Synthesis, crystal structure, anti-HIV, and antiproliferative activity of new oxadiazole and thiazole analogs

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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, crystal structure, anti-HIV, and antiproliferative activity of new oxadiazole and thiazole analogs

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Abstract A series of 2-adamantyl-5-arylthiazolyl-1,3,4-oxadiazoles **7a–x** together with thiazoles **13** and **14** were synthesized. Compounds **7a–l**, **13**, and **14** were tested in vitro with the aim of identifying novel lead compounds active against human immunodeficiency virus type-1 and human immunodeficiency virus type-2 activity in MT-4 cells. Title compounds were also tested against representatives of Gram-positive and Gram-negative bacteria (*Staphylococcus aureus*, *Salmonella* spp.), various mycobacterial strains (*Mycobacterium fortuitum* and *Mycobacterium smegmatis*), yeast (*Candida albicans*), and mold (*Aspergillus fumigatus*). None of the compounds showed antiviral or antimicrobial activity, except compounds **13** and **14** exhibited anti-human immunodeficiency virus-1 activity with EC_{50} values of 1.79 and 2.39 μM with Selectivity index = 18 and 4, respectively. On the other hand, compounds **7a** and **7j** showed a marked cytotoxicity against the human $CD4^+$ lymphocytes (MT-4). Therefore, **7a** and **7j** were evaluated for their antiproliferative activity against two solid tumor-derived cell lines, which exhibited IC_{50} values of 8.1 ± 0.10 μM and 4.8 ± 0.08 μM against Hep-G2 cell lines, respectively.

Keywords Anti-HIV activity · Antiproliferative activity · Adamantyl derivatives · Oxadiazole · Thiazoles

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Introduction

Reverse transcriptase (RT) is a key enzyme that plays an essential and multifunctional role in the replication of the human immunodeficiency virus type-1 (HIV-1), and thus constitutes an attractive target for the development of new drugs useful in acquired immune deficiency syndrome therapy (Jonckheere et al., 2000; De Clercq, 2009). Thiourea is an important building block of a number of heterocycles such as thiazoles (Dodson and King, 1945), where several heterocyclic thioureas have been reported as a new class of potent non-nucleoside reverse transcriptase inhibitors (NNRTIs) (Ahgren et al., 1995; Heinisch et al., 1997; Ren et al., 2000; D'Cruz et al., 2004; D'Cruz, 2006), one example being phenethylthiazolylthiourea (PETT) (Cantrell et al., 1996) (**1**). Uckun and Venkatachalam (2005) described the synthesis of a series of thiazole thioureas with alkyl, aryl, and heteroaryl substituents as

newly identified NNRTIs for HIV, including mutant strains of HIV, and effective in the treatment of multi-drug resistant HIV infection. However, significant resistance has been developed against the current NNRTIs and there is an urgent need to develop new anti-HIV agents that are effective against these resistant mutants (Wainberg et al., 2005; Imamichi, 2004). In this context, thiazolo thiourea derivatives appear as a promising class of compounds, since some 1,3-thiazole analogs exhibit remarkable anti-HIV activity (Xu et al., 2014; Zia et al., 2012) besides many other pharmacological activities such as anticancer (Dawood et al., 2013). Thiazole-containing drug molecules are currently being used in the treatment of various central nervous system disorders (Mishra et al., 2015). Furthermore, the adamantyl group has been revealed as a promising pharmacophore and some adamantyl derivatives are under clinical trial for 11β-hydroxysteroid dehydrogenase type 1 (Yu et al., 2013). Many other investigations have revealed the activity of its derivatives against HIV (Khan et al., 2012), hepatitis (Maynard et al., 2006), cancer (Cai et al., 2014), and some other biological disorders (Baxter et al., 2003).

In continuation of our attempts to develop new potent HIV-1 NNRTIs (Khan et al., 2010, 2012, 2015; Zahid et al., 2009; Akhtar et al., 2008), we report herein a new series of 2-adamantyl/adamantylmethyl-5-arylthiazolyl-1,3,4-oxadiazoles and two new thiazole thioureido analogs (Fig. 1), structurally similar to the powerful class of NNRTIs PETT analogs. Our aim was to investigate their anti-HIV, antifungal, and antibacterial activities, as well as antiproliferative activity against two solid-derived tumor cells.

Results and discussion

Chemistry

In the present work, a series of 2-adamantyl/adamantylmethyl-5-arylthiazolyl-1,3,4-oxadiazole derivatives **7a–x** were synthesized from aryl nitriles **2a–l** through a multi-step reaction sequence (Scheme 1). Aryl nitriles were converted to aryl thioamide derivatives **3a–l**, which upon cyclization with ethyl bromopyruvate, followed by hydrazinolysis yielded 2-aryl-1,3-thiazole-4-carbohydrazide analogs **5a–l**. Treatment of **5a–l** with adamantyl-1-carboxylic acid **6** in the presence of $POCl_3$ afforded **7a–l** (68–81 %). Similarly, treatment of **5a–l** with adamantylacetic acid **8** gave **7m–x** in 71–80 % yields.

The structures of **7a–x** were confirmed by infrared (IR), ^{1}H, and ^{13}C nuclear magnetic resonance (NMR) spectra.

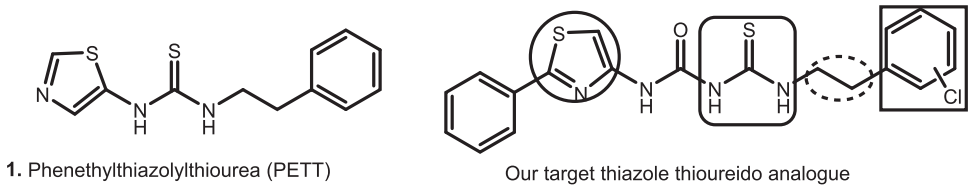
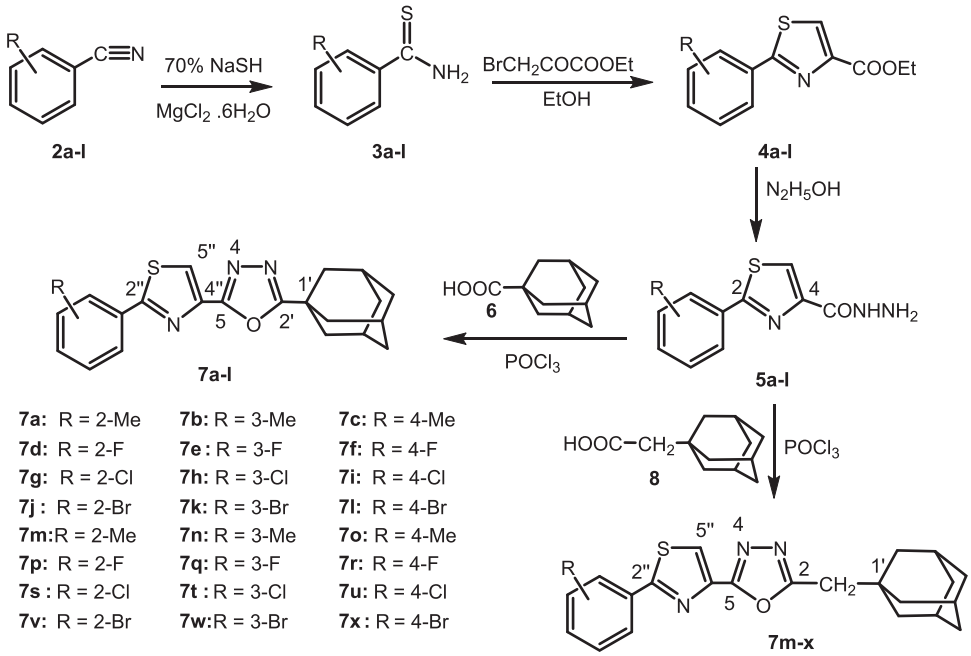


Fig. 1 Potent anti-HIV agents



Scheme 1 Synthesis of 2-adamantyl/adamantylmethyl-5-arylthiazolyl-1,3,4-oxadiazole derivatives **7a–x**

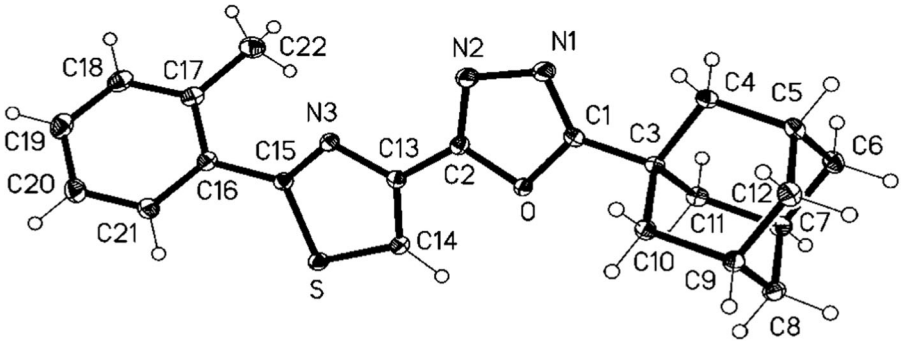


Fig. 2 The molecular structure of **7a** in the crystal, showing crystallographic numbering scheme. Displacement ellipsoids are drawn at 50 % probability level

In the ^{1}H NMR spectra, two signals integrating for 15 protons, in the region of δ 1.53–2.19 ppm, were assigned to adamantyl moiety, whereas the two methylene protons in **7m–x** appeared in the region of δ 2.69–2.76 ppm. H-5 of thiazole backbone resonated in the range of δ 7.79–8.28 ppm. In ^{13}C-NMR spectra, the resonances from δ 27.7 to 42.2 ppm were assigned to adamantyl carbon atoms, whereas the methylene carbon atoms in compounds **7m–x** appeared in the region of δ 39.5–39.6 ppm. C-2, C-4, and C-5 of the thiazole ring were observed in the regions δ 162.2–170.1, 140.1–141.6, and δ 120.9–123.0 ppm, respectively. The C-2 and C-5 of oxadiazole ring resonated in the regions δ 165.1–172.8 and 160.1–160.8 ppm, respectively. The electron ionization mass spectrometery (EI-MS) spectral data also supported the structures of **7a–x**, where molecular ion peaks were observed for all the synthesized compounds.

The structures of the synthesized compounds were unambiguously confirmed by single crystal X-ray diffraction study of compound **7a** as a representative molecule (Fig. 2); colorless crystals of **7a** were obtained from chloroform.

Next, our attention focused on synthesis of new thiazole thioureido derivatives as potentially active anti-HIV agents. Thus, treatment of acyl chloride **9** with NH_4SCN in acetone, following Kabbani's approach (Kabbani et al., 2005) afforded **10**, which was directly treated with the amines **11** and **12** to give, after purification, the thiazole thioureido derivatives **13** and **14** in 82 and 79 % yields, respectively. The synthetic reactions are summarized in Scheme 2.

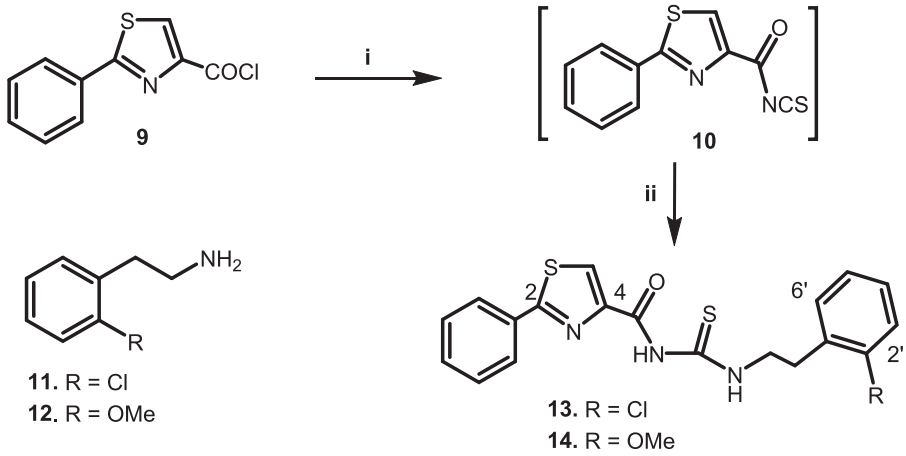
Structures of the newly synthesized compounds **13** and **14** were assigned using ^{1}H, ^{13}C-NMR, and mass spectral data. The ^{1}H NMR spectra showed similar patterns for the phenyl protons, while the two triplets at δ 2.94 and δ 3.83 ppm were attributed to CH_2Ph and CH_2N methylene protons ($J = 6.5$ Hz), respectively. H-5 of the thiazole ring appeared as a singlet at δ 9.12 and 9.09 ppm, respectively. In the ^{13}C-NMR spectra of **13** and **14**, the resonances at δ 30.1, 29.6 ppm and δ 45.6, 46.1 ppm were attributed to CH_2Ph and CH_2N methylene carbon atoms. Carbon atoms of the thiazole and phenyl moieties have been fully analyzed (*c.f.* Experimental section).

Compound **13** was selected for further NMR studies. The gradient heteronuclear multiple bond correlation spectrum (Willker et al., 1993) revealed a $^{3}J_{CH}$ coupling of NHCH_2 protons at δ_H 3.83 ppm with C = S at δ_C 178.9 ppm. In addition, the coupling between H-5 of thiazole ring at δ_H 9.12 ppm and C = O at δ_C 165.9 ppm was observed (Fig. 3).

In vitro anti-HIV activity

Compounds **7a–l**, **13**, and **14** were tested for their in vitro anti-HIV-1 and anti-HIV-2 activities in human T-lymphocyte (MT-4) cells based on Microculture Tetrazolium Assay (MTT) method (Pannecouque et al., 2008). The anti-HIV-1 activity was measured using strain III_B, while anti-HIV-2 activity was carried out on strain ROD. The results are given in Table 1, where the data for nevirapine (Hargrave et al., 1991) is included for comparison purposes. Compound-induced cytotoxicity was also measured in MT-4 cells parallel with the antiviral activity. All the compounds were found to be inactive except compounds **13** and **14**, which showed remarkable anti-HIV-1 activity with EC_{50} values of 1.79 and 2.93 μM, and CC_{50} values of 33.22 and 11.72 μM, resulting in SI values of 18 and 4, respectively.

With respect to structure-activity relationship studies, Bell et al. (1995) observed that *meta* and *ortho* substitutions generally triggers better activities, when compared to *para*, in the PETT analogs. As regards the electronic nature of the *ortho* substituents, both small electron-donating and small electron-withdrawing groups revealed good activities, and among these the preferred groups are: fluoro, chloro, azido, and methoxy (de Souza et al., 2011). Accordingly, the combined four portions (*o*-chlorophenyl moiety, ethyl group, thioureido residue, and thiazole scaffold) of compound **13** are considered as the optimal substituents that would give rise to the optimal activity. After proceeding with docking studies, it was observed that compounds **13** and **14** are well tolerated in the hydrophobic region of HIV RT and showed higher activity than those of **7a–x** analogs. In conclusion, compound **13** was found to be a potent agent



Scheme 2 *Reagents and conditions*: (i) NH_4SCN, acetone, reflux, 1 h; (ii) **11** or **12**, NaOH, reflux, 6 h

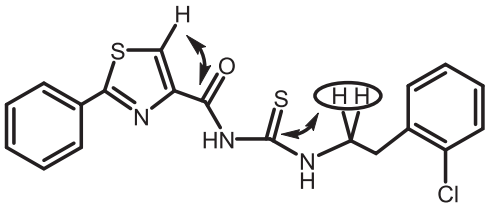


Fig. 3 $J_{C,H}$ correlations in the HMBC NMR spectrum of **13**

against HIV-1 and identified as a new candidate to act as a NNRTI; it might be considered a promising agent for further structural modifications and pharmacological evaluation.

In-vitro antiproliferative activity

Due to the marked cytotoxicity of compounds **7a** and **7j** against the human $CD4^+$ lymphocytes (MT-4) (Vicini et al., 2006), they were selected for their antiproliferative activity in vitro against two solid tumor-derived cell lines consisting Hep-G2 (human hepatocarcinoma) and MCF-7 (breast cancer) cell line using MTT assay (Alley et al., 1988). For comparative purposes, we evaluated the cytotoxic activities of the compounds relative to doxorubicin (Uyeki et al., 1981). However, both compounds were inactive against MCF-7 cell line ($IC_{50} > 50\,\mu M$). On the other hand, compound **7a** with *ortho* methyl ($IC_{50} = 8.1 \pm 0.10\,\mu M$) and **7j** with *ortho* bromo ($IC_{50} = 4.8 \pm 0.08\,\mu M$) moieties exerted cytotoxic effects towards Hep-G2 cell lines. Unfortunately, both compounds did not show superior activity than doxorubicin against Hep-G2 cell lines with IC_{50} value of 0.03 µM.

In vitro antimicrobial activity

Compounds **7a–x** were tested for their antifungal and antibacterial activities. Six fungal strains viz. *Trichphyton longifusus*, *Candida albicans*, *Aspergillus flavus*, *Microsporum canis*, *Fusarium solani*, and *Candida glabrata* were used to study antifungal activity. Antibacterial activity was evaluated against six bacterial strains, i.e., *Escherichia coli*, *Bacillus subtillus*, *Shigella flexenari*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Salmonella typhi*. However, at nontoxic concentrations (10 µM), the activities of the synthesized compounds were found to be non-significant against the tested fungi and bacteria.

Experimental

Chemistry

Melting points of the synthesized compounds were measured in open capillaries using Stuart SMP3 melting point apparatus and are uncorrected. The IR spectra were recorded on Schimadzu Fourier Transform Infra-red spectrophotometer (Model 270), using KBr disks. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 300 (^1H) and 75 MHz (^{13}C) spectrometers, unless otherwise stated, using $CDCl_3$ solvent containing tetramethylsilane as an internal standard (chemical shifts in δ, ppm). Microanalytical data were obtained with a Vario elemental apparatus (Shimadzu, Japan). The EI-MS was carried out using Agilent Technologies 6890N (GC) with an inert selective detector 5973 mass spectrometer. The reagents used were of analytical grade while the solvents were purified before use.

General procedure for the preparation of 2-adamantyl/adamantylmethyl-5-arylthiazolyl-1,3,4-oxadiazoles (**7a–x**)
Treatment of aryl nitriles **2** with 70 % NaSH in the presence of $MgCl_2.6H_2O$ afforded the corresponding aryl thioamides **3**, which cyclized to the thiazole ester derivatives **4** on treatment with ethyl bromopyruvate. Treatment of **4** with hydrazine hydrate afforded the corresponding 2-aryl-1,3-thiazole-4-carbohydrazides **5a–l** (Zia et al., 2012). A suspension of **5a–l** (0.50 mmol), adamantyl-1-carboxylic acid **6** (0.50 mmol) or adamantylacetic acid **8** (0.50 mmol)

Table 1 In vitro anti-HIV-1 and HIV-2 activity of 2-adamantyl/adamantylmethyl-5-arylthiazolyl-1,3,4-oxadiazoles **7a–l**, and the analogs **13** and **14**

Compounds	Virus strain	EC_{50} (μM)[a]	CC_{50} (μM)[b]	SI[c]
7a	III_B	>10.50	≥10.50	< or X1
	ROD	>10.50	≥10.50	< or X1
7b	III_B	>125.00	>125.00	X1
	ROD	>125.00	>125.00	X1
7c	III_B	>105.70	105.70	<1
	ROD	>105.70	105.70	<1
7d	III_B	>97.60	≥97.60	< or X1
	ROD	>97.60	≥97.60	< or X1
7e	III_B	>125.00	>125.00	X1
	ROD	>125.00	>125.00	X1
7f	III_B	>75.20	75.20	<1
	ROD	>75.20	75.20	<1
7g	III_B	>125.00	>125.00	X1
	ROD	>125.00	>125.00	X1
7h	III_B	>125.00	>125.00	X1
	ROD	>125.00	>125.00	X1
7i	III_B	>125.00	>125.00	X1
	ROD	>125.00	>125.00	X1
7j	III_B	>10.90	10.90	<1
	ROD	>10.90	10.90	<1
7k	III_B	>125.00	>125.00	X1
	ROD	>125.00	>125.00	X1
7l	III_B	>110.00	≥110.00	< or X1
	ROD	>110.00	≥110.00	< or X1
13	III_B	1.79	32.22	18
	ROD	>32.22	32.22	<1
14	III_B	2.93	11.72	4
	ROD	>11.72	11.72	<1
Nevirapine	III_B	0.05	>4	>80
	ROD	>4	>4	<1

Anti-HIV-1 activity measured on strain III_B

Anti-HIV-2 activity measured using strain ROD

[a]Compound concentration required to achieve 50 % protection of MT-4 cells from HIV-1 and HIV-2-induced cytopathogenic effects

[b]Compound concentration that reduces the viability of mock-infected MT-4 cells by 50 %

[c]Selectivity index (SI) (CC_{50}/EC_{50}). Data represent mean values (±S.D.) for two independent determinations

and $POCl_3$ (5 mL) was heated under reflux for 4 h (Khan et al., 2015). The reaction mixture was then cooled to room temperature, poured onto crushed ice and neutralized using solid K_2CO_3 and KOH to pH 8. The precipitated solid was filtered, washed with excess water, and purified through column chromatography (*n*-hexane-ethyl acetate; 7:3) to afford thiazolyloxadiazoles **7a–x**.

2-[(Adamantan-1-yl)-5-(2-(2-methylphenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7a**) From **5a** (117 mg). Yield: 141 mg (75 %); Mp 150–152 °C; FTIR (ν_{max}, cm^{-1}): 3097, 2904, 2849, 1604, 1556, 1203. ^1H NMR ($CDCl_3$): $\delta = 1.83$ (m, 6H, $H_{adamantane}$), 2.17 (m, 9H, $H_{adamantane}$), 2.64 (s, 3H, Ar–*Me*), 7.29–7.42 (m, 3H, $H_{arom.}$), 7.77 (m, 1H, $H_{arom.}$), 7.79 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): $\delta = 21.4$ (CH_3), 27.7, 34.5, 36.3, 39.9 ($10 \times C_{adamantane}$), 122.1 ($C^5{}_{thiazole}$), 126.2, 130.1, 130.2, 131.5, 132.1, 136.9 ($6 \times C_{arom.}$), 140.7 ($C^4{}_{thiazole}$), 160.4 ($C^5{}_{oxadiazole}$), 169.4 ($C^4{}_{thiazole}$), 172.7 ($C^2{}_{oxadiazole}$). EI-MS (*m/z*, %): 377 ($[M]^+$, 100), 202 (27), 174 (9), 135 (57), 117 (12), 107 (7), 93 (18), 91 (24), 79 (25). Anal. Calcd. for $C_{22}H_{23}N_3OS$: C, 70.00; H, 6.14; N, 11.13. Found: C, 69.85; H, 6.04; N, 10.93.

2-[(Adamantan-1-yl)-5-(2-(3-methylphenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7b**) From **5b** (117 mg). Yield: 134 mg (71 %); Mp 183–184 °C; FTIR (ν_{max}, cm^{-1}): 3102, 2904, 2850, 1607, 1560, 1205. ^1H NMR ($CDCl_3$): $\delta = 1.84$ (br s, 6H, $H_{adamantane}$), 2.18 (m, 9H, $H_{adamantane}$), 2.46 (s, 3H, Ar–*Me*), 7.30 (m, 1H, $H_{arom.}$), 7.38 (m, 1H, $H_{arom.}$), 7.84 (m, 1H, $H_{arom.}$), 7.91 (m, 1H, $H_{arom.}$), 8.09 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): $\delta = 21.4$ (CH_3), 27.8, 34.5, 36.3, 40.0 ($10 \times C_{adamantane}$), 121.3 ($C^5{}_{thiazole}$), 124.2, 127.5, 128.9, 131.7, 132.6, 138.9 ($6 \times C_{arom.}$), 141.3 ($C^4{}_{thiazole}$), 160.3 ($C^5{}_{oxadiazole}$), 170.1 ($C^2{}_{thiazole}$), 172.7 ($C^2{}_{oxadiazole}$). EI-MS (*m/z*, %): 377 ($[M]^+$, 100), 202 (13), 174 (9), 135 (31), 117 (12), 107 (10), 93 (11), 91 (7), 79 (20). Anal. Calcd. for $C_{22}H_{23}N_3OS$: C, 70.00; H, 6.14; N, 11.13. Found: C, 69.79; H, 6.01; N, 10.88.

2-[(Adamantan-1-yl)-5-(2-(4-methylphenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7c**) From **5c** (117 mg): Yield: 149 mg (79 %); Mp 196–198 °C; FTIR (ν_{max}, cm^{-1}): 3093, 2915, 2849, 1601, 1552, 1203. ^1H NMR ($CDCl_3$): $\delta = 1.84$ (br s, 6H, $H_{adamantane}$), 2.17 (m, 9H, $H_{adamantane}$), 2.43 (s, 3H, Ar–*Me*), 7.29 (d, 2H, $J = 8.1$ Hz, $H_{arom.}$), 7.96 (d, 2H, $J = 8.1$ Hz, $H_{arom.}$), 8.06 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): $\delta = 21.5$ (CH_3), 27.8, 34.5, 36.3, 39.7 ($10 \times C_{adamantane}$), 120.9 ($C^5{}_{thiazole}$), 125.8, 126.9, 129.7, 130.1 ($6 \times C_{arom.}$), 141.2 ($C^4{}_{thiazole}$), 160.3 ($C^5{}_{oxadiazole}$), 170.0 ($C^2{}_{thiazole}$), 172.6 ($C^2{}_{oxadiazole}$). EI-MS (*m/z*, %): 377 ($[M]^+$, 100), 202 (22), 174 (7), 135 (36), 117 (13), 107 (8), 93 (15), 91 (12), 79 (23). Anal. Calcd. for $C_{22}H_{23}N_3OS$: C, 70.00; H, 6.14; N, 11.13. Found: C, 69.80; H, 6.03; N, 10.98.

2-[(Adamantan-1-yl)-5-(2-(2-fluorophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7d**) From **5d** (119 mg). Yield: 130 mg (68 %); Mp 189–190 °C; FTIR (ν_{max}, cm^{-1}): 3080, 2919, 2881, 1577, 1552, 1203, 1195. ^1H NMR ($CDCl_3$): $\delta = 1.84$ (m, 6H, $H_{adamantane}$), 2.18 (m, 9H, $H_{adamantane}$), 7.24 (m, 1H, $H_{arom.}$), 7.33 (m, 1H, $H_{arom.}$), 7.47 (m, 1H, $H_{arom.}$), 8.18 (s, 1H, $H_{thiazole}$), 8.49 (m, 1H, Ar–H). ^{13}C NMR ($CDCl_3$): $\delta = 27.8$, 34.5, 36.3, 40.0 ($10 \times C_{adamantane}$), 116.1

(d, $J_{C\text{-}F} = 21.8$ Hz, $C^3_{arom.}$), 120.5 (d, $J_{C\text{-}F} = 11.3$ Hz, $C^1_{arom.}$), 121.3 ($C^5_{thiazole}$), 122.7 (d, $J_{C\text{-}F} = 9.8$ Hz, $C^6_{arom.}$), 124.8 (d, $J_{C\text{-}F} = 3.0$ Hz, $C^5_{arom.}$), 131.9 (d, $J_{C\text{-}F} = 9.0$ Hz, $C^4_{arom.}$), 140.3 ($C^4_{thiazole}$), 160.2 (d, $J_{C\text{-}F} = 251.3$ Hz, $C^2_{arom.}$), 160.3 ($C^5_{oxadiazole}$), 162.2 ($C^2_{thiazole}$), 172.7 ($C^2_{oxadiazole}$). EI-MS (*m/z*, %): 380/382 ($[M]^+$, 100), 206 (28), 178 (9), 135 (88), 121 (8), 107 (16), 93 (13), 79 (14). Anal. Calcd. for $C_{21}H_{20}FN_3OS$: C, 66.12; H, 5.28; N, 11.02. Found: C, 65.94; H, 5.21; N, 10.93.

2-[(Adamantan-1-yl)-5-(2-(3-fluorophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7e**) From **5e** (119 mg). Yield: 137 mg (72 %); Mp 180–183 °C; FTIR (ν_{max}, cm^{-1}): 3080, 2906, 2847, 1590, 1549, 1204, 1155. ^{1}H NMR ($CDCl_3$): $\delta = 1.84$ (m, 6H, $H_{adamantane}$), 2.18 (m, 9H, $H_{adamantane}$), 7.19 (m, 1H, $H_{arom.}$), 7.46 (m, 1H, $H_{arom.}$), 7.80–7.84 (m, 2H, $H_{arom.}$), 8.13 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): $\delta = 27.7$, 34.5, 36.3, 39.9 ($10 \times C_{adamantane}$), 113.8 (d, $J_{C\text{-}F} = 23.25$ Hz, $C^4_{arom.}$), 117.7 (d, $J_{C\text{-}F} = 21.0$ Hz, $C^2_{arom.}$), 121.8 ($C^5_{thiazole}$), 122.7 (d, $J_{C\text{-}F} = 3.0$ Hz, $C^6_{arom.}$), 130.7 (d, $J_{C\text{-}F} = 8.3$ Hz, $C^1_{arom.}$), 134.6 (d, $J_{C\text{-}F} = 8.3$ Hz, $C^5_{arom.}$), 141.6 ($C^4_{thiazole}$), 160.1 ($C^5_{oxadiazole}$), 163.1 (d, $J_{C\text{-}F} = 246.0$ Hz, $C^3_{arom.}$), 168.2 ($C^2_{thiazole}$), 172.8 ($C^2_{oxadiazole}$). EI-MS (*m/z*, %): 380/382 ($[M]^+$, 100), 206 (22), 178 (11), 135 (35), 121 (14), 107 (9), 93 (10), 79 (12). Anal. Calcd. for $C_{21}H_{20}FN_3OS$: C, 66.12; H, 5.28; N, 11.02. Found: C, 65.89; H, 5.18; N, 10.82.

2-[(Adamantan-1-yl)-5-(2-(4-fluorophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7f**) From **5f** (117 mg). Yield: 143 mg (75 %); Mp 204–205 °C; FTIR (ν_{max}, cm^{-1}): 3077, 2907, 2849, 1601, 1550, 1228, 1159. ^{1}H NMR ($CDCl_3$): $\delta = 1.84$ (m, 6H, $H_{adamantane}$), 2.18 (m, 9H, $H_{adamantane}$), 7.18–7.21 (m, 2H, $H_{arom.}$), 8.04–8.08 (m, 2H, $H_{arom.}$), 8.09 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): $\delta = 27.7$, 34.5, 36.3, 39.9 ($10 \times C_{adamantane}$), 116.2 (d, $J_{C\text{-}F} = 22.5$ Hz, $C^3_{arom.}$ + C-5), 121.3 ($C^5_{thiazole}$), 129.0 (d, $J_{C\text{-}F} = 9.0$ Hz, $C^2_{arom.}$ + C-6), 129.9 (d, $J_{C\text{-}F} = 3.0$ Hz, $C^1_{arom.}$), 141.4 ($C^4_{thiazole}$), 160.2 ($C^5_{oxadiazole}$), 164.3 (d, $J_{C\text{-}F} = 250.5$ Hz, $C^4_{arom.}$), 168.6 ($C^2_{thiazole}$), 172.7 ($C^2_{oxadiazole}$). EI-MS (*m/z*, %): 380/382 ($[M]^+$, 100), 206 (13), 178 (6), 135 (27), 121 (14), 107 (6), 93 (13), 79 (19). Anal. Calcd. for $C_{21}H_{20}FN_3OS$: C, 66.12; H, 5.28; N, 11.02. Found: C, 65.92; H, 5.15; N, 10.89.

2-[(Adamantan-1-yl)-5-(2-(2-chlorophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7g**) From **5g** (127 mg). Yield: 159 mg (80 %); Mp 146–148 °C; FTIR (ν_{max}, cm^{-1}): 3088, 2912, 2847, 1599, 1552, 1205, 1077. ^{1}H NMR ($CDCl_3$): $\delta = 1.84$ (m, 6H, $H_{adamantane}$), 2.19 (m, 9H, $H_{adamantane}$), 7.39–7.46 (m, 2H, $H_{arom.}$), 7.54 (m, 1H, $H_{arom.}$), 8.26 (s, 1H, $H_{thiazole}$), 8.42 (m, 1H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$): $\delta = 27.8$, 34.5, 36.3, 39.9 ($10 \times C_{adamantane}$), 123.0 ($C^5_{thiazole}$), 127.3, 130.6, 131.0, 131.1, 131.4, 132.1 ($6 \times$ Ar–C), 140.2 ($C^4_{thiazole}$), 160.3 ($C^5_{oxadiazole}$), 165.0 ($C^2_{thiazole}$), 172.7 ($C^2_{oxadiazole}$). EI-MS (*m/z*, %): 397/399 ($[M]^+$, 100), (69), 107 (5), 93 (9), 79 (11). Anal. Calcd. for $C_{21}H_{20}ClN_3OS$: C, 63.39; H, 5.15; N, 10.56. Found: C, 63.18; H, 5.03; N, 10.33.

2-[(Adamantan-1-yl)-5-(2-(3-chlorophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7h**) From **5h** (127 mg). Yield: 155 mg (78 %); Mp 198–200 °C; FTIR (ν_{max}, cm^{-1}): 3100, 2921, 2846, 1606, 1555, 1201, 1082. ^{1}H NMR ($CDCl_3$): $\delta = 1.84$ (m, 6H, $H_{adamantane}$), 2.19 (m, 9H, $H_{adamantane}$), 7.41–7.49 (m, 2H, $H_{arom.}$), 7.92 (m, 1H, $H_{arom.}$), 8.10 (m, 1H, $H_{arom.}$), 8.14 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): $\delta = 27.8$, 34.5, 36.3, 39.9 ($10 \times C_{adamantane}$), 121.8 ($C^5_{thiazole}$), 125.1, 126.9, 130.3, 130.8, 134.2, 135.2 ($6 \times C_{arom.}$), 141.6 ($C^4_{thiazole}$), 160.1 ($C^5_{oxadiazole}$), 168.1 ($C^2_{thiazole}$), 172.8 ($C^2_{oxadiazole}$). EI-MS (*m/z*, %): 397/399 ($[M+2]^+$, 49), 397/399 ($[M^+$, 100]), 224 (8), 222 (21), 196 (4), 194 (12), 135 (58), 107 (6), 93 (12), 79 (15). Anal. Calcd. for $C_{21}H_{20}ClN_3OS$: C, 63.39; H, 5.15; N, 10.56. Found: C, 63.22; H, 5.02; N, 10.40.

2-[(Adamantan-1-yl)-5-(2-(4-chlorophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7i**) From **5i** (127 mg). Yield: 161 mg (81 %); Mp 203–204 °C; FTIR (ν_{max}, cm^{-1}): 3081, 2910, 2845, 1604, 1557, 1206, 1079. ^{1}HNMR ($CDCl_3$): $\delta = 1.84$ (m, 6H, $H_{adamantane}$), 2.18 (m, 9H, $H_{adamantane}$), 7.45–7.49 (m, 2H, $H_{arom.}$), 7.99–8.03 (m, 2H, $H_{arom.}$), 8.12 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): $\delta = 27.8$, 34.5, 36.3, 39.9 ($10 \times C_{adamantane}$), 121.5 ($C^5_{thiazole}$), 128.2, 129.3, 131.2, 136.9 ($6 \times C_{arom.}$), 141.6 ($C^4_{thiazole}$), 160.1 ($C^5_{oxadiazole}$), 168.4 ($C^2_{thiazole}$), 172.7 ($C^2_{oxadiazole}$). EI-MS (*m/z*, %): 397/399 ($[M+2]^+$, 36), 396/398 ($[M^+$, 100]), 224 (6), 222 (16), 196 (4), 194 (11), 135 (41), 107 (4), 93 (6), 79 (11). Anal. Calcd. for $C_{21}H_{20}ClN_3OS$: C, 63.39; H, 5.15; N, 10.56. Found: C, 63.18; H, 5.00; N, 10.33.

2-[(Adamantan-1-yl)-5-(2-(2-bromophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7j**) From **5j** (149 mg). Yield: 166 mg (75 %); Mp 138–141 °C; FTIR (ν_{max}, cm^{-1}): 3088, 2917, 2844, 1600, 1559, 1212, 1044. ^{1}H NMR ($CDCl_3$): $\delta = 1.84$ (m, 6H, $H_{adamantane}$), 2.19 (m, 9H, $H_{adamantane}$), 7.34 (m, 1H, $H_{arom.}$), 7.47 (m, 1H, $H_{arom.}$), 7.74 (m, 1H, $H_{arom.}$), 8.22 (m, 1H, $H_{arom.}$), 8.27 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): $\delta = 27.7$, 34.5, 36.3, 39.9 ($10 \times C_{adamantane}$), 121.8 ($C^5_{thiazole}$), 123.1, 127.8, 131.3, 132.1, 133.2, 134.0 ($6 \times C_{arom.}$), 140.3 ($C^4_{thiazole}$), 160.3 ($C^5_{oxadiazole}$), 166.6 ($C^2_{thiazole}$), 172.8 ($C^2_{oxadiazole}$). EI-MS (*m/z*, %): 443 ($[M+2]^+$, 96), 441/443 [M^+, 100], 268 (8), 266 (10), 240 (6), 238 (7), 135 (48), 107 (12), 93 (5), 79 (13). Anal. Calcd. for $C_{21}H_{20}BrN_3OS$: C, 57.02; H, 4.56; N, 9.50. Found: C, 56.89; H, 4.48; N, 9.29.

2-[(Adamantan-1-yl)-5-(2-(3-bromophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7k**) From **5k** (149 mg). Yield: 168 mg (76 %); Mp 194–196 °C; FTIR (ν_{max}, cm^{-1}): 3078,

2911, 2847, 1602, 1551, 1218, 1052. ^{1}H NMR ($CDCl_3$): $\delta = 1.84$ (m, 6H, $H_{adamantane}$), 2.19 (m, 9H, $H_{adamantane}$), 7.37 (m, 1H, $H_{arom.}$), 7.62 (m, 1H, $H_{arom.}$), 7.97 (m, 1H, $H_{arom.}$), 8.14 (s, 1H, $H_{thiazole}$), 8.26 (m, 1H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$): $\delta = 27.7$, 34.5, 36.3, 39.9 ($10 \times C_{adamantane}$), 121.9 ($C^5{}_{thiazole}$), 123.2, 125.6, 129.7, 130.6, 133.7, 134.4 ($6 \times C_{arom.}$), 141.6 ($C^4{}_{thiazole}$), 160.1 ($C^5{}_{oxadiazole}$), 167.9 ($C^2{}_{thiazole}$), 172.8 ($C^2{}_{oxadiazole}$). EI-MS (*m/z*, %): 443 ([M +2]$^+$, 98), 441/443 ([M]$^+$, 100), 268 (10), 266 (12), 240 (4), 238 (3), 135 (79), 107 (6), 93 (14), 79 (14). Anal. Calcd. for $C_{21}H_{20}BrN_3OS$: C, 57.02; H, 4.56; N, 9.50. Found: C, 56.90; H, 4.50; N, 9.39.

2-[(Adamantan-1-yl)-5-(2-(4-bromophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7l**) From **5l** (149 mg). Yield: 179 mg (81 %); Mp 206–207 °C; FTIR (ν_{max}, cm^{-1}): 3091, 2922, 2848, 1603, 1552, 1208, 1049. ^{1}H NMR ($CDCl_3$): $\delta = 1.84$ (m, 6H, $H_{adamantane}$), 2.18 (m, 9H, $H_{adamantane}$), 7.61–7.64 (m, 2H, $H_{arom.}$), 7.93–7.96 (m, 2H, $H_{arom.}$), 8.12 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): $\delta = 27.7$, 34.5, 36.3, 39.9 ($10 \times C_{adamantane}$), 121.6 ($C^5{}_{thiazole}$), 125.3, 128.4, 131.6, 132.3 ($6 \times C_{arom.}$), 141.6 ($C^4{}_{thiazole}$), 160.1 ($C^5{}_{oxadiazole}$), 168.5 ($C^2{}_{thiazole}$), 172.7 ($C^2{}_{oxadiazole}$). EI-MS (*m/z*, %): 443/445 ([M+2]$^+$, 98), 440/442 ([M]$^+$, 100), 268 (10), 266 (11), 240 (3), 238 (3), 135 (45), 107 (4), 93 (7), 79 (6). Anal. Calcd. for $C_{21}H_{20}BrN_3OS$: C, 57.02; H, 4.56; N, 9.50. Found: C, 56.85; H, 4.47; N, 9.29.

2-[((Adamantan-1-yl)methyl)-5-(2-(2-methylphenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7m**) From **5a** (117 mg). Yield: 143 mg (73 %); Mp 152–154 °C; FTIR (ν_{max}, cm^{-1}): 3106, 2921, 2847, 1599, 1562, 1206. ^{1}H NMR ($CDCl_3$): $\delta = 1.61$–1.74 (m, 12H, $H_{adamantane}$), 2.01 (br s, 3H, $H_{adamantane}$), 2.65 (s, 3H, Ar–*Me*), 2.75 (s, 2H, CH_2), 7.29–7.42 (m, 3H, $H_{arom.}$), 7.78 (m, 1H, $H_{arom.}$), 8.19 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): $\delta = 21.5$ (CH_3), 28.5, 33.6, 36.5 ($7 \times C_{adamantane}$), 39.5 (CH_2), 42.2 ($3 \times C_{adamantane}$), 122.1 ($C^5{}_{thiazole}$), 126.2, 130.1, 131.5, 131.6, 132.0, 136.9 ($6 \times C_{arom.}$), 140.5 ($C^4{}_{thiazole}$), 160.8 ($C^5{}_{oxadiazole}$), 165.1 ($C^2{}_{thiazole}$), 169.5 ($C^2{}_{oxadiazole}$). EI-MS (*m/z*, %): 391 ([M]$^+$, 16), 202 (9), 174 (13), 135 (100), 117 (4), 107 (12), 93 (29), 91 (16), 79 (29). Anal. Calcd. for $C_{23}H_{25}N_3OS$: C, 70.56; H, 6.44; N, 10.73. Found: C, 70.33; H, 6.36; N, 10.54.

2-[((Adamantan-1-yl)methyl)-5-(2-(3-methylphenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7n**) From **5b** (117 mg). Yield: 155 mg (79 %); Mp 163–165 °C; FTIR (ν_{max}, cm^{-1}): 3083, 2896, 2844, 1581, 1561, 1229. ^{1}H NMR ($CDCl_3$): $\delta = 1.61$–1.74 (m, 12H, $H_{adamantane}$), 2.01 (br s, 3H, $H_{adamantane}$), 2.45 (s, 3H, Ar–*Me*), 2.75 (s, 2H, CH_2), 7.31–7.39 (m, 2H, $H_{arom.}$), 7.83 (m, 1H, $H_{arom.}$), 7.91 (m, 1H, $H_{arom.}$), 8.01 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): $\delta = 21.3$ (CH_3), 28.5, 33.6, 36.5 ($7 \times C_{adamantane}$), 39.6 (CH_2), 42.2 ($3 \times C_{adamantane}$), 121.3 ($C^5{}_{thiazole}$), 124.2, 127.5, 129.0, 131.7, 132.5, 139.0 ($6 \times C_{arom.}$), 141.1 ($C^4{}_{thiazole}$), 160.7 ($C^5{}_{oxadiazole}$), 165.0 ($C^2{}_{thiazole}$), 170.2 ($C^2{}_{oxadiazole}$). EI-MS (*m/z*, %): 391 ([M]$^+$, 28), 202 (19), 174 (4), 135 (100), 117 (3), 107 (7), 93 (18), 91 (11), 79 (10). Anal. Calcd. for $C_{23}H_{25}N_3OS$: C, 70.56; H, 6.44; N, 10.73. Found: C, 70.38; H, 6.37; N, 10.48.

2-[((Adamantan-1-yl)methyl)-5-(2-(4-methylphenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7o**) From **5c** (117 mg). Yield: 141 mg (72 %); Mp 188–190 °C; FTIR (ν_{max}, cm^{-1}): 3108, 2901, 2847, 1585, 1562, 1222. ^{1}H NMR ($CDCl_3$): $\delta = 1.61$–1.74 (m, 12H, $H_{adamantane}$), 2.01 (br s, 3H, $H_{adamantane}$), 2.43 (s, 3H, Ar–*Me*), 2.76 (s, 2H, CH_2), 7.29 (d, 2H, $J = 8.1$ Hz, $H_{arom.}$), 7.95 (d, 2H, $J = 8.1$ Hz, $H_{arom.}$), 8.07 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): $\delta = 21.5$ (CH_3), 28.5, 33.6, 36.6 ($7 \times C_{adamantane}$), 39.6 (CH_2), 42.2 ($3 \times C_{adamantane}$), 121.0 ($C^5{}_{thiazole}$), 126.9, 129.7, 130.0, 141.0 ($6 \times C_{arom.}$), 141.3 ($C^4{}_{thiazole}$), 160.8 ($C^5{}_{oxadiazole}$), 165.0 ($C^2{}_{thiazole}$), 170.2 ($C^2{}_{oxadiazole}$). EI-MS (*m/z*, %): 391 ([M]$^+$, 16), 202 (11), 174 (3), 135 (100), 117 (3), 107 (8), 93 (25), 91 (14), 79 (32). Anal. Calcd. for $C_{23}H_{25}N_3OS$: C, 70.56; H, 6.44; N, 10.73. Found: C, 70.29; H, 6.36; N, 10.56.

2-[((Adamantan-1-yl)methyl)-5-(2-(2-fluorophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7p**) From **5d** (119 mg). Yield: 140 mg (71 %); Mp 173–175 °C; FTIR (ν_{max}, cm^{-1}): 3096, 2905, 2845, 1604, 1563, 1207, 1192. ^{1}H NMR ($CDCl_3$): $\delta = 1.60$–1.72 (m, 12H, $H_{adamantane}$), 2.00 (br s, 3H, $H_{adamantane}$), 2.74 (s, 2H, CH_2), 7.18–7.32 (m, 2H, $H_{arom.}$), 7.44 (m, 1H, $H_{arom.}$), 8.21 (s, 1H, $H_{thiazole}$), 8.46 (m, 1H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$): $\delta = 28.5$, 33.6, 36.5 ($7 \times C_{adamantane}$), 39.6 (CH_2), 42.2 ($3 \times C_{adamantane}$), 116.1 (d, $J_{C\text{-}F} = 21.75$ Hz, $C^3{}_{arom.}$), 120.4 (d, $J_{C\text{-}F} = 11.25$ Hz, $C^1{}_{arom.}$), 121.2 ($C^5{}_{thiazole}$), 122.7 (d, $J_{C\text{-}F} = 9.75$ Hz, $C^6{}_{arom.}$), 124.8 (d, $J_{C\text{-}F} = 3.0$ Hz, $C^5{}_{arom.}$), 132.0 (d, $J_{C\text{-}F} = 9.0$ Hz, $C^4{}_{arom.}$), 140.2 ($C^4{}_{thiazole}$), 160.2 (d, $J_{C\text{-}F} = 250.5$ Hz, $C^2{}_{arom.}$), 160.8 ($C^5{}_{oxadiazole}$), 162.2 ($C^2{}_{thiazole}$), 165.1 ($C^2{}_{oxadiazole}$). EI-MS (*m/z*, %): 394/396 ([M]$^+$, 12), 206 (18), 178 (3), 135 (100), 121 (3), 107 (12), 93 (31), 79 (64). Anal. Calcd. for $C_{22}H_{22}FN_3OS$: C, 66.81; H, 5.61; N, 10.62. Found: C, 66.63; H, 5.58; N, 10.50.

2-[((Adamantan-1-yl)methyl)-5-(2-(3-fluorophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7q**) From **5e** (119 mg). Yield: 146 mg (74 %); Mp 156–158 °C; FTIR (ν_{max}, cm^{-1}): 3106, 2903, 2845, 1603, 1564, 1210, 1197. ^{1}H NMR ($CDCl_3$): $\delta = 1.61$–1.73 (m, 12H, $H_{adamantane}$), 2.01 (br s, 3H, $H_{adamantane}$), 2.76 (s, 2H, CH_2), 7.18 (m, 1H, $H_{arom.}$), 7.46 (m, 1H, $H_{arom.}$), 7.80 (m, 1H, $H_{arom.}$), 8.14 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): $\delta = 28.5$, 33.6, 36.5 ($7 \times C_{adamantane}$), 39.6 (CH_2), 42.2 ($3 \times C_{adamantane}$), 113.8 (d, $J_{C\text{-}F} = 23.3$ Hz, $C^4{}_{arom.}$), 117.8 (d, $J_{C\text{-}F} = 21.8$ Hz, $C^2{}_{arom.}$), 121.9 ($C^5{}_{thiazole}$), 130.8 (d, $J_{C\text{-}F} = 3.0$ Hz, $C^6{}_{arom.}$), 134.5

(d, $J_{C\text{-}F}$ = 8.3 Hz, $C^1_{arom.}$), 135.6 (d, $J_{C\text{-}F}$ = 8.3 Hz, $C^5_{arom.}$), 141.3 ($C^4_{thiazole}$), 160.6 ($C^5_{oxadiazole}$), 163.0 (d, $J_{C\text{-}F}$ = 246.0 Hz, $C^3_{arom.}$), 165.1 ($C^2_{thiazole}$), 168.4 ($C^2_{oxadiazole}$). EI-MS (*m/z*, %): 394/396 ($[M]^+$, 11), 206 (14), 178 (3), 135 (100), 121 (3), 107 (12), 93 (30), 79 (41). Anal. Calcd. for $C_{22}H_{22}FN_3OS$: C, 66.81; H, 5.61; N, 10.62. Found: C, 66.60; H, 5.53; N, 10.48.

2-[((Adamantan-1-yl)methyl)-5-(2-(4-fluorophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7r**) From **5f** (119 mg). Yield: 146 mg (74 %); Mp 202–204 °C; FTIR (ν_{max}, cm^{-1}): 3109, 2899, 2849, 1601, 1565, 1206, 1191. ^{1}H NMR ($CDCl_3$): δ = 1.58–1.71 (m, 12H, $H_{adamantane}$), 1.98 (br s, 3H, $H_{adamantane}$), 2.72 (s, 2H, CH_2), 7.11–7.17 (m, 2H, $H_{arom.}$), 8.00–8.04 (m, 2H, $H_{arom.}$), 8.06 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): δ = 28.5, 33.6, 36.5 (7 × $C_{adamantane}$), 39.5 (CH_2), 42.2 (3 × $C_{adamantane}$), 116.2 (d, $J_{C\text{-}F}$ = 22.5 Hz, $C^3_{arom.}$ + C-5), 121.4 ($C^5_{thiazole}$), 128.9 (d, $J_{C\text{-}F}$ = 9.0 Hz, $C^2_{arom.}$ + C-6), 129.9 (d, $J_{C\text{-}F}$ = 3.0 Hz, $C^1_{arom.}$), 141.2 ($C^4_{thiazole}$), 160.6 ($C^5_{oxadiazole}$), 164.3 (d, $J_{C\text{-}F}$ = 250.5 Hz, $C^4_{arom.}$), 165.0 ($C^2_{thiazole}$), 168.7 ($C^2_{oxadiazole}$). EI-MS (*m/z*, %): 395/396 ($[M]^+$, 15), 206 (12), 178 (3), 135 (100), 121 (3), 107 (11), 93 (28), 79 (37). Anal. Calcd. for $C_{22}H_{22}FN_3OS$: C, 66.81; H, 5.61; N, 10.62. Found: C, 66.59; H, 5.55; N, 10.42.

2-[((Adamantan-1-yl)methyl)-5-(2-(2-chlorophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7s**) From **5g** (127 mg). Yield: 165 mg (80 %); Mp 150–153 °C; FTIR (ν_{max}, cm^{-1}): 3088, 2911, 2844, 1600, 1560, 1206, 1076. ^{1}H NMR ($CDCl_3$): δ = 1.56–1.68 (m, 12H, $H_{adamantane}$), 1.98 (br s, 3H, $H_{adamantane}$), 2.72 (s, 2H, CH_2), 7.40–7.46 (m, 2H, $H_{arom.}$), 7.53 (m, 1H, $H_{arom.}$), 8.27 (s, 1H, $H_{thiazole}$), 8.42 (m, 1H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$): δ = 28.5, 33.6, 36.5 (7 × $C_{adamantane}$), 39.6 (CH_2), 42.2 (3 × $C_{adamantane}$), 121.4 ($C^5_{thiazole}$), 127.3, 130.4, 130.9, 131.0, 131.4, 132.6 (6 × $C_{arom.}$), 140.1 ($C^4_{thiazole}$), 160.3 ($C^5_{oxadiazole}$), 165.1 ($C^2_{thiazole}$), 168.8 ($C^2_{oxadiazole}$ 2). EI-MS (*m/z*, %): 413/415 ($[M+2]^+$, 7), 411/413 [M^+, 23], 224 (5), 222 (15), 135 (100), 107 (11), 93 (25), 79 (56). Anal. Calcd. for $C_{22}H_{22}ClN_3OS$: C, 64.14; H, 5.38; N, 10.20. Found: C, 63.95; H, 5.30; N, 10.03 %.

2-[((Adamantan-1-yl)methyl)-5-(2-(3-chlorophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7t**) From **5h** (127 mg). Yield: 152 mg (74 %); Mp 166–168 °C; FTIR (ν_{max}, cm^{-1}): 3084, 2900, 2846, 1593, 1563, 1191, 1081. ^{1}H NMR ($CDCl_3$): δ = 1.53–1.66 (m, 12H, $H_{adamantane}$), 1.93 (br s, 3H, $H_{adamantane}$), 2.69 (s, 2H, CH_2), 7.28–7.38 (m, 2H, $H_{arom.}$), 7.81 (m, 1H, $H_{arom.}$), 8.00 (m, 1H, $H_{arom.}$), 8.09 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): δ = 28.6, 33.4, 36.5 (7 × $C_{adamantane}$), 39.5 (CH_2), 42.2 (3 × $C_{adamantane}$), 121.6 ($C^5_{thiazole}$), 125.0, 126.7, 130.3, 130.7, 134.0, 135.1 (6 × $C_{arom.}$), 141.2 ($C^4_{thiazole}$), 160.5 ($C^5_{oxadiazole}$), 165.1 ($C^2_{thiazole}$), 168.1 ($C^2_{oxadiazole}$). EI-MS (*m/z*, %): 413/415 ($[M+2]^+$, 3), 411/413 [M^+, 8], 224 (4), 222 (10), 135 (100), 107 (9), 93 (25), 79 (33). Anal. Calcd. for $C_{22}H_{22}ClN_3OS$: C, 64.14; H, 5.38; N, 10.20. Found: C, 65.89; H, 5.29; N, 10.10.

2-[((Adamantan-1-yl)methyl)-5-(2-(4-chlorophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7u**) From **5i** (127 mg). Yield: 163 mg (79 %); Mp 184–187 °C; FTIR (ν_{max}, cm^{-1}): 3109, 2903, 2848, 1597, 1562, 1222, 1090. ^{1}HNMR ($CDCl_3$): δ = 1.56–1.69 (m, 12H, $H_{adamantane}$), 1.96 (br s, 3H, $H_{adamantane}$), 2.71 (s, 2H, CH_2), 7.41 (d, 2H, J = 8.7 Hz, $H_{arom.}$), 7.94 (d, 2H, J = 8.7 Hz, $H_{arom.}$), 8.06 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): δ = 28.5, 33.6, 36.5 (7 × $C_{adamantane}$), 39.5 (CH_2), 42.2 (3 × $C_{adamantane}$), 121.6 ($C^5_{thiazole}$), 128.1, 129.3, 131.1, 136.9 (6 × $C_{arom.}$), 141.3 ($C^4_{thiazole}$), 160.5 ($C^5_{oxadiazole}$), 165.0 ($C^2_{thiazole}$), 168.5 ($C^2_{oxadiazole}$). EI-MS (*m/z*, %): 413/415 ($[M+2]^+$, 4), 411/413 [M^+, 10], 224 (3), 222 (8), 135 (100), 107 (8), 93 (23), 79 (32). Anal. Calcd. for $C_{22}H_{22}ClN_3OS$: C, 64.14; H, 5.38; N, 10.20. Found: C, 65.90; H, 5.31; N, 9.98.

2-[((Adamantan-1-yl)methyl)-5-(2-(2-bromophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7v**) From **5j** (149 mg). Yield: 182 mg (80 %); Mp 185–187 °C; FTIR (ν_{max}, cm^{-1}): 3098, 2896, 2844, 1604, 1563, 1207, 1025. ^{1}H NMR ($CDCl_3$) δ = 1.59–1.73 (m, 12H, $H_{adamantane}$), 2.00 (br s, 3H, $H_{adamantane}$), 2.75 (s, 2H, CH_2), 7.32 (m, 1H, $H_{arom.}$), 7.45 (m, 1H, $H_{arom.}$), 7.72 (m, 1H, $H_{arom.}$), 8.20 (m, 1H, $H_{arom.}$), 8.26 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): δ = 28.5, 33.6, 36.6 (7 × $C_{adamantane}$), 39.6 (CH_2), 42.2 (3 × $C_{adamantane}$), 121.7 ($C^5_{thiazole}$), 123.1, 127.8, 131.3, 132.0, 133.1, 134.0 (6 × $C_{arom.}$), 140.1 ($C^4_{thiazole}$), 160.7 ($C^5_{oxadiazole}$), 165.1 ($C^2_{thiazole}$), 166.7 ($C^2_{oxadiazole}$). EI-MS (*m/z*, %): 457/459 ($[M+2]^+$, 6), 454/457 (M^+, 7), 268 (6), 266 (6), 135 (100), 107 (12), 93 (33), 79 (48). Anal. Calcd. for $C_{22}H_{22}BrN_3OS$: C, 57.90; H, 4.86; N, 9.21. Found: C, 57.71; H, 4.77; N, 8.96.

2-[((Adamantan-1-yl)methyl)-5-(2-(3-bromophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7w**) From **5k** (149 mg). Yield: 175 mg (77 %); Mp 172–173 °C; FTIR (ν_{max}, cm^{-1}): 3085, 2921, 2845, 1580, 1560, 1203, 993. ^{1}H NMR ($CDCl_3$): δ = 1.60–1.74 (m, 12H, $H_{adamantane}$), 2.01 (br s, 3H, $H_{adamantane}$), 2.76 (s, 2H, CH_2), 7.36 (m, 1H, H_{arom}), 7.61 (m, 1H, $H_{arom.}$), 7.95 (m, 1H, $H_{arom.}$), 8.13 (s, 1H, $H_{thiazole}$), 8.24 (m, 1H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$): δ = 28.5, 33.6, 36.5 (7 × $C_{adamantane}$), 39.6 (CH_2), 42.2 (3 × $C_{adamantane}$), 121.9 ($C^5_{thiazole}$), 123.2, 125.5, 129.7, 130.6, 133.7, 134.4 (6 × $C_{arom.}$), 141.4 ($C^4_{thiazole}$), 160.5 ($C^5_{oxadiazole}$), 165.1 ($C^2_{thiazole}$), 168.1 ($C^2_{oxadiazole}$). EI-MS (*m/z*, %): 457/459 ($[M+2]^+$, 6), 454/457 (M^+, 6), 268 (4), 266 (5), 135 (100), 107 (9), 93 (25), 79 (25). Anal. Calcd. for $C_{22}H_{22}BrN_3OS$: C, 57.90; H, 4.86; N, 9.21. Found: C, 57.79; H, 4.76; N, 9.02.

2-[((Adamantan-1-yl)methyl)-5-(2-(4-bromophenyl)-1,3-thiazol-4-yl)]-1,3,4-oxadiazole (**7x**) From **5l** (149 mg). Yield: 177 mg (78 %); Mp 190–192 °C; FTIR (ν_{max}, cm^{-1}): 3107, 2909, 2848, 1592, 1561, 1201, 989. ^1H NMR ($CDCl_3$): $\delta = 1.59–1.73$ (m, 12H, $H_{adamantane}$), 2.00 (br s, 3H, $H_{adamantane}$), 2.74 (s, 2H, CH_2), 7.61 (d, 2H, $J = 8.7$ Hz, $H_{arom.}$), 7.92 (d, 2H, $J = 8.7$ Hz, $H_{arom.}$), 8.10 (s, 1H, $H_{thiazole}$). ^{13}C NMR ($CDCl_3$): $\delta = 28.5$, 33.6, 36.5 (7 × $C_{adamantane}$), 39.6 (CH_2), 42.2 (3 × $C_{adamantane}$), 121.6 ($C^5{}_{thiazole}$), 125.3, 128.3, 131.5, 132.3 (6 × $C_{arom.}$), 141.4 ($C^4{}_{thiazole}$), 160.6 ($C^5{}_{oxadiazole}$), 165.1 ($C^2{}_{thiazole}$), 168.7 ($C^2{}_{oxadiazole}$). EI-MS (*m/z*, %): 457/459 ($[M+2]^+$, 6), 454/457 (M^+, 6), 268 (5), 266 (6), 135 (100), 107 (8), 93 (20), 79 (32). Anal. Calcd. for $C_{22}H_{22}BrN_3OS$: C, 57.90; H, 4.86; N, 9.21. Found: C, 57.67; H, 4.76; N, 8.88.

N-[(2-chlorophenethyl)carbamothioyl]-2-phenylthiazole-4-carboxamide (**13**) To a stirred solution of **9** (112 mg, 0.50 mmol) in acetone (7 mL), NH_4SCN (58 mg, 0.76 mmol) was added and the reaction mixture heated under reflux for 2 h. After cooling and filtration, the amine **11** (156 mg, 0.39 mmol) and NaOH (20 mg, 0.51 mmol) were added directly in dry form and the mixture heated under reflux for 6 h. After cooling, the reaction mixture was filtered, and the filtrate was evaporated to dryness. The residue was purified on a column of silica gel (10 g), using, in gradient, MeOH (0–10 %) and $CHCl_3$ as eluent to give **13** (139 mg, 69 %); Mp 159–162 °C. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 2.95$ (t, 2H, $J = 6.5$ Hz, CH_2Ph), 3.84 (t, 2H, $J = 6.5$ Hz, CH_2NH), 8.00–7.10 (m, 9H, $H_{arom.}$), 9.12 (s, 1H, $H_{thiazole}$), 8.90 (br s, 1H, NH), 10.11 (br s, 1H, NH). ^{13}C NMR (150.91 MHz, $CDCl_3$): $\delta = 30.1$ (CH_2Ph), 45.6 (CH_2N), 126.0, 126.3, 127.2, 128.0, 128.5, 128.8, 129.4, 132.8, 142.0 ($C_{arom.}$ + $C^5{}_{thiazole}$), 146.9 ($C^4{}_{thiazole}$), 165.0 ($C^2{}_{thiazole}$), 165.9 (C=O), 178.9 (C=S). FAB-MS (*m/z*, %): 401/403 $[M, 78]^+$. Anal. Calcd. for $C_{19}H_{16}ClN_3OS_2$: C, 56.78; H, 4.01; N, 10.45. Found: C, 56.59; H, 3.95; N, 10.28.

N-[(2-methoxyphenethyl)carbamothioyl]-2-phenylthiazole-4-carboxamide (**14**) This compound was prepared according to the procedure of prepartion of compound **13**, from **9** (112 mg, 0.50 mmol), NH_4SCN (58 mg, 0.76 mmol) in acetone followed by treatment with the amine **12** (59 mg, 0.39 mmol) and NaOH (20 mg, 0.51 mmol). Yield: 145 mg (73 %); Mp 149–151 °C. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 2.93$ (t, 2H, $J = 6.5$ Hz, CH_2Ph), 3.68 (s, 3H, OMe), 3.82 (t, 2H, $J = 6.5$ Hz, CH_2NH), 8.01–7.43 (m, 5H, $H_{arom.}$), 7.17–6.92 (m, 4H, $H_{arom.}$), 9.09 (s, 1H, $H_{thiazole}$), 9.10 (br s, 1H, NH), 10.15 (br s, 1H, NH). ^{13}C NMR (150.91 MHz, $CDCl_3$): $\delta = 29.6$ (CH_2Ph), 46.1 (CH_2N), 55.0 (OMe), 111.8, 119.6, 126.3, 128.0, 128.5, 129.0, 130.4, 131.0 ($C_{arom.}$ + $C^5{}_{thiazole}$), 147.0 ($C^4{}_{thiazole}$), 157.2 ($C_{arom.}$–OMe), 165.6 ($C^2{}_{thiazole}$), 166.3 (C=O), 181.1 (C=S). FAB-MS (*m/z*, %): 398 $([M+H]^+$, 88). Anal. Calcd. for $C_{20}H_{19}N_3O_2S_2$: C, 60.43; H, 4.82; N, 10.57. Found: C, 60.22; H, 4.61; N, 10.39.

Table 2 Summary of crystallographic data

Compound	**7a**
Formula	$C_{22}H_{23}N_3OS$
M_r	377.49
Habit	Colorless block
Cryst. size (mm)	0.4 × 0.35 × 0.25
Crystal system	Monoclinic
Space group	$P2_1/c$
Temperature (°C)	−173
Cell constants	
a (Å)	16.8868(5)
b (Å)	9.5584(3)
c (Å)	12.3345(4)
β (°)	109.184(4)
V (Å^3)	1880.36
Z	4
D_x (Mg m^{-3})	1.333
μ (mm^{-1})	0.19
F(000)	800
$2\theta_{max}$	62
Transmissions	0.963–1.000
Refl. measured	98225
Refl. indep.	5983
R_{int}	0.036
Parameters	245
$wR(F^2$, all refl.)	0.096
$R(F, >4\sigma(F))$	0.033
S	1.07
max. Δρ (e Å^{-3})	0.47

X-ray structure determinations

A colorless block of compound **7a** was mounted in inert oil on a glass fiber and transferred to the cold gas stream of the diffractometer (Oxford Diffraction Xcalibur E). Intensities were registered using monochromated Mo *K*α radiation (λ = 0.71073 Å). Absorption corrections were based on multi-scans. The structure was refined anisotropically on F^2 using the program SHELXL-97. Hydrogen atoms were included using a riding model starting from calculated positions. Table 2 presents the summary of crystallographic data.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-864706. Copies of the data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif.

Biological evaluation

In vitro anti-HIV assay Evaluation of the antiviral activity of compounds **7a–l**, **13**, and **14** against HIV-1 (III_B) and HIV-2 (ROD) strains in MT-4 cells was performed using an MTT assay as described previously (Pannecouque et al., 2008; Pauwles et al., 1988). In brief, stock solutions (10 times final concentration) of test compounds were added in 50-µl volumes to two series of triplicate wells to allow simultaneous evaluation of their effects on mock and HIV-infected cells at the beginning of each experiment. Serial 5-fold dilutions of test compounds were made directly in flat-bottomed 96-well microtiter trays using a Biomek 3000 robot (Beckman instruments). Untreated control, HIV-infected, and mock-infected cell samples were included for each sample. HIV-1 (III_B) (Popovic et al., 1984) or HIV-2 (ROD) (Barré-Sinoussi et al., 1993) stock (50 µl) at 100–300 $CCID_{50}$ (50 % cell culture infectious dose) or culture medium [10 % heat-inactivated Fetal Calf Serum (FCS), 2 mM-glutamine, 0.1 % sodium bicarbonate, and 20 µg/ml gentamicin] was added to either of the infected or mock-infected wells of the microtiter tray. Mock-infected cells were used to evaluate the effect of test compound on uninfected cells in order to assess the cytotoxicity of the test compounds. Exponentially growing MT-4 cells (Miyoshi et al., 1982) were centrifuged for 5 min at 1000 rpm (Minifuge T, rotor 2250; Heraeus, Germany), and the supernatant was discarded. The MT-4 cells were resuspended at 6 × 105 cells per ml, and 50 µl volumes were transferred to the microtiter tray wells. Five days after infection, the viability of the mock-infected and HIV-infected cells was examined spectrophotometrically.

Cytotoxicity assays Cell cultures were seeded at 1 × 105 cells per ml in 96 multiwell plates in specific media [RPMI-1640 medium with 20 mM HEPES buffer (Life Technologies)], supplemented with 10 % FCS and antibiotic (gentamicin), and incubated at 37 °C in a humidified CO_2 (5 %) atmosphere in the absence or presence of serial dilutions of test compounds. Cell viability was determined after 96 h at 37 °C by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) method (Pannecouque et al., 2008). Compounds were dissolved in dimethyl sulfoxide at 100 mM and then diluted into culture medium.

Conclusions

2-Adamantyl/adamantylmethyl-5-arylthiazolyl-1,3,4-oxadiazole derivatives **7a–x**, and 2-phenylthiazole-4-carboxamide analogs **13** and **14** were synthesized via several steps. Compounds **7a–l**, **13**, and **14** were screened for their inhibitory activity against HIV-1 and HIV-2, where **13** and **14** showed significant inhibition of HIV-1 with EC_{50} of 1.79 and 2.39 µM (SI = 18 and 4), respectively. The anti-HIV activity results suggest that compound **13** might act as a new candidate for NNRTIs. Furthermore, compounds **7a** and **7j** were tested against two solid tumor-derived cell lines consisting Hep-G2 (human hepatocarcinoma) and MCF-7 (breast cancer). Compound **7j** showed a moderate antitumor activity against Hep-G2 and led to be promising agent for further structural modification.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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