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Synthesis of novel triazoles bearing 1,2,4-oxadiazole and phenylsulfonyl groups by 1,3-dipolar cycloaddition of some organic azides and their biological activities

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Abstract: 1,3-Dipolar cycloaddition of 5-azidomethyl-3-*p*-substituted phenyl-1,2,4-oxadiazoles to phenyl vinyl sulfone and bismaleimide gives rise straightforwardly to 1-((3-(*p*-substituted) phenyl-1,2,4-oxadiazol-5-yl)methyl)-4-(phenylsulfonyl)-4,5-dihydro-1*H*-1,2,3-triazoles and bisdihydropyrrolo[3,4-d][1,2,3]triazole-4,6(*3aH,5H*)-diones. The structures of the new cycloadducts were elucidated by means of IR, NMR (^{1}H, ^{13}C, 2D), mass spectra, and physical characteristics (mp and R_f values). In addition, anticancer activities of the cycloadducts against MCF-7 cells were also investigated.

Key words: Azide, 1,3-dipolar cycloaddition, 1,2,4-oxadiazole, 1,2,3-triazole, pyrrole, anticancer activity

1. Introduction

Organic azides have recently been playing a significant role in the preparation of heterocyclic scaffolds of triazoles. They have potency to undergo a variety of organic reactions and are important components in click chemistry.[1−16] They received considerable attention in the 1950s and 1960s in industrial applications such as rubber, polymers, dyes, plastics technology, and especially in pharmacological usages.

Some examples are azidothymidine (zidovudine), an azidonucleoside (in the treatment of AIDS), azapride (dopamine antagonist), azidamfenicol (for the treatment of bacterial infections in eyes), and azidomorphine (analgesic, sedative) (Figure 1).[17−24]

Furthermore, heterocyclic compounds carrying 1,2,4-oxadiazole units are also of pharmaceutical importance and some of them have been found to be active against cancer cells and various types of tumors and to inhibit enzymes like tyrosine kinase and monoamine oxidase. These compounds are also effective as muscarinic agonists, histamine H3 antagonists, and antiinflammatory agents. Heterocycles bearing 1,2,4-oxadiazole moiety have also been assayed as heterocyclic amide and ester bioisosteres in the construction of new peptide mimics and dipeptidomimetics.[25−28] Two recently reported antimycobacterium tuberculosis agents containing a 1,2,4-oxadiazole ring are shown below (Figure 2).[29,30]

Heterocyclic compounds containing 1,2,3- and 1,2,4-triazole rings have found increasing attention in organic syntheses, biochemistry, and medicinal chemistry research due to their activity as antifungal and anticonvulsant agents including being popular mimics in designing anticancer molecules (Figure 3).[31−39]

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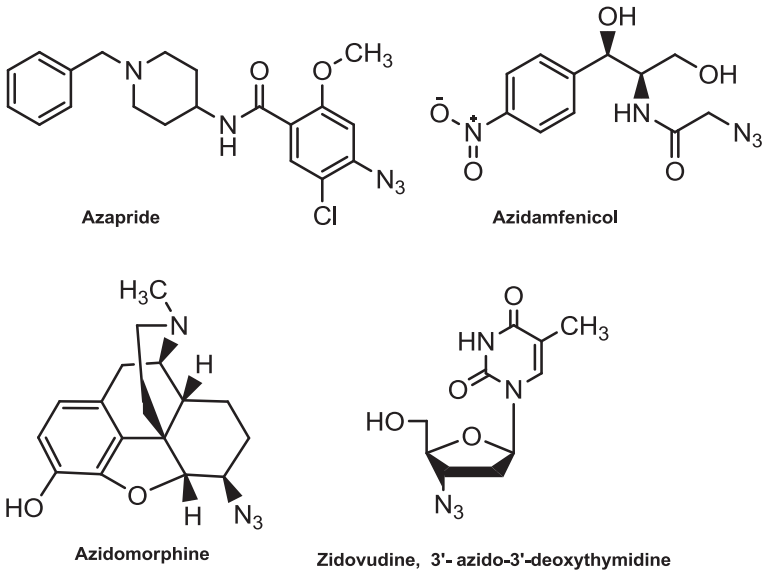


Figure 1. Some important organic azides.

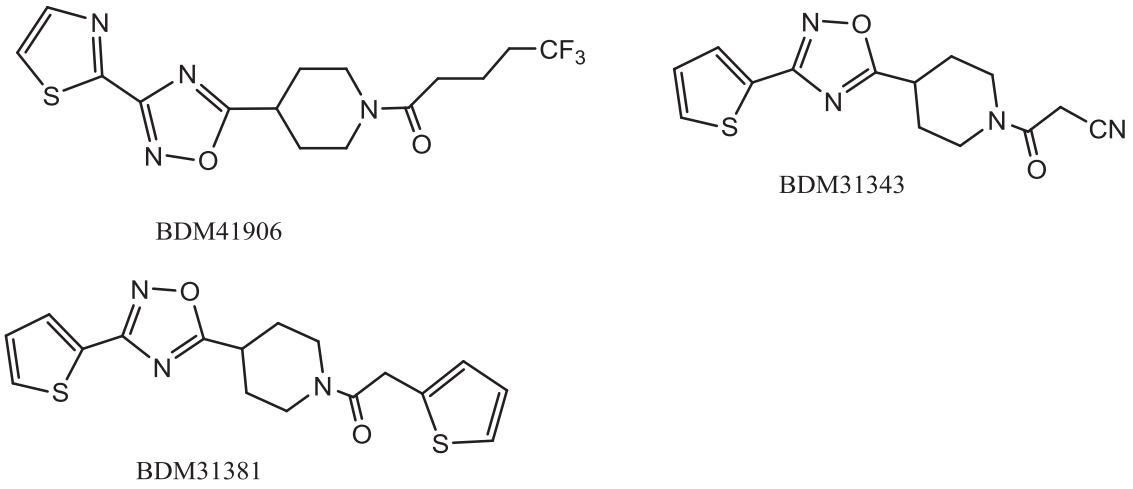


Figure 2. Some important 1,2,4-oxadiazoles.

Sulfones are known as an important class of compounds and various sulfone containing heterocycles have been shown to possess diversified bioactivities such as antibacterial, antimalarial, anthelmintic, antilepral, antineoplastic, antiinflammatory, and antidiabetic activities.[40]

In reference to the reasons mentioned above and our ongoing interest in 1,3-dipolar cycloaddition reactions of the various types of ylides,[41] 1,2,4-oxadiazolyl substituted azides,[42] and phenyl vinyl sulfone,[43] and due to very infrequent studies on the cycloaddition reactions between organic azides with dipolarophiles such as phenyl vinyl sulfone and bismaleimide, we have focused on the synthesis of a series of pyrrolotriazole derivatives carrying 1,2,4-oxadiazole and phenylsulfonyl groups and their biological activities.

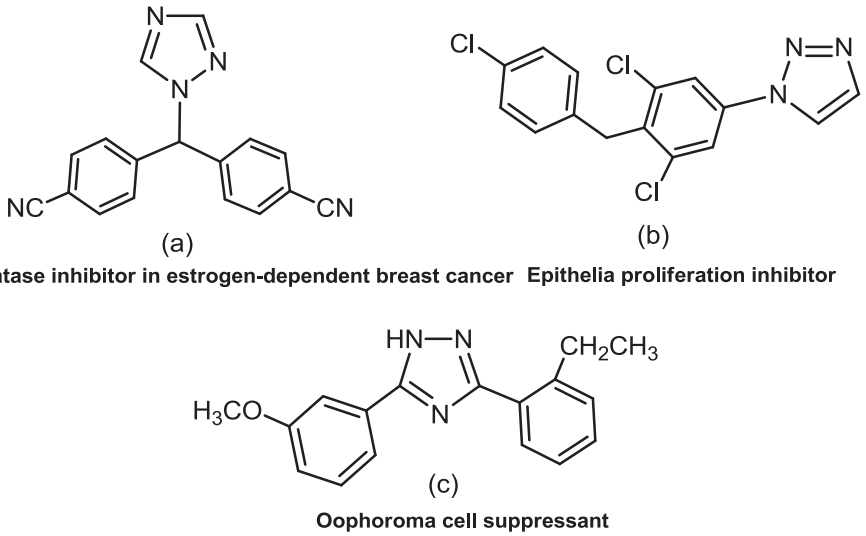


Figure 3. Some important triazoles.

2. Results and discussion

2.1. Chemistry

To the best of our knowledge, there are a number of examples of cycloaddition reactions of organic azides with electron-deficient alkenes, but those with organic azides (**3a**–**k**) bearing a 1,2,4-oxadiazole ring have not been reported previously. The synthetic sequence of the preparation of the target cycloadducts is shown below (Scheme 1). The exact structures of the novel cycloadducts **4a**–**k** were identified by IR, NMR (^{1}H, ^{13}C, COSY, NOESY, HMBC, and HSQC), mass spectra (low and high resolution), mp, and R_f characteristics. In the IR spectra, the disappearance of the N=N=N absorption of the corresponding starting azides **3a**–**k** at around 2100–2200 cm^{-1} and the appearance of the symmetric (1160–1120 cm^{-1}) and asymmetric (1300-1350 cm^{-1}) stretching absorptions of the sulfone group are evidence for 4-(phenylsulfonyl)-4,5-dihydro-[1,2,3]triazoles **4a**–**k**.

In the ^{1}H NMR spectra of these compounds, the relevant H-atoms labeled as H_a, H_b, H_c, H_d, and H_e in Figure 4 exhibited different splitting patterns.

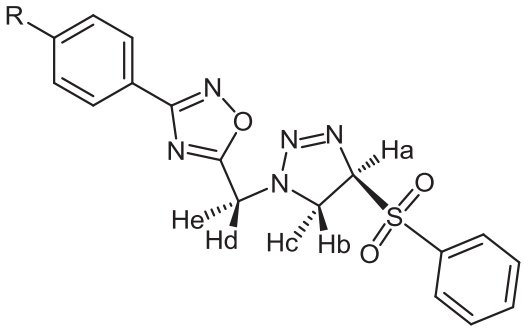
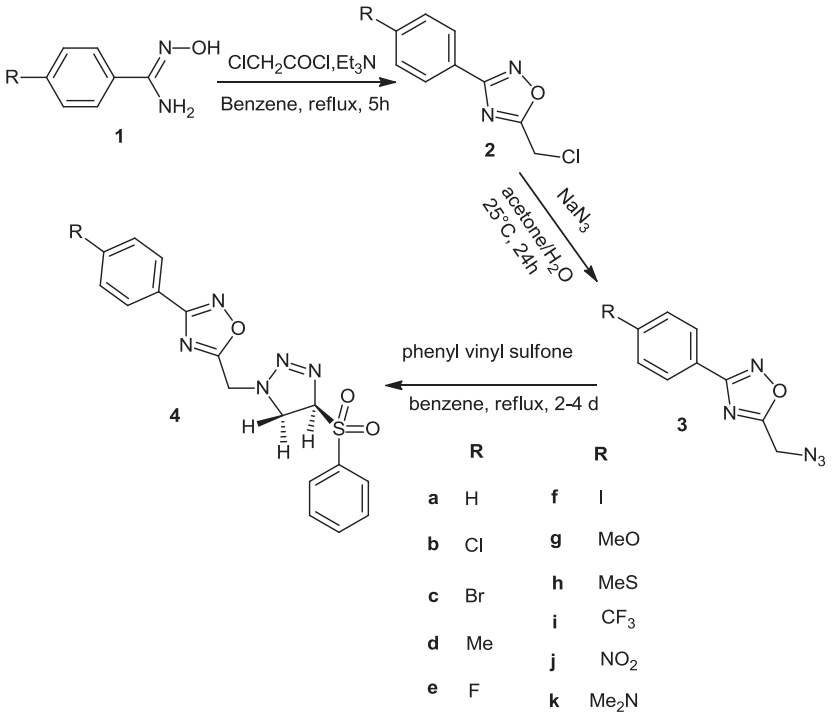


Figure 4. Aliphatic protons of **4a**–**k**.

The H_a proton, which has been found most deshielded due to the electron-withdrawing phenylsulfonyl group, appeared as a doublet of doublets induced by vicinal H_b and H_c protons, approximately at around 5.80 ppm with J= 12.5, 7.9 Hz. Two doublets at around 5.30 and 5.20 ppm with J = 17.0 Hz can be attributed to

the geminal H_d and H_e (AB system) protons. However, when compounds **4j** and **4k** were recorded in DMSO-d_6 they gave a singlet proton resonance signal corresponding to 2 hydrogens. An interesting splitting pattern was observed for geminal H_b and H_c protons at around 4.0 ppm with $J = 12.0$ Hz (Figure 5).



Scheme 1. Synthesis of oxadiazolylmethyltriazoles carrying phenylsulfone.

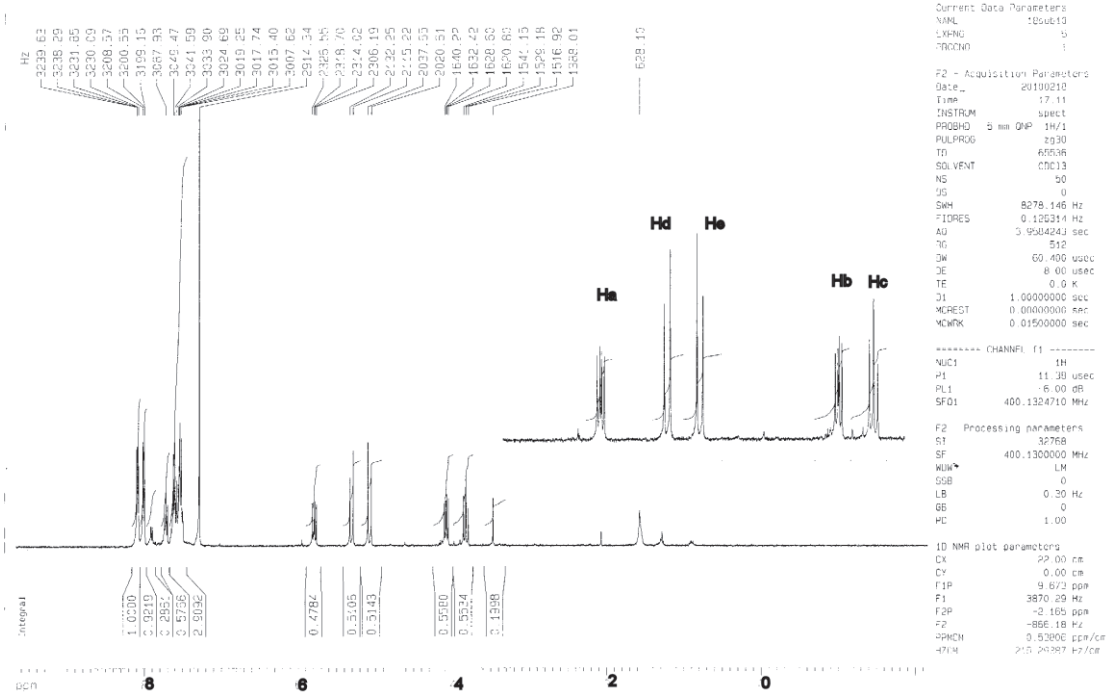


Figure 5. ^{1}H NMR spectrum of **4a**.

As for ^{13}C NMR assignments, iminic carbons of the oxadiazole ring resonated at around 173 (C-3 carbon of oxadiazole) and 168 ppm (C-5 carbon of oxadiazole). The carbon atom of the triazole ring, which is attached to the phenyl sulfonyl group, arose at around 95 ppm. The CH_2 group of the triazole ring and the bridge CH_2 resonate at around 45 and 44 ppm, respectively. From the HMBC and HSQC spectra, it can be seen that Ha is attached to the carbon atom bearing the phenyl sulfone group and Hb and Hc protons belong to the triazole CH_2 group (Figures 6 and 7).

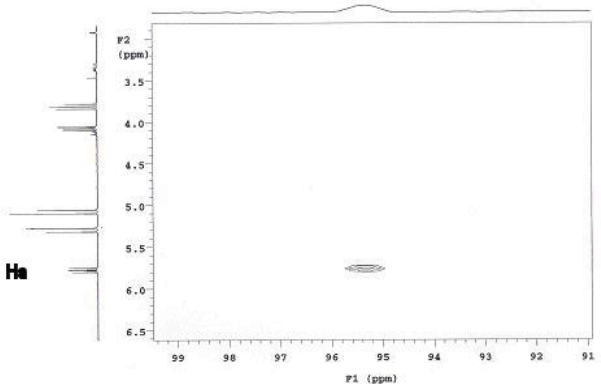


Figure 6. Partial HMBC spectrum of **4b**.

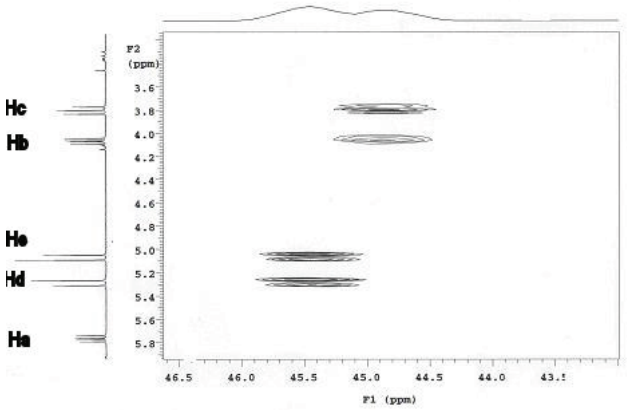
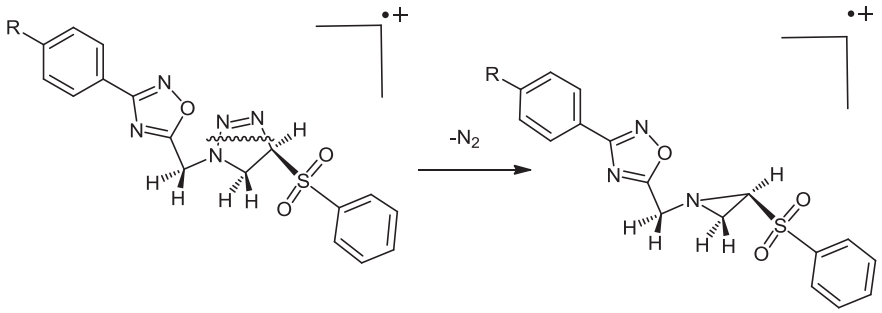


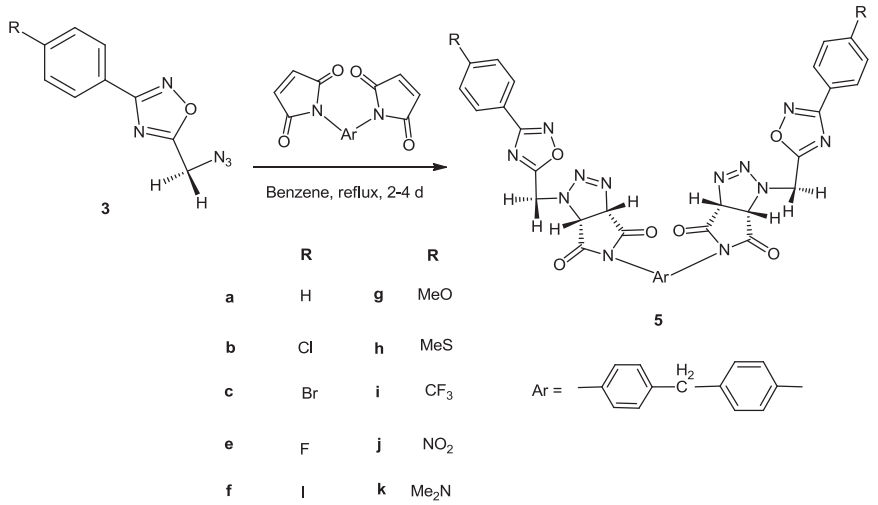
Figure 7. Partial HSQC spectrum of **4b**.

In the electron impact mass spectra of the cycloadducts **4a**–**k**, molecular ions (M^+) were not observed. The major peaks with the relatively intense abundances of these cycloadducts appeared as $[M–N_2]^+$, which can be considered as aziridine radical cations. These are most likely generated by the loss of N_2 from the molecules (Scheme 2). These fragments appeared mostly as base peaks. There are also peaks related to the $PhSO_2$ extrusion from the molecular ion with low abundances.



Scheme 2. Mass spectral fragmentation of **4a**–**k**.

As the second part of this work, we synthesized bis pyrrolo[3,4-d]- triazolediones **5** by the 1,3-dipolar cycloaddition of organic azides **3** to 4,4'-methylene bis(*N*-phenyl maleimide) as another electron-deficient alkene (Scheme 3). Thus, 10 new compounds were obtained and their structures were identified by spectroscopic/physical data. **5d** (*p*-tolyl substituted cycloadduct) cannot be obtained by the conducted synthetic procedure as a material of sufficient purity.



Scheme 3. Synthesis of bistriazolopyrrolidines carrying oxadiazole moiety.

In the IR spectra of these compounds, strong absorptions appeared at around 1715 cm^{-1} related to the C=O groups, which originated from bismaleimide. The ^{1}H NMR spectra show the bridge protons 3a–3a' at around 4.80 ppm as a doublet, 6a–6a' appeared at around 5.90 ppm as a doublet, and the CH_2 group between oxadiazole and triazole rings appeared as a singlet at around 5.60 ppm; the one between 2 Ph rings resonated at around 4.0 ppm (Figure 8).

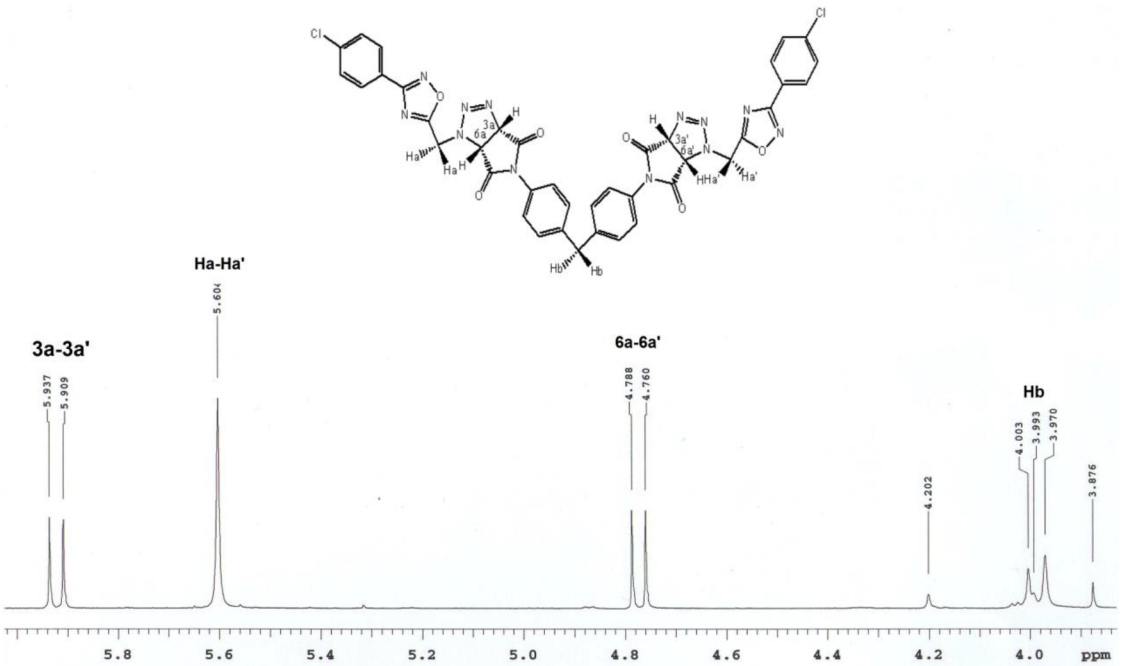


Figure 8. Aliphatic proton signals of **5b**.

2.2. Anticancer activity assay

4,5-Dihydro-1*H*-1,2,3-triazoles (**4a**–**k**) carrying phenylsulfonyl and oxadiazolylmethyl groups and bisdihydropyrrolo[3,4-d][1,2,3]triazole-4,6(3a*H*,5*H*)-diones (**5a**–**k**) carrying oxadiazolylmethyl groups were screened in vitro

for anticancer activity against human breast cancer cell lines, MCF-7, at a concentration of 1×10^{-3} M and the results are summarized below (Tables 1–3), indicating that among the phenylsulfonyl substituted triazoles **4a** and **4d** exhibited much higher activities against breast cancer cells (MCF-7). MCF-7 cells were maintained in Dulbeccos's Modified Eagle's Medium (DMEM) F-12 (Invitrogen) supplemented with 10 % (v/v) fetal bovine serum (FBS) (Invitrogen) and 1% antibiotic-antimycotic (penicillin streptomycin amphotericin B, Panbiotech).

Table 1. Cytotoxic activities of **4a**–**k** against MCF-7 cells[a].

Compd	R	IC_{50} (M)	Anticancer activity (% growth at a concentration of 1×10^{-3} M.
4a	H	7.2×10^{-4} [b]	34.0 ± 7.5
4b	Cl		77.0 ± 4.7
4c	Br		47.6 ± 5.7
4d	Me	2.5×10^{-4} [b]	40.5 ± 4.8
4e	F		66.3 ± 1.2
4f	I		51.4 ± 1.3
4g	MeO		95.2 ± 10.0
4h	MeS		74.2 ± 6.3
4i	CF_3		64.5 ± 3.5
4j	NO_2		> 100
4k	NMe_2		> 100

[a] Compounds tested in triplicate, data expressed as mean value ± SD of 3 independent experiments. [b] 50% growth inhibition as determined by MTT assay.

Table 2. Cytotoxic activities of **4a**–**k** against MCF-7 cells (WST-1 assay)[a].

Compd	R	Anticancer activity (% growth at a concentration of 1×10^{-3} M)
4a	H	31.7 ± 3.8
4b	Cl	72.0 ± 2.6
4c	Br	57.8 ± 1.4
4d	Me	45.7 ± 12.5
4e	F	79.7 ± 7.1
4f	I	54.3 ± 3.6
4g	MeO	80.0 ± 4.4
4h	MeS	49.3 ± 5.5
4i	CF_3	68.4 ± 6.9
4j	NO_2	> 100
4k	NMe_2	> 100

[a] Compounds tested in triplicate, data expressed as mean value ± SD of 3 independent experiments.

Except for the doses of 1×10^{-3} and 5×10^{-4} M, the ratio of DMSO was less than 5 per thousand. Doses were compared to controls containing the same amount of DMSO. The MCF-7 cells were then placed into 96-well plates (20,000 cells per well in 100?μL of DMEM F-12 with 10% heat-inactivated fetal calf serum and 1% antibiotic-antimycotic). After the cells adhered to the wells, different doses of the compounds were exposed to the cells for 24 h. After 24 h of incubation at 37 °C and in 5% CO_2 atmosphere, MTT measurement was conducted. MTT (Roche) solution (5 mL of MTT; (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium

bromide) labeling reagent (1×), 5 mg/mL in phosphate buffered saline) providing the final concentration 1/10 was added to all samples. Afterwards, 100 μL of solubilization solution (10% SDS in 0.01 M HCl) was added to each well, and the plate was incubated overnight at 37 °C. The optical densities of the wells were measured at a wavelength of 570 nm with reference of 690 nm using an ELISA microplate reader (Thermo Scientific Multiskan FC).[44] The results were calibrated with optical density measured without cells in the wells.

Table 3. Cytotoxic activities of **5a**–**k** against MCF-7 cells[a].

Compd	R	IC_{50} (M)	Anticancer activity (% growth at a concentration of 1×10^{-3} M)
5a	H		100.0 ± 3.4
5b	Cl	2.5×10^{-4}[b]	39.4 ± 4.2
5c	Br	4.3×10^{-4}[b]	26.3 ± 3.6
5e	F	4.8×10^{-4}[b]	20.5 ± 0.6
5f	I	1.7×10^{-4}[b]	41.9 ± 4.1
5g	MeO	2.6×10^{-4}[b]	26.5 ± 1.9
5h	MeS	1.7×10^{-4}[b]	33.3 ± 1.7
5i	CF_3	6.0×10^{-4}[b]	45.3 ± 2.1
5j	NO_2	4.9×10^{-4}[b]	34.0 ± 1.9
5k	NMe_2		> 100

[a] Compounds tested in triplicate, data expressed as mean value ± SD of 3 independent experiments. [b] 50% growth inhibition as determined by MTT assay.

2.3. WST-1 assay

MCF-7 cells were seeded at a concentration of 20,000 cells/well in 100 μL of DMEM F-12 (Invitrogen) with 10% heat-inactivated fetal bovine serum (Invitrogen) and 1% antibiotic-antimycotic (penicillin streptomycin amphotericin B, Panbiotech). After the treatment of the cells with the compounds, they were incubated for 24 h. Then 10 μL of WST-1 (Roche-Cell Proliferation Reagent WST-1) was added to each well and incubated for 4 h at 37 °C and in the presence of 5% CO_2 atmosphere. Wells were measured at a wavelength of 450 nm with using an ELISA microplate reader (Thermo Scientific Multiskan FC) (Table 3).[45]

When we take a look at the inhibitory values obtained from the MTT assay for compounds **5a**–**k**, we see that the better activity results are obtained from the MeO, I, NO_2, CF_3, Cl, and F substituted cycloadducts. Among them, fluorine substituted bisdihydropyrrolotriazoledione **5e** showed the best activity against MCF-7 cells (Table 3).

3. Experimental

3.1. General

All reactions were carried out under argon in dried solvents. All reagents were purchased from Merck (Germany) and Alfa-Aesar (Germany) and used without purification. ^{1}H, ^{13}C, and 2D-NMR spectra were recorded on Bruker and Varian (400 MHz for ^{1}H; 100 MHz for ^{13}C) spectrometers; δ in ppm relative to Me_4Si as internal standard, J in Hz. IR spectra were recorded on a Shimadzu FTIR 8400-S instrument;?in cm^{-1}. Mass spectra were run on a Waters 2695 Alliance Micromass ZQ LC/MS instrument; in m/z (rel. %). High resolution mass measurements were performed on a Waters Synapt MS instrument. Melting points were determined on

a Meltemp apparatus and are uncorrected. Flash column chromatography was performed on silica gel (Merck, 230–400 mesh ASTM). TLC was done using silica gel precoated plates with fluorescent indicator (Merck 5735). A Chromatotron 7924T rotary TLC apparatus (T-Squared Technology, Inc. San Bruno, CA, USA) was utilized for further separation and purifications. The stain solutions of permanganate and iodine were used for visualization of the TLC spots. Compounds **1**, **2**, and **3** were synthesized according to methods described previously.[42,46]

3.1.1. Typical procedure for the preparation of 1-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-4-(phenylsulfonyl)-4,5-dihydro-1H-1,2,3-triazole (4a)

A mixture of phenyl vinyl sulfone (0.087 g, 0.504 mmol) and 5-(azidomethyl)-3-phenyl-1,2,4-oxadiazole **3a** (0.100 g, 0.500 mmol) was stirred in benzene (25 mL) and the mixture was heated under reflux for 2 days. The reaction was monitored by TLC. The reaction mixture was concentrated in vacuo, and the crude residue was purified by flash column chromatography (*n*-hexane/ethyl acetate; 2:1) to give **4a** as a white solid (0.083 g, 45%); mp 120–122 °C. R_f: 0.52 (*n*-hexane/ethyl acetate; 1:1). IR (KBr, cm^{-1})v_{max} 3064, 1597, 1573 (C=N), 1477, 1446, 1309 (SO_2-asym), 1153 (SO_2-sym), 742. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J= 9.5 Hz, 2H), 8.00 (d, J= 8.0 Hz, 2H), 7.56 (m, 6H), 5.79 (dd, J= 12.5, 7.8 Hz, 1H, CH-SO_2), 5.31 (d, J= 17.0 Hz, 1H), 5.07 (d, J= 17.0 Hz, 1H), 4.08 (dd, J= 11.6, 7.8 Hz, 1H, CH_2-triazole), 3.82 (t, J= 12.0 Hz, 1H, CH_2-triazole). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 (C=N) 168.2 (C=N), 137.2, 135.5, 134.3, 131.1, 129.1, 129.0, 128.7, 128.4, 127.6, 127.4, 127.0, 125.5, 94.6, (C-SO_2), 44.7 (CH_2-triazole), 44.2 (CH_2). LC-MS (70 eV) (m/z, %) = 342 (M^+- N_2, 100), 278 (32), 200 (15), 172 (53), 121 (27). HRMS (TOF MS ES$^+$): Measured; 392.0781 Calculated for $C_{17}H_{15}N_5O_3S$ + Na; 392.0793.

3.1.2. 1-((3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4-(phenylsulfonyl)-4,5-dihydro-1H-1,2,3-triazole (4b)

White solid (0.141 g, 70%); mp 125–126 °C. R_f: 0.53 (n-hexane/ethyl acetate; 1:1). IR (KBr, cm^{-1}) v_{max} 3061, 1597, 1566 (C=N), 1416, 1410, 1309 (SO_2-asym), 1153 (SO_2-sym), 742. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (t, J = 7.5 Hz, 4H), 7.73 (t, J = 7.4 Hz, 1H), 7.60 (t, J = 7.7 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 5.78 (dd, J = 12.5, 7.8 Hz, 1H, CH-SO_2), 5.29 (d, J = 17.0 Hz, 1H), 5.08 (d, J = 17.0 Hz, 1H), 4.10 (dd, J = 13.9, 10.7 Hz, 1H, CH_2-triazole), 3.80 (t, J = 12.0 Hz, 1H, CH_2-triazole). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6 (C=N) 168.8 (C=N), 137.9, 136.1, 134.8, 129.7, 129.6, 129.4, 129.2, 128.8, 128.7, 128.4, 124.5, 125.2, 95.7, (C-SO_2), 45.3 (CH_2-triazole), 44.9 (CH_2). LC-MS (70 eV) (m/z, %) = 375 (M^+- N_2, 65), 312 (53), 206 (100), 171 (11). HRMS (TOF MS ES$^+$): Measured; 426.0395; Calculated for $C_{17}H_{14}N_5O_3SCl$ + Na; 426.0404.

3.1.3. 1-((3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4-(phenylsulfonyl)-4,5-dihydro-1H-1,2,3-triazole (4c)

Light yellow solid (0.067 g, 42%); mp 158–160 °C. R_f: 0.49 (n-hexane/ethyl acetate; 1:1). IR (KBr, cm^{-1}) v_{max} 2955, 1595, 1566 (C=N), 1446, 1408, 1346 (SO_2-asym), 1155 (SO_2-sym), 840, 738. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.2 Hz, 2H), 7.96 (d, J = 8.6 Hz, 2H), 7.72 (t, J = 7.4 Hz, 1H), 7.68 (d, J = 8.6 Hz, 2H), 7.61 (t, J = 7.2 Hz, 2H), 5.75 (dd, J = 12.5, 7.9 Hz, 1H, CH-SO_2), 5.30 (d, J = 17.0 Hz, 1H), 5.07 (d, J = 17.0 Hz, 1H), 4.07 (dd, J = 11.5, 7.9 Hz, 1H, CH_2-triazole), 3.80 (t, J = 12.0 Hz, 1H, CH_2-triazole). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6 (C=N), 168.9 (C=N), 136.8, 135.6, 134.8, 133.1, 130.3, 130.0, 129.8, 128.8, 128.2, 128.0,

127.0, 125.7, 95.7, (C-SO_2), 45.5 (CH_2-triazole), 44.9 (CH_2). LC-MS (70 eV) (m/z, %) = 451 (M^+, 100), 417 (11), 282 (10), 226 (13). HRMS (TOF MS ES^+): Measured; 448.0079; Calculated for $C_{17}H_{14}N_5O_3BrS$; 448.0079.

3.1.4. 4-(Phenylsulfonyl)-1-((3-p-tolyl-1,2,4-oxadiazol-5-yl)methyl)-4,5-dihydro-1H-1,2,3-triazole (4d)

Light yellow solid (0.093 g, 48%); mp 152–154 °C. R_f: 0.48 (n-hexane/ethyl acetate; 1:1). IR (KBr, cm^{-1}) v_{max} 2980, 1593, 1570 (C=N), 1448, 1343 (SO_2-asym), 1153 (SO_2-sym), 829, 742. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–7.95 (m, 3H), 7.80 (t, J = 7.8 Hz, 1H), 7.70 (t, J = 7.4 Hz, 1H), 7.59 (t, J = 6.9 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 5.79 (dd, J = 12.5, 7.7 Hz, 1H, CH-SO_2), 5.28 (d, J = 17.0 Hz, 1H), 5.05 (d, J = 17.0 Hz, 1H), 4.06 (dd, J = 11.6, 7.7 Hz, 1H, CH_2-triazole), 3.81 (t, J = 12.1 Hz, 1H, CH_2-triazole), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1 (C=N), 171.2, 168.6 (C=N), 142.0, 141.9, 135.9, 134.7, 129.6, 129.5, 129.2, 128.3, 127.4, 127.3, 123.1, 95.1 (C-SO_2), 45.2 (CH_2-triazole), 44.8 (CH_2), 21.6 (CH_3). LC-MS (70 eV) (m/z, %) = 356 (M^+- N_2, 100), 242 (22), 214 (16), 186 (8). HRMS (TOF MS ES^-): Measured; 406.0959; Calculated for $C_{18}H_{17}N_5O_3NaS$; 406.0950.

3.1.5. 1-((3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4-(phenylsulfonyl)-4,5-dihydro-1H-1,2, 3-triazole (4e)

Yellow solid (0.059 g, 30%); mp 120–122 °C. R_f: 0.61 (n-hexane/ethyl acetate; 1:1). IR (KBr, cm^{-1}) v_{max} 2926, 1597, 1546 (C=N), 1448, 1419, 1325 (SO_2-asym), 1153 (SO_2-sym), 854. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, J = 8.4, 5.6 Hz, 2H), 7.97 (d, J = 7.6 Hz, 1H), 7.70 (t, J = 7.4 Hz, 1H), 7.58 (t, J = 7.8 Hz, 2H), 7.32 (t, J = 3.0 Hz, 1H), 7.17 (t, J = 8.6 Hz, 2H), 5.77 (dd, J = 12.4, 4.0 Hz, 1H, CH-SO_2), 5.27 (d, J = 17.2 Hz, 1H), 5.06 (d, J = 17.2 Hz, 1H), 4.06 (dd, J = 12.2, 4.0 Hz, 1H, CH_2-triazole), 3.79 (t, J = 12.2 Hz, 1H, CH_2-triazole). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 173.7 (C=N), 168.0 (C=N), 165.0 (d, J_{CF} = 250.7 Hz), 137.6, 136.2, 135.0, 134.0, 130.0, 129.9, 129.7, 129.5, 129.2, 128.6, 95.4 (C-SO_2), 54.2 (CH_2-triazole), 45.5 (CH_2). LC-MS (80 eV) (m/z, %) = 410 ([M^+- N_2 +H], 100). HRMS (TOF MS ES^+): Measured; 461.1874 Calculated for $C_{18}H_{14}FN_5O_3S$+H+Na; 461.1899.

3.1.6. 1-((3-(4-Iodophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4-(phenylsulfonyl)-4,5-dihydro-1H-1,2,3-triazole (4f)

Light yellow solid (0.100 g, 40%); mp 119–121 °C. R_f: 0.48 (n-hexane/ethyl acetate; 1:1). IR (KBr, cm^{-1}) v_{max} 2934, 1593, 1565 (C=N), 1458, 1400, 1316 (SO_2-asym), 1151 (SO_2-sym), 738. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.72 (t, J = 7.4 Hz, 1H), 7.60 (dd, J = 15.8, 7.8 Hz, 2H), 5.76 (dd, J = 12.6, 7.8 Hz, 1H, CH-SO_2), 5.27 (d, J = 17.2 Hz, 1H, CH_2), 5.06 (d, J = 17.2 Hz, 1H, CH_2), 4.05 (dd, J = 11.8, 7.8 Hz, 1H, CH_2-triazole), 3.79 (t, J = 12.2 Hz, 1H, CH_2, triazole). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5 (C=N), 168.0 (C=N), 138.2, 135.9, 134.8, 134.5, 129.7, 129.5, 129.2, 128.9, 128.2, 128.0, 125.4, 99.4 (C-I), 95.1 (C-SO_2), 49.4 (CH_2-triazole), 45.2 (CH_2). LC-MS (80 eV) (m/z, %) = 468 (M^+-N_2, 100), 496 (M^++H, 60), 518 (36), 559 (44). HRMS (TOF MS ES^+): Measured; 517.9758; Calculated for $C_{17}H_{14}N_5O_3SI$+ Na; 517.9760.

3.1.7. 1-((3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)-4-(phenylsulfonyl)-4,5-dihydro-1H-1,2,3-triazole (4g)

Light yellow oil (0.102 g, 60%). R_f: 0.37 (n-hexane/ethyl acetate; 1:1). IR (KBr, cm^{-1}) ν_{max} 2964, 1597, 1546 (C=N), 1481, 1425, 1309 (SO_2-asym), 1155 (SO_2-sym), 736. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.97 (m, 4H), 7.70 (t, J = 7.4 Hz, 1H), 7.58 (t, J = 7.6 Hz, 2H), 7.00 (dd, J = 6.8 Hz, 2H), 5.77 (dd, J = 12.8, 7.6 Hz, 1H, CH-SO_2), 5.26 (d, J = 16.8 Hz, 1H, CH_2), 5.03 (d, J = 16.8 Hz, 1H, CH_2), 4.05 (dd, J = 11.8, 7.8 Hz, 1H, CH_2-triazole), 3.87 (s, 3H, OCH_3) 3.79 (t, J = 12.2 Hz, 1H, CH_2-triazole). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1 (C=N), 168.5 (C=N), 162.4 (C-OCH_3), 136.1 (2C), 135.0, 129.8 (2C), 129.5, 129.4, 118.6 (2C), 114.6 (2C), 95.3 (C-SO_2), 55.6 (OCH_3), 45.4 (CH_2-triazole), 45.0 (CH_2). LC-MS (80 eV) (m/z, %) = 468 (M^+-N_2, 100), 496 (M^++H, 60), 518 (36), 559 (44). HRMS (TOF MS ES^+): Measured; 422.0912; Calculated for $C_{18}H_{17}N_5O_4S$+Na; 422.0899.

3.1.8. 1-((3-(4-Methylthiophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4-(phenylsulfonyl)-4,5-dihydro-1H-1,2,3-triazole (4h)

Light yellow solid (0.092 g, 37%); mp 99–101 °C. R_f: 0.45 (n-hexane/ethyl acetate; 1:1). IR (KBr, cm^{-1}) ν_{max} 2924, 1599, 1570 (C=N), 1458, 1419, 1305 (SO_2-asym), 1151 (SO_2-sym), 740. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (td, J = 9.2, 8.0, 1.2 Hz, 2H), 7.89–7.52 (m, 5H), 7.31 (d, J = 8.4 Hz, 2H), 5.77 (dd, J = 12.4, 7.6 Hz, 1H, CH-SO_2), 5.25 (d, J = 17.2 Hz, 1H, CH_2), 5.04 (d, J = 17.2 Hz, 1H, CH_2), 4.05 (dd, J = 11.6, 7.8 Hz, 1H, CH_2-triazole), 3.78 (t, J = 12.4 Hz, 1H, CH_2-triazole), 2.53 (s, 3H, SCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4 (C=N), 168.4 (C=N), 143.8, 138.2, 136.1, 134.9, 134.7, 134.0, 129.7, 129.4, 128.2, 127.9, 126.0, 125.9, 95.3 (C-SO_2), 54.1 (CH_2-triazole), 49.7 (CH_2), 15.2 (SCH_3). LC-MS (80 eV) (m/z, %) = 388 (M^+ - N_2, 100), 410 (37), 416 (M^++H, 22), 451 (18), 479 (15). HRMS (TOF MS ES^+): Measured; 438.0658; Calculated for $C_{18}H_{17}N_5O_3S_2$+ Na; 438.0671.

3.1.9. 1-((3-(4-Trifluoromethylphenyl)-1,2,4-oxadiazol-5-yl)methyl)-4-(phenylsulfonyl)-4,5-dihydro-1H-1,2,3-triazole (4i)

Yellow solid (0.080 g, 34%); mp 104–106 °C. R_f: 0.55 (n-hexane/ethyl acetate; 1:1). IR (KBr, cm^{-1}) ν_{max} 2926, 1597, 1546 (C=N), 1448, 1419, 1325 (SO_2-asym), 1153 (SO_2-sym), 854. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.8 Hz, 2H), 7.82–7.79 (m, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.31 (t, J =3.2 Hz, 3H), 5.77 (dd, J = 12.6, 7.8 Hz, 1H, CH-SO_2), 5.30 (d, J = 17.2 Hz, 1H, CH_2), 5.10 (d, J = 17.2 Hz, 1H, CH_2), 4.10 (dd, J = 12.0, 4.0 Hz, 1H, CH_2-triazole), 3.80 (t, J = 12.2 Hz, 1H, CH_2-triazole). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7 (C=N), 167.3 (C=N), 137.6, 135.0, 134.0, 129.7, 129.5, 129.2, 128.6, 128.1, 127.9, 127.2, 126.1, 126.0, 110.0, 95.4 (C-SO_2), 54.2 (CH_2-triazole), 52.2 (CH_2). LC-MS (80 eV) (m/z, %) = 410 (M^+ - N_2, 100), 435 (25), 473 (25), 576 (23), 593 (40). HRMS (TOF MS ES^+): Measured; 461.1874; Calculated for $C_{18}H_{14}F_3N_5O_3S$+H+Na; 461.0745.

3.1.10. 1-((3-(4-Nitrophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4-(phenylsulfonyl)-4,5-dihydro-1H-1,2,3-triazole (4j)

Yellow solid (0.133 g, 51%); mp 126–128 °C. R_f: 0.37 (n-hexane/ethyl acetate; 1:1). IR (KBr, cm^{-1}) ν_{max} 2941, 1581, 1529 (C=N), 1448, 1415, 1342 (SO_2-asym), 1153 (SO_2-sym), 854. ^{1}H NMR (400 MHz, DMSO-

d_6) δ 8.42 (d, J = 8.8 Hz, 2H), 8.26 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 7.2 Hz, 2H), 7.77 (t, J = 7.0 Hz, 1H), 7.66 (t, J = 7.8 Hz, 2H), 6.35 (dd, J = 12.4, 7.2 Hz, 1H, CH-SO_2), 5.39 (s, 2H, CH_2), 3.90 (dd, J = 12.0, 7.6 Hz, 1H, CH_2-triazole), 3.73 (t, J = 12.6 Hz, 1H, CH_2-triazole). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.1 (C=N), 166.7 (C=N), 149.9, 136.6, 135.2, 135.0, 134.8, 132.0, 129.8, 129.6, 129.2, 128.8, 128.7, 128.6, 128.2, 124.7, 124.4, 94.4 (C-SO_2), 51.5 (CH_2-triazole), 45.0 (CH_2-oxadiazolylmethyl). LC-MS (80 eV) (m/z, %) = 415 (M+H, 35], 387 (M^+ - N_2, 100), 374 (47), 267 (60). HRMS (TOF MS ES^+): Measured; 409.0584; Calculated for $C_{17}H_{14}N_6O_5S$+Na; 409.0583.

3.1.11. 1-((3-(4-Dimethylaminophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4-(phenylsulfonyl)-4,5-dihydro-1H-1,2,3-triazole (4k)

Yellow solid (0.117 g, 57%); mp 102–104 °C. R_f: 0.55 (n-hexane/ethyl acetate; 1:1). IR (KBr, cm^{-1}) v_{max} 2926, 1581, 1558 (C=N), 1489, 1431, 1344 (SO_2-asym), 1193 (SO_2-sym), 736. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (dd, J = 8.4, 1.2 Hz, 1 H), 7.81–7.44 (m, 5 H), 6.80 (dt, J = 10.0, 5.2, 2.8 Hz, 3H), 6.33 (dd, J = 12.8, 7.6 Hz, 1H, CH-SO_2), 5.28 (s, 2H, CH_2), 3.88 (dd, J = 7.2, 4.4 Hz, 1H, CH_2-triazole), 3.70 (t, J = 12.6, Hz, 1H, CH_2-triazole), 3.00 (s, 6H, NMe_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.5 (C=N), 168.1 (C=N), 152.6, 136.6, 135.1, 134.3, 129.8, 129.6, 129.4, 128.6, 128.5, 128.2, 112.2, 112.1, 94.3 (C-SO_2), 53.9 (CH_2-triazole), 51.7 (CH_2-oxadiazolylmethyl), 44.7 ($N(CH_3)_2$). LC-MS (80 eV) (m/z, %) = 413 [M+H, 25], 407 (58), 385 (M - N_2, 100). HRMS (TOF MS ES^+) Measured; 410.1681 Calculated for $C_{19}H_{20}N_6O_3S$-2H; 410.1695.

3.1.12. Typical procedure for the preparation of (3aS,6aR)-5-(4-((9S,10R)-4-((3aS,6aR)-4,6-Dioxo-1-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-3a,4,6,6a-tetrahydropyrrolo[3,4-d][1,2,3] triazol-5(1H)-yl)benzyl)phenyl)-1-((3-phenyl-1,2,4-oxadiazol-5-yl) methyl)-1,6a-dihydropyrrolo[3,4-d][1,2,3]triazole-4,6(3aH,5H)-dione (5a)

A mixture of 4,4-methylene bis(N-phenyl maleimide) (0.090 g, 0.250 mmol) and 5-(azidomethyl)-3-phenyl-1,2,4-oxadiazole 3a (0.100 g, 0.500 mmol) was stirred in benzene (25 mL) and the mixture was heated under reflux for 4 days. The reaction was monitored by TLC. The reaction mixture was concentrated in vacuo, and the crude residue was washed with hexane to give 5a as a white solid (0.095 g, 50%); mp 172–174 °C. R_f: 0.63 (n-hexane/ethyl acetate; 1:1). IR (KBr, cm^{-1}) v_{max} 3074, 1718 (C=O), 1595, 1572 (C=N), 1348, 1192, 719. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 4 H), 7.44 (m, 6H), 7.13 (d, J = 10.1 Hz, 8H), 5.85 (d, J = 10.5 Hz, 2H), 5.50 (dd, J = 33.0, 17.4 Hz, 4H), 4.74 (d, J = 10.5 Hz, 2H), 3.94 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3 (C=O), 171.3 (C=O), 170.0 (C=N), 168.2 (C=N), 141.3, 131.7, 129.8, 129.5, 129.2, 127.4, 126.8, 126.2, 83.8 (CH), 58.1 (CH), 44.5 (CH_2), 29.5 (Ph-CH_2-Ph). HRMS (TOF MS ES^+): Measured; 760.2262; Calculated for $C_{39}H_{28}N_{12}O_6$; 760.2255.

3.1.13. (3a*S*,6a*R*)-1-((3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-5-(4-(4-((3a*R*,6a*S*)-1-((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-d][1,2,3]triazol-5(1*H*)-yl)benzyl)phenyl)-1,6a-dihydropyrrolo[3,4-d][1,2,3]triazole-4,6(3a*H*,5*H*)-dione (5b)

Yellow solid (0.155 g, 75%); mp 148–150 °C. R_f: 0.63 (*n*-hexane/ethyl acetate; 1:2). IR (KBr, cm^{-1}) v_{max} 2958, 1716 (C=O), 1591, 1512 (C=N), 1379, 1186, 744. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, J = 8.8

Hz, 5H), 7.63 (m, 5H), 7.11 (d, J = 8.0 Hz, 6H), 5.92 (d, J = 11.2 Hz, 2H), 5.60 (s, 4 H), 4.77 (d, J = 11.2 Hz, 2H), 3.97 (d, J = 13.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.7 (C=O), 172.3 (C=O), 170.8 (C=N), 167.5 (C=N), 142.4, 142.1, 141.0, 137.2, 135.3, 130.2, 129.9, 129.5, 127.4, 125.3, 84.1 (CH), 58.7 (CH), 44.8 (CH_2), 41.2 (Ph-CH_2-Ph). LC-MS (80 eV) (m/z, %) = 917 (100), 910 (81), 883 (63), 855 (56), 561 (93). HRMS (TOF MS ES$^+$): Measured; 828.1460; Calculated for $C_{39}H_{26}Cl_2N_{12}O_6$; 828.1475.

3.1.14. (3a*S*,6a*R*)-1-((3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)methyl)-5-(4-(4-((3a*R*,6a*S*)-1-((3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-d][1,2,3]triazol-5(1*H*)-yl)benzyl)phenyl)-1,6a-dihydropyrrolo[3,4-d][1,2,3]triazole-4,6(3a*H*,*5H*)-dione (5c)

Yellow solid (0.130 g, 70%); mp 146–148 °C. R_f: 0.60 (n-hexane/ethyl acetate; 1:2). IR (KBr, cm^{-1}) ν_{max} 3039, 1720 (C=O), 1597, 1566 (C=N), 1381, 1184, 742. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, J = 9.2 Hz, 4H), 7.90 (d, J = 8.4 Hz, 4H), 7.78 (m, 8H), 5.92 (d, J = 10.8 Hz, 2H), 5.60 (s, 4H), 4.77 (d, J = 11.2 Hz, 2H), 4.00 (d, J = 13.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ175.9 (C=O), 171.5 (C=O), 170.0 (C=N), 166.8 (C=N), 134.5, 132.4, 132.3, 129.1, 128.9, 126.6, 125.3, 124.9, 83.2 (CH), 57.9 (CH), 44.0 (CH_2), 33.6 (Ph-CH_2-Ph). LC-MS (80 eV) (m/z, %) = 970 (100), 926 (81), 907 (57), 746 (31), 503 (55). HRMS (TOF MS ES$^-$): Measured; 889.0679 Calculated for $C_{39}H_{25}N_{10}O_6Br_2$ [M-H-N_2]; 889.0672.

3.1.15. (3a*S*,6a*R*)-1-((3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-5-(4-(4-((3a*R*,6a*S*)-1-((3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-d][1,2,3]triazol-5(1*H*)-yl)benzyl)phenyl)-1,6a-dihydropyrrolo[3,4-d][1,2,3]triazole-4,6(3a*H*,5*H*)-dione (5e)

Orange solid (0.157 g, 79%); mp 142–144 °C. R_f: 0.40 (n-hexane/ethyl acetate; 1:2). IR (KBr, cm^{-1}) ν_{max} 2985, 1720 (C=O), 1579, 1514 (C=N), 1381, 1186, 750. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (m, 6 H), 7.35 (m, 10 H), 5.93 (d, J = 11.2 Hz, 2 H), 5.60 (s, 4 H), 4.77 (d, J = 10.8 Hz, 2 H), 3.98 (d, J = 12.8 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.8 (C=O), 171.5 (C=O), 170.1 (C=N), 166.7 (C=N), 163.9 (d, J = 248.4 Hz) (C-F), 141.2, 134.6, 129.6, 129.5, 129.1, 128.2, 126.6, 116.5, 116.3, 83.2 (CH), 57.9 (CH), 44.0 (CH_2), 33.5 (Ph-CH_2-Ph). LC-MS (80 eV) (m/z, %) = 851 (100), 825 (67), 786 (82), 775 (44), 604 (73). HRMS (TOF MS ES$^+$): Measured; 795.1988; Calculated for $C_{39}H_{25}N_{12}O_6F_2$; 795.1988.

3.1.16. (3a*S*,6a*R*)-1-((3-(4-Iodophenyl)-1,2,4-oxadiazol-5-yl)methyl)-5-(4-(4-((3a*R*,6a*S*)-1-((3-(4-iodophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-d][1,2,3]triazol-5(1*H*)-yl)benzyl)phenyl)-1,6a-dihydropyrrolo[3,4-d][1,2,3]triazole-4,6(3a*H*,5*H*)-dione (5f)

Yellow solid (0.100 g, 64%); mp 160–162 °C. R_f: 0.55 (n-hexane/ethyl acetate; 1:2). IR (KBr, cm^{-1}) ν_{max} 2956, 1720 (C=O), 1593, 1512 (C=N), 1402, 1182, 831. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96–7.70 (m, 6H), 7.40–7.05 (m, 10H), 5.91 (d, J = 10.4 Hz, 2H, 2 × CH), 5.60 (s, 4H, 2 × CH_2), 5.19 (s, 2H, Ph-CH_2-Ph), 4.75 (d, J = 10.8 Hz, 2H, 2 × CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.6, 176.4 (C=O), 172.2 (C=O), 170.7, 170.6 (C=N), 168.2, 167.8 (C=N), 138.9, 138.8, 135.3, 129.9, 129.8, 129.4, 127.5, 127.4, 125.7, 100.0, 99.8 (C-I),

84.0 (CH), 58.6 (CH), 44.9 (CH_2), 34.3 (Ph-CH_2-Ph). LC-MS (80 eV) (m/z, %) = 1019 (92), 959 (44), 904 (75), 687 (93), 391 (100). HRMS (TOF MS ES$^+$): Measured; 1013.0266; Calculated for $C_{39}H_{26}N_{12}O_6I_2$; 1013.0266.

3.1.17. (3a*S*,3a'*S*,6a*R*,6a'*R*)-5,5'-(4,4'-Methylenebis(4,1-phenylene))bis(1-((3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)-1,6a-dihydropyrrolo[3,4-d][1,2,3]triazole-4,6(3a*H*,5*H*)-dione) (5g)

Light yellow solid (0.202 g, 78%); mp 154–156 °C. R_f: 0.42 (*n*-hexane:ethyl acetate; 1:2). IR (KBr, cm^{-1}) ν_{max} 2937, 1720 (C=O), 1573, 1512 (C=N), 1381, 1255, 750. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, J = 11.6 Hz, 4H), 7.28–7.15 (m, 8H), 6.96 (d, J= 9.2 Hz, 4H), 5.85 (d, J = 10.8 Hz, 2H, 2×CH), 5.58 (d, J = 18.0 Hz, 2H), 5.30 (d, J = 18.0 Hz, 2H), 4.78 (d, J = 10.8 Hz, 2H, 2×CH), 4.02 (d, J = 7.2 Hz, 2H, Ph-CH_2-Ph), 3.86 (s, 6H, 2×OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.7 (C=O), 170.9 (C=O), 168.8 (C=N), 168.5 (C=N), 141.7, 134.4, 130.1, 129.9, 129.4, 129.0, 128.6, 126.5, 118.6, 114.6, 83.1, 57.3, 55.7 (CH_2), 44.6 (Ph-CH_2-Ph). LC-MS (80 eV) (m/z, %) = 902 (66), 871 (100), 797 (M$^+$-N_2, 18), 594 (70). HRMS (TOF MS ES$^+$): Measured; 820.2470, Calculated for $C_{41}H_{32}N_{12}O_8$; 820.2466.

3.1.18. (3a*S*,3a'*S*,6a*R*,6a'*R*)-5,5'-(4,4'-Methylenebis(4,1-phenylene))bis(1-((3-(4-(methylthio) phenyl)-1,2,4-oxadiazol-5-yl)methyl)-1,6a-dihydropyrrolo[3,4-d][1,2,3]triazole-4,6(3a*H*, 5*H*)-dione) (5h)

Light yellow solid (0.190 g, 92%); mp 147–149 °C. R_f: 0.45 (*n*-hexane:ethyl acetate; 1:2). IR (KBr, cm^{-1}) ν_{max} 2976, 1716 (C=O), 1593, 1512 (C=N), 1379, 1184, 744. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.8 Hz, 2 H), 7.36 (s, 2 H), 7.26 (m, 12 H), 5.84 (d, J = 10.8 Hz, 2H, 2×CH), 5.58 (d, J = 17.6 Hz, 2H, CH_2), 5.30 (d, J = 18.0 Hz, 2H, CH_2), 4.76 (d, J = 10.8 Hz, 2H, 2×CH), 4.00 (d, J = 8.8 Hz, 2H, Ph-CH_2-Ph), 2.51 (s, 6H, 2×SCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9 (C=O), 170.8 (C=O), 168.7 (C=N), 168.4 (C=N), 143.8, 142.0, 141.6, 140.2, 134.4, 130.0, 129.9, 129.0, 128.5, 128.0, 126.4, 126.3, 126.1, 126.0, 122.3, 83.1 (CH), 57.2 (CH), 44.5 (CH_2), 41.2 (Ph-CH_2-Ph 15.3 (CH_3S). LC-MS (80 eV) (m/z, %) = 870 (100), 610 (73), 825 (M$^+$-N_2, 14), 875 (M$^+$+Na, 30). HRMS (TOF MS ES$^+$): Measured; 853.2066; Calculated for $C_{41}H_{33}N_{12}O_6S_2$, 853.2087.

3.1.19. (3a*S*,3a'*S*,6a*R*,6a'*R*)-5,5'-(4,4'-Methylenebis(4,1-phenylene))bis(1-((3-(4-(trifluoromethyl) phenyl)-1,2,4-oxadiazol-5-yl)methyl)-1,6a-dihydropyrrolo[3,4-d][1,2,3]triazole-4,6(3a*H*,5*H*)-dione) (5i)

Light yellow solid (0.140 g, 63%); mp 158–160 °C. R_f: 0.58 (*n*-hexane/ethyl acetate; 1:2). IR (KBr, cm^{-1}) ν_{max} 2976, 1716 (C=O), 1595, 1512 (C=N), 1325, 1124, 758. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 8.0 Hz, 4H), 7.93 (d, J = 8.0 Hz, 4H), 7.30–7.07 (m, 8H), 5.92 (d, J = 10.8 Hz, 2H, 2×CH), 5.63 (s, 4H, 2×CH_2), 4.78 (d, J = 10.8 Hz, 2H, 2×CH), 3.94 (t, J = 20.2 Hz, 2H, Ph-CH_2-Ph). ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.0 (C=O), 172.2 (C=O), 170.7 (C=N), 170.6, 167.3 (C=N), 142.1, 135.3, 132.3, 130.3, 130.0, 129.9, 129.8, 128.6, 127.4, 127.0, 84.0 (CH), 58.7 (CH), 44.9 (CH_2), 41.1 (Ph-CH_2-Ph). LC-MS (80 eV) (m/z, %) = 952 (100), 919 (M$^+$+Na, 93), 879 (M$^+$-N_2, 18), 707 (59). HRMS (TOF MS ES$^+$): Measured; 896.2016; Calculated for $C_{41}H_{26}F_6N_{12}O_6$, 896.2002.

3.1.20. (3a*S*,3a'*S*,6a*R*,6a'*R*)-5,5'-(4,4'-Methylenebis(4,1-phenylene))bis(1-((3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1,6a-dihydropyrrolo[3,4-d][1,2,3]triazole-4,6(3a*H*,5*H*)-dione) (5j)

Yellow solid (0.146 g, 69%); mp 148–150 °C. R_f: 0.38 (*n*-hexane/ethyl acetate; 1:2). IR (KBr, cm^{-1}) ν_{max} 3099, 1720 (C=O), 1581, 1514 (C=N), 1336, 1124, 723. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (dd, J = 7.6, 2.4 Hz, 4 H), 8.23 (t, J = 1.6 Hz, 4 H), 7.30 (m, 4 H), 7.10 (t, J = 7.6 Hz, 4 H), 5.94 (d, J = 10.8 Hz, 2 H), 5.65 (s, 4 H), 4.79 (d, J = 10.8 Hz, 2 H), 3.95 (d, J = 17.6 Hz, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.3 (C=O), 172.3 (C=O), 170.8 (C=N), 167.0 (C=N), 150.0, 142.2, 135.3, 132.2, 129.9, 129.2, 127.4, 125.2, 84.1 (CH), 58.7 (CH), 44.8 (CH_2), 31.6 (CH_2). LC-MS (80 eV) (m/z, %) = 905 (78), 851 (M^++H, 39), 824 (M^+-N_2, 30), 610 (73), 413 (93), 229 (100). HRMS (TOF MS ES$^+$): Measured; 850.2001; Calculated for $C_{39}H_{26}N_{14}O_{10}$, 850.1956.

3.1.21. (3a*S*,3a'*S*,6a*R*,6a'*R*)-5,5'-(4,4'-Methylenebis(4,1-phenylene))bis(1-((3-(4-(dimethylamino) phenyl)-1,2,4-oxadiazol-5-yl)methyl)-1,6a-dihydropyrrolo[3,4-d][1,2,3]triazole-4,6(3a*H*,5*H*)-dione) (5k)

Brown solid (0.131 g, 75%); mp 168–170 °C. R_f: 0.33 (*n*-hexane/ethyl acetate; 1:2). IR (KBr, cm^{-1})υ_{max} 2901, 1724 (C=O), 1614, 1512 (C=N), 1348, 1193, 752. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83–7.74 (m, 3H), 7.30–7.23 (m, 3H), 7.12–7.09 (m, 3H), 6.83–6.76 (m, 3H), 5.90 (d, J= 10.4 Hz, 2H, 2 × CH), 5.53 (s, 4H), 5.53 (s, 4H, 2 × CH_2), 4.75 (d, J= 10.4 Hz, 2H, 2 × CH), 3.98 (d, J= 6.0 Hz, 2H, Ph-CH_2-Ph), 2.98 (m, 12H, 2 × NMe_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.4 (C=O), 172.2 (C=O), 170.8 (C=N), 168.3 (C=N), 152.8, 130.1, 129.9, 129.0, 128.9, 128.8, 127.4, 112.9, 112.5, 112.3, 83.9 (CH), 58.7 (CH), 44.8 (CH_2). LC-MS (80 eV) (m/z, %) = 819 (M^+-N_2, 34), 719 (17), 693 (100), 433 (74), 410 (87). HRMS (TOF MS ES$^+$): Measured; 847.3181; Calculated for $C_{43}H_{39}N_{14}O_6$, 847.3177.

4. Conclusions

A simple and practical method for the preparation of 11 novel phenylsulfonyl substituted triazoles carrying a 3-*p*-substituted phenyl-1,2,4-oxadiazole unit and 10 novel bis dihydropyrrolo[3,4-d][1,2,3]triazole-4,6(*3aH,5H*)-diones carrying a 3-*para*-substituted phenyl-1,2,4-oxadiazole unit is introduced. The target compounds were assayed against MCF-7 breast cancer cells, but IC_{50} values were not low. It was found that especially when R = H, Me, MeO, I, NO_2, F, and Cl in both series compounds show somewhat higher cytotoxicity against these cells.

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References

1. Ding, S.; Jia, G.; Sun, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 1877–1880.
2. Gao, J.; Zhang, X.; Xu, S.; Tan, F.; Li, X.; Zhang, Y.; Qu, Z.; Quan, X.; Liu, J. *Chem. Eur. J.* **2014**, *20*, 1957–1963.
3. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599.

4. Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin,V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210–216.
5. White, J. D.; Osborn, M. F.; Moghaddam, A. D.; Guzman, L. E.; Haley, M. M.; DeRose, V. J. *J. Am. Chem. Soc.* **2013**, *135*, 11680–11683.
6. Fu, T-H.; Li, Y.; Thaker, H. D.; Scott, R. W.; Tew, G. N. *ACS Med. Chem. Lett.* **2013**, *4*, 841–845.
7. Kushwaha, D.; Tiwari, V. K. *J. Org. Chem.* **2013**, *78*, 8184–8190.
8. Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905–4979.
9. Li, X.; Tu, Z.; Li, H.; Liu, C.; Li, Z.; Sun, Q.; Yao, Y.; Liu, J.; Jiang, S. *ACS Med. Chem. Lett.* **2013**, *4*, 132–136.
10. Suzuki, T.; Ota, Y.; Ri, M.; Bando, M.; Gotoh, A.; Itoh, Y.; Tsumoto, H.; Tatum, P. R.; Mizukami, T.; Nakagawa, H.; et al. *J. Med. Chem.* **2012**, *55*, 9562–9575.
11. Beghdadi, S.; Miladi, I. A.; Romdhane, H. B.; Bernard, J.; Drockenmuller, E. *Biomacromolecules* **2012**, *13*, 4138–4145.
12. Früh, S. M.; Steuerwald, D.; Simon, U.; Vogel, V. *Biomacromolecules* **2012**, *13*, 3908–3911.
13. Zolotarskaya, O. Y.; Wagner, A. F.; Beckta, J. M.; Valerie, K.; Wynne, K. J.; Yang, H. *Mol. Pharmaceutics* **2012**, *9*, 3403–3408.
14. Odds, F. C.; Brown, A. J. P.; Gow, N. A. *Trends Microbiol.* **2003**, *11*, 272–279.
15. Wan, J.; Zhang, L.; Yang, G. F. *J. Comput. Chem.* **2004**, *25*, 1827–1832.
16. Yang, B.; He, Q. J.; Zhu, D. Y.; Lou, Y. J.; Fang, R. Y. *Cancer Chemother. Pharmacol.* **2006**, *57*, 268–273.
17. Bräse, S.; Banert, K. *Organic Azides: Syntheses and Applications.* Wiley: West Sussex, UK, 2010.
18. Lin, T. S.; Prusoff, W. H. *J. Med. Chem.* **1978**, *21*, 106–109.
19. Lowema, C. K.; Nissan, R. A.; Wilson, W. S. *J. Org. Chem.* **1990**, *55*, 3755–3761.
20. D'Anna, F.; Marullo, S.; Noto, R. *J. Org. Chem.* **2008**, *73*, 6224–6228.
21. Huang, X.; Shen, R.; Zhang, T. *J. Org. Chem.* **2007**, *72*, 1534–1537.
22. Zhou, Y.; Murphy, P. V. *Org. Lett.* **2008**, *10*, 3777–3780.
23. Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247–12275.
24. Zhang, F. Z.; Moses, J. E. *Org. Lett.* **2009**, *11*, 1587–1590.
25. Nicolaides, D. N.; Fylaktakidou, K. C.; Litinas, K. E.; Hadjipavlou-Litina, D. *Eur. J. Med. Chem.* **1998**, *33*, 715–724.
26. Leite, A. C. L.; Vieira, R. F.; De Faria, A. R.; Wanderley, A. G.; Afiatpour, P.; Ximenes, E. C. P. A.; Srivastava, R. M.; De Oliveira, C. F.; Antunes, M. V.; Medeiros, E.; et al. *Farmaco* **2000**, *55*, 719–724.
27. Yang, X.; Liu, G.; Li, H.; Zhang, Y.; Song, D.; Li, C., Wang, R.; Liu, B.; Liang, W.; Jing, Y.; et al. *J. Med. Chem.* **2010**, *53*, 1015–1022.
28. Luthman, K.; Borg, S.; Hacksell, U. *Methods Mol. Med.* **1999**, *23*, 1–23.
29. Flipo, M.; Desroses, M.; Lecat-Guillet, N.; Villemagne, B.; Blondiaux, N.; Leroux, F.; Piveteau, C.; Mathys, V.; Flament, M-P.; Siepmann, J.; et al. *J. Med. Chem.* **2012**, *55*, 68–83.
30. Flipo, M.; Desroses, M.; Lecat-Guillet, N.; Dirie, B.; Carette, X.; Leroux, F.; Piveteau, C.; Demirkaya, F.; Lens, Z.; Rucktooa, P.; et al. *J. Med. Chem.* **2011**, *54*, 2994–3010.
31. Kale, P.; Johnson, L. B. *Drugs Today* **2005**, *41*, 91–105.
32. Torres, H. A.; Hachem, R. Y.; Chemaly, R. F.; Kontoyiannis, D. P.; Raad, I, I. *Lancet Infect. Dis.* **2005**, *5*, 775–785.
33. Keating, G. M. *Drugs* **2005**, *65*, 1553–1567.
34. Cuzick, J. *Drugs Today* **2005**, *41*, 227–239.
35. Howell, A.; Buzdar, A. *J. Steroid Biochem. Mol. Biol.* **2005**, *93*, 237–247.

36. Geisler, J.; Lønning, P. E. *J. Steroid Biochem. Mol. Biol.* **2005**, *95*, 75–81.
37. Brueggemeier, R.W.; Hackett, J.C.; Diaz-Cruz, E. S. *Endocr. Rev.* **2005**, *26*, 331–345.
38. Moody, T. W.; Chiles, J.; Moody, E.; Sieczkiewicz, G. J.; Kohn, E. C. *Lung Cancer* **2003**, *39*, 279–288.
39. Yang, B.; He, Q. J.; Zhu, D. Y.; Lou, Y. J.; Fang, R. Y. *Cancer Chemother. Pharmacol.* **2006**, *57*, 268–273.
40. Pandeya, S. N.; Ojha, T. N.; Srivastava, V. *J. Sci. Ind. Res.* **1985**, *44*, 150–162.
41. Dürüst, Y.; Sağırlı, A.; Fronczek, F. R. *Mol. Divers.* **2011**, *15*, 799–808.
42. Dürüst, Y.; Karakuş, H.; Kaiser, M.; Tasdemir, D. *Eur. J. Med. Chem.* **2012**, *47*, 296–304.
43. Dürüst, Y.; Altuğ, C.; Sinkkonen, J.; Martiskainen, O.; Pihlaja, K. *J. Heterocycl. Chem.* **2006**, *43*, 1267–1274.
44. Berridge, M. V.; Tan, A. S. *Arch. Biochem. Biophys.* **1993**, *303*, 474–482.
45. Yin, L. M.; Wei, Y.; Wang, Y.; Xu, Y. D.; Yang Y. Q. *Int. J. Med. Sci.* **2013**, *10*, 68–72.
46. Ağırbaş, H.; Sümengen, D.; Dürüst, Y.; Dürüst, N. *Synth. Commun.* **1992**, *22*, 209–217.