8.04 (d, 2H, Ar-H-3, Ar-H-5). $^{13}$C-NMR (CDCl$_3$): $\delta$ 28.5, 36.3, 39.9, 43.0 (C$_{adamant}$); 121.1 (C$_5$thiazole); 122.7, 126.4, 128.5 (C$_{arom}$); 132.3 (C$_4$thiazole); 139.2 (C$_4$thiazole); 160.9 (C$_2$oxadiazole); 163.6 (C$_5$oxadiazole); 183.7 (C$_2$thiazole). El-MS (m/z; %): 443 (M+2, 100), 441 (M+, 100), 362 (5), 246 (12), 217 (2), 185 (14), 183 (15), 157 (10), 155 (9), 135 (20), 121 (5), 107 (7), 93 (18), 79 (25).

2-(2-Adamantyl-1,3-thiazol-4-yl)-5-(3-bromophenyl)-1,3,4-oxadiazole (6h). From 3-bromobenzoic acid (0.20 g). Yield: 0.28 g (63%); mp 171-173 °C; Rf: 0.57; IR ($v_{max}$, KBr, cm$^{-1}$): 1590, 1545, 1260, 1084; $^1$H-NMR (CDCl$_3$): $\delta$ 1.84 (m, 6H, CH$_2$-4, CH$_2$-6, CH$_2$-10); 2.16 (m, 9H, CH$_2$-2, CH-3, CH-5, CH-7, CH$_2$-8, CH$_2$-9); 7.42 (t, 1H, $J_{5,6} = 7.8$ Hz, Ar-H-5); 7.69 (m, 2H, Ar-H-2, Ar-H-4); 8.10 (m, 1H, Ar-H-6); 8.12 (s, 1H, H$_3$thiazole). $^{13}$C-NMR (CDCl$_3$): $\delta$ 28.5, 36.4, 39.9, 43.0 (C$_{adamant}$); 121.2 (C$_5$thiazole); 123.0, 125.7, 129.9, 130.5, 134.6 (C$_{arom}$); 139.1 (C$_4$thiazole); 161.0 (C$_2$oxadiazole); 163.0 (C$_5$oxadiazole); 183.8 (C$_2$thiazole). El-MS (m/z; %): 443 (M+2, 100), 441 (M+, 100), 362 (5), 246 (10), 217 (10), 185 (10), 183 (10), 157 (12), 155 (12), 135 (18), 121 (3), 107 (10), 93 (19), 79 (25).

2-(2-Adamantyl-1,3-thiazol-4-yl)-5-(2-bromophenyl)-1,3,4-oxadiazole (6i). From 2-bromobenzoic acid (0.20 g). Yield: 0.28 g (64%); mp 186-188 °C; Rf: 0.51. IR ($v_{max}$, KBr, cm$^{-1}$): 1592, 1489, 1262, 1013; $^1$H-NMR (CDCl$_3$): $\delta$ 1.83 (m, 6H, CH$_2$-4, CH$_2$-6, CH$_2$-10); 2.16 (m, 9H, CH$_2$-2, CH-3, CH-5, CH-7, CH$_2$-8, CH$_2$-9); 7.41 (m, 1H, Ar-H-4); 7.49 (m, 1H, Ar-H-5); 7.78 (m, 2H, Ar-H-3, Ar-H-6); 8.09 (s, 1H, H$_3$thiazole). $^{13}$C-NMR (CDCl$_3$): $\delta$ 28.5, 36.4, 39.9, 43.0 (C$_{adamant}$); 121.2 (C$_5$thiazole); 121.8 (C$_2$arom); 125.3, 127.5, 131.8, 132.5 (C$_{arom}$); 134.4 (C$_1$arom); 139.2 (C$_4$thiazole); 161.2 (C$_2$oxadiazole); 163.6 (C$_5$oxadiazole); 183.8 (C$_2$thiazole). El-MS (m/z; %): 443 (M+2, 98), 441 (M+, 100), 362 (10), 246 (20), 217 (10), 185 (15), 183 (15), 157 (10), 155 (10), 135 (25), 121 (3), 107 (10), 93 (19), 79 (22).

2-(2-Adamantyl-1,3-thiazol-4-yl)-4-(4-flourophenyl)-1,3,4-oxadiazole (6j). From 4-fluorobenzoic acid (0.14 g). Yield: 0.24 g (63%); mp 213-215 °C; Rf: 0.47. IR ($v_{max}$, KBr, cm$^{-1}$): 1606, 1497, 1262, 1222; $^1$H-NMR (CDCl$_3$): $\delta$ 1.83 (m, 6H, CH$_2$-4, CH$_2$-6, CH$_2$-10); 2.16 (m, 9H, CH$_2$-2, CH-3, CH-5, CH-7, CH$_2$-8, CH$_2$-9); 7.23 (t, 2H, $J = 8.4$ Hz, Ar-H-3, Ar-H-5); 8.08 (s, 1H, H$_3$thiazole); 8.20 (dd, 2H, $J_{2',3'} = 9.0$ Hz, $J_{2',6'} = 5.4$ Hz, Ar-H-2, Ar-H-6). $^{13}$C-NMR (CDCl$_3$): $\delta$ 28.5,
36.4, 39.9, 43.0 (C_{adaman}); 116.3 (d, J_{C,F} = 22.5 Hz, C^{3,5}_{arom}); 120.1 (C^5_{thiazol}); 129.8 (d, J_{C,F} = 9.0 Hz, C^2_{arom}); 139.3 (C^4_{thiazol}); 161.0 (C^2_{oxadiazole}); 163.1 (C^5_{oxadiazole}); 163.7 (d, J_{C,F} = 252.2 Hz, C^4_{arom}); 183.8 (C^2_{thiazole}). EI-MS (m/z; %): 381 (M^+, 100), 246 (11), 217 (2), 164 (15), 135 (10), 121 (4), 107 (4), 95 (7), 93 (6), 79 (8).

2-(2-Adamantyl-1,3-thiazol-4-yl)-5-(3-flourophenyl)-1,3,4-oxadiazole (6k). From 3-fluorobenzoic acid (0.14 g). Yield: 0.25 g (66%); mp 158-160 °C; Rf: 0.52. IR (v_{max}, KBr, cm^{-1}): 1587, 1551, 1259, 1225; ^1H-NMR (CDCl3): δ 1.82 (m, 6H, CH2-4, CH2-6, CH2-10); 2.16 (m, 9H, CH2-2, CH-3, CH-5, CH-7, CH2-8, CH2-9); 7.26 (dt, 1H, J_{4,5} = 8.1 Hz, J_{4,6} = 2.4 Hz, J_{4,F} = 8.3 Hz, Ar-H-4), 7.52 (m, 2H, Ar-H-2, Ar-H-5), 7.88 (s, 1H, H^5_{thiazol}); 7.99 (m, 1H, Ar-H-6). ^13C-NMR (CDCl3): δ 28.5, 36.4, 39.9, 43.0 (C_{adaman}); 113.6 (C^5_{thiazole}); 114.1 (d, J_{C2,F} = 24.0 Hz, C^2_{arom}); 115.3 (d, J_{C4,F} = 21.0 Hz, C^4_{arom}); 122.9 (d, J_{C6,F} = 3.0 Hz, C^6_{arom}); 125.6 (d, J_{C5,F} = 8.2 Hz, C^5_{arom}); 130.8 (d, J_{C1,F} = 7.1 Hz, C^1_{arom}); 161.1 (C^2_{oxadiazole}); 162.8 (d, J_{C2,F} = 246.0 Hz, C^3_{arom}); 163.3 (C^5_{oxadiazole}); 183.8 (C^2_{thiazole}). EI-MS (m/z; %): 381 (M^+, 100), 246 (11), 217 (2), 164 (15), 135 (10), 121 (4), 107 (4), 95 (7), 93 (6), 79 (8).

2-(2-Adamantyl-1,3-thiazol-4-yl)-5-(2-flourophenyl)-1,3,4-oxadiazole (6l). From 2-fluorobenzoic acid (0.14 g). Yield: 0.25 g (65%); mp 175-177 °C; Rf: 0.53. IR (v_{max}, KBr, cm^{-1}): 1596, 1467, 1256, 1228; ^1H-NMR (CDCl3): δ 1.82 (m, 6H, CH2-4, CH2-6, CH2-10); 2.15 (m, 9H, CH2-2, CH-3, CH-5, CH-7, CH2-8, CH2-9); 7.24-7.34 (m, 2H, Ar-H-3, Ar-H-5); 7.59 (m, 1H, Ar-H-4); 8.09 (s, 1H, H^5_{thiazol}); 8.17 (t, 1H, J_{H6,F} = 8.4 Hz, Ar-H-6). ^13C-NMR (CDCl3): δ 28.5, 36.4, 39.9, 43.0, (C_{adaman}); 112.3 (C^5_{thiazole}); 116.9 (d, J_{C3,F} = 21.0 Hz, C^3_{arom}); 124.6 (d, J_{C1,F} = 21.2 Hz, C^1_{arom}); 130.0 (d, J_{C5,F} = 3.70 Hz, C^5_{arom}); 133.5 (d, J_{C6,F} = 9.0 Hz, C^6_{arom}); 139.2 (d, J_{C4,F} = 9.2 Hz, C^4_{arom}); 160.0 (d, J_{C2,F} = 257.2 Hz, C^2_{arom}); 161.0 (C^2_{oxadiazole}); 161.1 (C^5_{oxadiazole}); 183.7 (C^2_{thiazole}). EI-MS (m/z; %): 381 (M^+, 100), 246 (11), 217 (2), 164 (15), 135 (10), 121 (4), 107 (4), 95 (7), 93 (6), 79 (8).

Cytotoxicity assays

Cell cultures were seeded at 1x10^5 cells/mL in 96 multiwell plates in specific media supplemented (5%) atmosphere supplemented with 10% FCS and antibiotics then incubated at 37 °C in a humidified CO2 in the absence or presence of serial dilutions of test compounds. Cell viability was determined after 96 hrs at 37 °C by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) method. Compounds were dissolved in DMSO at 100 mM and then diluted into culture medium.

References