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Synthesis and structure elucidation of 2-(1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-yl)thio)-1-arylethan-1-ones

Bakr F. Abdel-Wahab [a], Mohammed A Baashen [b], Mohamed S. Bekheit [c], Benson M. Kariuki [d], Gamal A. El-Hiti [e,]*

[a] Applied Organic Chemistry Department, Chemical Industries Research Institute, National Research Center, Dokki, Giza 12622, Egypt

[b] Department of Chemistry, Science and Humanities College, Shaqra University, Al-Dawadmi 11911, Saudi Arabia

[c] Department of Pesticide Chemistry, National Research Center, Dokki, Giza 12622, Egypt

[d] School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff CF10 3AT, UK

[e] Department of Optometry, College of Applied Medical Sciences, King Saud University, Riyadh 11433, Saudi Arabia

ABSTRACT

Several new 2-(1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-yl)thio)-1-arylethan-1-ones were synthesized in excellent yields using simple procedures. Reaction of 1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carbohydrazide (**1**) and carbon disulfide in ethanol and in the presence of potassium hydroxide at 0 °C to room temperature for 6 hours gave potassium 2-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carbonyl)hydrazine-1-carbodithioate (**2**) as an intermediate. In situ treatment of **2** with aqueous ethanol under reflux for 6 h, followed by neutralization with hydrochloric acid, gave 5-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1,3,4-oxadiazole-2-thiol (**3**) in 70% yield. Reactions of thiol **3** with various phenacyl bromides **4** in ethanol in basic medium under reflux for 5 hours gave the corresponding 2-(1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-yl)thio)-1-arylethan-1-ones **5a**–**f** in 83-88% yields. The structures of the newly synthesized heterocycles were elucidated using spectroscopic data and single-crystal X-ray structure determination.

Keywords: 1,2,3-Triazole; Hydrazide; Phenacyl bromides; Benzofuran; X-ray crystallography, 1,3,4-Oxadiazole

1. Introduction

1,3,4-Oxadiazole is one of the four isomers of oxadiazole [1]. 1,3,4-Oxadiazoles exhibit a wide range of pharmaceutical and biological activities, including antimicrobial, antifungal, anti-inflammatory, and antihypertensive effects [2–6]. 1,3,4-Oxadiazoles with three or more conjugated rings have been used in various applications as luminescent compounds [7]. They are also used in clinical medicine to treat various disorders. Figure 1 shows some 1,3,4-oxadiazoles with medicinal uses. For example, raltegravir is an antiretroviral medication used as part of HIV/AIDS therapy and tiodazosin is an α1-adrenergic receptor antagonist. Zibotentan is a potential anticancer agent which, when combined with dapagliflozin, reduces albuminuria with an acceptable tolerability and safety profile [8]. Various 1,3,4-oxadiazoles exhibit antibacterial, antitubercular, anti-inflammatory, antifungal, and anticancer activity [9].

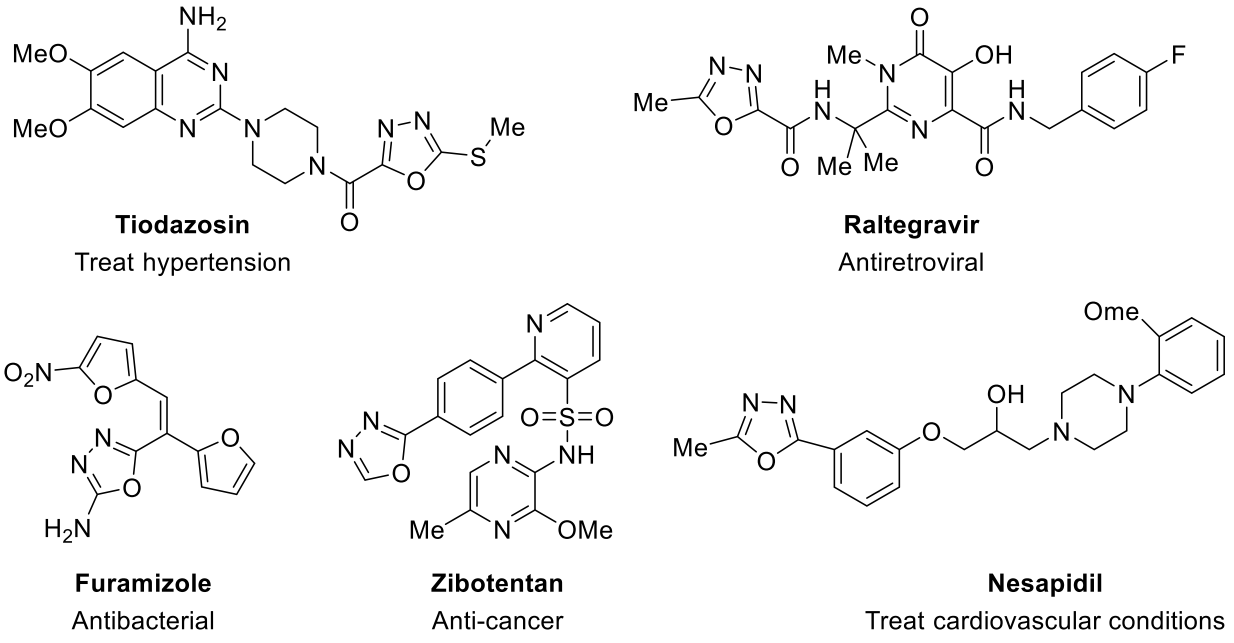
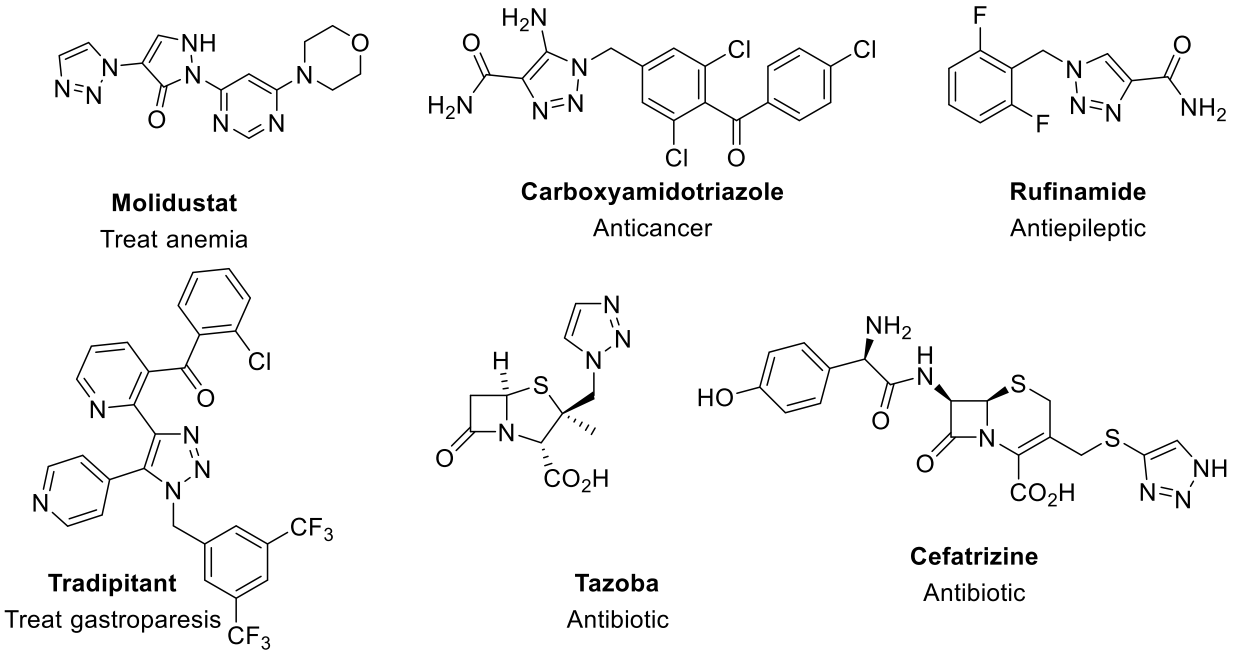


Figure 1. Examples of 1,3,4-oxadiazole with medicinal uses.

Common methods for synthesizing 1,3,4-oxadiazoles include reactions of suitable hydrazides with phosgene [2], carboxylic acids [10,11], α-bromo nitroalkanes [12,13], or carbon disulfide [14,15]. Oxidative cyclization of *N*-acylhydrazones or 1,2-diacylhydrazines is achieved using dehydrating agents [16–21].

Triazoles and their derivatives have been shown to exhibit diverse pharmacological activities, including analgesic, antiasthematic, diuretic, antihypertensive, and antiinflammatory properties [22,23]. 1,2,3-Triazole has three tautomeric isomers: 1*H*-1,2,3-triazole, 2*H*-1,2,3-triazole, and 4*H*-1,2,3-triazole [24]. 1,2,3-Triazole is a bioisostere used as a building block in the synthesis of many drugs, especially those with antimicrobial, antiviral, and anticancer properties [25,26]. Figure 2 shows some examples of 1,2,3-triazoles with medicinal uses. 1,2,3-Triazole is readily synthesized via the copper-catalyzed azide-alkyne cycloaddition click reaction [27–29].



Molidustat
Treat anemia

Carboxyamidotriazole
Anticancer

Rufinamide
Antiepileptic

Tradipitant
Treat gastroparesis

Tazoba
Antibiotic

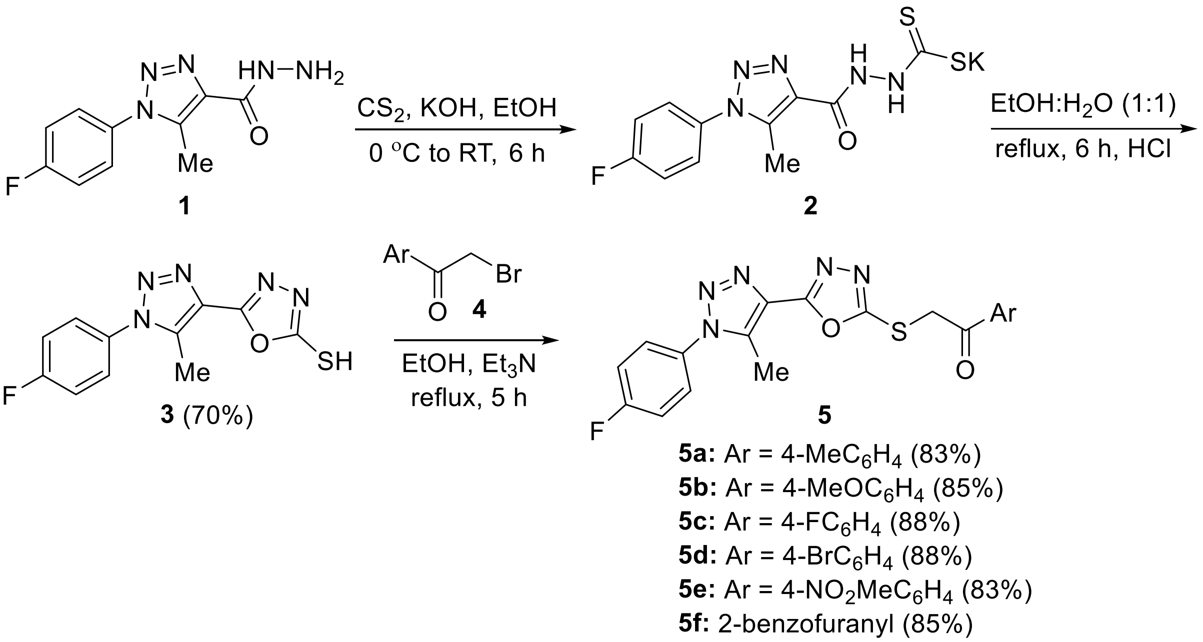
Cefatrizine
Antibiotic

Figure 2. Examples of 1,2,3-triazoles with medicinal uses.

Considering these the importance of the two moieties, syntheses of compounds combining 1,2,3-triazole and 1,3,4-oxadiazole groups were performed. The resulting products were characterized by single-crystal structure analysis to confirm their molecular structures their intermolecular interactions within the crystals of the compounds were examined using Hirshfeld surfaces.

2. Results and Discussion

Reaction of 1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carbohydrazide (**1**) and carbon disulfide in ethanol and in the presence of potassium hydroxide at 0 °C to room temperature for 6 hours gave potassium 2-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carbonyl)hydrazine-1-carbodithioate (**2**) as an intermediate. In situ treatment of **2** with aqueous ethanol under reflux for 6 h, followed by neutralization with hydrochloric acid, gave 5-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1,3,4-oxadiazole-2-thiol (**3**) in 70% yield (Scheme 1).



Scheme 1. Synthesis of 2-(1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-yl)thio)-1-arylethan-1-ones **5a**–**f**.

The FTIR spectrum of **3** exhibits absorption bands associated with the C–H, C=N, and C=C groups. The ^{1}H NMR spectrum of **3** shows a singlet signal at a very low field (14.37 ppm), corresponding to the SH proton. Additionally, the methyl protons appear as a singlet at a high field (2.51 ppm). The four aromatic protons appear as an apparent doublet (8.6 Hz) and a multiplet, with two protons each at 7.52 and 7.76 ppm, respectively. The presence of multiple signals instead of two doublets indicates coupling between fluorine atoms and aromatic protons. The ^{13}C NMR spectrum of **3** shows the methyl carbon at 10.0 ppm, while C5 of the oxadiazolyl ring appears at 177.5 ppm. The spectrum shows the coupling between the aryl carbons and the fluorine atom. The C4 of the 4-fluorophenyl ring appears at 163.2 ppm as a doublet with a coupling constant of 246.8 Hz, while the C2/C6 carbons are observed at 128.3 ppm as a doublet with a coupling constant of 9.5 Hz. The C3/C5 carbons appear at 117.3 ppm as a doublet, with a coupling constant of 23.9 Hz.

Reactions of thiol **3** with various phenacyl bromides **4** under basic conditions in boiling ethanol for 5 hours produced the corresponding 2-(1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-yl)thio)-1-arylethan-1-ones **5a-f** with yields of 83-88% (Scheme 1). The structures of 2-(1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-yl)thio)-1-arylethan-1-ones **5a**–**f** were confirmed through NMR spectroscopy and X-ray crystallography.

The FTIR spectra of compounds **5a**–**f** show several distinct absorption bands, including C–H stretching (3363–3033 and 2977–2900 cm^{-1}), C=O (1691–1668 cm^{-1}), C=N (1640–1598 cm^{-1}), and C=C groups (1601–1571 cm^{-1}). The ^{1}H NMR spectra of compounds **5a**–**f** show two distinct singlets at 2.41–2.55 ppm (3 protons) and 507-5.18 ppm (2 protons) corresponding to the methyl and methylene protons, respectively. The four protons of the 4-fluorophenyl ring appear as apparent doublets and multiplets, indicating coupling between the aryl protons and the fluorine atom. The ^{13}C NMR spectra of **5a**–**f** show the carbonyl carbon in the range 183.2–192.4 ppm and the CH_2 carbon in the range 41.1–41.4 ppm. They also show the coupling between the aryl carbons and the fluorine atom. The C4 of the 4-fluorophenyl ring appears at 162.2–163.2 ppm as a doublet with a coupling constant of 245.6–246.8 Hz, while the C2/C6 carbons are observed at 128.3–132.0 ppm as a doublet with a coupling constant of 8.3–9.5 Hz. The C3/C5 carbons appear at 117.3 ppm as a doublet, with a coupling constant of 22.7–23.9 Hz. The Supplementary Materials include IR and NMR spectra and crystallographic data for the synthesized heterocycles.

Crystal structures

The molecule of **5a** (Figure 3a) contains fluorophenyl (FP, C1–C6, F1), methyltriazolyl (MT, C7–C9, N1–N3), oxadiazolyl (OD, C10, C11, N4, N5, O1), sulfanylacetaldehyde (SA, C12, C13, O2, S1) and methylphenyl (MB, C14–C20) groups. The fluorophenyl, oxadiazolyl, and sulfanylacetaldehyde groups are almost coplanar with FP/OD/SA dihedral angles of 5.4(1)°/11.0(1)°. The orientations of the methyltriazolyl and methyphenyl groups deviate from this plane with dihedral angles FP/MT and OD/MB of 41.1(1)° and 20.0(1)°, respectively. In the crystal, the molecules pack with their axes aligned to [–1, 0, 1] crystallographic direction. Intermolecular contacts of type C–H…O [C3–H3...O2 angle of 130.0°, C3…O2 distance of 3.282(3)Å] and C–H…N [C5–H5...N4 angle of 160.5°, C5…N4 distance of 3.480(3)Å and C7–H7C...N4 angle of 153.6°, C7…N4 distance of 3.505(3) Å] are observed between neighboring molecules (Figure 3b).

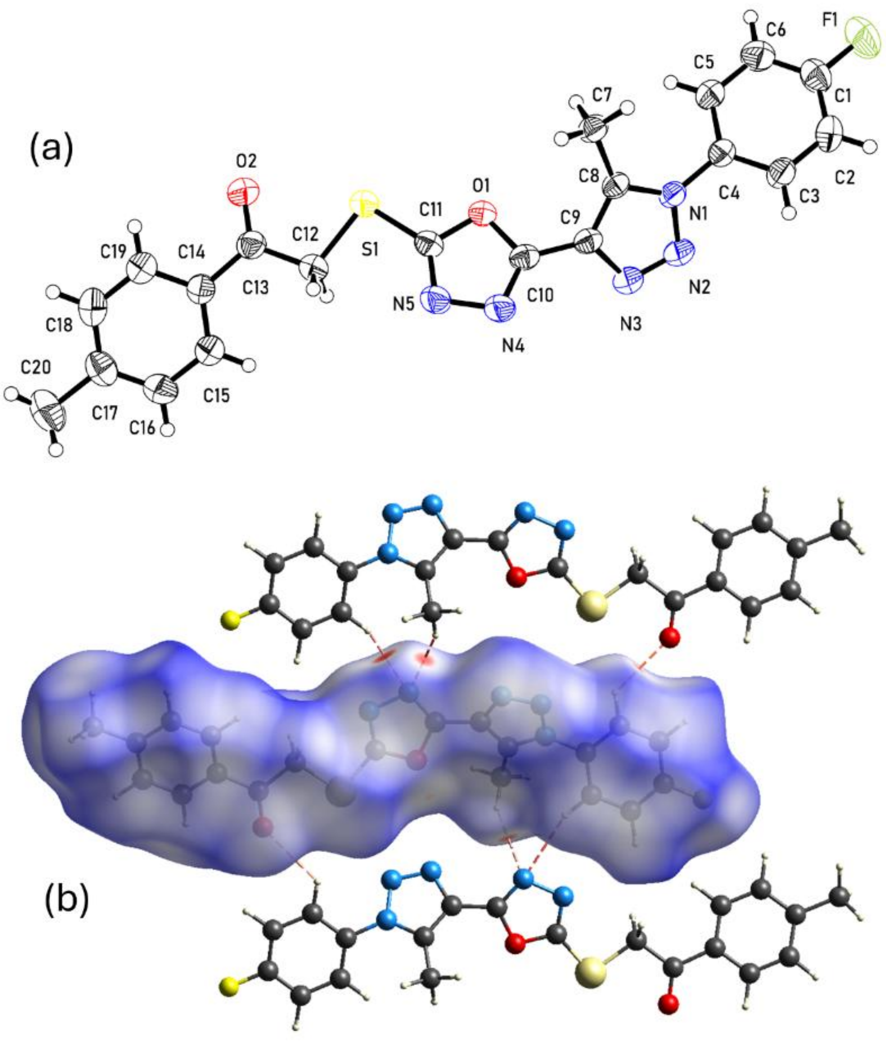


Figure 3. (a) The symmetric unit derived from the crystal structure of **5a**, displaying atomic displacement parameters at a 50% probability level. (b) The Hirshfeld surface of the molecule is shown, with close intermolecular contacts indicated by dashed lines.

The molecule of **5b** (Figure 4a) contains fluorophenyl (FP, C1–C6, F1), methyltriazolyl (MT, C7–C9, N1–N3), oxadiazolyl (OD, C10, C11, N4, N5, O1), sulfanylacetaldehyde (SA, C12, C13, O2, S1) and methoxyphenyl (MP, C14–C19, F2) groups. The dihedral angles FP/MT/OD/SA/MP between the fluorophenyl, methyltriazolyl, oxadiazolyl, sulfanylacetaldehyde, and the ring of the methoxyphenyl groups are 40.8(1)°/12.6(1)°/12.9(1)°/12.3(1)°. The torsion angle C20–O3–C17–C18 of the methoxyphenyl group is 9.0(2)°. In the crystal, intermolecular contacts of type C–H…O [C2–H2...O3 angle of 162.9°, C2…O2 distance of 3.398(2)] and C–H…S [C12–H12A...S1 angle of 160.5°, C12…S1 distance of 3.798(2) Å] are observed (Figure 4b).

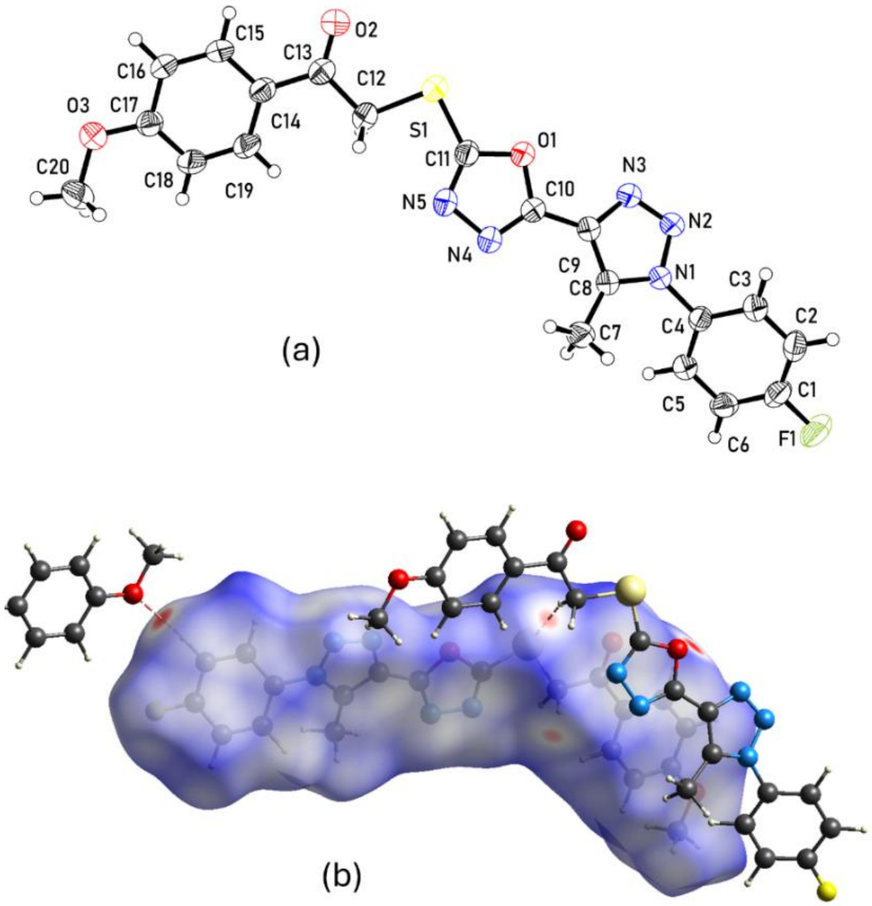


Figure 4. (a) The symmetric unit derived from the crystal structure of **5b**, displaying atomic displacement parameters at a 50% probability level. (b) The Hirshfeld surface of the molecule is shown, with close intermolecular contacts indicated by dashed lines.

The molecule of **5c** (Figure 5a) contains fluorophenyl (FP1, C1–C6, F1), methyltriazolyl (MT, C7–C9, N1–N3), oxadiazolyl (OD, C10, C11, N4, N5, O1), sulfanylacetaldehyde (SA, C12, C13, O2, S1) segments and a second fluorophenyl (FP2, C14–C19, F2) group. The two fluorophenyls, oxadiazolyl, and sulfanylacetaldehyde groups are almost coplanar with FP1/OD/SA/FP2 dihedral angles of 6.4(1)°/11.1(1)°/5.7(1)°. The orientation of the methyltriazolyl group deviates from this plane with dihedral angles FP1/MT and MT/OD of 41.8(1)° and 39.9.0(1)°.

In the crystal, the molecular axes are aligned parallel to [–1, 0, 1] crystallographic direction. Intermolecular contacts of type C–H…O [C7–H7b...O1 angle of 121.1°, C3…O2 distance of 3.209(2)Å], C–H…N [C5–H5...N4 angle of 158.0°, C5…N4 distance of 3.449(2)Å and C7–

H7C...N4 angle of 153.5°, C7…N4 distance of 3.520(2) Å] and C–H…F [C16–H16...F1 angle of 151.3°, C16…F1 distance of 3.471(3)Å] are observed between neighboring molecules (Figure 5b). Crystal packing of **5c** is similar to that of **5a**, which accounts for the same symmetry and similar unit cell parameters (Table 1).

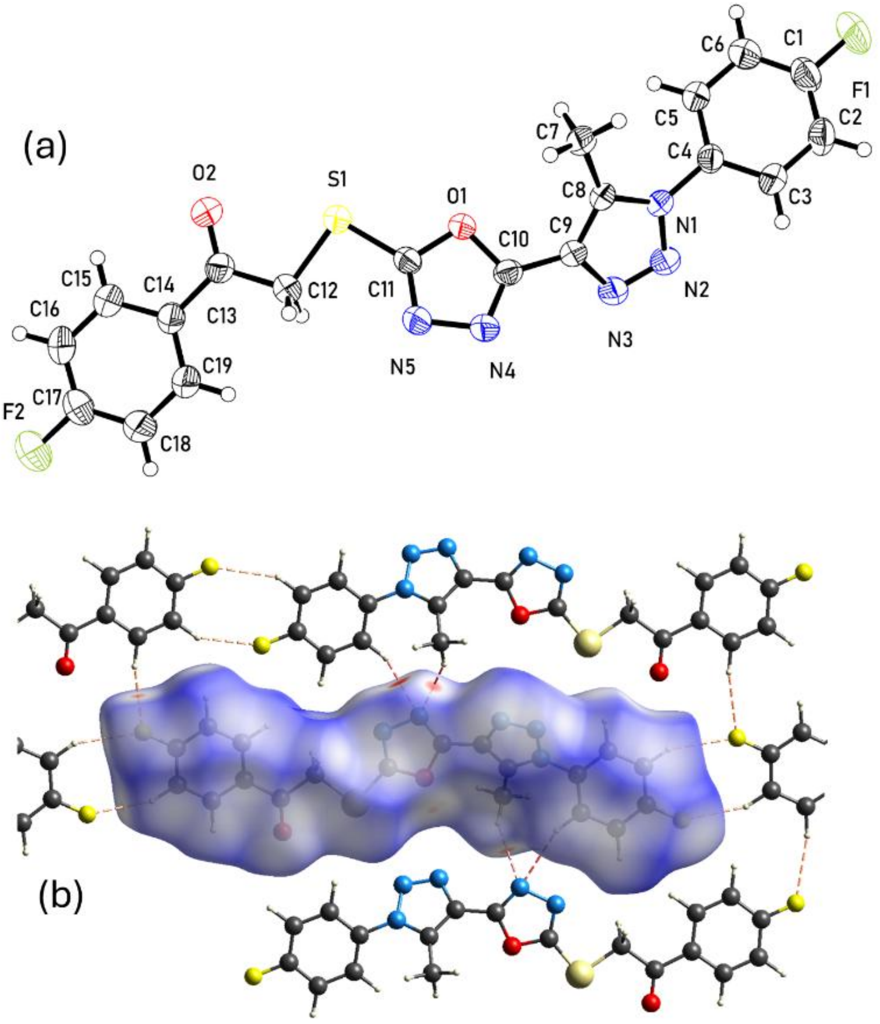


Figure 5. (a) The symmetric unit derived from the crystal structure of **5c**, displaying atomic displacement parameters at a 50% probability level. (b) The Hirshfeld surface of the molecule is shown, with close intermolecular contacts indicated by dashed lines.

The molecule of **5d** (Figure 6a) contains fluorophenyl (FP, C1–C6, F1), methyltriazolyl (MT, C7–C9, N1–N3), oxadiazolyl (OD, C10, C11, N4, N5, O1), sulfanylacetaldehyde (SA, C12, C13, O2, S1) and bromophenyl (BP, C14–C19, Br1) groups. The oxadiazolyl, sulfanylacetaldehyde, and bromophenyl groups are almost coplanar with OD/SA/BP dihedral angles of 3.3(1)°/13.0(1)°. The fluorophenyl (FP, C1–C6, F1) and methyltriazolyl groups are twisted from this plane with FP/MT and MT/OD dihedral angles of 33.7(1)° and 17.7(1)°, respectively. In the crystal, the molecules pack with their molecular axes parallel to [2, 0, 3] crystallographic direction. Close intermolecular contacts of type C–H…N [C5–H5...N2 angle of 158.2°, C5…N2 distance of 3.579(3)Å; C5–H5...N3 angle of 130.1°, C5…N3 distance of 3.266(3) Å and C7–H7C...N2 angle of 146.5°, C7…N2 distance of 3.494(4) Å] are found in the structure (Figure 6b).

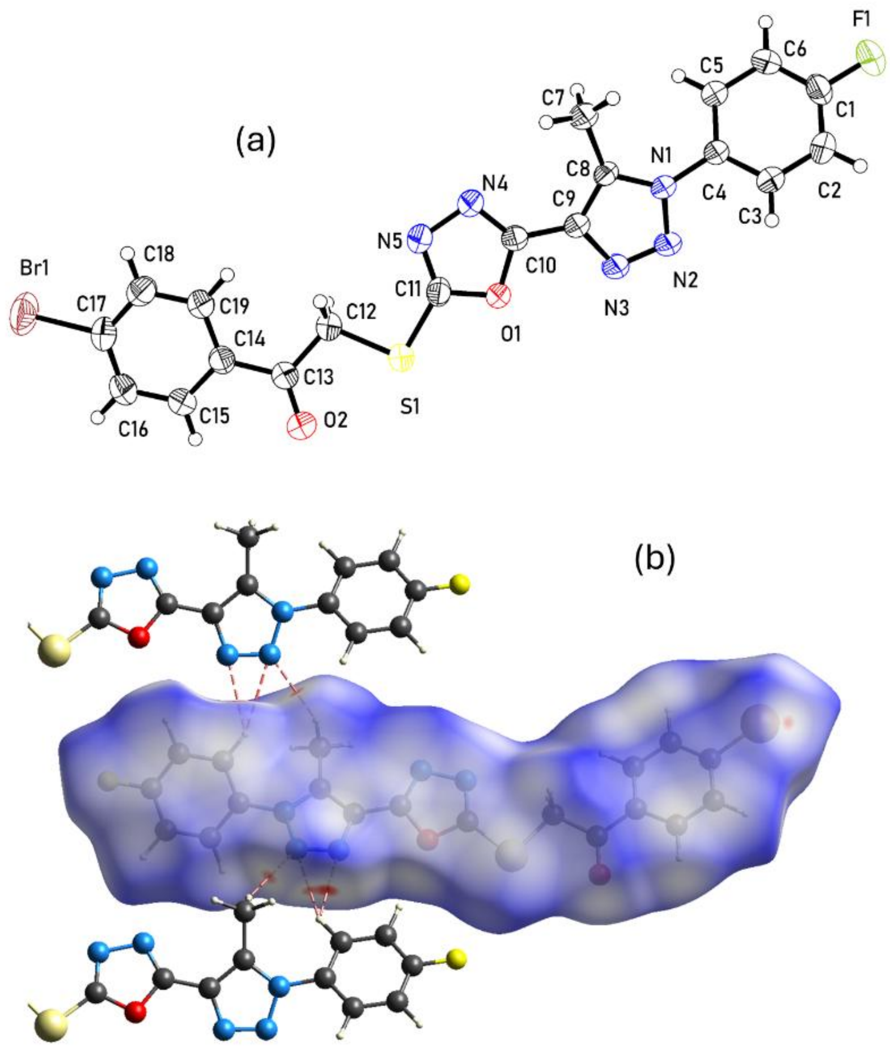


Figure 6. (a) The symmetric unit derived from the crystal structure of **5d**, displaying atomic displacement parameters at a 50% probability level. (b) The Hirshfeld surface of the molecule is shown, with close intermolecular contacts indicated by dashed lines.

The molecule of **5e** (Figure 7a) contains fluorophenyl (FP, C1–C6, F1), methyltriazolyl (MT, C7–C9, N1–N3), oxadiazolyl (OD, C10, C11, N4, N5, O1), sulfanylacetaldehyde (SA, C12, C13, O2, S1) and nitrophenyl (NP, C14–C19, N6, O3, O4) groups. The FP/MT/OD/SA/NP dihedral angles between the groups are 43.3(1)°/37.9(1)°/10.5(1)°/13.2(1)°. In the crystal, the molecules pack with their molecular axes parallel to [5, 0, –1] crystallographic direction. Intermolecular contacts of type C–H...O [C18–H18...O4 angle of 119.9°, C18...O4 distance of 3.126(3)Å] and C–H...N [C12–H12B...N2 angle of 159.9°, C12...N2 distance of 3.486(3)Å] are observed between neighboring molecules (Figure 7b).

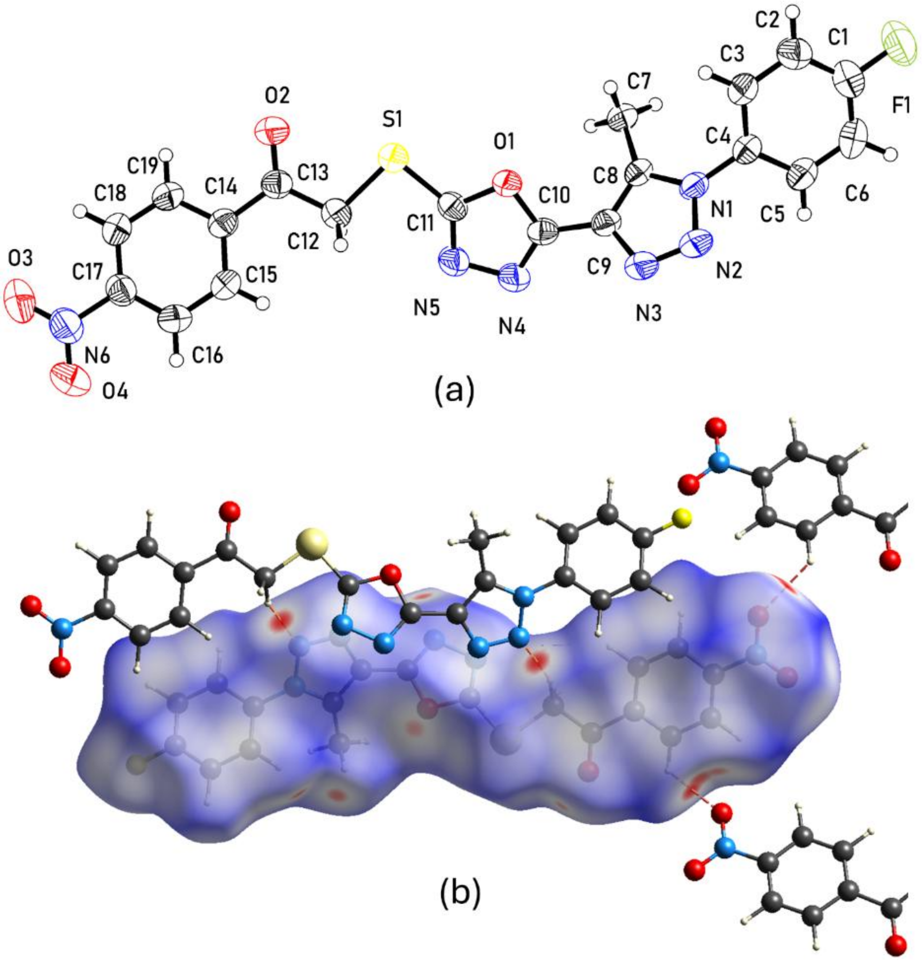


Figure 7. (a) The symmetric unit derived from the crystal structure of **5e**, displaying atomic displacement parameters at a 50% probability level. (b) The Hirshfeld surface of the molecule is shown, with close intermolecular contacts indicated by dashed lines.

The molecule of **5f** (Figure 8a) contains fluorophenyl (FP, C1–C6, F1), methyltriazolyl (MT, C7–C9, N1–N3), oxadiazolyl (OD, C10, C11, N4, N5, O1), sulfanylacetaldehyde (SA, C12, C13, O2, S1) and benzofuranyl (BF, C14–C21, O3) groups. The methyltriazolyl, oxadiazolyl, sulfanylacetaldehyde, and benzofuranyl groups are almost coplanar with MT/OD/SA/BF dihedral angles of 9.8(1)°/9.7(1)°/3.5(1)°. The fluorophenyl group is twisted further with a FP/Mt dihedral angle of 41.4(1)°. In the crystal, the molecules pack with the planar segments parallel to the *ab* plane. Intermolecular contacts of type C–H…O [C18–H18...O3 angle of 171.1°, C18…O3 distance of 3.587(2)Å], C–H…F [C20–H20...F1 angle of 125.8°, C20…F1 distance of 3.158(2)Å] are observed between neighboring molecules (Figure 8b).

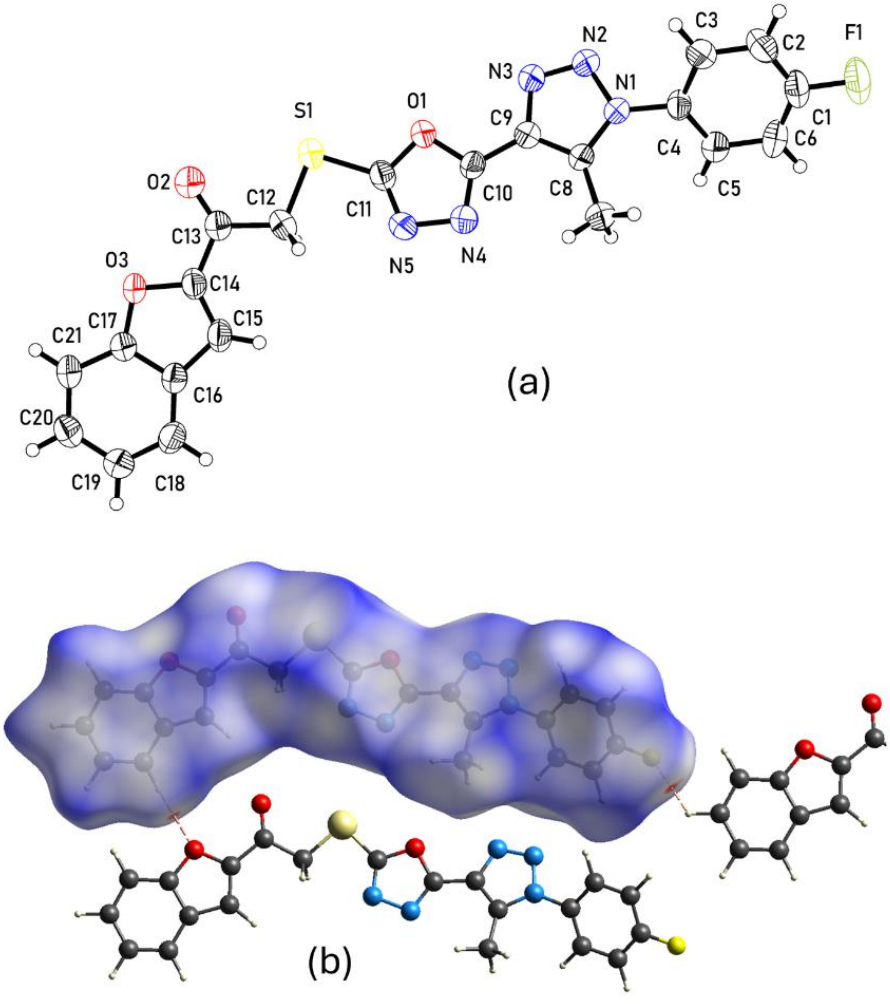


Figure 8. (a) The symmetric unit derived from the crystal structure of **5f**, displaying atomic displacement parameters at a 50% probability level. (b) The Hirshfeld surface of the molecule is shown, with close intermolecular contacts indicated by dashed lines.

3. Experimental

3.1. General

Analytical or HPLC-grade solvents were sourced from Merck and Fischer and used without alteration. An electrothermal melting-point apparatus was used to determine the melting points of the synthesized heterocycles. The infrared (IR) spectra were recorded using a Bruker Invenio-S FTIR spectrometer over the range 4000–400 cm^{-1}, with calibration using a polystyrene film to ensure accuracy. For nuclear magnetic resonance (NMR) analysis, the samples were dissolved in deuterated dimethyl sulfoxide (DMSO-d_6). The NMR spectra were acquired on a JEOL spectrometer, operating at 125 MHz and 500 MHz for ^{13}C and ^{1}H NMR, respectively. The coupling constants obtained were expressed in hertz (Hz), and the chemical shifts were reported in parts per million (ppm). Compounds **1** [29], **4a**–**e** [30], and **4f** [31] were obtained from the NRC-Fine Organic Chemicals Unit at the National Research Center, Egypt, in accordance with established procedures.

*3.2. 5-(1-(4-Fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1,3,4-oxadiazole-2-thiol (**3**)*

To a mixture of **1** (4.7 g, 20 mmol) and KOH (2.24 g, 40 mmol) in dry EtOH (50 mL), CS_2 (5 mL) was added, and the mixture was stirred at RT for 12 h. The mixture was transferred to a round-bottom flask, water (50 mL) was added, and the mixture was heated under reflux for 5 h. The mixture was left to cool to room temperature, then poured into ice water; acidified with HCl, and the pH was adjusted to 4. The white solid produced was collected by filtration, dried, and recrystallized from ethanol. Yield 70%, mp 265–267 °C. FTIR (ν_{max}; cm^{-1}): 3100, 2922, 2788, 1684, 1634, 1604, 1562. ^{1}H NMR (δ, ppm): 2.51 (s, 3H, Me), 7.52 (app. t, 8.6 Hz, 2H, H3 & H5 of 4-fluorophenyl), 7.76 (m, 2H, H2 & H6 of 4-fluorophenyl), 14.36 (s, 1H, SH). ^{13}C NMR (δ, ppm): 10.0 (Me), 117.3 (d, 23.9 Hz, C3 & C5 of 4-fluorophenyl), 128.3 (d, 9.5 Hz, C2 & C6 of 4-fluorophenyl), 130.6 (C1 of 4-fluorophenyl), 131.8 (C4 of triazolyl), 137.0 (C5 of triazolyl), 155.5

(C2 of oxadiazolyl), 163.2 (d, 246.8 Hz, C4 of 4-fluorophenyl), 177.4 (C5 of oxadiazolyl). Anal. Calcd. for $C_{11}H_8FN_5OS$ (277.28): C, 47.65; H, 2.91; N, 25.26. Found: C, 47.78; H, 3.19; N, 25.41%.

*3.3. Synthesis of **5a**–**f***

A mixture of **3** (0.55 g, 2.0 mmol), appropriate phenacyl bromides **4a**–**f** (2.0 mmol), dry EtOH (20 mL), and triethylamine (0.5 mL) was heated under reflux for 5 h. The mixture was left to cool to room temperature. The colorless solid formed was collected, dried, and recrystallized from DMF to give pure **5a**–**f**.

*3.3.1. 2-((5-(1-(4-Fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-yl)thio)-1-(4-tolyl)ethan-1-one (**5a**)*

Yield 83%, mp 160–162 °C. FTIR (ν_{max}; cm^{-1}): 3336, 3033, 2906, 1677, 1603, 1571. ^{1}H NMR (δ, ppm): 2.41 (s, 3H, Me), 2.54 (s, 3H, Me), 5.16 (s, 2H, CH_2), 7.39 (d, 8.1 Hz, 2H, H2 & H6 of 4-tolyl), 7.52 (app. t, 8.6 Hz, 2H, H3 & H5 of 4-fluorophenyl), 7.77 (m, 2H, H2 & H6 of 4-fluorophenyl), 7.97 (d, 8.1 Hz, 2H, H3 & H5 of 4-tolyl). ^{13}C NMR (δ, ppm): 10.0 (Me), 21.8 (Me), 41.2 (CH_2), 117.3 (d, 23.9 Hz, C3 & C5 of 4-fluorophenyl), 128.4 (d, 9.5 Hz, C2 & C6 of 4-fluorophenyl), 129.1 (C2 & C6 of 4-tolyl), 130.0 (C3 & C5 of 4-tolyl), 131.1 (C1 of 4-fluorophenyl), 132.0 (C1 of 4-tolyl), 133.0 (C4 of triazolyl), 137.0 (C4 of 4-tolyl)., 145.2 (C5 of triazolyl), 159.8 (C2 of oxadiazolyl), 163.2 (d, 246.8 Hz, C4 of 4-fluorophenyl), 163.7 (C5 of oxadiazolyl), 192.4 (C=O). Anal. Calcd. for $C_{20}H_{16}FN_5O_2S$ (409.43): C, 58.67; H, 3.94; N, 17.11. Found: C, 58.89; H, 4.17; N, 17.39%.

*3.3.2. 2-((5-(1-(4-Fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-yl)thio)-1-(4-methoxyphenyl)ethan-1-one (**5b**)*

Yield 85%, mp 184–186 °C. FTIR (ν_{max}; cm^{-1}): 3124, 3075, 2977, 1668, 1571. ^{1}H NMR (δ, ppm): 2.55 (s, 3H, Me), 3.87 (s, 3H, OMe), 5.14 (s, 2H, CH_2), 7.10 (d, 9.0 Hz, 2H, H3 & H5 of 4-anisyl), 7.52 (app. t, 8.6 Hz, 2H, H3 & H5 of 4-fluorophenyl), 7.77 (m, 2H, H2 & H6 of 4-fluorophenyl), 8.04 (d, 9.0 Hz, 2H, H2 & H6 of 4-anisyl). ^{13}C NMR (δ, ppm): 10.0 (Me), 41.1 (CH_2), 56.2 (OMe), 114.6 (C3 & C5 of 4-anisyl), 117.3 (d, 22.7 Hz, C3 & C5 of 4-fluorophenyl), 128.3 (C1, C2 & C6 of 4-anisyl), 131.1 (C4 of triazolyl), 131.4 (C1 of 4-fluorophenyl), 132.0 (d, 9.5 Hz, C2 & C6 of 4-fluorophenyl), 137.0 (C5 of triazolyl), 159.8 (C2 of oxadiazolyl), 162.3 (d, 246.8 Hz, C4 of 4-fluorophenyl), 163.7 (C4 of 4-anisyl), 164.3 (C5 of oxadiazolyl), 191.1 (C=O). Anal. Calcd. for $C_{20}H_{16}FN_5O_3S$ (425.44): C, 56.46; H, 3.79; N, 16.46. Found: C, 56.58; H, 3.99; N, 16.64%.

*3.3.3. 1-(4-Fluorophenyl)-2-((5-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one (**5c**)*

Yield 88%, mp 174–176 °C. FTIR (ν_{max}; cm^{-1}): 3345, 3082, 2906, 1680, 1639, 1596. ^1H NMR (δ, ppm): 2.54 (s, 3H, Me), 5.18 (s, 2H, CH_2), 7.43 (app. t, 8.6 Hz, 2H, H3 & H5 of 4-fluorophenyl), 7.51 (app. t, 8.6 Hz, 2H, H3 & H5 of 4-fluorophenyl), 7.76 (m, 2H, H2 & H6 of 4-fluorophenyl), 8.16 (m, 2H, H2 & H6 of 4-fluorophenyl). ^{13}C NMR (δ, ppm): 10.0 (Me), 41.2 (CH_2), 116.5 (d, 21.5 Hz, C3 & C5 of 4-fluorophenyl), 117.3 (d, 22.7 Hz, C3 & C5 of 4-fluorophenyl), 128.4 (d, 9.5 Hz, C2 & C6 of 4-fluorophenyl), 131.0 (C1 of 4-fluorophenyl), 132.0 (C1 of 4-fluorophenyl), 132.1 (d, 9.5 Hz, C2 & C6 of 4-fluorophenyl), 133.3 (C4 of triazolyl), 137.0 (C5 of triazolyl), 159.8 (C2 of oxadiazolyl), 162.2 (d, 245.6 Hz, C4 of 4-fluorophenyl), 163.6 (C5 of oxadiazolyl), 166.0 (d, 251.6 Hz, C4 of 4-fluorophenyl), 191.6 (C=O). Anal. Calcd. for $C_{19}H_{13}F_2N_5O_2S$ (413.40): C, 55.20; H, 3.17; N, 16.94. Found: C, 55.42; H, 3.25; N, 17.20%.

*3.3.4. 1-(4-Bromophenyl)-2-((5-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one (**5d**)*

Yield 88%, mp 196–198 °C. FTIR (ν_{max}; cm^{-1}): 3354, 3094, 2961, 1682, 1627, 1584. ^1H NMR (δ, ppm): 2.55 (s, 3H, Me), 5.18 (s, 2H, CH_2), 7.52 (app. t, 8.6 Hz, 2H, H3 & H5 of 4-fluorophenyl), 7.77 (m, 2H, H2 & H6 of 4-fluorophenyl), 7.81 (d, 8.6 Hz, 2H, H2 & H6 of 4-bromophenyl), 8.00 (d, 8.6 Hz, 2H, H3 & H5 of 4-bromophenyl). ^{13}C NMR (δ, ppm): 10.0 (Me), 41.2 (CH_2), 117.3 (d, 23.9 Hz, C3 & C5 of 4-fluorophenyl), 128.3 (d, 9.5 Hz, C2 & C6 of 4-fluorophenyl), 128.8 (C4 of 4-bromophenyl), 130.9 (C3 & C5 of 4-bromophenyl), 131.0 (C1 of 4-fluorophenyl), 131.9 (C1 of 4-bromophenyl), 132.5 (C2 & C6 of 4-bromophenyl), 134.5 (C4 of triazolyl), 137.0 (C5 of triazolyl), 159.9 (C2 of oxadiazolyl), 163.1 (d, 246.8 Hz, C4 of 4-fluorophenyl), 163.5 (C5 of oxadiazolyl), 192.3 (C=O). Anal. Calcd. for $C_{19}H_{13}BrFN_5O_2S$ (474.31): C, 48.11; H, 2.76; N, 14.77. Found: C, 48.36; H, 2.99; N, 14.93%.

*3.3.5. 2-((5-(1-(4-Fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-yl)thio)-1-(4-nitrophenyl)ethan-1-one (**5e**)*

Yield 83%, mp 178–180 °C. FTIR (ν_{max}; cm^{-1}): 3364, 3083, 2900, 1691, 1601, 1507. ^{1}H NMR (δ, ppm): 2.50 (s, 3H, Me), 5.26 (s, 2H, CH_2), 7.52 (app. t, 8.6 Hz, 2H, H3 & H5 of 4-fluorophenyl), 7.76 (m, 2H, H2 & H6 of 4-fluorophenyl), 8.35 (d, 8.6 Hz, 2H, H2 & H6 of 4-nitrophenyl), 8.39 (d, 8.6 Hz, 2H, H3 & H5 of 4-nitrophenyl). ^{13}C NMR (δ, ppm): 10.0 (Me), 41.4 (CH_2), 117.3 (d, 23.8 Hz, C3 & C5 of 4-fluorophenyl), 124.5 (C3 & C5 of 4-nitrophenyl), 128.3 (d, 8.3 Hz, C2 & C6 of 4-fluorophenyl), 130.4 (C2 & C6 of 4-nitrophenyl), 131.0 (C1 of 4-fluorophenyl), 131.9 (C1 of 4-nitrophenyl), 137.1 (C4 of triazolyl), 140.2 (C5 of triazolyl), 150.8 (C4 of 4-nitrophenyl), 159.9 (C2 of oxadiazolyl), 162.2 (d, 246.8 Hz, C4 of 4-fluorophenyl), 163.3 (C5 of oxadiazolyl), 192.5 (C=O). Anal. Calcd. for $C_{19}H_{13}FN_6O_4S$ (440.41): C, 51.82; H, 2.98; N, 19.08. Found: C, 51.84; H, 3.20; N, 19.20%.

*3.3.6. 1-(Benzofuran-2-yl)-2-((5-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one (**5f**)*

Yield 85%, mp 171–173 °C. FTIR (ν_{max}; cm^{-1}): 3115, 3068, 2968, 1676, 1617, 1547. ^{1}H NMR (δ, ppm): 2.54 (s, 3H, Me), 5.07 (s, 2H, CH_2), 7.41 (t, 7.4 Hz, 1H, H5 of benzofuranyl), 7.51 (app. t, 8.5 Hz, 2H, H3 & H5 of 4-fluorophenyl), 7.59 (t, 7.4 Hz, 1H, H6 of benzofuranyl), 7.77–7.75 (m, 3H, H2 & H6 of 4-fluorophenyl & H7 of benzofuranyl), 7.89 (d, 7.4 Hz, 1H, H4 of benzofuranyl), 8.15 (s, 1H, H3 of benzofuranyl). ^{13}C NMR (δ, ppm): 10.0 (Me), 41.4 (CH_2), 112.8 (C3 of benzofuranyl), 116.2 (C7 of benzofuranyl), 117.3 (d, 22.7 Hz, C3 & C5 of 4-fluorophenyl), 124.4 (C4 of benzofuranyl), 124.8 (C5 of benzofuranyl), 127.2 (C6 of benzofuranyl), 128.3 (d, 9.5 Hz, C2 & C6 of 4-fluorophenyl), 129.5 (C3a of benzofuranyl), 131.0 (C1 of 4-fluorophenyl), 131.9 (C4 of triazolyl), 137.0 (C5 of triazolyl), 151.0 (C2 of benzofuranyl), 155.7 (C2 of oxadiazolyl), 160.0 (C7a of benzofuranyl), 163.1 (d, 246.8 Hz, C4 of 4-fluorophenyl), 163.3 (C5 of oxadiazolyl), 183.3

(C=O). Anal. Calcd. for $C_{21}H_{14}FN_5O_3S$ (435.43): C, 57.93; H, 3.24; N, 16.08. Found: C, 58.11; H, 3.36; N, 16.23%.

3.3. Crystal structure determination

Single-crystal X-ray diffraction data were collected on an Agilent SuperNova Dual Atlas diffractometer equipped with a mirror monochromator, using either Cu or Mo radiation. An Oxford Cryosystems cooling apparatus was used for temperature regulation. The data were processed using CrysAlisPro [32] and the crystal structures were solved using SHELXT [33] and refined using SHELXL [34]. Non-hydrogen atoms were refined with anisotropic displacement parameters and. in the final cycles of refinement, hydrogen atom geometry was idealized, and a riding model was used, with U_{iso} set to 1.2 or 1.5 times U_{eq} for the atom to which the hydrogen atoms are bonded. Crystal and data collection parameters are shown in Table 1. Hirshfeld surfaces were obtained and examined using CrystalExplorer [35]. The data have been deposited in the CSD with reference numbers CCDC 2502433-2502438.

Table 1. Crystal data and structure refinement for **5a–f**.

	5a	**5b**	**5c**	**5d**	**5e**	**5f**
	$C_{20}H_{16}FN_5O_2S$	$C_{20}H_{16}FN_5O_3S$	$C_{19}H_{13}F_2N_5O_2S$	$C_{19}H_{13}BrFN_5O_2S$	$C_{19}H_{13}FN_6O_4S$	$C_{21}H_{14}FN_5O_3S$
FW	409.44	425.44	413.40	474.31	440.41	435.43
T (K)	293(2)	267(2)	293(2)	293(2)	293(2)	293(2) K
λ (Å)	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_1/c$	C 2/c	$P2_1/c$	$P2_1/c$	$P2_1/c$	Pna21
a (Å)	20.3627(10)	20.6022(12)	19.2302(10)	11.4228(7)	19.3447(11)	21.4682(10)
b (Å)	12.0250(5)	6.7668(3)	12.0011(5)	11.8435(6)	12.2325(5)	13.4803(8)
c (Å)	7.6896(4)	29.0351(18)	7.7356(4)	14.6544(10)	8.2081(5)	6.6207(3)
α (°)	90	90	90	90	90	90
β (°)	93.510(4)	110.204(7)	94.358(5)	104.423(7)	101.883(6)	90
γ (°)	90	90	90	90	90	90
V (Å^3)	1879.35(16)	3798.7(4)	1780.09(15)	1920.1(2)	1900.69(18)	1916.02(17)
Z	4	8	4	4	4	4
Density (calc) (Mg/m^3)	1.447	1.488	1.543	1.641	1.539	1.509
Absorption coeff. (mm^{-1})	0.210	0.215	0.230	2.286	0.223	0.215
F(000)	848	1760	848	952	904	896
Crystal size (mm^3)	0.51x0.40 x 0.02	0.47 x 0.40 x 0.27	0.49 x 0.29 x 0.05	0.49 x 0.26 x 0.20	0.48 x 0.31 x 0.05	0.60 x 0.08 x 0.05
Refs collected	19108	15253	15578	18200	17192	17433
Independent refs	4756	4679	4437	4765	4806	4833
R(int)	0.0366	0.0318	0.0291	0.0381	0.0353	0.0427
Goodness-of-fit on F^2	1.058	1.051	1.060	1.011	1.076	1.069

R1 ($I>2\sigma(I)$)	0.0507	0.0439	0.0444	0.0425	0.0492	0.0520
wR2 ($I>2\sigma(I)$)	0.1105	0.1126	0.1032	0.0802	0.1138	0.1052
Largest diff. peak/hole (e.Å^{-3})	0.192/ –0.286	0.288/ -0.349	0.236/ -0.240	0.382/ –0.542	0.213/ –0.258	0.176/ –0.181

4. Conclusion

Six new 2-(1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-yl)thio)-1-arylethan-1-ones were synthesized by transforming 1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carbohydrazide into 1,3,4-oxadiazole-2-thiol, followed by reaction with various phenacyl bromide derivatives. The process is simple, straightforward, and produces high yields. The molecular structures of the newly synthesized heterocycles were confirmed using NMR spectroscopy and X-ray crystallography and their intermolecular in the crystal structures explored.

Ethics and informed consent

Not applicable.

CRediT authorship contribution statement

Bakr F. Abdel-Wahab: Conceptualization, formal analysis, investigation, methodology, funding acquisition, original draft writing, and editing. **Mohammed A Baashen:** Formal analysis, methodology, original draft writing, and editing. **Mohamed S. Bekheit:** Formal analysis, methodology, original draft writing, and editing. **Benson M. Kariuki:** Conceptualization, formal analysis, methodology, original draft writing, and editing. **Gamal A. El-Hiti:** Conceptualization, formal analysis, methodology, funding acquisition, original draft writing, and editing.

Declaration of Competing Interest

There are no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version.

Data availability

The data are contained within the manuscript and the supplementary material.

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