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

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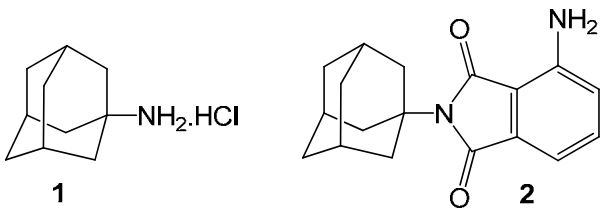
Abstract

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 μM, respectively. Compound **6l** showed activity against CCRF-SB cell lines with CC_{50} = 51 μM. 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[1-3] 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.[4,5] 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-aminophthalimide **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

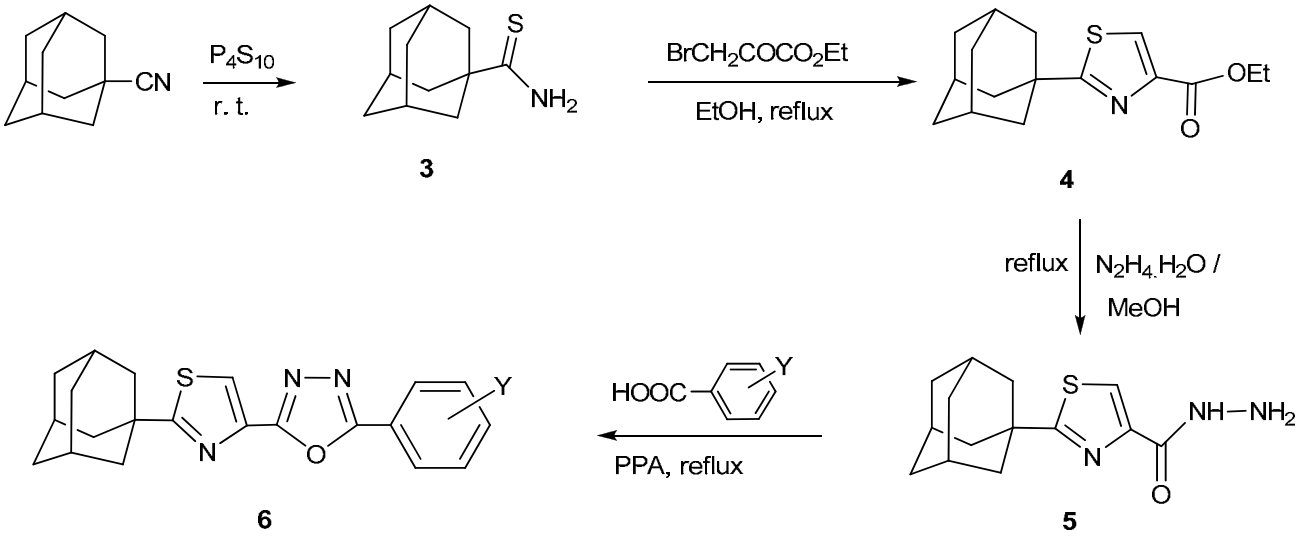


typical non-nucleoside reverse transcriptase inhibitors.[7,8] Burstein *et al.*[9] developed adamantane derivatives, in which the adamantane moiety is chemically linked to a water soluble polyanionic matrix. These derivatives proved to be good inhibitors of replication in early stages of HIV-1. In addition, the activity of some adamantane derivatives has recently improved their use in clinical therapeutic efficacy of interferon/ribavirin combination against hepatitis C.[10] Some other adamantyl derivatives have been used as anti-inflammatory,[11-14] antimicrobial,[15-17] antimalarial[18] and antidepressant[19] agents as well as inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1).[20]

We have recently reported the synthesis and biological activities of various azoles.[21-23] In the present study, we selected three pharmacophores *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 P_4S_{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.



a: Y = 4-CH_3; **b:** Y = 3-CH_3; **c:** Y = 2-CH_3;
d: Y = 4-Cl; **e:** Y = 3-Cl; **f:** Y = 2-Cl;
g: Y = 4-Br; **h:** Y = 3-Br; **i:** Y = 2-Br;
j: Y = 4-F; **k:** Y = 3-F; **l:** Y = 2-F

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 ν_{max} 3424 and 3323 cm^{-1} characteristic of the primary NH_2 group were observed. The ^{1}H-NMR spectrum exhibited two singlets at δ 7.95 and 7.10 attributed to the NH_2 protons. In the ^{13}C-NMR spectrum, the downfield signal at δ 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 ν_{max} 1732 and 1663 cm^{-1}, respectively. In the ^{13}C-NMR spectra, the signals at δ 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 δ 8.48 was assigned to the NH_2 group. Additional support for formation of **4** and **5** were obtained by appearence 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 ν_{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 δ 7.33-8.33 ppm. The singlets in the range δ 7.88-8.12 were assigned to H-5 of the thiazole moiety. In the ^{13}C-NMR spectra, the resonances in the region δ ~161.0 and δ ~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 δ 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 δ_H 8.09 showed a $^3J_{C,H}$

couplings with C-2 of the thiazole ring at δ_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 δ_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 μM, respectively. Compound **6l** exhibited activity against CCRF-SB cell lines with CC_{50} = 51 μM.

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). N MR 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 δ). 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, Kieslgel 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_4S_{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_2Cl_2 (3 x 50 mL). The combined organic extracts were dried (Na_2SO_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; R_f: 0.54. IR (υ_{max}, KBr, cm^{-1}): 3424, 3323, 2907, 2848, 1656, 1449, 1384, 1181. ^{1}H-NMR ($CDCl_3$): δ 1.79 (m, 6H, CH_2-4, CH_2-6, CH_2-10), 2.18 (m, 9H, CH_2-2, CH-3, CH-5, CH-7, CH_2-8, CH_2-9), 7.10 (bs, 1H, N-H), 7.95 (1H, bs, N-H). ^{13}C-NMR ($CDCl_3$): δ 28.4, 36.2, 41.7, 45.6 ($C_{adamant.}$); 218.9 (C=S). EI-MS (m/z, %): 195 ($M^{+\cdot}$, 80), 135 (100), 121 (5), 107 (15), 93 (27), 60 (16). Anal. calcd. for $C_{11}H_{17}NS$: C, 67.64; H, 8.77; N, 7.17. Found: C, 67.54; H, 8.72; N, 7.38.

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 CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford **3** as a yellow oil (0.35 g, 80 %), R_f: 0.73. IR (υ_{max}, film, cm^{-1}): 3117, 2906, 2850, 1732, 1605, 1497, 1477, 1451, 1368, 1093. ^{1}H-NMR ($CDCl_3$): δ 1.40 (t, 3H, J = 7.2 Hz, $OCH_2\mathit{CH_3}$), 1.79 (m, 6H, CH_2-4, CH_2-6, CH_2-10), 2.18 (m, 9H, CH_2-2, CH-3, CH-5, CH-7, CH_2-8, CH_2-9), 4.41 (2H, q, J = 7.2 Hz, $O\mathit{CH_2}CH_3$), 8.05 (1H, s, H-12). ^{13}C-NMR ($CDCl_3$): δ 14.4 ($OCH_2\mathit{CH_3}$); 28.5, 36.4, 39.8, 41.7 ($C_{adamant.}$); 61.2 ($O\mathit{CH_2}CH_3$); 125.9 ($C^5_{thiazole}$); 146.6 ($C^4_{thiazole}$); 161.7 (C=O); 182.3 ($C^2_{thiazole}$). EI-MS (m/z, %): 291 ($M^{+\cdot}$, 90), 246 (100), 135 (45), 121 (3), 107 (9), 93 (15), 71, (50), 45 (10).

2-Adamantyl-1,3-thiazole-4-carbohydrazide (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 (Na_2SO_4) and recrystallized from aq. EtOH to give (**5**) (0.27 g, 75%); mp 179-181 ºC; R_f 0.73 (petroleum ether : acetone; 2:3). IR (υ_{max}, KBr, cm^{-1}): 3424, 3323, 3184, 1663, 1541, 1491. ^{1}H-NMR ($CDCl_3$): δ 1.79 (m, 6H, CH_2-4, CH_2-6, CH_2-10), 2.04 (m, 9H, CH_2-2, CH-3, CH-5, CH-7, CH_2-8, CH_2-9), 4.08 (bs, 2H, NH_2), 7.99 (s, 1H, H-12), 8.48 (bs, 1H, N-H). ^{13}C-NMR ($CDCl_3$): δ 28.4, 36.4, 39.6, 43.1 ($C_{adamant.}$); 121.8 ($C^5_{thiazole}$); 147.9 ($C^4_{thiazole}$); 162.2 (C=O); 182.1 ($C^2_{thiazole}$). EI-MS (m/z, %): 277 ($M^{+\cdot}$, 95), 246 (100), 219 (10), 179 (5), 135 (47), 121 (3), 107 (9), 93 (15). Anal. calcd. for $C_{14}H_{19}N_3SO$: 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-l)

A mixture of **5** (0.50 g, 1.8 mmol) and substituted benzoic acid (1.8 mmol) was heated at 100-120 °C in presence of excess polyphosphoric acid (PPA) for 4 h. After cooling, the mixture was poured into crushed ice, and neutralized with 5% aq. $NaHCO_3$ 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, R_f: 0.57. IR (υ_{max}, KBr, cm^{-1}): 1600, 1497, 1261. ^{1}H-NMR ($CDCl_3$): δ 1.84 (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); 2.46 (s, 3H, Ph-$\mathit{CH_3}$); 7.35 (d, 2H, $J_{2,3} = J_{5,6}$ = 9.0 Hz, Ar-H-3, Ar-H-5); 8.07 (s, 1H, $H^5_{thiazole}$); 8.08 (d, 2H, Ar-H-2, Ar-H-6). ^{13}C-NMR ($CDCl_3$): δ 21.7 (Ph-$\mathit{CH_3}$);

28.5, 36.4, 39.9, 43.1 ($C_{adaman.}$); 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 ($C^2_{oxadiazole}$); 164.6 ($C^5_{oxadiazole}$); 183.5 ($C^2_{thiazole}$). EI-MS (m/z; %): 377 ($M^{+\cdot}$, 100), 246 (10), 160 (33), 135 (15), 121 (10), 119 (25), 107 (3), 93 (7), 91 (27), 79 (15), 65 (10). Anal. calcd. for $C_{22}H_{23}N_3SO$: 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; R_f: 0.55. IR (υ_{max}, KBr, cm^{-1}): 1590, 1549, 1263. ^{1}H-NMR ($CDCl_3$): δ 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, $H^5_{thiazole}$); 8.08 (d, 1H, Ar-H-6). ^{13}C-NMR ($CDCl_3$): δ 22.3 (Ph-*CH*$_3$); 28.6, 36.5, 39.9, 43.1 ($C_{adaman.}$); 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 ($C^2_{thiazole}$). EI-MS (m/z; %): 377 ($M^{+\cdot}$, 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-methylphenyl)-1,3,4-oxadiazole (6c). From 2-methylbenzoic acid (0.25 g). Yield: 0.43 g (64%); mp 151-153 ºC; R_f: 0.61. IR (υ_{max}, KBr, cm^{-1}): 1601, 1536, 1261. ^{1}H-NMR ($CDCl_3$): δ 1.84 (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); 2.78 (s, 3H, Ph-*CH*$_3$); 7.34-7.45 (m, 3H, Ar-H-3, Ar-H-4, Ar-H-5); 8.07 (m, 2H, Ar-H-6, $H^5_{thiazole}$). ^{13}C-NMR ($CDCl_3$): δ 22.1 (Ph-*CH*$_3$); 28.5, 36.4, 39.9, 43.1 ($C_{adaman.}$); 120.7 ($C^5_{thiazole}$); 122.9, 126.1, 129.2, 131.2 ($C_{arom.}$); 138.6 ($C^2_{arom.}$); 139.5 ($C^4_{thiazole}$); 160.4 ($C^2_{oxadiazole}$); 164.6 $C^5_{oxadiazole}$); 183.6 ($C^2_{thiazole}$). EI-MS (m/z; %): 377 ($M^{+\cdot}$, 100), 246 (13), 160 (10), 135 (17), 121 (4), 119 (15), 107 (2), 93 (2), 91 (20), 65 (8).

2-(2-Adamantyl-1,3-thiazol-4-yl)-5-(4-chlorophenyl)-1,3,4-oxadiazole (6d). From 4-chlorobenzoic acid (0.16 g). Yield: 0.26 g (64%); mp 181-183 ºC; R_f: 0.47. IR (υ_{max}, KBr, cm^{-1}): 1596, 1543, 1262, 1019. ^{1}H-NMR ($CDCl_3$): δ 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, $H^5_{thiazol}$); 8.13 (d, 2H, Ar-H-3, Ar-H-5). ^{13}C-NMR ($CDCl_3$): δ 28.5, 36.4, 39.9, 43.1 ($C_{adaman.}$); 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 ($C^2_{thiazole}$). EI-MS (m/z; %): 399 (M+2, 33), 397 ($M^{+\cdot}$, 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; R_f: 0.52. IR (υ_{max}, KBr, cm^{-1}): 1576, 1547, 1262, 1086. ^{1}H-NMR ($CDCl_3$): δ 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 ($CDCl_3$): δ 28.6, 36.2, 39.9, 43.0 ($C_{adaman.}$); 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($C^2_{thiazole}$). EI-MS (m/z; %): 399 (M+2, 33), 397 ($M^{+\cdot}$, 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 (6f). From 2-chlorobenzoic acid (0.16 g). Yield: 0.24 g (62%); mp 148-150 ºC; R_f: 0.50. IR (υ_{max}, KBr, cm^{-1}):

1596, 1532, 1262, 1088. ^{1}H-NMR ($CDCl_3$): δ 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, $J_{3,4} = 7.7$ Hz, $J_{3,5} = 1.5$ 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, $H^5_{thiazole}$). ^{13}C-NMR ($CDCl_3$): δ 28.5, 36.4, 39.9, 43.1 ($C_{adaman.}$); 121.3 ($C^5_{thiazole}$); 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 ($C^2_{thiazole}$). EI-MS (m/z; %): 399 (M+2, 33), 397 ($M^{+\cdot}$, 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 (6g). From 4-bromobenzoic acid (0.20 g). Yield: 0.27 g (61%); mp 188-190 ºC; R_f: 0.53. IR (υ_{max}, KBr, cm^{-1}): 1593, 1474, 1102, 1075; ^{1}H-NMR ($CDCl_3$): δ 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, $H^5_{thiazol}$); 8.04 (d, 2H, Ar-H-3, Ar-H-5). ^{13}C-NMR ($CDCl_3$): δ 28.5, 36.3, 39.9, 43.0, ($C_{adaman.}$); 121.1 ($C^5_{thiazole}$); 122.7, 126.4, 128.5 (C_{arom}); 132.3 ($C^4_{arom.}$); 139.2($C^4_{thiazole}$); 160.9 ($C^2_{oxadiazole}$); 163.6 ($C^5_{oxadiazole}$); 183.7 ($C^2_{thiazole}$). EI-MS (m/z; %): 443 (M+2, 100), 441 ($M^{+\cdot}$, 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 ºC; R_f: 0.57; IR (υ_{max}, KBr, cm^{-1}): 1590, 1545, 1260, 1084; ^{1}H-NMR ($CDCl_3$): δ 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, $H^5_{thiazole}$). ^{13}C-NMR ($CDCl_3$): δ 28.5, 36.4, 39.9, 43.0 ($C_{adaman.}$); 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 ($C^2_{thiazole}$). EI-MS (m/z; %): 443 (M+2, 100), 441 ($M^{+\cdot}$, 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 ºC; R_f: 0.51. IR (υ_{max}, KBr, cm^{-1}): 1592, 1489, 1262, 1013. ^{1}H-NMR ($CDCl_3$): δ 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, $H^5_{thiazole}$). ^{13}C-NMR ($CDCl_3$): δ 28.5, 36.4, 39.9, 43.0 ($C_{adaman.}$);, 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 ($C^2_{thiazole}$). . EI-MS (m/z; %): 443 (M+2, 98), 441 ($M^{+\cdot}$, 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)-5-(4-flourophenyl)-1,3,4-oxadiazole (6j). From 4-fluorobenzoic acid (0.14 g). Yield: 0.24 g (63%); mp 213-215 ºC; R_f: 0.47. IR (υ_{max}, KBr, cm^{-1}): 1606, 1497, 1262, 1222. ^{1}H-NMR ($CDCl_3$): δ 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, $H^5_{thiazol}$); 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 ($CDCl_3$): δ 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, $C^{2,6}_{arom.}$); 139.3 ($C^{4}_{thiazole}$); 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 ($M^{+\cdot}$, 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 ºC; R_f: 0.52. IR (υ_{max}, KBr, cm^{-1}): 1587, 1551, 1259, 1225; ^{1}H-NMR ($CDCl_3$): δ 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);, 7.26 (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). ^{13}C-NMR ($CDCl_3$): 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 ($M^{+\cdot}$, 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-flurobenzoic acid (0.14 g). Yield: 0.25 g (65%); mp 175-177 ºC; R_f: 0.53. IR (υ_{max}, KBr, cm^{-1}): 1596, 1467, 1256, 1228. ^{1}H-NMR ($CDCl_3$): δ 1.82 (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); 7.24-7.34 (m, 2H, Ar-H-3, Ar-H-5); 7.59 (m, 1H, Ar-H-4), 8.09 (s, 1H, $H^{5}_{thiazole}$); 8.17 (t, 1H, $J_{H6,F}$ = 8.4 Hz, Ar-H-6). ^{13}C-NMR ($CDCl_3$): 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, $J_{C5,F}$ = 3.7.0 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 ($M^{+\cdot}$, 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 atand antibiotics and incubated at 37 °C in a humidified CO_2 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.[25]

Compounds were dissolved in DMSO at 100 mM and then diluted into culture medium.

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