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ORIGINAL ARTICLE

Synthesis and biological evaluation of novel tamoxifen-1,2,4-triazole conjugates

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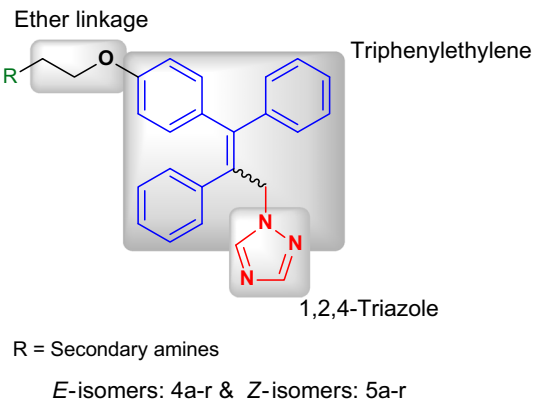
Abstract A new class of compounds, structurally related to the breast cancer drug tamoxifen, was designed and synthesized. The McMurry coupling reaction was used as the key synthetic step in the preparation of these analogs, and the structural assignments were made on the basis of ^{1}H NMR, ^{13}C NMR, and HRMS studies. The absolute stereochemistry of *E* and *Z* isomers was unambiguously confirmed by a single-crystal X-ray diffraction analysis. Water was found to be an inexpensive nontoxic and effective medium for the C–N bond formation. Utilizing this protocol, various tamoxifen derivatives were synthesized in good yields. Environmental acceptability, low cost, and high yields are the important features of this protocol. These compounds were evaluated for their antiproliferative activity on five human tumor cell lines. Compound **4p** (GI_{50} = 0.23 μM) showed improved antiproliferative activity against breast cancer cell line (MDA-MB-231) compared to tamoxifen (GI_{50} = 0.24 μM), while the compound **4o** (GI_{50} = 0.12 μM) exhibited similar activity against SiHa compared to the reference drug, tamoxifen (GI_{50} = 0.12 μM). In addition, these analogs were investigated for their antibacterial activity against six bacterial strains. Preliminary results indicate that some of the newly synthesized title compounds exhibited promising antibacterial activity compared with the standard drug, vancomycin.

Graphical Abstract A new class of compounds were designed rationally by the replacement of a ethyl group in tamoxifen with a methylene (1*H*-1,2,4-triazole) group. The absolute stereochemistry of *E* and *Z* isomers were unambiguously confirmed by a single-crystal X-ray diffraction analysis. The title compounds were evaluated for their antiproliferative and antibacterial activities.



Keywords Tamoxifen · 1,2,4-Triazole · McMurry coupling · Piperazines · Antibacterial

Introduction

Cancer is one of the major health problems in the world for decades. Breast cancer is the most commonly diagnosed cancer and the leading cause of morbidity and mortality in

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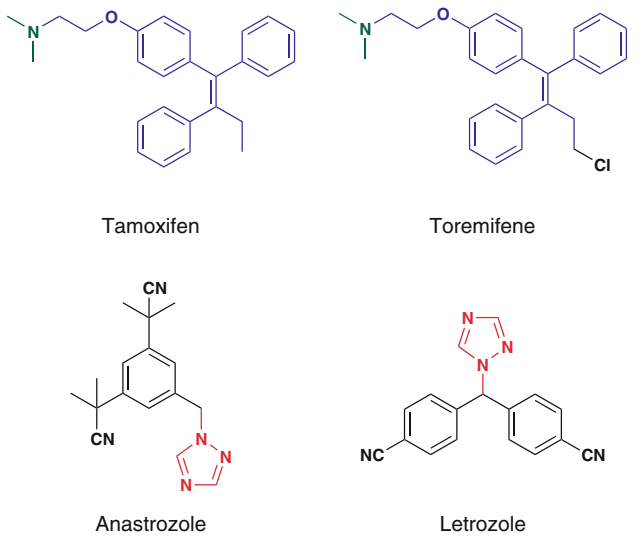


Fig. 1 Structures of the selective estrogen receptor modulators (SERMs) tamoxifen and toremifene, and the aromatase inhibitors (AIs) anastrozole and letrozole

women worldwide [1]. It is generally believed that estrogen can directly stimulate the growth of breast cancer; therefore, its inhibition with antiestrogens at the estrogen receptor (ER) can provide a particularly useful strategy for the treatment of hormone-dependent breast cancer. Antiestrogens (AEs) and aromatase inhibitors (AIs) are used clinically to arrest estrogen-dependent growth of breast cancer. Moreover, triphenylethylene antiestrogens, which have more recently been designated as selective estrogen receptor modulators (SERMs), are widely used to treat all stages of breast cancer [2]. Tamoxifen is a synthetic nonsteroidal triphenylethylene antiestrogen drug and is widely used in the treatment of breast cancer (Fig. 1) [3,4]. Tamoxifen is an SERM, which acts as either an agonist or an antagonist depending on the target tissue. Toremifene is a chlorinated derivative of tamoxifen, which is an alternative to tamoxifen in the first-line treatment of hormone-responsive metastatic breast cancer (Fig. 1) [5,6].

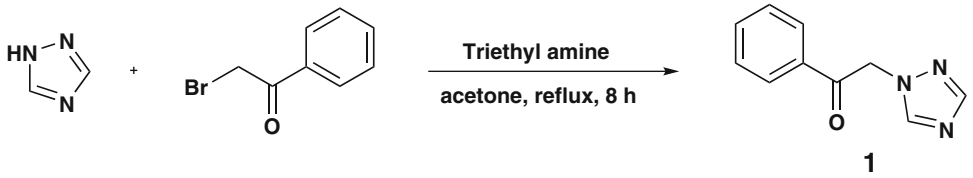
Aromatase inhibitors lower the production of estrogen levels in the body by blocking aromatase, an enzyme that converts the hormone androgen into estrogen. Suppression of estrogen biosynthesis by aromatase inhibition is a valuable approach for the treatment of hormone-responsive breast cancer. The third-generation nonsteroidal aromatase inhibitors have shown important benefits in postmenopausal women with estrogen receptor-positive (ER+) breast cancer. The reversible nonsteroidal AIs anastrozole and letrozole (1,2,4-triazole derivatives) (Fig. 1) are widely accepted as alternatives to tamoxifen as an initial therapy in postmenopausal women with advanced breast cancer, because of their improved clinical effectiveness [7,8]. Accordingly, here we describe the synthesis of novel tamoxifen derivatives containing a 1,2,4-triazole moiety.

The McMurry coupling reaction is an important methodology for the synthesis of functionalized olefins and has been used for the synthesis of title compounds that mimic the structural core of tamoxifen [9–13]. A structural characteristic of most nonsteroidal antiestrogens is the presence of basic ether side chain/group at a given position in space, which is required for the molecule to be an effective estrogen antagonist [14,15]. The basic group may be important in evoking estrogen antagonism due to its ionic interaction with an acidic amino acid residue in the binding site of the estrogen receptor [16]. To probe the importance of the aminoethyl side chain, we evaluated the antiproliferative activity of a newly prepared series of tamoxifen analogs in which the side chain basicity was varied over a wide range.

The triphenylethylene moiety and the side chain are prerequisites for tamoxifen binding to the ER, although modification of the ethyl group linked to the ethylenic carbon does not seem to drastically affect the affinity for the antiestrogen binding site [17]. Toremifene differs from tamoxifen by the introduction of a chlorine atom for a hydrogen atom in the ethyl group and has been proven to be clinically effective [18]. The fluorotamoxifen analogs with fluorine atom positioned on the ethyl substituent of tamoxifen had similar or superior binding affinities compared with tamoxifen [19]. They were found to be most active on the MCF-7 cell line [20]. Based on these observations, new tamoxifen analogs **4a**–**r** and **5a**–**r** were designed rationally by the replacement of an ethyl group in tamoxifen with a methylene (1*H*-1,2,4-triazole) group to furnish novel tamoxifen analogs with high antiproliferative activity.

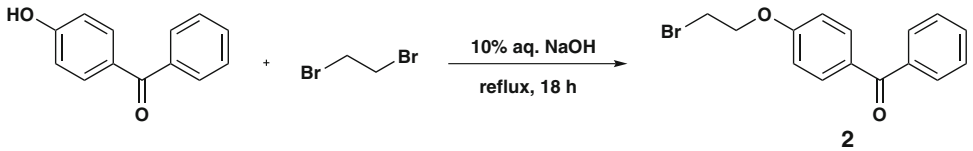
The construction of the C–N bond is of great importance because of its relevance in compounds with interesting and diverse biological activities [21]. The classical methods for the C–N bond formation involves the use of strong bases like alkali metal hydroxides, carbonates, and phosphates as well as organic bases like DBU or tertiary amines. Hence, the construction of the C–N bond employing mild and inexpensive reaction conditions is of particular interest. Water is a unique medium to perform catalyst-free organic reactions [22] and also offers practical advantages over organic solvents because it is readily available, safe, nontoxic, nonflammable, and environmentally benign. Herein, we report an environmentally friendly and efficient method for the formation of C–N bond under catalyst-free conditions in aqueous medium. In addition, the title compounds were evaluated for their in vitro antiproliferative activity against five human tumor cell lines, SiHa (cervical cancer), MDA-MB-231 (breast cancer), PANC-1 (pancreatic carcinoma), IMR-32 (neuroblastoma), and Hep G2 (liver carcinoma). All the compounds were subjected to in vitro antibacterial activity against *Bacillus subtilis*, *Bacillus megaterium*,

Scheme 1 Synthesis of 1-phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone



1

Scheme 2 Synthesis of (4-(2-bromoethoxy)benzophenone



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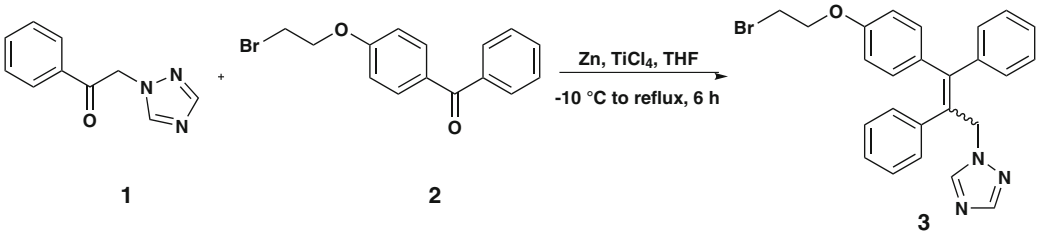
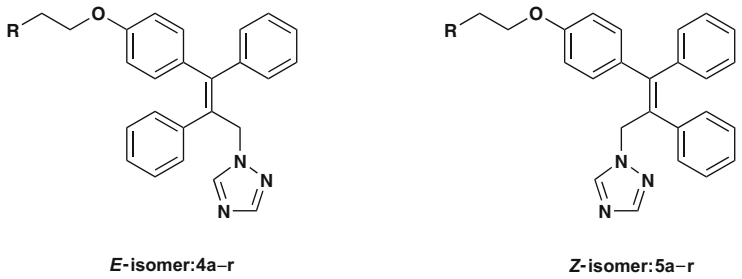


1 2 3



E-isomer:4a–r *Z*-isomer:5a–r

R= Secondary amines

Scheme 3 Synthesis of tamoxifen containing 1,2,4-triazole and its side chain analogs. Compounds **4a**–**r** are presented as *E*-isomers and compounds **5a**–**r** are presented as *Z*-isomers

Micrococcus luteus, *Escherichia coli*, *Salmonella typhi*, and *Pseudomonas aeruginosa* and their minimal inhibitory concentrations were determined.

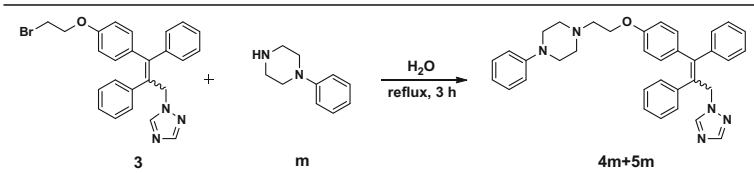
Results and discussion

Chemistry

The synthetic routes adopted for the preparation of target molecules (**4a**–**r** & **5a**–**r**) are shown in Schemes 1, 2, and 3. McMurry coupling was used as the key synthetic step in the preparation of these compounds. The required ketones **1** and **2** necessary for the McMurry coupling reaction were prepared as outlined in Schemes 1 and 2. The triazole-ketone **1** was prepared by the reaction of 1*H*-1,2,4-triazole with phenacyl bromide in the presence of Et_3N [23]. The synthesis of 4-(2-bromoethoxy)benzophenone **2** was accomplished by the reaction of 4-hydroxybenzophenone with 1,2-dibromoethane using sodium hydroxide [24]. The (*E*,*Z*)-1-(3-(4-(2-bromoethoxy)phenyl)-2,3-diphenylallyl)-1*H*-1,2,4-triazole **3** was afforded via implementation of the titanium tetrachloride/zinc-mediated McMurry coupling reaction of 1-phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone **1** with 4-(2-bromoethoxy)benzophenone **2** [10]. The mixture of *E*, *Z* isomers **3** proved difficult to separate by column chromatography. However, upon alkylation, the resulting *E*, *Z* isomers **4a**–**r** and **5a**–**r** were readily separable.

Initially, compound **3** and phenyl piperazine were selected as the model substrates to determine the optimized reac-

Table 1 Optimization of the reaction conditions



3 m 4m+5m

Entry	Solvent	Temperature (°C)	Yield[a] (%)
1	H_2O	rt	0
2	H_2O	50	28
3	**H_2O**	**100**	**82**
4	CH_3CN	82	42
5	DCM	40	39
6	DMSO	100	43
7	DMF	100	47
8	1,4-Dioxan	100	54
9	Toluene	100	51
10	PEG-400	100	63

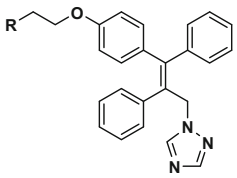
Reaction conditions: **3** (0.0005 mol), **m** (0.001 mol) in solvent (3 mL) were refluxed for 3 h
Bold value indicates the best optimized reaction conditions
[a] Isolated yield after column chromatography

tion conditions and the results are summarized in Table 1. The reaction proceeds under catalyst-free conditions and, in order to ascertain the effect of solvent on *N*-alkylation, the reaction was carried out using different solvents (Table 1, entries 3–10). The results, as shown in Table 1, unveil that water is superior to the other solvent systems. In aqueous medium, no reaction was observed at room temperature but by performing the reaction at 50 °C (Table 1, entry 2) encouragingly the reaction afforded the corresponding product in 28 % yield. With a further increase in temperature to 100 °C, the yield increased to 82 % (Table 1, entry 3). Thus, the best result was obtained when the reaction was pursued at 100 °C under catalyst-free conditions in water for 3 h. In order to investigate the scope of this reaction, a variety of secondary amines were subjected to this reaction (Table 2, entries 1–18) which afforded the corresponding products in good yields. The results suggest that, irrespective of the nature of the secondary amine, the reaction proceeds well in the optimized conditions (Table 2). The C–N bond formation reaction provided a mixture of *E*, *Z* isomers (**4a**–**r** and **5a**–**r**) that were separated by column chromatography in good yields (74–82 %).

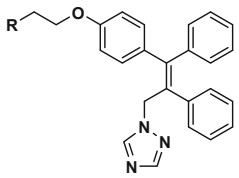
The configuration of final compounds was readily assigned on the basis of the relative chemical shift of basic side chain *O*-methylene protons in NMR spectra. In *trans*-tamoxifen, the resonance of the *O*-methylene protons is at higher field compared to *cis*-tamoxifen due to the shielding influence of unsubstituted phenyl rings [25]. This relation holds for all tamoxifen derivatives and related triphenylethylenes [26,27]. Accordingly, the stereochemistry of series **4a**–**r** was determined to be in the *E* configuration based on its chemical shift between 3.92 and 4.03 ppm. Similarly, the chemical shift between 4.07 and 4.18 ppm establishes the stereochemical assignment of series **5a**–**r** to be in the *Z* configuration (*trans* (*E*) and *cis* (*Z*) are used in this paper to designate the relative positions of the methylene (1*H*-1,2,4-triazole) group and the ring bearing the aminoethyl side chain). The same pattern was observed for *N*-methylene protons attached to the triazole ring (chemical shift between 5.13 and 5.15 ppm for series **4a**–**r** and 5.19 and 5.21 ppm for series **5a**–**r**). Single-crystal X-ray diffraction of compounds **4h**, **4i**, and **5k** (each recrystallized from EtOAc) confirms the stereochemical assignment for these compounds (Fig. 2).

The analysis of the *E* and *Z* isomers of the tamoxifen derivatives by reversed-phase high-performance liquid chromatography (RP-HPLC) has been reported. A typical chromatogram of compound **3** spiked with *E* and *Z* isomers is shown in Fig. 3a. The retention times of *E* and *Z* were 17.7 and 18.9 min, respectively. The signals were provisionally assigned on the basis of UV spectra of compound **3**. The separation of the isomers in compound **3** is not possible at this stage and hence the precise identification of individual signals is difficult. However, after alkylation of **3** it is possible to discriminate between each of the isomers on the basis of ^{1}H NMR data of tamoxifen derivatives **4m** and **5m** (Table 2, entry 13). Both compounds **4m** and **5m** exhibited signals with well- separated retention times of 20.7 and 24.2 min, respectively, as shown in Fig. 3b. The spectrum of **4m** contained an *O*-methylene triplet centered at δ 4.03 ppm. This was assigned to the *E* configuration (retention time of 20.7,

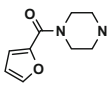
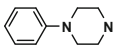
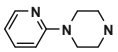
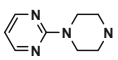
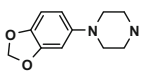
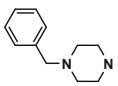
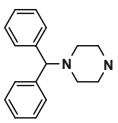
Table 2 Synthesis of (*EZ*)-2-(4-(1,2-diphenyl-3-(1*H*-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl amines (**4a–r** and **5a–r**)



***E*- isomer: 4a–r**



***Z*- isomer: 5a–r**

Entry	R		Product[a]	Yield[b] (%)	E:Z ratio[c]
1		a	4a+5a	78	2.8:1
2		b	4b+5b	81	3:1
3		c	4c+5c	79	2.9:1
4		d	4d+5d	76	3.2:1
5		e	4e+5e	80	3.1:1
6		f	4f+5f	77	3:1
7		g	4g+5g	75	4.8:1
8		h	4h+5h	82	4.1:1
9		i	4i+5i	81	3.3:1
10		j	4j+5j	79	3.2:1
11		k	4k+5k	80	3:1
12		l	4l+5l	74	3.1:1
13		m	4m+5m	82	3.3:1
14		n	4n+5n	79	3.6:1
15		o	4o+5o	79	2.7:1
16		p	4p+5p	78	2.9:1
17		q	4q+5q	80	3.5:1
18		r	4r+5r	77	2.8:1

[a] Reaction conditions: **3** (0.0005 mol), **RH** (0.001 mol) in water (3 mL) were refluxed for 3 h

[b] Isolated yield after column chromatography

[c] E/Z ratio determined from the integral of the respective NCH_2 singlet in the NMR spectra

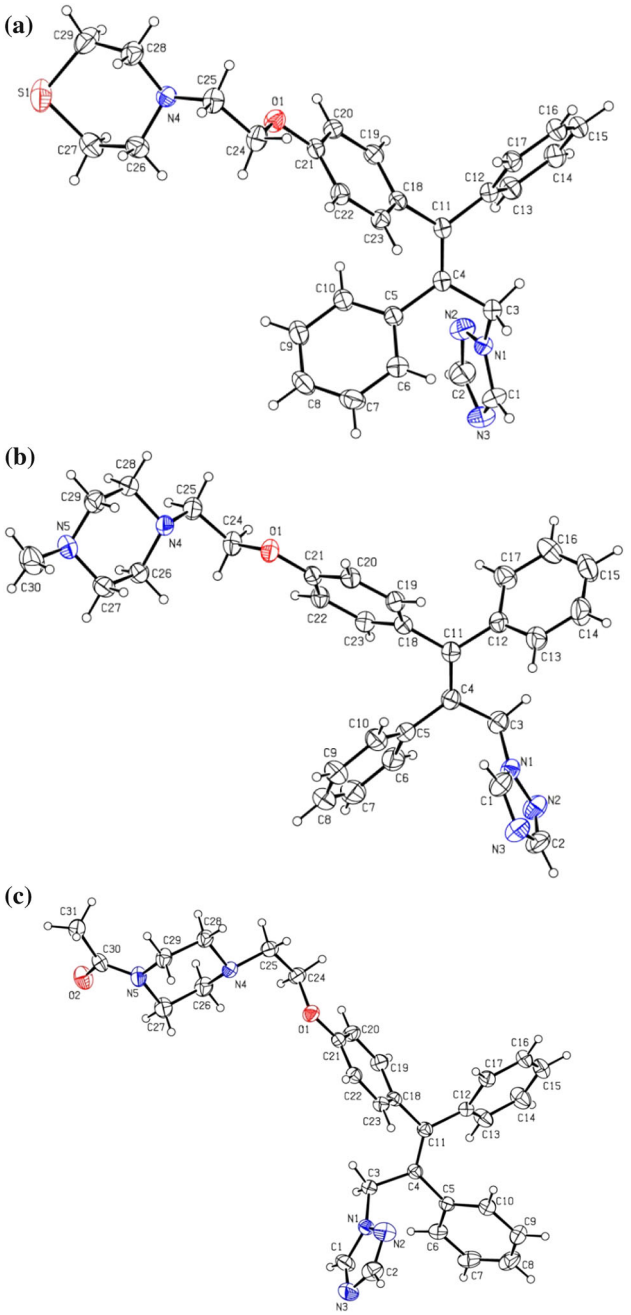


Fig. 2 ORTEP diagram of compounds **a 4h**, CCDC number 1028923, **b 4i**, CCDC number 1028922, and **c 5k**, CCDC number 1028921 with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30 % probability level and H atoms are shown as small spheres of arbitrary radius

Fig. 3c). The triplet at δ 4.18 ppm is due to the OCH_2 of compound **5m**, which was assigned as the *Z* configuration (retention time of 23.8, Fig. 3d). On this basis, the signal identities were further established by the retention times of compounds **4m** and **5m**.

Biological evaluation

Antiproliferative activity

The title compounds were evaluated by an in vitro assay, which was carried out with a panel of five human cancer cell lines including cervical cancer (SiHa), breast cancer (MDA-MB-231), pancreatic carcinoma (PANC-1), neuroblastoma (IMR-32), and liver carcinoma (Hep G2), using tamoxifen as a reference compound. The screening procedure was based on the standard SRB assay. The results are summarized in Table 3 and expressed as the concentration, in μM, of drug inhibiting the cell growth by 50 % (GI_{50}).

The investigation of the antiproliferative effect on estrogen independent human tumor cell lines SiHa, MDA-MB-231, PANC-1, IMR-32, and Hep G2 showed a significant decrease of sensitivity toward tamoxifen. A direct comparison of antiproliferative activity of compound **4a** containing the *N*-dimethyl basic side chain to the activity recorded for tamoxifen resulted in a significant loss in activity indicating that the replacement of an ethyl group in tamoxifen for a methylene (1*H*-1,2,4-triazole) group may not be necessary. Interestingly, compound **4p** bearing a piperonyl piperazine moiety showed a slight increase in activity ($GI_{50} = 0.23\ \mu M$) against the breast cancer cell line (MDA-MB-231) compared to tamoxifen. Compound **4o** having a pyrimidyl piperazine group maintained similar activity against SiHa compared to the reference drug. Compound **4m**, with phenyl piperazine group, was close to the standard ($GI_{50} = 0.39\ \mu M$) in IMR-32. Among the screened tamoxifen derivatives, compound **4e**, with a homopiperidine substitution, was found to be active against PANC-1 and Hep G2. It is well known that *E*-tamoxifen (*cis* isomer) is not antiestrogenic but functions as an estrogen agonist, whereas *Z*-tamoxifen (*trans* isomer) behaves as an antagonist and is effective in treating estrogen-dependent breast cancer [28]. The antiproliferative activity results of title compounds revealed that *E*-tamoxifen derivatives were more active toward the tested cells compared to *Z*-tamoxifen derivatives (Table 3).

Antibacterial activity

In addition to antiproliferative activity studies, we studied the antibacterial properties of the new tamoxifen derivatives. Thus, the newly synthesized compounds and tamoxifen were screened for their in vitro activity against three Gram-positive (*B. subtilis*, *B. megaterium*, *M. luteus*) and three Gram-negative (*E. coli*, *S. typhi*, *Pseudomonas aeruginosa*) bacterial strains using the well diffusion and microdilution methods. Antibacterial activity was determined by measuring the diameter of inhibition zone in mm. The minimum inhibitory concentration (MIC) was noted by considering the lowest concentration of the drug at which there was no visi-

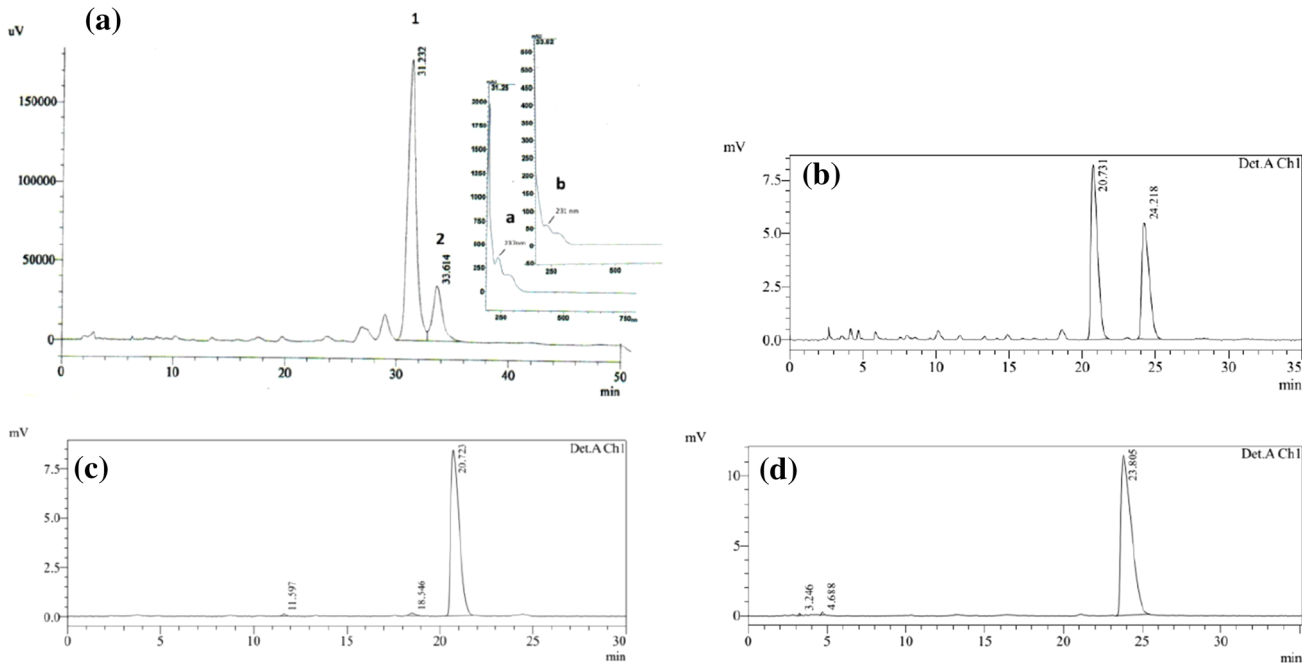


Fig. 3 HPLC chromatograms (**a**) of compound **3**, (**b**) reaction mixture of **4m**:**5m**, (**c**) compound **4m**, and (**d**) compound **5m**

ble growth. The activity of each compound was compared to vancomycin (standard). The inhibitory effects of compounds **4a–r** and **5a–r** against these organisms are summarized in Table 4.

The screening results from Table 4 indicate that some of the compounds exhibited moderate to good antibacterial activity when compared with the standard drug, vancomycin. Among the tested organisms, the compounds showed twofold better activity for Gram-positive bacteria (*B. subtilis and B. megatherium*) than the Gram-negative bacteria (*E. coli* and *S. typhi*). This may be due to their diffusibility nature against the cell wall bacteria. One of the Gram-negative bacteria (*P. aeruginosa*) was resistant to almost all compounds along with the standard drug, vancomycin. Among the newly synthesized compounds, the inhibitory efficiency of compounds **4a** and **4d** with MIC = 125 μg/mL against Gram-negative bacteria, *E. coli*, and compounds **4a**–**4e**, **5d**, and **5e** each having MIC = 31.25 μg/mL against *S. typhi* were comparable to that of the standard drug, vancomycin. Further observation of the data indicated that compound **4e** (MIC = 62.5 μg/mL) showed twofold more potent activity than the standard drug, vancomycin (MIC = 125 μg/mL) against *E. coli*. In general, the resistance to naturally available drugs may be associated with the tough cell wall and spore forming nature of gram-positive organisms. It was observed from Table 4 that the compounds **4a**–**4d**, **4i**, **4j**, and **5c** each having MIC = 125 μg/mL showed equivalent antibacterial activity against *B. subtilis*, compounds **4a**, **4d**, **5d**, **5e**, and **5k** each having MIC = 125 μg/mL against *B. megatherium*, and compounds **5d** and **5e** with MIC = 31.25 μg/mL against *M. luteus* when compared with the standard drug, vancomycin. Besides, the compounds **4e**, **5d**, and **5e** each having MIC = 62.5 μg/mL against *B. subtilis*, compound **4e** (MIC = 62.5 μg/mL) against *B. megatherium* exhibited exceptional activity compared to the standard drug, vancomycin. Compounds **4a** and **4e** showed potent and broad-spectrum antibacterial activity against representatives of both Gram-positive and Gram-negative bacteria except *P. aeruginosa*.

The antibacterial activity results revealed that the title compounds with dimethyl amine, piperidine, and homopiperidine substitutions exhibited promising antibacterial activity compared to other substituted tamoxifen derivatives. In addition, taking the stereochemistry into consideration, *E* isomers **4a**–**r** proved to be more active toward the tested bacterial strains, with respect to *Z* isomers **5a**–**r**. The data from Table 4 indicate that tamoxifen has *in vitro* antibacterial properties against *E. coli*, *B. subtilis*, and *B. megatherium* when compared with the standard drug, vancomycin. Tamoxifen exhibited potent antibacterial activity against *B. megatherium* (MIC = 62.5 μg/mL). Overall, the data from Table 4 suggest that tamoxifen and some of its derivatives may represent attractive new chemical entities (NCEs) for antibacterial drug development.

Conclusions

In summary, we have developed a straightforward synthetic strategy for the preparation of novel tamoxifen scaffolds incorporating a methylene (1*H*-1,2,4-triazole) with good yields. The replacement of a dimethyl amino moiety in

Table 3 Growth inhibition activity of compounds **4a**–**r** and 5a–**r** on five different human cancer cell lines

Compound	Antiproliferative activity (GI_{50} in μM)				
	SiHa	MDA-MB-231	PANC-1	IMR-32	Hep G2
4a	**0.21 ± 0.01**	11.99 ± 0.02	5.44 ± 0.02	7.32 ± 0.01	16.39 ± 0.07
4b	5.19 ± 0.02	7.47 ± 0.01	7.02 ± 0.01	2.61 ± 0.09	6.14 ± 0.08
4c	4.45 ± 0.01	4.81 ± 0.02	**0.41 ± 0.02**	3.21 ± 0.07	3.42 ± 0.06
4d	0.59 ± 0.02	15.96 ± 0.01	5.62 ± 0.01	6.47 ± 0.03	12.43 ± 0.02
4e	3.69 ± 0.03	0.93 ± 0.02	**0.31 ± 0.02**	2.01 ± 0.04	**0.71 ± 0.01**
4f	7.24 ± 0.02	20.53 ± 0.02	3.26 ± 0.01	24.68 ± 0.02	12.68 ± 0.01
4g	3.75 ± 0.01	**0.44 ± 0.03**	1.67 ± 0.03	5.67 ± 0.03	2.45 ± 0.05
4h	0.59 ± 0.02	9.59 ± 0.01	1.51 ± 0.02	5.49 ± 0.08	6.19 ± 0.03
4i	3.50 ± 0.01	**0.51 ± 0.02**	9.41 ± 0.03	6.98 ± 0.06	7.64 ± 0.02
4j	9.15 ± 0.03	14.12 ± 0.01	5.99 ± 0.01	7.54 ± 0.09	12.95 ± 0.07
4k	8.99 ± 0.02	0.59 ± 0.03	4.41 ± 0.02	4.92 ± 0.07	2.87 ± 0.03
4l	5.19 ± 0.01	2.03 ± 0.01	8.37 ± 0.01	6.92 ± 0.07	5.36 ± 0.03
4m	**0.31 ± 0.02**	**0.51 ± 0.01**	**0.61 ± 0.01**	**0.39 ± 0.03**	**0.94 ± 0.01**
4n	3.87 ± 0.01	5.62 ± 0.02	7.49 ± 0.02	6.39 ± 0.09	4.83 ± 0.06
4o	**0.12 ± 0.02**	5.48 ± 0.01	0.49 ± 0.03	2.88 ± 0.01	3.76 ± 0.04
4p	3.34 ± 0.03	**0.23 ± 0.01**	3.13 ± 0.02	3.75 ± 0.06	4.95 ± 0.03
4q	8.35 ± 0.02	5.32 ± 0.02	1.34 ± 0.01	7.95 ± 0.06	4.74 ± 0.02
4r	7.02 ± 0.01	4.17 ± 0.03	0.71 ± 0.02	6.33 ± 0.05	5.11 ± 0.09
5a	3.63 ± 0.02	3.85 ± 0.02	9.71 ± 0.01	8.13 ± 0.03	6.54 ± 0.04
5b	12.48 ± 0.01	4.33 ± 0.01	14.67 ± 0.03	11.84 ± 0.07	9.73 ± 0.06
5c	6.81 ± 0.02	2.73 ± 0.02	5.38 ± 0.02	9.42 ± 0.05	3.58 ± 0.01
5d	3.00 ± 0.01	11.04 ± 0.03	7.27 ± 0.01	16.7 ± 0.04	14.61 ± 0.02
5e	12.79 ± 0.02	18.63 ± 0.02	18.01 ± 0.02	13.42 ± 0.06	10.92 ± 0.03
5f	2.05 ± 0.01	1.53 ± 0.01	5.11 ± 0.03	3.35 ± 0.01	6.75 ± 0.03
5g	2.04 ± 0.03	3.39 ± 0.02	0.73 ± 0.02	4.81 ± 0.09	5.11 ± 0.02
5h	4.13 ± 0.02	1.77 ± 0.01	3.64 ± 0.01	1.58 ± 0.01	8.78 ± 0.02
5i	0.89 ± 0.01	12.41 ± 0.02	11.89 ± 0.02	9.57 ± 0.05	16.42 ± 0.01
5j	11.15 ± 0.02	1.88 ± 0.02	3.81 ± 0.01	6.32 ± 0.08	9.36 ± 0.01
5k	2.12 ± 0.03	2.04 ± 0.03	0.89 ± 0.03	1.45 ± 0.07	0.93 ± 0.03
5l	8.65 ± 0.02	7.10 ± 0.02	3.02 ± 0.02	4.19 ± 0.02	8.37 ± 0.02
5m	1.91 ± 0.02	4.71 ± 0.01	7.66 ± 0.01	5.97 ± 0.05	4.95 ± 0.03
5n	2.07 ± 0.01	5.99 ± 0.02	2.29 ± 0.01	9.74 ± 0.06	11.46 ± 0.01
5o	3.03 ± 0.02	1.63 ± 0.02	4.21 ± 0.03	3.43 ± 0.08	6.25 ± 0.02
5p	12.84 ± 0.01	8.65 ± 0.01	1.77 ± 0.02	3.12 ± 0.01	13.58 ± 0.03
5q	8.68 ± 0.02	9.03 ± 0.02	1.03 ± 0.01	6.31 ± 0.09	7.12 ± 0.01
5r	12.49 ± 0.03	4.57 ± 0.02	1.49 ± 0.02	10.82 ± 0.05	8.94 ± 0.03
Tamoxifen	0.12 ± 0.01	0.24 ± 0.01	0.15 ± 0.02	0.35 ± 0.01	0.54 ± 0.02

Bold value indicates the most potent compounds

tamoxifen by various secondary amines can be used as a tool to prepare novel tamoxifen analogs with high antiproliferative activity. We have also developed a simple, convenient, and effective method for the facile C–N bond formation in aqueous medium. The new tamoxifen analogs **4a**–**r** and **5a**–**r** were designed for evaluation as antiproliferative agents. Compound **4p** bearing a piperonyl piperazine moiety showed a slight increase in activity ($GI_{50} = 0.23\,\mu M$) against breast cancer cell line (MDA-MB-231) compared to tamoxifen. Compound **4o** having a pyrimidyl piperazine group maintained similar activity against SiHa compared to the reference drug, tamoxifen. In addition, all the synthesized compounds were evaluated for their *in vitro* antimicrobial activity and compounds **4a**, **4d**, **4e**, **5d**, and **5e** were found to be promising antibacterial agents.

Table 4 In vitro antibacterial activity of compounds **4a**–**r** and **5a**–**r** on different bacterial strains

Compounds	Antibacterial activity (zone of inhibition in mm and MIC in mg/mL)					
	Gram-positive bacteria			Gram-negative bacteria		
	B. subtilis	*B. megaterium*	*M. luteus*	*E. coli*	*S. typhi*	*P. aeruginosa*
4a	**17** (**125**)	**15** (**125**)	19 (62.5)	16 (125)	23 (31.25)	0
4b	15 (125)	12	17	14	**24** (**31.25**)	0
4c	**17** (**125**)	12	17	14	**25** (**31.25**)	0
4d	**16** (**125**)	**15** (**125**)	16	**17** (**125**)	23 (31.25)	0
4e	**20** (**62.5**)	**18** (**62.5**)	19 (62.5)	**19** (**62.5**)	**25** (**31.25**)	0
4f	12	12	0	13	15	0
4g	11	10	0	11	14	0
4h	0	0	0	0	13	0
4i	15 (125)	0	15	12	21 (62.5)	0
4j	15 (125)	10	17	13	22 (62.5)	0
4k	0	0	0	10	13	0
4l	0	0	0	0	12	0
4m	0	0	0	0	0	0
4n	0	0	0	12	0	0
4o	0	0	0	0	0	0
4p	0	0	0	10	12	0
4q	0	0	11	0	11	0
4r	0	0	0	0	0	0
5a	13	0	12	0	18	0
5b	11	0	0	0	10	0
5c	**16** (**125**)	0	15	0	22 (62.5)	0
5d	**18** (**62.5**)	**14** (**125**)	**21** (**31.25**)	14	**25** (**31.25**)	0
5e	**18** (**62.5**)	**15** (**125**)	**21** (**31.25**)	14	**25** (**31.25**)	0
5f	14	13	16	15	21 (62.5)	0
5g	12	12	16	0	18	0
5h	0	12	13	0	11	0
5i	13	12	17	0	22 (62.5)	0
5j	12	12	17	0	21 (62.5)	0
5k	11	15 (125)	14	0	16	0
5l	0	0	0	0	12	0
5m	0	0	0	0	11	0
5n	0	0	12	0	14	0
5o	0	0	13	0	15	14
5p	0	0	15	0	14	12
5q	0	0	16	0	16	0
5r	0	0	11	0	0	0
DMSO	0	0	0	0	0	0
Tamoxifen	15 (125)	17 (62.5)	20 (125)	17 (125)	18 (125)	0
Vancomycin	16 (125)	14 (125)	22 (31.25)	17 (125)	24 (31.25)	0

The table shows the zone of inhibition in mm and the corresponding MIC values in μg/mL
Bold value indicates the most potent compounds

Experimental

Chemistry

General Information

All chemicals and reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran was dried over Na metal and distilled prior to use. Glassware was oven-dried, assembled while hot, and cooled under an inert atmosphere. Unless otherwise noted, all reactions were conducted in an inert atmosphere. The progress of the reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel glass plate (60 F254, 0.25 mm), and TLC plates were visualized by UV light (254 nm) or I_2 stain. Column chromatography was carried out with Merck 60–120 sized mesh silica gel or aluminum oxide active neutral with 100–300 mesh using ethyl acetate and hexane as an eluent. All products were characterized by their NMR, IR, and HRMS spectra. The ^{1}H NMR spectra were recorded on a Bruker Avance 500 (500 MHz) Nuclear Magnetic Resonance spectrometer or on a Bruker Avance spectrometer (300 MHz), and ^{13}C NMR spectra were recorded on a Bruker Avance 500 (126 MHz) Nuclear Magnetic Resonance spectrometer or on a Bruker Avance spectrometer (75 MHz) taking the compounds in $CDCl_3$ using TMS as an internal standard. The chemical shifts (δ) were reported in parts per million (ppm) downfield from TMS, and the values of coupling constants ^nJ were expressed in Hz. The following abbreviations are used for NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, qd = quartet of doublets, ddd = doublet of doublet of doublets, dqd = doublet of quartet of doublets. IR spectra (KBr) were recorded on a Thermo Nicolet Nexus 670 FTIR Spectrometer (ν in cm^{-1}). HRMS spectra were recorded on a Thermo Scientific Exactive Orbitrap Mass Spectrometer under Electron Spray Ionization conditions preparing sample solution in methanol. Melting points were measured on an Electro thermal 9100 Melting point apparatus and are uncorrected.

Synthetic methods and spectroscopic data

Synthesis of 1-phenyl-2-(1H-1,2,4-triazol-1-yl)ethanone (**1**)
To a cooled solution of 1,2,4-1*H*-triazole (1.52 g, 0.022 mol) and Et_3N (2.02 g, 0.02 mol) in acetone (5 mL) was added dropwise a solution of phenacyl bromide (3.98 g, 0.02 mol) in acetone (10 mL). The reaction mixture was heated to reflux for 6 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, indicated by TLC, the reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure, and the resulting residue was partitioned between EtOAc and H_2O. The aqueous phase was further extracted with EtOAc, and the combined organic phases were successively washed with H_2O, brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, the resulting residue was purified by column chromatography using ethyl acetate/hexane (8:2) as an eluent to get pure compound as a yellow crystalline solid (52 % yield).

M.p. 114–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (s, 1H), 8.10–7.91 (m, 3H), 7.68 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.5 Hz, 2H), 5.69 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.6, 151.9, 144.9, 134.6, 134.0, 129.2, 128.1, 55.1; MS (ESI) 188 ($M+H^+$).

Synthesis of 4-(2-bromoethoxy)benzophenone (**2**)
To a solution of 4-hydroxybenzophenone (5.0 g, 0.025 mol), tetra-n-butyl ammonium iodide (0.37 g, 0.001 mol), and sodium hydroxide (2.0 g, 0.05 mol) in water (15 mL), 1,2-dibromoethane (9.4 g, 0.05) was added. The mixture was heated to reflux and stirred for 18 h. The cooled solution was partitioned between ethyl acetate and water. The organic layer was washed with water, brine, and dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by silica gel chromatography using ethyl acetate/hexane (20:1) as an eluent to give pure compound as a white solid (63 % yield).

M.p. 68–69 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89–7.69 (m, 4H), 7.58 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.4 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 4.38 (t, J = 6.2 Hz, 2H), 3.68 (t, J = 6.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 195.5, 161.7, 138.1, 132.6, 132.4, 132.1, 130.8, 129.8, 128.4, 128.3, 114.2, 67.9, 28.7; MS (ESI) 306 ($M+H^+$).

Synthesis of (E,Z)-1-(3-(4-(2-bromoethoxy)phenyl)-2,3-diphenylallyl)-1H-1,2,4-triazole (**3**)
Zinc powder (1.56 g, 0.024 mol) was suspended in dry THF (10 mL), and the mixture was cooled to −10 °C. $TiCl_4$ (1.32 mL, 0.012 mol) was added dropwise under nitrogen. When the addition was completed, the reaction mixture was heated to reflux for 2 h. A solution of 1-phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone (0.75 g, 0.004 mol) and 4-(2-bromoethoxy) benzophenone (1.22 g, 0.004 mol) in dry THF (10 mL) was added to a cooled suspension of the titanium reagent at 0 °C, and the reaction mixture was heated to reflux for 2.5 h. After cooling to 25 °C, the reaction mixture was poured into a 10 % aqueous K_2CO_3 solution (30 mL), this mixture was stirred vigorously for 15 min, and the dispersed insoluble material was filtered off. The organic fraction was separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic fractions were dried (Na_2SO_4). Removal of the solvent in vacuo gave a residue which was purified by silica gel column chromatography using EtOAc:hexane (1:3) as an eluent to furnish a mixture of the E:Z stereoisomers in a ratio of 3:1 (^{1}H NMR integrals) in 44 % yield (1.0 g), m.p. 125–126 °C. All attempts to separate these stereoisomers by fractional crystallization from

solvents of different polarity (diethyl ether, ethyl acetate, isopropanol, and ethanol) were unsuccessful. Therefore, this mixture was used for a subsequent reaction without further purification.

General procedure for the synthesis of (E & Z)-2-(4-(1,2-diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy) ethyl amines (**4a**–**r** & **5a**–**r**)

The mixture of (*E*) and (*Z*) stereoisomers **3** (0.0005 mol) was added to an appropriate secondary amine (0.001 mol) in water (3 mL). The mixture was heated under reflux for 3 h. After completion of the reaction, indicated by TLC, the reaction mixture was cooled to room temperature. The aqueous phase was extracted with EtOAc (3 × 10 mL), and then the combined organic phases were successively washed with H_2O, brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give the crude product, which was purified by neutral alumina column chromatography using ethyl acetate/hexane (1:4) as an eluent to give the separated (*E*)-(**4a**–**r**) and (*Z*)-(**5a**–**r**) stereoisomers.

(E)-2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)-N,N-dimethyl ethanamine (**4a**)

Yellow oil; IR (KBr) ν/cm^{-1} 3054, 2924, 1605, 1508, 1240, 1137; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.69 (s, 1H), 7.43–7.31 (m, 5H), 7.17–7.03 (m, 5H), 6.85–6.80 (m, 2H), 6.62–6.56 (m, 2H), 5.14 (s, 2H), 3.95 (t, J = 5.7 Hz, 2H), 2.67 (t, J = 5.7 Hz, 2H), 2.30 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.7, 151.7, 145.2, 143.3, 141.8, 139.4, 134.0, 131.9, 131.4, 129.6, 129.5, 128.7, 128.5, 127.8, 127.2, 113.7, 65.7, 58.2, 54.1, 45.8; HRMS (ESI) calcd for $C_{27}H_{29}ON_4$, 425.23341 $[M+H]^+$; found, 425.23339.

(E)-2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)-N,N-diethyl ethanamine (**4b**)

Yellow oil; IR (KBr) ν/cm^{-1} 2924, 1605, 1508, 1245, 1138; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.70 (s, 1H), 7.43–7.31 (m, 5H), 7.18–7.05 (m, 5H), 6.84–6.80 (m, 2H), 6.60–6.55 (m, 2H), 5.14 (s, 2H), 3.92 (t, J = 6.4 Hz, 2H), 2.79 (t, J = 6.4 Hz, 2H), 2.59 (q, J = 7.1 Hz, 4H), 1.02 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.5, 151.7, 145.1, 143.3, 141.8, 139.3, 134.0, 131.9, 131.4, 129.6, 129.5, 128.7, 128.5, 127.8, 127.2, 113.7, 65.9, 54.0, 51.5, 47.8, 11.4; HRMS (ESI) calcd for $C_{29}H_{33}ON_4$, 453.26342 $[M+H]^+$; found, 453.26320.

(E)-1-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)pyrrolidine (**4c**)

Yellow oil; IR (KBr) ν/cm^{-1} 3036, 2930, 1606, 1508, 1246, 1145; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.69 (s, 1H), 7.45–7.29 (m, 5H), 7.19–7.04 (m, 5H), 6.86–6.79 (m, 2H), 6.63–6.55 (m, 2H), 5.14 (s, 2H), 3.98 (t, J = 6.0 Hz, 2H), 2.82 (t, J = 6.0 Hz, 2H), 2.62–2.54 (m, 4H), 1.81–1.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7, 151.7, 145.1, 143.3, 141.8, 139.3, 133.8, 131.9, 131.4, 129.6, 129.5, 128.6, 128.6, 128.5, 127.8, 127.2, 113.7, 66.9, 55.1, 54.8, 54.0, 23.5; HRMS (ESI) calcd for $C_{29}H_{31}ON_4$, 451.24820 $[M+H]^+$; found, 451.24827.

(E)-1-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)piperidine (**4d**)

White crystalline solid, M.p. 155–156 °C; IR (KBr) ν/cm^{-1} 3031, 2924, 1603, 1507, 1247; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.69 (s, 1H), 7.44–7.30 (m, 5H), 7.18–7.04 (m, 5H), 6.82 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 8.8 Hz, 2H), 5.14 (s, 2H), 3.99 (t, J = 6.0 Hz, 2H), 2.71 (t, J = 6.0 Hz, 2H), 2.48 (s, 4H), 1.62–1.54 (m, 4H), 1.43 (d, J = 5.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.7, 151.7, 145.2, 143.3, 141.8, 139.4, 133.9, 131.9, 131.4, 129.6, 129.5, 128.7, 128.5, 127.8, 127.2, 113.7, 65.7, 57.9, 55.1, 54.1, 25.9, 24.2; HRMS (ESI) calcd for $C_{30}H_{33}ON_4$, 465.26400 $[M+H]^+$; found, 465.26403.

(E)-1-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)azepane (**4e**)

Yellow oil; IR (KBr) ν/cm^{-1} 3050, 2933, 1605, 1508, 1247, 1142; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.69 (s, 1H), 7.46–7.29 (m, 5H), 7.12 (tt, J = 7.8, 4.3 Hz, 5H), 6.82 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 8.8 Hz, 2H), 5.14 (s, 2H), 3.94 (t, J = 6.2 Hz, 2H), 2.87 (t, J = 6.2 Hz, 2H), 2.78–2.65 (m, 4H), 1.58 (s, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 151.7, 145.1, 143.3, 141.8, 139.4, 133.8, 131.9, 131.3, 129.6, 129.5, 128.6, 128.5, 127.8, 127.2, 113.7, 66.3, 56.3, 55.9, 54.0, 27.9, 27.1; HRMS (ESI) calcd for $C_{31}H_{35}ON_4$, 479.27858 $[M+H]^+$; found, 479.27863.

(E)-4-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)morpholine (**4f**)

White solid, M.p. 105–106 °C; IR (KBr) ν/cm^{-1} 3035, 2931, 1604, 1507, 1245, 1145; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.69 (s, 1H), 7.44–7.31 (m, 5H), 7.19–7.04 (m, 5H), 6.83 (d, J = 8.7 Hz, 2H), 6.58 (d, J = 8.7 Hz, 2H), 5.14 (s, 2H), 3.98 (t, J = 5.7 Hz, 2H), 3.73–3.67 (m, 4H), 2.72 (t, J = 5.7 Hz, 2H), 2.53 (d, J = 4.1 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.5, 151.7, 145.0, 143.3, 141.7, 139.3, 134.0, 131.9, 131.5, 129.6, 129.5, 128.6, 128.5, 127.8, 127.2, 113.7, 66.9, 65.6, 57.6, 54.1, 54.0; HRMS (ESI) calcd for $C_{29}H_{31}ON_4$, 467.24432 $[M+H]^+$; found, 467.24442.

(E)-4-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)-2,6-dimethylmorpholine (**4g**)

Yellow oil; IR (KBr) ν/cm^{-1} 2972, 1606, 1508, 1245, 1140; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.69 (s, 1H), 7.43–7.32 (m, 5H), 7.17–7.02 (m, 5H), 6.86–6.81 (m, 2H), 6.60–6.56 (m, 2H), 5.14 (s, 2H), 3.98 (t, J = 5.8 Hz, 2H), 3.68 (dqd, J = 12.5, 6.3, 2.0 Hz, 2H), 2.77 (t, J = 9.1 Hz, 2H), 2.73–2.68 (m, 2H), 1.88–1.80 (m, 2H), 1.14 (d, J = 6.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.6, 151.7, 145.0, 143.3, 141.7, 139.3, 134.0, 131.9, 131.5, 130.9, 130.6, 129.6, 129.5, 128.6, 128.5, 127.8, 127.2, 113.7, 71.6, 65.5, 59.8, 57.2, 54.0, 19.2; HRMS (ESI) calcd for $C_{31}H_{35}O_2N_4$, 495.27360 $[M + H]^+$; found, 495.27353.

(E)-4-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)thiomorpholine (**4h**)

White crystalline solid, M.p. 166–167 °C; IR (KBr) ν/cm^{-1} 3033, 2930, 1601, 1505, 1242, 1139; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.69 (s, 1H), 7.42–7.31 (m, 5H), 7.18–7.05 (m, 5H), 6.86–6.80 (m, 2H), 6.60–6.54 (m, 2H), 5.14 (s, 2H), 3.95 (t, J = 5.8 Hz, 2H), 2.80 (dd, J = 6.1, 3.9 Hz, 4H), 2.76 (t, J = 5.8 Hz, 2H), 2.67–2.63 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5, 151.7, 145.0, 143.3, 141.7, 139.3, 134.0, 131.9, 131.4, 129.6, 129.5, 128.6, 128.5, 127.8, 127.2, 113.7, 65.5, 57.9, 55.3, 54.0, 27.9; HRMS (ESI) calcd for $C_{29}H_{31}ON_4S$, 483.21801 $[M+H]^+$; found, 483.21836.

(E)-1-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)-4-methylpiperazine (**4i**)

Yellow crystalline solid, M.p. 165–166 °C; IR (KBr) ν/cm^{-1} 3052, 2935, 1607, 1509, 1241, 1155; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.69 (s, 1H), 7.43–7.30 (m, 5H), 7.17–7.05 (m, 5H), 6.85–6.80 (m, 2H), 6.60–6.55 (m, 2H), 5.14 (s, 2H), 3.97 (t, J = 5.8 Hz, 2H), 2.74 (t, J = 5.8 Hz, 2H), 2.65–2.35 (m, 8H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.7, 151.7, 145.1, 143.3, 141.8, 139.4, 134.0, 131.9, 131.4, 129.6, 129.5, 128.7, 128.5, 127.8, 127.2, 113.7, 65.8, 57.2, 55.0, 54.0, 53.6, 46.0; HRMS (ESI) calcd for $C_{30}H_{34}ON_5$, 480.27404 $[M+H]^+$; found, 480.27395.

(E)-1-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)-4-ethylpiperazine (**4j**)

Yellow oil; IR (KBr) ν/cm^{-1} 3055, 2942, 1606, 1508, 1237, 1144; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.69 (s, 1H), 7.44–7.30 (m, 5H), 7.12 (qd, J = 8.2, 4.2 Hz, 5H), 6.83 (d, J = 8.7 Hz, 2H), 6.57 (d, J = 8.8 Hz, 2H), 5.14 (s, 2H), 3.98 (t, J = 5.8 Hz, 2H), 2.81–2.31 (m, 12H), 1.13–1.01 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.6, 151.7, 145.0, 143.3, 141.7, 139.3, 133.9, 131.8, 131.4, 129.5, 129.5, 128.6, 128.5, 127.7, 127.2, 113.7, 65.7, 57.1, 54.0, 53.6, 52.7, 52.3, 12.0; HRMS (ESI) calcd for $C_{31}H_{36}ON_5$, 494.28999 $[M+H]^+$; found, 494.28997.

(E)-1-(4-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl) piperazin-1-yl)ethanone (**4k**)

Yellow oil; IR (KBr) ν/cm^{-1} 2926, 1607, 1508, 1244, 1138; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.69 (s, 1H), 7.46–7.31 (m, 5H), 7.19–7.03 (m, 5H), 6.87–6.80 (m, 2H), 6.61–6.54 (m, 2H), 5.14 (s, 2H), 3.98 (t, J = 5.6 Hz, 2H), 3.67–3.56 (m, 2H), 3.49–3.39 (m, 2H), 2.75 (t, J = 5.5 Hz, 2H), 2.58–2.44 (m, 4H), 2.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.9, 157.5, 151.7, 145.0, 143.3, 141.7, 139.3, 134.1, 131.9, 131.6, 129.6, 129.5, 128.6, 128.5, 127.8, 127.2, 113.7, 65.7, 57.1, 54.0, 53.7, 53.2, 46.3, 41.4, 21.3; HRMS (ESI) calcd for $C_{31}H_{34}O_2N_5$, 508.26905 $[M+H]^+$; found, 508.26892.

(E)-(4-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl) piperazin-1-yl)(furan-2-yl) methanone (**4l**)

Yellow oil; IR (KBr) ν/cm^{-1} 3056, 2925, 1508, 1244, 1138; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.69 (s, 1H), 7.49–7.45 (m, 1H), 7.43–7.31 (m, 5H), 7.17–7.05 (m, 5H), 6.98 (d, J = 3.5 Hz, 1H), 6.84 (d, J = 8.6 Hz, 2H), 6.58 (d, J = 8.7 Hz, 2H), 6.48–6.45 (m, 1H), 5.14 (s, 2H), 3.99 (t, J = 5.5 Hz, 2H), 3.80 (s, 4H), 2.77 (t, J = 5.5 Hz, 2H), 2.63–2.54 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.1, 157.5, 151.7, 148.0, 145.0, 143.7, 143.4, 141.7, 139.3, 134.2, 131.9, 131.6, 129.6, 129.5, 128.7, 128.5, 127.8, 127.2, 116.5, 113.7, 111.3, 65.7, 57.1, 54.0; HRMS (ESI) calcd for $C_{34}H_{34}O_3N_5$, 560.26467 $[M+H]^+$; found, 560.26470.

(E)-1-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)-4-phenylpiperazine (**4m**)

Yellow oil; IR (KBr) ν/cm^{-1} 3057, 2931, 1601, 1503, 1241, 1141; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.69 (s, 1H), 7.44–7.31 (m, 5H), 7.29–7.23 (m, 3H), 7.18–7.05 (m, 5H), 6.92 (d, J = 8.3 Hz, 2H), 6.88–6.81 (m, 3H), 6.60 (t, J = 5.7 Hz, 2H), 5.14 (s, 2H), 4.03 (t, J = 5.7 Hz, 2H), 3.23–3.16 (m, 4H), 2.80 (t, J = 5.7 Hz, 2H), 2.74–2.66 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.6, 151.8, 151.3, 145.1, 143.4, 141.8, 139.4, 134.1, 131.9, 131.5, 129.6, 129.5, 129.2, 128.7, 128.6, 127.8, 127.3, 119.9, 116.2, 113.8, 65.8, 57.3, 54.1, 53.7, 49.2; HRMS (ESI) calcd for $C_{35}H_{36}ON_5$, 542.29135 $[M+H]^+$; found, 542.29135.

(E)-1-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)-4-(pyridin-2-yl)piperazine (**4n**)

Yellow oil; IR (KBr) ν/cm^{-1} 3054, 2925, 1595, 1505, 1244, 1139;^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (ddd, J = 4.9, 1.9, 0.7 Hz, 1H), 7.87 (s, 1H), 7.68 (s, 1H), 7.49–7.31 (m, 6H), 7.18–7.05 (m, 5H), 6.87–6.81 (m, 2H), 6.65–6.56 (m, 4H), 5.14 (s, 2H), 4.02 (t, J = 5.7 Hz, 2H), 3.56–3.51 (m, 4H), 2.78 (t, J = 5.7 Hz, 2H), 2.67–2.61 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 159.5, 157.6, 151.7, 148.0, 145.0, 143.3, 141.7, 139.3, 137.5, 134.0, 131.9, 131.5, 129.5, 129.5, 128.6, 128.5, 127.7, 127.2, 113.7, 113.3, 107.1, 65.7, 57.3, 54.0, 53.4, 45.1; HRMS (ESI) calcd for $C_{34}H_{35}ON_6$, 543.28671 $[M+H]^+$; found, 543.28718.

(E)-2-(4-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl) prop-1-en-1-yl)phenoxy)ethyl) piperazin-1-yl)pyrimidine (**4o**)

Yellow oil; IR (KBr) ν/cm^{-1} 2926, 1585, 1505, 1245, 1139; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (d, J = 4.7 Hz, 2H), 7.87 (s, 1H), 7.69 (s, 1H), 7.45–7.31 (m, 5H), 7.18–7.05 (m, 5H), 6.87–6.80 (m, 2H), 6.63–6.56 (m, 2H), 6.48 (t, J = 4.7 Hz, 1H), 5.15 (s, 2H), 4.03 (t, J = 5.7 Hz, 2H), 3.88–3.78 (m, 4H), 2.79 (t, J = 5.7 Hz, 2H), 2.65–2.56 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.6, 157.7, 157.5, 151.6, 145.0, 143.3, 141.7, 139.3, 134.0, 131.8, 131.4, 129.5, 129.5, 128.6, 128.5, 127.7, 127.2, 113.7, 109.9, 65.6, 57.3, 54.0, 53.5, 43.6; HRMS (ESI) calcd for $C_{33}H_{34}ON_7$, 544.28159 $[M+H]^+$; found, 544.28161.

(E)-1-(Benzo[d][1,3]dioxol-5-ylmethyl)-4-(2-(4-(1,2-diphenyl-3-(1H-1,2,4-triazol-1-yl) prop-1-en-1-yl)phenoxy) ethyl)piperazine (**4p**)

Yellow oil; IR (KBr) ν/cm^{-1} 2927, 1605, 1505, 1244, 1138; ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.69 (s, 1H), 7.42–7.31 (m, 5H), 7.17–7.04 (m, 4H), 6.86–6.79 (m, 3H), 6.74 (d, J = 7.6 Hz, 3H), 6.56 (d, J = 8.8 Hz, 2H), 5.94 (d, J = 10.5 Hz, 2H), 5.14 (s, 2H), 3.97 (t, J = 5.8 Hz, 2H), 3.43–3.37 (m, 2H), 2.74 (t, J = 5.8 Hz, 2H), 2.66–2.31 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.6, 151.7, 147.6, 146.6, 145.1, 143.3, 141.7, 139.3, 133.9, 131.8, 131.4, 129.5, 129.5, 128.6, 128.5, 127.7, 127.2, 122.3, 113.7, 109.6, 107.9, 100.9, 65.6, 62.7, 57.1, 54.0, 53.6, 52.8; HRMS (ESI) calcd for $C_{37}H_{38}O_3N_5$, 600.29795 $[M+H]^+$; found, 600.29780.

(E)-1-Benzyl-4-(2-(4-(1,2-diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy) ethyl)piperazine (**4q**)

Yellow oil; IR (KBr) ν/cm^{-1} 3027, 2935, 1604, 1504, 1243, 1139; ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.69 (s, 1H), 7.42–7.21 (m, 11H), 7.16–7.05 (m, 5H), 6.85–6.78 (m, 2H), 6.59–6.53 (m, 2H), 5.14 (s, 2H), 3.96 (t, J = 5.9 Hz, 2H), 3.50 (s, 2H), 2.73 (t, J = 5.9 Hz, 2H), 2.65–2.39 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$): δ157.6, 151.7, 145.1, 143.3, 141.8, 139.3, 138.0, 133.9, 131.9, 131.4, 129.6, 129.5, 129.3, 128.6, 128.5, 128.3, 127.8, 127.2, 127.1, 113.7, 65.7, 63.1, 57.2, 54.0, 53.6, 53.0; HRMS (ESI) calcd for $C_{36}H_{38}ON_5$, 556.30799 $[M+H]^+$; found, 556.30779.

(E)-1-Benzhydryl-4-(2-(4-(1,2-diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)piperazine (**4r**)

White solid, M.p. 166–167 °C; IR (KBr) ν/cm^{-1} 3026, 2959, 1603, 1504, 1252, 1137; ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.69 (s, 1H), 7.43–7.30 (m, 9H), 7.28–7.22 (m, 5H), 7.19–7.03 (m, 7H), 6.84–6.78 (m, 2H), 6.58–6.52 (m, 2H), 5.13 (s, 2H), 4.20 (s, 1H), 3.96 (t, J = 5.9 Hz, 2H), 2.73 (t, J = 5.8 Hz, 2H), 2.66–2.24 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.7, 151.7, 145.1, 143.3, 142.8, 141.8, 139.4, 133.9, 131.9, 131.4, 129.6, 129.5, 128.7, 128.5, 128.0, 127.8, 127.2, 127.0, 113.7, 76.3, 65.8, 57.2, 54.1, 54.0, 51.9; HRMS (ESI) calcd for $C_{42}H_{42}ON_5$, 632.33720 $[M+H]^+$; found, 632.33729.

(Z)-2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)-N,N-dimethylethanamine (**5a**)

Yellow oil; IR (KBr) ν/cm^{-1} 2924, 1606, 1508, 1243, 1142; ^1H NMR (300 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.71 (s, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.15–7.00 (m, 8H), 6.93 (d, J = 8.5 Hz, 4H), 5.21 (s, 2H), 4.11 (t, J = 5.7 Hz, 2H), 2.78 (t, J = 5.6 Hz, 2H), 2.37 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.4, 151.7, 145.4, 143.4, 141.9, 139.3, 134.0, 132.0, 130.9, 130.6, 129.5, 128.4, 127.7, 127.2, 126.9, 114.6, 65.7, 58.0, 54.1, 45.6; HRMS (ESI) calcd for $C_{27}H_{29}ON_4$, 425.23167 $[M+H]^+$; found, 425.23188.

(Z)-2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)-N,N-diethyl ethanamine (**5b**)

Yellow oil; IR (KBr) ν/cm^{-1} 3053, 2925, 1606, 1507, 1245, 1138; ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, J = 3.9 Hz, 1H), 7.71 (s, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.18–6.99 (m, 10H), 6.96–6.89 (m, 4H), 5.21 (s, 2H), 4.07 (t, J = 6.3 Hz, 2H), 2.90 (t, J = 6.3 Hz, 2H), 2.66 (q, J = 7.1 Hz, 4H), 1.08 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.35, 151.75, 145.37, 143.40, 141.91, 139.29, 134.01, 132.00, 130.95, 130.66, 129.53, 128.45, 127.69, 127.26, 126.94, 114.57, 66.06, 54.09, 51.60, 47.76, 11.46; HRMS (ESI) calcd for $C_{29}H_{33}ON_4$, 453.26318 $[M+H]^+$; found, 453.26290.

(Z)-1-(2-(4-(1,2-diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)pyrrolidine (**5c**)

Yellow oil; IR (KBr) ν/cm^{-1} 3053, 2928, 1606, 1508, 1244, 1138; ^1H NMR (500 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.71 (s, 1H), 7.34 (d, J = 8.6 Hz, 2H), 7.15–7.02 (m, 8H), 6.97–6.89 (m, 4H), 5.20 (s, 2H), 4.15 (t, J = 5.6 Hz, 2H), 2.88–2.88 (m, 2H), 2.63–2.48 (s, 4H), 1.70–1.57 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.0, 151.7, 145.3, 143.4, 141.9, 139.3, 132.1, 131.0, 130.6, 129.5, 128.4, 127.7, 127.3, 127.0, 114.6, 54.7, 54.6, 54.1, 23.5; HRMS (ESI) calcd for $C_{29}H_{31}ON_4$, 451.24741 $[M+H]^+$; found, 451.24743.

(Z)-1-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)piperidine (**5d**)

Yellow oil; IR (KBr) ν/cm^{-1} 2924, 1605, 1503, 1244, 1137; ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.71 (s, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.13–7.00 (m, 8H), 6.93 (dd, J = 9.1, 4.3 Hz, 4H), 5.20 (s, 2H), 4.14 (t, J = 6.0 Hz, 2H), 2.80 (t, J = 6.0 Hz, 2H), 2.54 (s, 4H), 1.68–1.56 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.5, 151.8, 145.4, 143.4, 141.9, 139.3, 134.0, 132.0, 130.9, 130.7, 129.6, 128.4, 127.7, 127.3, 126.9, 114.7, 65.9, 57.9, 55.1, 54.1, 25.8, 24.1; HRMS (ESI) calcd for $C_{30}H_{33}ON_4$, 465.26585 $[M+H]^+$; found, 465.26568.

(Z)-1-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl) azepane (**5e**)

Yellow oil; IR (KBr) ν/cm^{-1} 3056, 2923, 1607, 1509, 1247, 1137; ^1H NMR (500 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.71 (s, 1H), 7.36–7.31 (m, 2H), 7.14–7.02 (m, 8H), 6.95–6.90 (m, 4H), 5.21 (s, 2H), 4.09 (t, J = 6.2 Hz, 2H), 2.97 (t, J = 6.2 Hz, 2H), 2.82–2.76 (m, 4H), 1.67 (s, 4H), 1.63–1.58 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.6, 151.7, 145.4, 143.4, 141.9, 139.3, 133.8, 132.0, 130.9, 130.6, 129.5, 128.4, 127.7, 127.2, 126.9, 114.6, 66.5, 56.4, 55.9, 54.1, 27.9, 27.1; HRMS (ESI) calcd for $C_{31}H_{35}ON_4$, 479.27940 $[M+H]^+$; found, 479.27936.

(Z)-4-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)morpholine (**5f**)

White solid, M.p. 129–130 °C; IR (KBr) ν/cm^{-1} 3036, 2929, 1606, 1508, 1243, 1137; ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.70 (s, 1H), 7.35 (d, J = 8.6 Hz, 2H), 7.09 (dd, J = 12.8, 7.8 Hz, 8H), 6.92 (d, J = 8.6 Hz, 4H), 5.20 (s, 2H), 4.13 (t, J = 5.6 Hz, 2H), 3.79–3.70 (m, 4H), 2.82

(t, J = 5.6 Hz, 2H), 2.65–2.54 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.4, 151.8, 145.3, 143.4, 141.9, 139.3, 134.0, 132.0, 130.9, 130.6, 129.5, 128.4, 127.7, 127.2, 126.9, 114.6, 67.0, 65.8, 57.7, 54.2, 54.1; HRMS (ESI) calcd for $C_{29}H_{31}ON_4$, 467.24442 $[M+H]^+$; found, 467.24480.

(Z)-4-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)-2,6-dimethylmorpholine **(5g)**

Yellow oil; IR (KBr) ν/cm^{-1} 2932, 1607, 1508, 1244, 1141; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.71 (s, 1H), 7.35 (d, J = 8.6 Hz, 2H), 7.16–6.99 (m, 8H), 6.97–6.87 (m, 4H), 5.21 (s, 2H), 4.13 (t, J = 5.7 Hz, 2H), 3.81–3.64 (m, 2H), 2.82 (dd, J = 14.8, 8.9 Hz, 4H), 1.90 (t, J = 10.8 Hz, 2H), 1.17 (d, J = 6.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.4, 151.8, 145.4, 143.4, 141.9, 139.3, 134.0, 132.0, 130.9, 130.6, 129.5, 128.4, 127.7, 127.3, 126.9, 114.6, 71.6, 65.7, 59.9, 57.3, 54.1, 19.3; HRMS (ESI) calcd for $C_{31}H_{35}O_2N_4$, 495.27357 $[M+H]^+$; found, 495.27378.

(Z)-4-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)thiomorpholine **(5h)**

White solid, M.p. 135–136 °C; IR (KBr) ν/cm^{-1} 3035, 2921, 1607, 1508, 1242, 1136; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.70 (s, 1H), 7.35 (d, J = 8.6 Hz, 2H), 7.08 (dd, J = 19.0, 4.9 Hz, 8H), 6.93 (dd, J = 9.9, 5.7 Hz, 4H), 5.20 (s, 2H), 4.11 (t, J = 5.6 Hz, 2H), 2.86 (s, 6H), 2.75–2.66 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.4, 151.8, 145.4, 143.4, 141.9, 139.3, 134.1, 132.0, 130.9, 130.6, 129.5, 128.4, 127.7, 127.3, 126.9, 114.6, 65.8, 58.0, 55.4, 54.1, 28.0; HRMS (ESI) calcd for $C_{29}H_{31}ON_4S$, 483.22230 $[M+H]^+$; found, 483.22226.

(Z)-1-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)-4-methylpiperazine **(5i)**

Yellow solid, M.p. 135–136 °C; IR (KBr) ν/cm^{-1} 2927, 1609, 1506, 1245, 1169; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.71 (s, 1H), 7.36–7.32 (m, 2H), 7.14–7.01 (m, 8H), 6.95–6.89 (m, 4H), 5.20 (s, 2H), 4.15–4.10 (m, 2H), 2.85 (t, J = 5.7 Hz, 2H), 2.77–2.51 (m, 8H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 151.6, 145.3, 143.3, 141.8, 139.2, 134.0, 131.9, 130.9, 130.6, 129.5, 128.4, 127.6, 127.2, 126.9, 114.5, 65.7, 56.9, 54.3, 54.0, 52.7, 45.2; HRMS (ESI) calcd for $C_{30}H_{34}ON_5$, 480.27390 $[M+H]^+$; found, 480.27384.

(Z)-1-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)-4-ethylpiperazine **(5j)**

Yellow oil; IR (KBr) ν/cm^{-1} 2929, 1606, 1508, 1245, 1138; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.71 (s, 1H), 7.34 (d, J = 8.6 Hz, 2H), 7.17–7.00 (m, 8H), 6.93 (t, J = 6.8 Hz, 4H), 5.20 (s, 2H), 4.13 (t, J = 5.7 Hz, 2H), 2.91–2.33 (m, 12H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.4, 151.7, 145.4, 143.4, 141.9, 139.3, 133.9, 132.0, 130.9, 130.6, 129.5, 128.4, 127.7, 127.2, 126.9, 114.6, 65.9, 57.2, 54.1, 53.5, 52.7, 52.3, 11.9; HRMS (ESI) calcd for $C_{31}H_{36}ON_5$, 494.28996 $[M+H]^+$; found, 494.28983.

(Z)-1-(4-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl) piperazin-1-yl)ethanone **(5k)**

Yellow crystalline solid, M.p. 167–168 °C; IR (KBr) ν/cm^{-1} 3055, 2921, 1508, 1246, 1138; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.70 (s, 1H), 7.38–7.32 (m, 2H), 7.14–7.02 (m, 8H), 6.96–6.89 (m, 4H), 5.20 (s, 2H), 4.13 (t, J = 5.5 Hz, 2H), 3.68–3.62 (m, 2H), 3.52–3.46 (m, 2H), 2.85 (t, J = 5.5 Hz, 2H), 2.62–2.53 (m, 4H), 2.09 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.0, 158.3, 151.8, 145.3, 143.4, 141.9, 139.3, 134.1, 132.1, 130.9, 130.6, 129.5, 128.4, 127.7, 127.3, 126.9, 114.6, 65.9, 57.2, 54.1, 53.7, 53.2, 46.3, 41.4, 21.4; HRMS (ESI) calcd for $C_{31}H_{34}O_2N_5$, 508.26889 $[M+H]^+$; found, 508.26919.

(Z)-(4-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)piperazin-1-yl)(furan-2-yl) methanone **5l**)

Yellow oil; IR (KBr) ν/cm^{-1} 2924, 1605, 1508, 1243, 1138; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.70 (s, 1H), 7.48 (t, J = 2.6 Hz, 1H), 7.37–7.33 (m, 2H), 7.15–7.02 (m, 8H), 7.01–6.99 (m, 1H), 6.96–6.90 (m, 4H), 6.48 (dd, J = 3.4, 1.8 Hz, 1H), 5.20 (s, 2H), 4.15 (t, J = 5.5 Hz, 2H), 3.91–3.79 (m, 4H), 2.88 (t, J = 5.5 Hz, 2H), 2.70–2.64 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 151.7, 148.0, 145.3, 143.7, 143.4, 141.9, 139.3, 134.1, 132.1, 131.0, 130.6, 129.5, 128.4, 127.7, 127.3, 126.9, 116.5, 114.6, 111.3, 65.9, 57.2, 54.1; HRMS (ESI) calcd for $C_{34}H_{34}O_3N_5$, 560.26318 $[M+H]^+$; found, 560.26253.

(Z)-1-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)-4-phenylpiperazine **(5m)**

Yellow oil; IR (KBr) ν/cm^{-1} 3040, 2922, 1600, 1507, 1239, 1150; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.71 (s, 1H), 7.35 (d, J = 8.7 Hz, 2H), 7.30–7.23 (m, 4H), 7.14–7.01 (m, 7H), 6.94 (d, J = 7.7 Hz, 6H), 6.86 (t, J = 7.3 Hz, 1H), 5.21 (s, 2H), 4.18 (t, J = 5.7 Hz, 2H), 3.26–3.21 (m, 4H), 2.90 (t, J = 5.6 Hz, 2H), 2.81–2.73 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.4, 151.8, 151.3, 145.4, 143.4, 141.9, 139.3, 134.0, 132.1, 130.9, 130.6, 129.5, 129.2, 128.4, 127.7, 127.3, 126.9, 119.8, 116.2, 114.7, 66.0, 57.3, 54.1, 53.8, 49.2; HRMS (ESI) calcd for $C_{35}H_{36}ON_5$, 542.29166 $[M+H]^+$; found, 542.29176.

(Z)-1-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)-4-(pyridin-2-yl)piperazine **(5n)**

White solid, M.p. 135–136 °C; IR (KBr) ν/cm^{-1} 2923, 1599, 1507, 1243, 1150; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (dd, J = 4.9, 1.2 Hz, 1H), 7.88 (s, 1H), 7.70 (s, 1H), 7.48 (ddd, J = 8.9, 7.2, 2.0 Hz, 1H), 7.37–7.33 (m, 2H), 7.14–7.02 (m, 8H), 6.96–6.91 (m, 4H), 6.67–6.61 (m, 2H), 5.20 (s, 2H), 4.19 (t, J = 5.5 Hz, 2H), 3.60 (s, 4H), 2.91 (t, J = 5.4 Hz, 2H), 2.74 (s, 4H);^{13}C NMR (126 MHz, $CDCl_3$): δ 159.6, 158.4, 151.8, 148.0, 145.4, 143.4, 141.9, 139.3, 137.5, 134.0, 132.0, 130.9, 130.6, 129.5, 128.4, 127.7, 127.2, 126.9, 114.6, 113.4, 107.1, 66.0, 57.4, 54.1, 53.5, 45.2; HRMS

(ESI) calcd for $C_{34}H_{35}ON_6$, 543.28634 $[M+H]^+$; found, 543.28658.

(Z)-2-(4-(2-(4-(1,2-Diphenyl-3-(1H-1,2,4-triazol-1-yl) prop-1-en-1-yl)phenoxy)ethyl) piperazin-1-yl)pyrimidine (**5o**)

Yellow oil; IR (KBr) ν/cm^{-1} 3031, 1588, 1506, 1245, 1149; ^1H NMR (300 MHz, $CDCl_3$): δ 8.32 (t, J = 5.9 Hz, 2H), 7.89 (s, 1H), 7.71 (s, 1H), 7.37 (t, J = 7.9 Hz, 2H), 7.16–7.01(m, 8H), 6.99–6.89 (m, 4H), 6.48 (t, J = 4.7 Hz, 1H), 5.21 (s, 2H), 4.17 (t, J = 5.7 Hz, 2H), 3.92–3.82 (m, 4H), 2.88 (t, J = 5.7 Hz, 2H), 2.71–2.61 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.7, 158.4, 157.8, 151.7, 145.3, 143.4, 141.9, 139.3, 134.0, 132.1, 130.9, 130.6, 129.6, 129.5, 128.4, 127.7, 127.2, 126.9, 114.6, 109.9, 65.9, 57.4, 54.1, 53.6, 43.7; HRMS (ESI) calcd for $C_{33}H_{34}ON_7$, 544.28177 $[M+H]^+$; found, 544.28179.

(Z)-1-(Benzo[d][1,3]dioxol-5-ylmethyl)-4-(2-(4-(1,2-diphenyl-3-(1H-1,2,4-triazol-1-yl) prop-1-en-1-yl)phenoxy) ethyl)piperazine (**5p**)

Yellow oil; IR (KBr) ν/cm^{-1} 2923, 1605, 1505, 1244, 1138; ^1H NMR (500 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.71 (s, 1H), 7.37–7.31 (m, 2H), 7.15–7.01 (m, 8H), 6.96–6.88 (m, 4H), 6.85 (d, J = 6.0 Hz, 1H), 6.78–6.70 (m, 2H), 5.96–5.92 (m, 2H), 5.20 (s, 2H), 4.13 (q, J = 6.0 Hz, 2H), 3.44 (d, J = 4.1 Hz, 2H), 2.85 (t, J = 5.7 Hz, 2H), 2.76–2.40 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.4, 151.8, 147.7, 146.7, 145.4, 143.4, 141.9, 139.3, 134.0, 132.0, 130.9, 130.6, 129.5, 128.4, 127.7, 127.2, 126.9, 122.4, 114.6, 109.7, 108.0, 101.0, 65.9, 62.8, 57.2, 54.1, 53.6, 52.8; HRMS (ESI) calcd for $C_{37}H_{38}O_3N_5$, 600.29795 $[M+H]^+$; found, 600.29774.

(Z)-1-Benzyl-4-(2-(4-(1,2-diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy) ethyl)piperazine (**5q**)

Yellow oil; IR (KBr) ν/cm^{-1} 3029, 2934, 1603, 1504, 1244, 1136; ^1H NMR (500 MHz,$CDCl_3$): δ 7.88 (s, 1H), 7.71 (s, 1H), 7.35–7.29 (m, 6H), 7.14–7.00 (m, 9H), 6.95–6.88 (m, 4H), 5.20 (s, 2H), 4.12 (t, J = 5.8 Hz, 2H), 3.53 (s, 2H), 2.84 (t, J = 5.8 Hz, 2H), 2.76–2.42 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.4, 151.8, 145.4, 143.4, 141.9, 139.3, 138.0, 133.9, 132.0, 130.9, 130.6, 129.5, 129.3, 128.4, 128.3, 127.7, 127.2, 127.2, 126.9, 114.6, 65.9, 63.1, 57.2, 54.1, 53.7, 53.0; HRMS (ESI) calcd for $C_{36}H_{38}ON_5$, 556.30793 $[M+H]^+$; found, 556.30775.

(Z)-1-Benzhydryl-4-(2-(4-(1,2-diphenyl-3-(1H-1,2,4-triazol-1-yl)prop-1-en-1-yl)phenoxy)ethyl)piperazine (**5r**)

White solid, M.p. 201–202 °C; IR (KBr) ν/cm^{-1} 3025, 2961, 1604, 1507, 1249, 1136; ^1H NMR (500 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.70 (s, 1H), 7.41 (d, J = 7.7 Hz, 4H), 7.33 (d, J = 8.4 Hz, 2H), 7.29–7.24 (m, 7H), 7.17 (t, J = 7.3 Hz, 2H), 7.13–7.07 (m, 2H), 7.03 (t, J = 4.1 Hz, 4H), 6.95–6.86 (m, 4H), 5.19 (s, 2H), 4.22 (s, 1H), 4.14–4.08 (m, 2H), 2.83 (s, 2H), 2.72–2.34 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.4, 151.8, 145.4, 143.4, 142.8, 141.9, 139.3, 134.0, 132.0, 130.9, 130.6, 129.5, 128.6, 128.4, 128.0, 127.7, 127.2, 127.0, 126.9, 114.6, 76.3, 66.0, 57.2, 54.1, 54.0, 51.9; HRMS (ESI) calcd for $C_{42}H_{42}ON_5$, 632.33770 $[M+H]^+$; found, 632.33769.

*X-ray crystallographic data of compounds **4h**, **4i** and **5k***

Crystal data for compound 4h $C_{29}H_{30}N_4OS$, M = 482.63, colorless block, 0.42 × 0.40 × 0.31 mm^3, monoclinic, space group *Pc* (No. 7), a = 8.8130(4) Å, b = 15.0717(8) Å, c = 10.3342(5) Å, β = 112.0480(10)°, V = 1272.28(11) $Å^3$, Z = 2, D_c = 1.260 g/cm^3, F_{000} = 512, λ = 0.71073 Å, CCD area detector, Mo K α radiation, T = 293(2)K, $2\theta_{max}$ = 50.0°, 12,027 reflections collected, 4461 unique (R_{int} = 0.0204), final *GooF* = 1.046, R1 = 0.0283, wR2 = 0.0738, R indices based on 4344 reflections with I > 2σ(I) (refinement on F^2), 316 parameters, μ = 0.156 mm^{-1}, CCDC number 1028923.

*Crystal data for compound **4i*** $C_{30}H_{33}N_5O$, M = 479.61, colorless block, 0.43 × 0.38 × 0.26 mm^3, monoclinic, space group *Pn* (No. 7), a = 9.1314(5) Å, b = 15.5515(9) Å, c = 10.3830(6) Å, β = 115.6080(10)°, V = 1329.63(13) $Å^3$, Z = 2, D_c = 1.198 g/cm^3, F_{000} = 512, CCD area detector, Mo K α λ = 0.71073 Å, radiation, T = 293(2) K, $2\theta_{max}$ = 50.0°, 12,624 reflections collected, 2349 unique (R_{int} = 0.0208), final *GooF* = 1.146, R1 = 0.0265, wR2 = 0.0709, R indices based on 2301 reflections with I > 2σ(I) (refinement on F^2), 326 parameters, μ = 0.075 mm^{-1}, CCDC number 1028922.

*Crystal data for compound **5k*** $C_{31}H_{33}N_5O_2$, M = 507.62, colorless block, 0.49 × 0.38 × 0.33 mm^3, triclinic, space group $P(\bar{1})$ (No. 2), a = 9.3539(7) Å, b = 10.3002(8) Å, c = 14.5900(11) Å, α = 104.8220(10)°, β = 90.9440(10)°, γ = 90.1160(10)°, V = 1358.72(18) $Å^3$, Z = 2, D_c = 1.241 g/cm^3, F_{000} = 540, CCD area detector, MoK α λ = 0.71073 Å, radiation, T = 293(2) K, $2\theta_{max}$ = 50.0°, 13,168 reflections collected, 4788 unique (R_{int} = 0.0181), final *GooF* = 1.031, R1 = 0.0464, wR2 = 0.1191, R indices based on 4093 reflections with I > 2σ(I) (refinement on F^2), 344 parameters, μ = 0.080 mm^{-1}, CCDC number 1028921.

Experimental biology

Cell culture, maintenance, and antiproliferative evaluation

The cell lines, SiHa, MDA-MB-231, PANC1, IMR-32, and Hep G2 which were used in this study were procured from American Type Culture Collection (ATCC), United States. The synthesized test compounds were evaluated for their in vitro antiproliferative activity against five different human cancer cell lines. A protocol of 48-h continuous drug exposure was used, and a sulforhodamine B (SRB) cell proliferation assay was used to estimate cell viability or growth. All cell lines were grown in Dulbecco's mod-

ified Eagle's medium (containing 10 % fetal bovine serum (FBS) in a humidified atmosphere of 5 % CO_2 at 37 °C). Cells were trypsinized when sub-confluent from T25 flasks/60-mm dishes and seeded in 96-well plates in 100 − μL aliquots at plating densities depending on the doubling time of individual cell lines. The microtiter plates were incubated at 37 °C, 5 % CO_2, 95 % air, and 100 % relative humidity for 24 h prior to addition of experimental drugs and were incubated for 48 h with different doses (0.01, 0.1, 1, 10, 100 μM) of the prepared derivatives. After 48-h incubation at 37 °C, cell monolayers were fixed by the addition of 10 % (wt/vol) cold trichloroacetic acid, incubated at 4 °C for 1 h, and then stained with 0.057 % SRB dissolved in 1 % acetic acid for 30 min at room temperature. Unbound SRB was washed with 1 % acetic acid. The protein-bound dye was dissolved in 10 mM Tris base solution for OD determination at 510 nm using a microplate reader (Enspire, Perkin Elmer, USA). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth was calculated at each of the drug concentrations levels. Percentage growth inhibition was calculated as

$[(\mathrm{Ti}-\mathrm{Tz})/(\mathrm{C}-\mathrm{Tz})] \times 100$ for concentrations for which $\mathrm{Ti} > / = \mathrm{Tz}$

$[(\mathrm{Ti}-\mathrm{Tz})/\mathrm{Tz}] \times 100$ for concentrations for which $\mathrm{Ti} < \mathrm{Tz}$.

The dose–response parameters were calculated for each experimental agent. Growth inhibition of 50 % (GI_{50}) was calculated from $[(\mathrm{Ti}-\mathrm{Tz})/(\mathrm{C}-\mathrm{Tz})] \times 100 = 50$, which is the drug concentration resulting in a 50 % reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The values were calculated for this parameter if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter was expressed as greater or less than the maximum or minimum concentration tested.

Microorganisms and growth conditions

The newly synthesized compounds were screened for their antibacterial activity against three Gram-positive (*B. subtilis* MTCC 736, *B. megaterium* MTCC 2412, *M. luteus* MTCC 106) and three Gram-negative (*E. coli* MTCC 40, *S. typhi* Isolated strain, *Pseudomonas aeruginosa* MTCC 4673) bacterial strains by well diffusion method. The microdilution method for estimation of MIC value (the lowest concentration of compound required to inhibit the growth of the tested microorganism) was applied to evaluate the antibacterial activity. The MTCC (Microbial Type Culture Collection) cultures were provided by the Institute of Microbial Technology, Chandigarh. All the compounds were dissolved in dimethylsulfoxide (DMSO) to get a final concentration of one mg/mL. The antibacterial potency of the compounds under conditions was compared with the activity of the antibacterial drug vancomycin 50 μg/mL. In order to ensure that the solvent had no effect on bacteria, a control test was also performed with DMSO.

Disk diffusion method

The antibacterial activity of the synthesized compounds was evaluated by the disk diffusion method. A standard inoculum ($1 - 2 \times 10^7$ cfu/mm 0.5 McFarland standards) was introduced onto the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculum. The disks measuring 6 mm in diameter were prepared from Whatman no. 1 filter paper and sterilized by dry heat at 140 °C for an hour. The sterile disks previously soaked in a known concentration of the test compounds (in DMSO) were placed in nutrient agar medium. Solvent and growth controls were kept. The plates were inverted and incubated for 24 h at 37 °C. After incubation, the zone of growth inhibition was measured using a calibrated scale and expressed in mm. Experiment was performed in triplicate to minimize the deviations, and the average values are reported in Table 4.

Microdilution broth method

The minimal inhibitory concentration (MIC) values for the tested compounds were determined using the microdilution broth method. The inoculum of microorganisms was prepared from 24-h broth cultures, and the suspensions were adjusted to 0.5 McFarland standard turbidity. The test compounds dissolved in DMSO were diluted to the highest concentration (1000 μg/mL) to be tested. Then serial twofold dilutions were made in the concentration range from 1.95 to 1000 μg/mL in 10-mL sterile tubes. A prepared suspension of the standard microorganisms was added to each dilution in a 1:1 ratio. Growth of the microorganisms was determined visually after incubation for 24 h at 37 °C. It corresponds to the well with the lowest concentration of the tested substance where microbial growth was clearly inhibited. The MIC values (in micro molars) are shown in Table 4.

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