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FULL-LENGTH PAPER

Parallel synthesis of novel antitumor agents: 1,2,3-triazoles bearing biologically active sulfonamide moiety and their 3D-QSAR

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Abstract A 60-member 1,2,3-triazoles bearing biologically active sulfonamide moiety library was synthesized via azide–alkyne cycloaddition and examined for cytotoxic activity against human leukemia cell line HL-60. 25 of them were evaluated further in four additional cancer cell lines (HepG2, A549, PC3, SGC7901). Most of the 25 compounds showed moderate cytotoxic activities against the tested cell lines. Furthermore, the structure–activity relationships were discussed and a reliable 3D-QSAR model with good prediction $\left(r^2_{cv} = 0.64,\ r^2 = 0.958\right)$ was generated on the basis of our synthesized 1,2,3-triazoles for their cytotoxic activities against the HL-60 cell line. The contour map of the CoMFA should aid in the design of new antitumor agents.

Keywords 1,2,3-Triazoles · Sulfonamide · Antitumor · 3D-QSAR · Azide–alkyne cycloaddition

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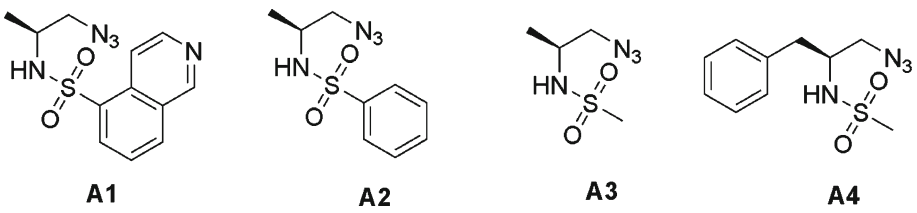
Introduction

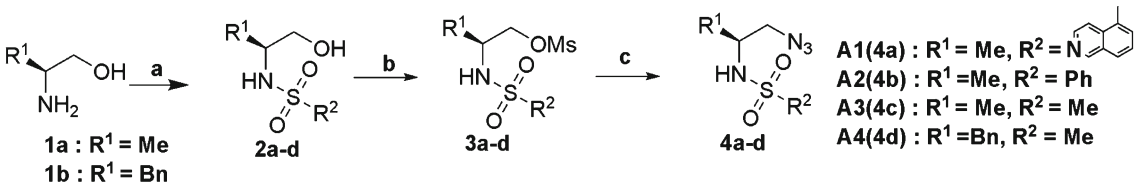
Cancer is the second largest cause of death in the world. Various chemotherapeutic drugs have been used in cancer clinics. However, due to multi-drug resistance, there has been a growing interest in the discovery of novel anti-cancer substances with high efficacy, low toxicity, and minimum side effects. 1,2,3-Triazoles are a very important class of heterocycles, which have been well-recognized for their broad range of pharmacological properties, such as antiviral [1], antifungal [2,3], and antitubercular activities [4]. Particularly noteworthy in the context of this report is their antitumor activity [5–8]. On the other hand, sulfonamides have attracted great attention for their interesting antitumor activity [9–12]. In continuation of our research program on anticancer agents and efforts directed toward parallel synthesis of heterocyclic compound, herein, we wish to report the synthesis of novel 1,2,3-triazoles bearing biologically active sulfonamide moiety using azide–alkyne cycloaddition as well as their antitumor activity evaluation. In addition, a comparative molecular field analysis (CoMFA) was performed using the cytotoxic data against HL-60 cell line as a template to probe the 3D-quantitative structure–activity relationships (3D-QSAR) of these compounds.

Chemistry

The synthesis of azides **A1**–**A4** (Fig. 1) is outlined in Scheme 1. The *N*-sulfonation of L-alaninol (**1a**) or L-phenylalaninol (**1b**) to yield **2a**–**d** was followed by the generation of the *O*-methylsulfonyls (**3a**–**d**), and finally azidation with NaN_3 to obtain **4a**–**d** (**A1**–**A4**) [13,14]. As for the alkyne-containing fragments **B1**–**B18** (Fig. 2), it is illustrated in Scheme 2. Compounds **B1**–**B5** were prepared by the

Fig. 1 Azide building blocks





Reagent and conditions: (a) R^2SO_2Cl, DMAP, Et_3N, CH_2Cl_2, 0 ℃ to rt, overnight; (b) MsCl, Et_3N, CH_2Cl_2, 0 ℃ to rt , 2h; (c) NaN_3, DMF, 60 ℃, 16h.

Scheme 1 Synthesis of azide building blocks (**A1**–**A4**). Reagent and conditions: (a) R^2SO_2Cl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, overnight; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h; (c) NaN_3, DMF, 60 °C, 16 h

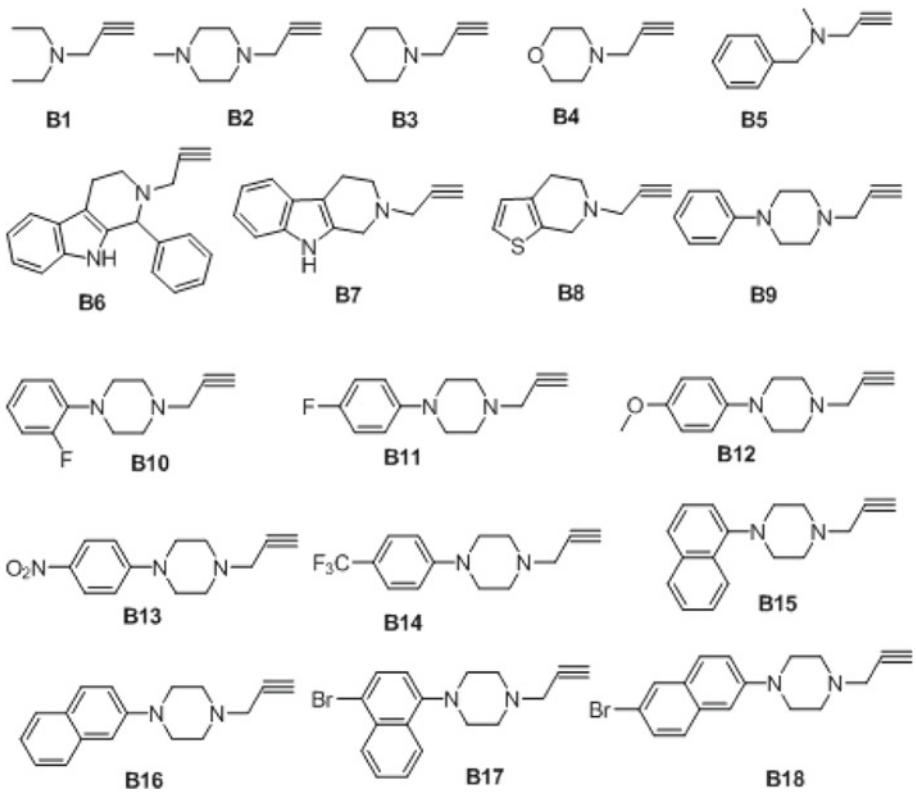
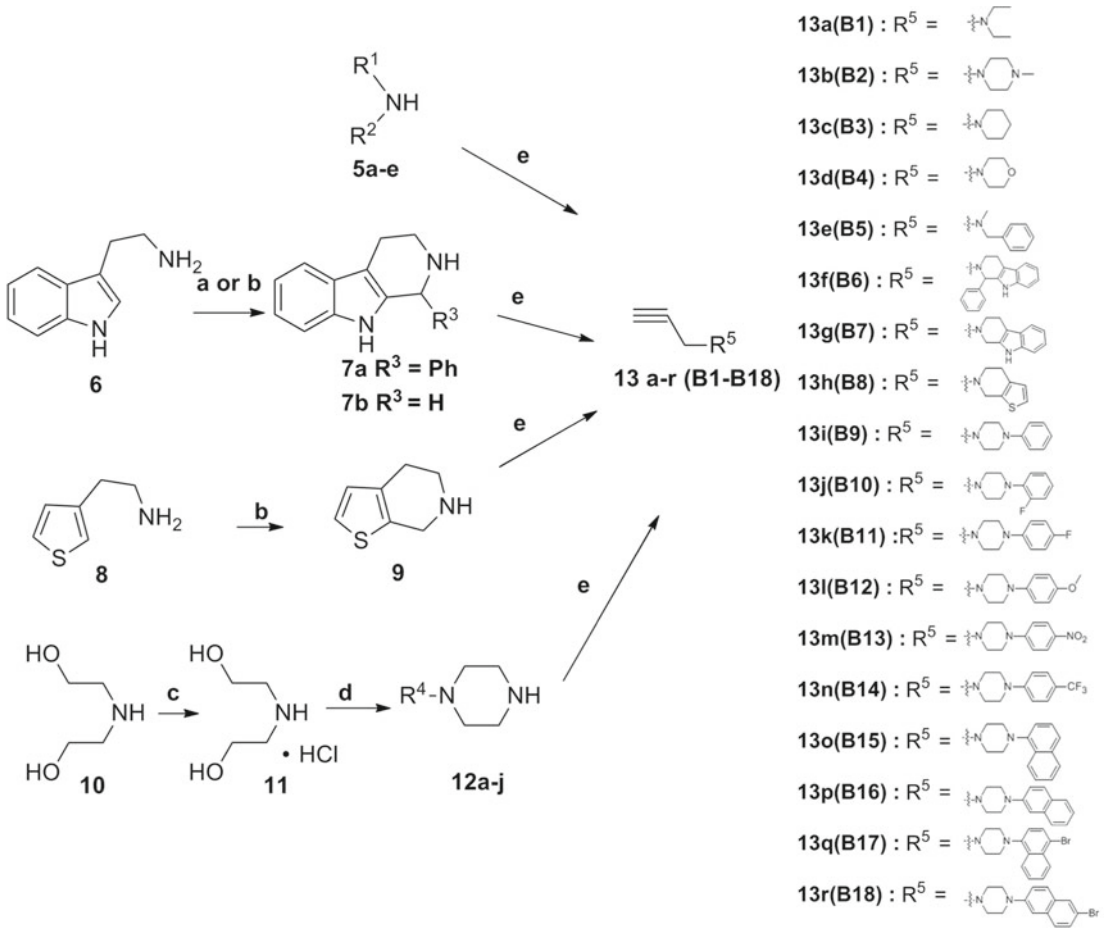


Fig. 2 Alkyne building blocks

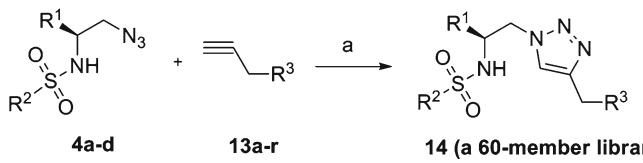
reaction of diethylamine, *N*-methyl piperazine, piperidine, morpholine, *N*-methyl-benzylamine with propargyl bromide and K_2CO_3 in acetone [15]. These propargylated compounds were purified by vacuum distillation. Using tryptamine or 3-thienylmethylamine as a starting material, we employed the classical Pictet–Spengler reaction followed by propargylation to achieve compounds **B6**–**B8** [16–18]. Synthesis of compounds **B9**–**B18** started with the preparation of bis-β-chloroethylamine hydrochloride from diethanolamine. The *N*-arylpiperazines hydrochloride (**12a**–**j**) were prepared



Reagent and conditions: (a) benzaldehyde, TFA, CH_2Cl_2, 0 ℃ to rt, overnight; (b) paraformaldehyde, HCl, C_2H_5OH, rt; (c) $SOCl_2$, $CHCl_3$, rt to 60 ℃; (d) R^4NH_2, K_2CO_3, nBuOH, 48h;(e) propargyl bromide, K_2CO_3, acetone, overnight.

Scheme 2 Synthesis of alkyne building blocks (**B1**–**B18**). Reagent and conditions: (a) benzaldehyde, TFA, CH_2Cl_2, 0 °C to rt, overnight; (b) paraformaldehyde, HCl, C_2H_5OH, rt; (c) $SOCl_2$, $CHCl_3$, rt to 60 °C; (d) R^4NH_2, K_2CO_3, *n*-BuOH, 48 h; (e) propargyl bromide, K_2CO_3, acetone, overnight

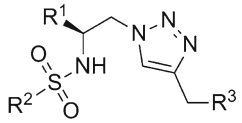
Scheme 3 Synthesis of a 60-member 1,2,3-triazoles library. Reagent and conditions: (a) copper(II) sulfate/sodium ascorbate, *t*-BuOH/H_2O (1:1), rt, 24 h

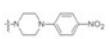
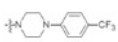
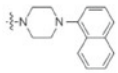
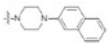
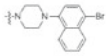
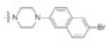
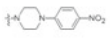
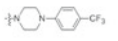
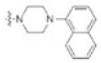
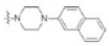
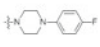
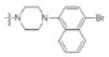
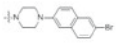
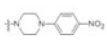


Reagent and conditions: (a) copper (II) sulphate/sodium ascorbate, *t*-BuOH/H_2O (1:1), rt , 24h.

by condensing the appropriate anilines with bis-β-chloroethylamine hydrochloride [19,20], then propargylated with propargyl bromide and K_2CO_3 in acetone. With these building blocks at hand, we performed the azide–alkyne cycloaddition reaction [21] using copper(II) sulfate/sodium ascorbate as the catalyst in *t*-BuOH/H_2O (1:1) at room temperature to obtain the focused library of 1,2,3-triazoles (Scheme 3).

Table 1 Cytotoxic effects of all the synthesized 1,2,3-triazoles against human leukemia cell line (HL-60) in vitro



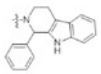
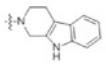
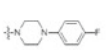
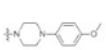
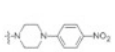
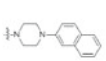
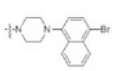
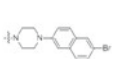
Compd	R^1	R^2	R^3	IC_{50} (μM)	Compd	R^1	R^2	R^3	IC_{50} (μM)
A1B1	Me			82.9	**A2B13**	Me	Ph		15.6
A1B2	Me			3940	**A2B14**	Me	Ph		2.35
A1B3	Me			61.2	**A2B15**	Me	Ph		7.08
A1B4	Me			173	**A2B16**	Me	Ph		9.78
A1B5	Me			18.0	**A2B17**	Me	Ph		1.30
A1B6	Me			8.14	**A2B18**	Me	Ph		3.34
A1B7	Me			2.39	**A3B13**	Me	Me		161
A1B8	Me			18.6	**A3B14**	Me	Me		44.4
A1B9	Me			24.1	**A3B15**	Me	Me		180
A1B10	Me			76.6	**A3B16**	Me	Me		115
A1B11	Me			>50	**A3B17**	Me	Me		10.2
A1B12	Me			36.0	**A3B18**	Me	Me		4.91
A1B13	Me			14.0	**A4B1**	Bn	Me		2.01×10^3
A1B14	Me			5.84	**A4B2**	Bn	Me		3.21×10^6

Results and discussion

Biological activities

All the synthesized compounds were initially examined for in vitro cytotoxic activity against the human leukemia cell line HL-60. Table 1 lists the IC_{50} values obtained for these compounds in the HL-60 cell line MTT assay. The data show that the compounds containing **A3** azide building block exhibited on average less activity in comparison to the other compounds containing **A1**, **A2**, and **A4** fragments, when the **B** fragment was held constant. For example, **A3B18** is less

Table 1 continued

A1B15	Me			6.38	**A4B3**	Bn	Me		290
A1B16	Me			10.9	**A4B4**	Bn	Me		1.00×10^6
A1B17	Me			4.71	**A4B5**	Bn	Me		57.7
A1B18	Me			1.45	**A4B6**	Bn	Me		7.21
A2B1	Me	Ph		29.0	**A4B7**	Bn	Me		6.24
A2B2	Me	Ph		3180	**A4B8**	Bn	Me		1.37×10^4
A2B3	Me	Ph		11.8	**A4B9**	Bn	Me		144
A2B4	Me	Ph		121	**A4B10**	Bn	Me		374
A2B5	Me	Ph		73.5	**A4B11**	Bn	Me		7.83
A2B6	Me	Ph		2.66	**A4B12**	Bn	Me		27.6
A2B7	Me	Ph		19.8	**A4B13**	Bn	Me		35.0
A2B8	Me	Ph		145	**A4B14**	Bn	Me		2.19
A2B9	Me	Ph		42.0	**A4B15**	Bn	Me		4.97
A2B10	Me	Ph		4.14	**A4B16**	Bn	Me		3.76
A2B11	Me	Ph		11.1	**A4B17**	Bn	Me		8.31
A2B12	Me	Ph		72.0	**A4B18**	Bn	Me		2.23

MTT assays: 72 h of drug exposure; values are means of three experiments

active than **A1B18**, **A2B18**, and **A4B18**. This indicates that the aromatic group might be an essential feature for activity in the azide component of the compounds. As for the three series of alkyne building blocks (series 1 is **B1**–**B5**, series 2 is **B6**–**B8**, and series 3 is **B9**–**B18**), the compounds contained in series 1 produced on average the least cytotoxic activity. Among the compounds containing the fragment **B6**, **B7**, and **B8** (series 2), cytotoxic activity was reduced if the indole group of β-carboline (**B7**) or phenyl substituted β-carboline (**B6**) was replaced with thiophene (**B8**). Seventy percent (28 of 40) of the compounds in the third series (compounds containing the fragments **B9**–**B18**) produced moderate cytotoxic activity against HL-60 ($IC_{50} \leq 50\,\mu M$). In order to further investigate the antitumor activities of the synthesized 1,2,3-triazoles, 25 1,2,3-triazoles were chosen for in vitro cytotoxic examination against four additional human cancer cell lines:

Table 2 Cytotoxic effects of 25 selected 1,2,3-triazoles against five human cell lines in vitro

Compound	Cytotoxicity IC_{50} (μM)[a]				
	HL-60	HepG-2	A549	SGC7901	PC-3
A1B6	8.14	>50	>50	>50	15.1
A1B7	2.39	>50	31.3	21.3	12.4
A1B12	36.0	>50	>50	>50	>50
A1B13	14.0	>50	>50	>50	29.6
A1B14	5.84	>50	>50	39.3	21.3
A1B15	6.38	19.8	44.5	27.6	19.4
A1B16	10.9	>50	>50	>50	46.7
A1B17	4.71	6.52	17.3	19.9	8.94
A1B18	1.45	20.7	9.06	19.6	16.8
A2B6	2.66	46.3	44.4	19.6	22.6
A2B7	19.8	48.4	>50	>50	22.6
A2B14	2.35	16.8	9.99	12.7	13.3
A2B15	7.08	14.4	29.4	15.5	10.4
A2B16	9.78	>50	25.2	32.9	25.7
A2B17	1.30	17.3	13.0	14.7	10.9
A2B18	3.34	21.0	6.78	20.0	6.4
A3B17	10.2	9.35	20.9	19.2	21.9
A3B18	4.91	36.1	18.6	43.4	16.8
A4B6	7.21	>50	21.5	>50	>50
A4B7	6.24	26.0	>50	>50	17.8
A4B14	2.19	16.6	>50	33.0	8.25
A4B15	4.97	8.99	26.2	13.7	9.15
A4B16	3.76	>50	>50	28.72	>50
A4B17	8.31	4.99	14.66	20.17	34.67
A4B18	2.23	3.77	24.53	36.79	>50
Taxol[b]	<0.08	0.19	2.67	0.17	1.64

[a] MTT assays: 72 h of drug exposure; values are means of three experiments
[b] Positive control

HepG2, A549, PC3, SGC7901. Table 2 lists the IC_{50} values obtained for these compounds including taxol (positive control). Interesting results were obtained from the MTT assay with respect to the compounds with β-carboline or 1-phenyl substituted β-carboline groups. When the azide building block was **A1**, the β-carboline containing compound (**A1B7**) was more potent than the 1-phenyl substituted β-carboline compound (**A1B6**). However, when the azide building block is **A2**, the opposite result was obtained: **A2B6** > **A2B7**. Evaluating the 1,2,3-triazoles with arylpiperazine groups, specifically **A1B14** and **A1B12**, the introduction of an electron withdrawing group at the *para* position of the phenyl ring was favored over the introduction of an electron donating group in the following order: **A1B14** > **A1B12**. In general, replacing the substituted phenyl with naphthyl or bromo-substituted naphthyl was beneficial for antitumoral activity. For example, compounds bearing an α-naphthyl group exhibited better activity than those with β-naphthyl group; **A1B15** > **A1B16** (in all 5 cell lines), **A2B15** > **A2B16** (in 4 of 5 cell lines), and **A4B15** > **A4B16** (in 4 of 5 cell lines). Additionally, introducing bromo into the naphthyl enhanced the antitumor activity as shown by **A1B17** > **A1B15**, **A1B18** > **A1B16**, and **A2B18** > **A2B16** (in all 5 cell lines); **A4B18** > **A4B16** and **A2B17** > **A2B15** (in 3 of 5 cell lines); **A4B17** > **A4B15** (in 2 cell lines). Overall, compounds **A1B17**, **A2B17**, **A2B14** exhibited good inhibition activities of IC_{50} < 20 μM against all the tumor cell lines.

3D-QSAR study

To further investigate the SARs of 1,2,3-triazoles in more detail, the cytotoxic data of 58 bioactive compounds against HL-60 cell line were used to build a 3D-QSAR model. All of the compounds have significant variation of their IC_{50} values ranging four orders of magnitude, which would be useful to generate a good 3D-QSAR model. These compounds were divided into a training set with 27 compounds, and a test set with 31 compounds. The compounds of the training and test sets were carefully selected in order to ensure appropriate property coverage on the entire range of pIC_{50} values.

All molecular modeling studies were performed using Tripos Sybyl 6.9 on a SGI computer [22]. Since compound **A1B7** has good cytotoxicity against the HL-60 cell, it was chosen as the template molecule to do MD/MM simulations in order to sample various molecular conformations at its local-minima energy landscapes. At first, the initial structure of **A1B7** was drawn by using Sybyl/Sketch module in the Sybyl molecular modeling package, and minimized using the Tripos force field. MD/MM simulations were then carried out to get the sample conformations. MD simulations were performed at 298 K with the time length set of 300,000 fs and time step of 1 fs. 300 snapshots were finally collected at a rate of 1 ps/snapshot for postprocessing analysis. The collected 300 conformations were further minimized with the steepest descent method until the maximum derivative was less than 0.001 kcal/(mol Å) using Tripos force field and Gasteiger–Hückel atomic charge with a distance-dependent dielectric function. The optimized 300 conformations were then superimposed with each other on all of heavy atom. Conformations with RMS values less than 1.0 Å were classified into the same family of conformers. This operation resulted in the convergence of these conformers into 10 families. Each of the minimum-energy conformations in these 10 families are represented in Fig. 3, and the energetical characterization of the 10 preferred conformations described in Table 3. The energy difference among these 10 conformers is less than 10.10 kcal/mol. Therefore, all of these 10 conformers are possibly present for compound **A1B7**.

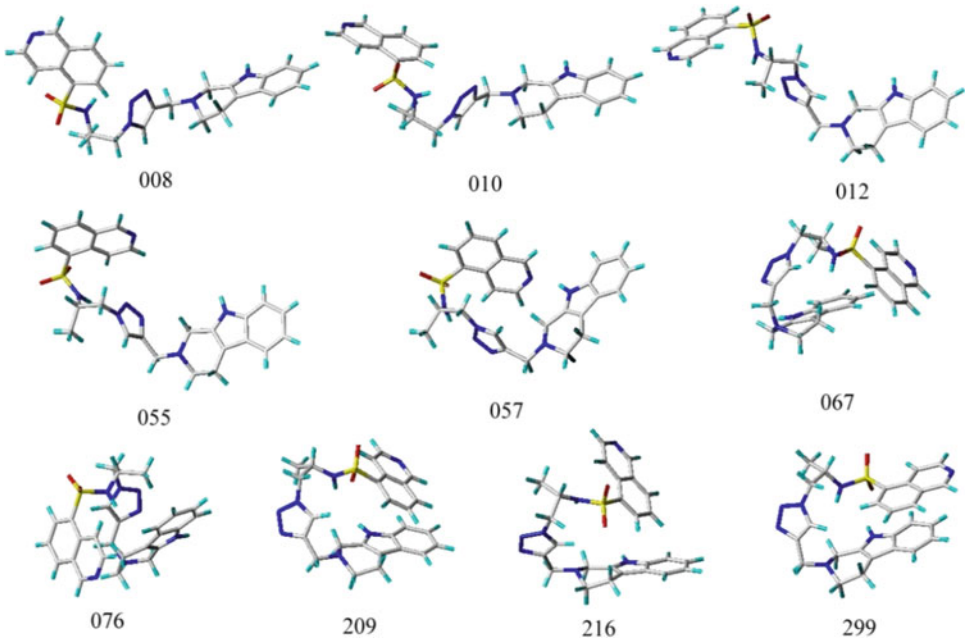


Fig. 3 Representation of 10 favored conformations of **A1B7** on the basis of the energy minimization of structures occurring along the molecular dynamics trajectory

Table 3 Energetical characterization of 10 preferred conformations of A1B7

Conformation	Energy (kcal/mol)
008	32.5
010	31.7
012	31.0
055	29.5
057	25.2
067	22.4
076	23.0
209	23.0
216	25.9
299	23.9

For the CoMFA analyses, each of the 10 conformers of **A1B7** obtained from MD/MM simulations was, respectively, used as a template for structural alignment of all compounds in the training database. After examination of structural similarity and diversity of compounds in the training set, four functional groups were selected as a basis for the structural superimposition of all ligands: 1,2,3-triazole ring; S, O, N atoms of the sulfonamide group; the heavy atoms in the R^3 group; and the heavy atoms in the R^2 group. It is reasonable to assume that ligands do not necessarily bind to the receptors in their global minimum-energy conformations because some degree of bond rotation may be required to adapt an electrostatic and hydrophobic match that would yield the lowest energy drug–protein complexes [23]. Therefore, the previously obtained local minimum-energy conformations of each compound would be regarded as starting points from which the possible binding conformation candidates could be found for the compound. In order to provide for optimal structural alignment, all single bonds in each molecule must be rotated slightly in order to have a fine superimposition of all compounds on the structural template. On the other hand, it is important to note that the allowed change of each compound's conformation must be restricted to those that can be obtained upon binding within reasonable energy limits [24]. Typically, a 10 kcal/mol difference between the local minimum conformational energy and the aligned conformational energy of each compound provided superimposition in structural alignment. For example, Fig. 4 shows the structural superimpositions of 27 compounds in the training set based on conformer 010. After structural alignment, the CoMFA study was performed using the Sybyl/CoMFA module. All the aligned molecules in the training set were placed in a rectangular box which was 4 Åbeyond longer than any molecule in X, Y, Z directions. The steric and electrostatic field energies (AM1 charge) were calculated on the basis of interaction between a probe of an sp^3 carbon atom with a +1 charge and the atoms of each compound located at all intersections of a regularly spaced grid (2.0 Å). Steric and electrostatic contributions were truncated at 30 kcal/mol. The dielectric constant was applied with distance dependence. All the initial partial least squares (PLS) analyses were performed using the "leave-one-out (LOO)" cross-validation method [25]. A cross-validated r^2_{cv} is defined as cross-validated

$$r^2_{cv} = (\mathrm{SD} - \mathrm{PRESS})/\mathrm{SD}$$

where SD is the sum of the squared deviations of each biological property value from their mean,

$$\mathrm{SD} = \sum[(\text{target data value}) - (\text{target data mean})]^2$$

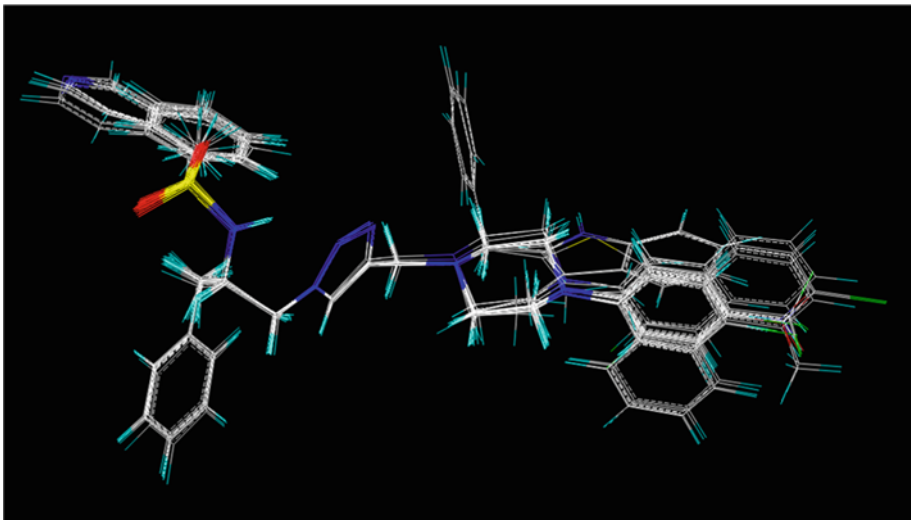


Fig. 4 Conformer-010 based structural alignment of the compounds in the training set for constructing 3D-QSAR CoMFA model

and PRESS is the sum, over all compounds, of the squared differences between the experimental and 'model-predicted' biological property values.

$$\text{PRESS} = \sum[(\text{target data value}) - (\text{corresp. predicted data value})]^2$$

The standard deviation of predictions, s_{PRESS}, is calculated from PRESS, the sum of the squared errors of these predictions, considering the number of degrees of freedom. SDEP (the standard deviation of the error of predictions) corresponds to s_{PRESS} but the number of degrees of freedom is not considered in the calculation of the SDEP value. As described by Kubinyi [26], as long as only significant components are extracted in the PLS analysis, PRESS, SDEP, and s_{PRESS} will decrease; if too many components are derived, overprediction results and PRESS, SDEP, and s_{PRESS} increase. Therefore, the number of components would be accepted from 3 to 5 in a PLS analysis for a good CoMFA-generated 3D-QSAR model.

In the current studies, the optimum number of components was set as default of 6. In order to reduce the noise, the minimum column filtering σ value was set to 2.0 kcal/mol. Then, the non-cross-validated conventional analysis was performed for the model which had the highest cross-validated r^2_{cv} of 0.64, and the optimum number of components was equal to the number obtained by the LOO method of the same model.

In each instance, a cross-validated PLS analysis was run to generate a corresponding 3D-QSAR model. Table 4 lists all of the cross-validated r^2_{cv} values and the optimal components from PLS statistical analyses based on the 10 conformers of **A1B7**, obtained from MD/MM simulations, respectively. As described in the Sybyl 6.9 QSAR manual [22], there is a generally accepted criterion for CoMFA statistical validity of $r^2_{\text{cv}} \geq 0.6$. Among our 10 CoMFA models, only the one based on conformer 010 exceeded this criterion. Therefore, the CoMFA-generated 3D-QSAR model is only good enough when conformer 010 is used. As indicated in our result, only a reliable 3D-QSAR model can be constructed to line the quantitative relationship between the biological data of compound in the training database and their electrostatic and steric field, which are dependent on the molecular conformation and important factors to interact with their receptor, computed based on MD/MM-simulated conformer 10 of **A1B7**. It can follow that conformer 010 is the most likely conformer of **A1B7** when it binds to its receptor. According to the results from the CoMFA analyses, we hypothesize that **A1B7** directly interacts with the receptor without a big change in its conformation.

Table 4 Cross-validated analyses of the CoMFA model based on the A1B7 conformations

Template conformation	LOO r^2_{cv}	Optimal component
008	0.55	5
010	0.64	5
012	0.51	4
021	0.52	4
055	0.16	6
057	0.44	5
067	0.47	4
203	0.58	6
216	0.43	4
299	0.48	6

Using the optimum component number 5 obtained from cross-validated PLS analysis, the non-cross-validated analysis of this model yielded an r^2 of 0.958, and the estimated standard error is 0.197. Table 5 lists observed and predicted pIC_{50} values of molecules in the training set. These data show that, the CoMFA model is reliable and accurate.

Table 5 Observed and CoMFA-predicted pIC_{50} values of molecules in the training set

Compound	pIC_{50} (obsd)	pIC_{50} (pred)	Residual
A1B1	4.08	4.24	−0.16
A1B5	4.75	4.87	−0.12
A1B7	5.62	5.36	0.26
A1B9	4.62	4.68	−0.06
A1B10	4.12	3.99	0.13
A1B12	4.44	4.51	−0.07
A1B18	5.84	6.04	−0.20
A2B1	4.54	4.31	0.23
A2B2	2.50	2.66	−0.16
A2B4	3.92	3.93	−0.01
A2B6	5.58	5.27	0.31
A2B7	4.70	4.89	−0.19
A2B12	4.14	4.11	0.03
A2B14	5.63	5.39	0.24
A2B15	5.15	5.38	−0.23
A2B16	5.01	5.25	−0.24
A3B13	3.79	3.68	0.11
A3B14	4.35	4.37	−0.02
A3B17	4.99	4.93	0.06
A3B18	5.31	5.13	0.18
A4B3	3.54	3.42	0.12
A4B8	2.86	2.87	−0.01
A4B10	3.43	3.59	−0.16
A4B11	5.11	4.93	0.18
A4B15	5.30	5.22	0.08
A4B16	5.42	5.38	0.04
A4B17	5.08	5.44	−0.36

CoMFA model: $r^2 = 0.958$, standard error of estimate = 0.197, $F = 95.220$

Table 6 Experimental (obsd) and CoMFA-predicted (pred) pIC_{50} values of molecules in the test set

Compound	pIC_{50} (obsd)	pIC_{50} (pred)	Residual
A1B2	2.40	2.76	−0.36
A1B3	4.21	4.27	−0.06
A1B4	4.76	4.65	0.11
A1B6	5.09	5.07	0.02
A1B8	4.73	3.88	0.85
A1B13	4.85	4.81	0.04
A1B14	5.23	5.54	−0.31
A1B15	5.20	5.17	0.03
A1B16	4.96	5.28	−0.32
A1B17	5.33	5.70	−0.37
A2B3	4.93	4.35	0.58
A2B5	4.13	4.11	0.02
A2B8	3.84	3.87	−0.03
A2B9	4.38	4.47	−0.09
A2B10	5.38	4.42	0.96
A2B11	4.95	4.89	0.06
A2B13	4.81	4.80	0.01
A2B17	5.89	5.69	0.20
A2B18	5.48	5.49	−0.01
A3B12	3.86	3.65	0.21
A3B15	3.74	4.11	−0.37
A3B16	3.94	4.08	−0.14
A4B1	2.70	3.04	−0.34
A4B5	4.24	3.92	0.33
A4B6	5.14	4.88	0.26
A4B7	5.20	5.33	−0.13
A4B9	3.84	4.17	−0.33
A4B12	4.56	4.53	0.03
A4B13	4.46	4.66	−0.20
A4B14	5.66	5.35	0.31
A4B18	5.65	5.56	0.09

The predictive capability of the CoMFA model was also evaluated and examined by using a test set containing an additional 31 compounds that we synthesized. (Table 6). Figure 5 illustrates CoMFA-predicted and experimental pIC_{50} values of the compounds both in the training and test set for the non-cross-validated analysis. The linearity of the plot also demonstrated that our CoMFA model has a very good prediction capability. Thus, the result indicated that our CoMFA-generated
3D-QSAR model has reliable capability of predicting bioactivity in the range of magnitude included in the present paper. We could use pharmacophoric features induced in the 3D-QSAR model to design and predict more potent new compound.

Figure 6 shows the steric–electrostatic contour map of the CoMFA model. The CoMFA contour is helpful in identifying important features contributing to interactions between ligand and receptor. The green areas indicate the regions where steric bulky groups would increase activity; whereas, yellow contours depict regions where steric bulky groups would not be favored. The levels of these two fields are 87 and 13%, respectively. The red and blue regions show important areas where the enhanced cytotoxic activity is associated with increasing and decreasing negatively charged groups, respectively. For instance, the red and green areas around the isoquinoline ring indicate that the presence of a negatively charged bulky group is expected to enhance bioactivity of the compound. The MTT data shows that the compounds containing the **A3** azide building block exhibited on average less activity to the relative **A1**, **A2**, or **A4** fragment containing compounds. This points to the necessity of the aromatic groups (or bulky group) in the azides fragments which agree with our CoMFA analyses. In the region around the

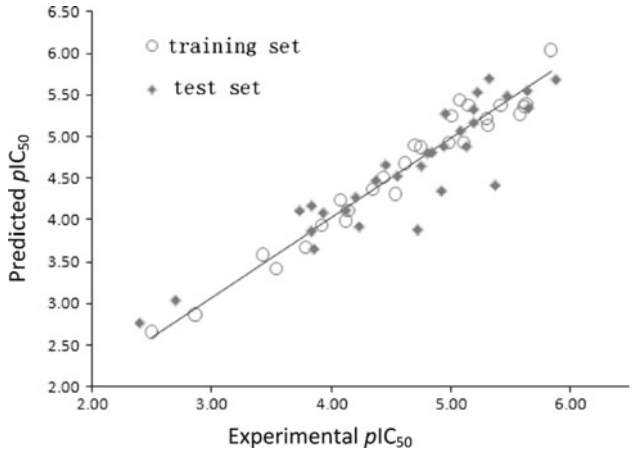


Fig. 5 CoMFA-predicted and experimental pIC_{50} values of the compounds both in training and test set

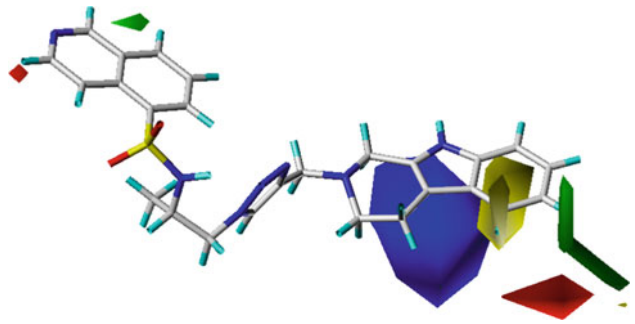


Fig. 6 CoMFA contour map. Sterically favored areas (contribution level of 87%) are in *green*. Sterically unfavored areas (contribution level of 13%) are in *yellow*. Positive potential favored areas (contribution level of 87%) are in *blue*. Positive potential unfavored areas (contribution level of 13%) are in *red*. (Color figure online)

R^3 group, the blue contour indicates that a positively charged group is favored for bioactivity in the triazoles. The red and green contours in this region imply that a negatively charged bulky group could increase the bioactivity. This was validated by our experimental data, as it was observed that the introduction of an electron withdrawing group in the *para* position of the phenyl ring increased activity over an electron donating group (**A1B14** > **A1B12**). Additionally, in general, replacing a substituted phenyl ring with a naphthyl group (increasing bulkiness) was beneficial for the antitumor activity. Furthermore, introducing bromide into the naphthyl (a negatively charged group on a bulky group) enhanced the antitumoral activity (**A1B17** > **A1B15**, **A1B18** > **A1B16**).

Conclusion

In summary, we have synthesized a 60-member 1,2,3-triazole library bearing a biologically active sulfonamide moiety via azide–alkyne cycloaddition. In addition, the effects of all the 1,2,3-triazoles on inhibition activities against the HL-60 cell line were examined. Twenty-five of the 1,2,3-triazoles were further evaluated for cytotoxic activities against four other human cancer cell lines, including HepG2, A549, PC3, SGC7901. Most of the obtained compounds showed moderate antitumor activities against all the tested cell lines. According to 10 conformations of **A1B7** obtained from MD/MM simulation, we successfully conducted a 3D-QSAR/CoMFA of our synthesized 1,2,3-triazoles based on their cytotoxic activities against the HL-60 cell line. By PLS analyses, a 3D-QSAR model was generated based on one of the ten conformations. Utilizing our other synthesized 1,2,3-triazoles in the test database, our generated 3D-QSAR model was confirmed to have a good predictive capabilities. The CoMFA results and contour can be utilized in rational drug design both to explain and predict the cytotoxic activities of 1,2,3-triazoles, and also as a guide to enhance the activity and selectivity of analogues by chemical modification. Moreover, the study on the antitumor mechanism of these compounds is underway and the results will be reported in due course.

Experimental section

Chemistry

Melting points were measured with a B-540 Büchi melting-point apparatus and are uncorrected. Mass spectra (MS) were recorded in ESI mode on Waters Acquity TQD LC–MS system. NMR spectra were recorded at either 500, 400 MHz (^{1}H NMR), or 125 MHz (^{13}C NMR) using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. The values of chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. The following NMR abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet). Dichloromethane (CH_2Cl_2) was dried by distillation over P_2O_5. Triethylamine (Et_3N) was dried by distillation over KOH. All other solvents were used as received and were reagent grade where available. Compounds **2a**–**2d**, **3a**–**3d** were obtained according to the literature [13,14].

*General procedure for preparation of azides (***A1–A4***)*

To a solution of **3** (1.0 equiv) in DMF (5 mL/mmol) was added NaN_3 (1.4 equiv). The reaction was heated to 60 °C for 16 h before being cooled to room temperature, diluted with Et_2O (15 mL/mmol), and washed with H_2O (5 × 15 mL/mmol) and then with brine (2 × 15 mL/mmol). The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. The crude residue was fairly pure for further use. To obtain the product's ^{1}H NMR a sample was purified by flash

chromatography (10% EtOAc in cyclohexane). Typical characterization data were as follows:

*(S)-N-(1-Azidopropan-2-yl)isoquinoline-5-sulfonamide (***A1***)* Yield: 55%. White solid. Mp: 125–128 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.71 (d, J = 6.0 Hz, 1H), 8.48 (d, J = 7.0 Hz, 1H), 8.40 (d, J = 6.0 Hz, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.73–7.70 (m, 1H), 5.17 (d, J = 7.5 Hz, 1H), 3.53–3.50 (m, 1H), 3.25 (dd, J = 12.5, 5.0 Hz, 1H), 3.20 (dd, J = 12.5, 5.0 Hz, 1H), 1.05 (d, J = 5.2 Hz, 3H).

*(S)-N-(1-Azidopropan-2-yl)benzenesulfonamide (***A2***)* Yield: 70%. White solid. Mp: 78–81 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–7.89 (m, 2H), 7.61–7.58 (m, 1H), 7.54–7.51 (m, 2H), 4.96 (d, J = 7.0 Hz, 1H), 3.53–3.47 (m, 1H), 3.31–3.24 (m, 2H), 1.09 (d, J = 7.0 Hz, 3H).

*(S)-N-(1-Azido-3-phenylpropan-2-yl)methanesulfonamide (***A4***)* Yield: 74%. White solid. Mp: 94–95 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.33 (m, 2H), 7.29–7.27 (m, 1H), 7.22–7.21 (m, 2H), 4.54 (d, J = 8.5 Hz, 1H), 3.74–3.71 (m, 1H), 3.54 (dd, J = 12.5, 5 Hz, 1H), 3.46 (dd, J = 12.5, 4.5 Hz, 1H), 2.92 (dd, J = 14, 6.0 Hz, 1H), 2.80 (dd, J = 14, 8.0 Hz, 1H), 2.54 (s, 3H).

*Procedure for 1-phenyl-2,3,4,9-tetrahydro-1H-β-carboline (***7a***)*

A solution of tryptamine (2.4 g, 15 mmol) and benzaldehyde (1.74 g, 16.5 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C, then TFA (2.4 mL, 30 mmol) was slowly added. The mixture was stirred at room temperature overnight and then alkalified with saturated aq. sodium bicarbonate, extracted with DCM (50 mL × 3). The organic phase was washed with saturated sodium chloride solution (30 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a crude solid, which was purified by column chromatography on silica gel (ethyl acetate) to give **6a** as white solid. Yield: 60%, Mp: 173–175 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 7.5 Hz, 1H), 7.52 (s, 1H), 7.36–7.31 (m, 5H), 7.22 (d, J = 7.0 Hz, 1H), 7.16–7.12 (m, 2H), 5.18 (s, 1H), 3.41–3.37 (m, 1H), 3.19–3.13 (m, 1H), 2.96–2.84 (m, 1H), 2.83–2.81 (m, 1H), 1.90 (s, 1H).

*Procedure for 2,3,4,9-tetrahydro-1H-β-carboline (***7b***)*

A mixture of tryptamine (2.4 g, 15 mmol) and paraformaldehyde (0.54 g, 18 mmol) in ethanol (150 mL) was stirred at room temperature for 3 h. The resulting mixture was adjusted to pH 2–3 with 2 N HCl, then left to react for another 10 h. Ethanol was removed partly under reduced pressure, and then the reaction mixture was filtered, washed several times with ethanol/CH_2Cl_2. The filter cake was basified to pH 10–11 with 4 M NaOH at 0 °C, extracted with CH_2Cl_2 (50 mL × 3), and the combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give the pure product. Yield: 58%. White solid. Mp: 208–210 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.16–7.08 (m, 2H), 4.02 (s, 2H), 3.19 (t, J = 5.5 Hz, 2H), 2.76 (t, J = 5.5 Hz, 2H).

*4,5,6,7-Tetrahydrothieno[2,3-c]pyridine (***9***)*

Compound **9** was obtained by the treatment of thiophene-3-ethanamine as described for compound **7b**. Yield: 62%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, J = 5.0 Hz, 1H), 6.78 (d, J = 5.0 Hz, 1H), 4.03 (s, 2H), 3.11 (t, J = 5.5 Hz, 2H), 2.65 (t, J = 5.5 Hz, 2H).

*General procedure for preparation of (***12a–j***)*

A mixture of bis(β-chloroethyl)amine hydrochloride (0.09 mol), the appropriate aniline (0.09 mol) and K_2CO_3 (2.07 g, 0.015 mol) in *n*-BuOH (60 mL) was refluxed for 12 h. The mixture was cooled, K_2CO_3 (2.07 g, 0.015 mol) was added, and the refluxing was continued for another 12 h. After adding K_2CO_3 (2.07 g, 0.015 mol) for the third time, the mixture continued refluxing for another 24 h. The reaction mixture was cooled, filtered, and washed several times with methanol. For compounds **10a–f**, the organic phase was concentrated in vacuo to give a crude solid, which was purified by column chromatography on silica gel (EtOAc/methanol, 1:1) to get the target compound, while compounds **10g–j** were obtained from the filter cake directly without further purification.

General procedure for preparation of **11a–j** *(***B1–B18***)*

To a mixture of a secondary amine (3 mmol) and K_2CO_3 (3.6 mmol) in acetone (15 mL), propargyl bromide (3.6 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered and the filtrate was removed under reduced pressure to yield the crude product, which was purified by vacuum distillation or column chromatography over silica gel (EtOAc/cyclohexane). Typical characterization data were as follows:

*2-(Prop-2-ynyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (***B7***)* Yellow solid, yield: 51%. Mp: 190–192 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, NH), 7.47 (d, J = 7.5 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.15–7.08 (m, 2H), 3.82 (s, 2H),

3.58 (s, 2H), 2.96 (t, $J = 5.5$ Hz, 2H), 2.86 (t, $J = 5.5$ Hz, 2H), 2.30 (s, 1H).

*1-(2-Fluorophenyl)-4-(prop-2-ynyl)piperazine (***B10***)* White solid, yield: 73%. Mp: 40–42 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07–6.91 (m, 4H), 3.37 (d, $J = 2.5$ Hz, 2H), 3.16 (t, $J = 4.5$ Hz, 4H), 2.77 (t, $J = 4.5$ Hz, 4H), 2.28 (t, $J = 2.5$ Hz, 1H).

*1-(4-Methoxyphenyl)-4-(prop-2-ynyl)piperazine (***B12***)* White solid, yield: 71%. Mp: 75–78 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (d, $J = 9.0$ Hz, 2H), 6.84 (d, $J = 9.0$ Hz, 2H), 3.77 (s, 3H), 3.37 (d, $J = 2.5$ Hz, 2H), 3.14 (t, $J = 5.0$ Hz, 4H), 2.76 (t, $J = 5.0$ Hz, 4H), 2.28 (d, $J = 2.5$ Hz, 1H).

*1-(4-Bromonaphthalen-1-yl)-4-(prop-2-ynyl) piperazine (***B17***)* Brown solid, yield : 68%. Mp: 78–80 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25–8.21 (m, 2H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.58–7.52 (m, 2H), 6.96 (d, $J = 8.0$ Hz, 1H), 3.44 (d, $J = 2.5$ Hz, 2H), 3.16 (t, $J = 5.0$ Hz, 4H), 2.87 (t, $J = 5.0$ Hz, 4H), 2.33 (t, $J = 2.5$ Hz, 1H).

*1-(6-Bromonaphthalen-2-yl)-4-(prop-2-ynyl)piperazine (***B18***)* Brown solid, yield: 60%. Mp: 148–151 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, $J = 1.5$ Hz, 1H), 7.63 (d, $J = 9.0$ Hz, 1H), 7.55 (d, $J = 9.0$ Hz, 1H), 7.46 (dd, $J = 8.5$, 2.0 Hz, 1H), 7.29 (dd, $J = 9.0$, 2.0 Hz, 1H), 7.07 (d, $J = 2.5$ Hz, 1H), 3.41 (d, $J = 2.0$ Hz, 2H), 3.35 (t, $J = 5.0$ Hz, 4H), 2.80 (t, $J = 5.0$ Hz, 4H), 2.30 (t, $J = 2.0$ Hz, 1H).

General "Click Reaction" procedure for library synthesis

Each azide (0.3 mmol) and each alkyne (0.36 mmol) were suspended in a 1:1 mixture of water and *tert*-butyl alcohol (4 mL). Sodium ascorbate (6 mg, 0.03 mmol, 0.1 mL of freshly prepared 0.3 M solution in water) was added, followed by copper(II) sulfate pentahydrate (0.75 mg, 0.003 mmol, 0.1 mL of 0.03 M solution in water). The resulting mixture was stirred at room temperature for 24 h. Then the reaction was diluted with water, extracted with CH_2Cl_2 (10 mL × 3), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a crude product, which was purified by column chromatography on silica gel (EtOAc/methanol) to obtain the pure product.

*(S)-N-(1-(4-((Diethylamino)methyl)-1H-1,2,3-triazol-1-yl) propan-2-yl)isoquinoline-5-sulfonamide (***A1B1***)* Yellow oil, yield: 64%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.59 (d, $J = 6.0$ Hz, 1H), 8.38–8.36 (m, 2H), 8.22 (s, 1H), 8.15 (d, $J = 8.0$ Hz, 1H), 7.64 (t, $J = 8.0$ Hz, 1H), 4.43–4.35 (m, 2H), 4.11 (d, $J = 14.0$ Hz, 1H), 3.90 (d, $J = 14.0$ Hz, 1H), 3.77–3.73 (m, 1H), 2.98–2.89 (m,4H), 1.24 (t, $J = 7.0$ Hz, 6H), 1.01 (d, $J = 6.5$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 403.3.

*(S)-N-(1-(4-((4-Methylpiperazin-1-yl)methyl) -1H-1,2,3-triazol-1-yl)propan-2-yl) isoquinoline-5-sulfonamide (***A1B2***)* Yellow oil, yield: 54%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.55 (d, $J = 6.5$ Hz, 1H), 8.39 (d, $J = 7.0$ Hz, 1H), 8.35 (d, $J = 6.0$ Hz, 1H), 8.18 (d, $J = 8.0$ Hz, 1H), 7.66 (t, $J = 8.0$ Hz, 1H), 7.52 (s, 1H), 4.39 (dd, $J = 14$ Hz, 4.5 Hz, 1H), 4.34 (dd, $J = 14$ Hz, 5.5 Hz, 1H), 3.76–3.72 (m, 1H), 3.53 (s, 2H), 2.50 (m, 8H), 2.21 (s, 3H), 0.98 (d, $J = 6.5$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 430.3.

*(S)-N-(1-(4-(Piperidin-1-ylmethyl) -1H-1,2,3-triazol-1-yl) propan-2-yl) isoquinoline-5-sulfonamide (***A1B3***)* Yellow oil, yield: 59%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.58 (d, $J = 6.0$ Hz, 1H), 8.40 (d, $J = 7.0$ Hz, 1H), 8.36 (d, $J = 6.0$ Hz, 1H), 8.18 (d, $J = 8.0$ Hz, 1H), 7.67 (t, $J = 8.0$ Hz, 1H), 7.60 (s, 1H), 4.37 (d, $J = 5.0$ Hz, 1H), 3.80–3.74 (m, 1H), 3.51–3.44 (m, 2H), 2.41 (t, $J = 5.0$ Hz, 4H), 1.53–1.51 (m, 4H), 1.39 (m, 2H), 0.98 (d, $J = 7.0$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 415.2.

*(S)-N-(1-(4-(Morpholinomethyl) -1H-1,2,3-triazol-1-yl) propan-2-yl) isoquinoline-5-sulfonamide (***A1B4***)* Yellow oil, yield: 59%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.61 (d, $J = 6.0$ Hz, 1H), 8.41 (d, $J = 7.0$ Hz, 1H), 8.36 (d, $J = 6.0$ Hz, 1H), 8.20 (d, $J = 8.0$ Hz, 1H), 7.76 (s, 1H), 7.69 (t, $J = 8.0$ Hz, 1H), 4.43–4.37 (m, 2H), 3.77–3.74 (m, 6H), 3.68–3.65 (m, 1H), 2.68–2.64 (m, 4H), 0.99 (d, $J = 6.5$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 417.2.

*(S)-N-(1-(4-((Benzyl(methyl)amino)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl) isoquinoline-5-sulfonamide (***A1B5***)* White solid, yield: 52%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.66 (d, $J = 6.0$ Hz, 1H), 8.42 (dd, $J = 7.5$, 1.0 Hz, 1H), 8.33 (d, $J = 6.0$ Hz, 1H), 8.17 (d, $J = 8.5$ Hz, 1H), 7.68–7.66 (m, 1H), 7.44 (s, 1H), 7.33–7.32 (m, 4H), 7.28–7.25 (m, 1H), 4.37 (dd, $J = 14$ Hz, 4.5 Hz, 1H), 4.32 (dd, $J = 14$ Hz, 5.5 Hz, 1H), 3.81–3.77 (m, 1H), 3.62 (d, $J = 15$ Hz, 1H), 3.58 (d, $J = 15$ Hz, 1H), 3.54 (s, 2H), 2.20 (s, 3H), 2.04 (d, $J = 7.0$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 451.3.

*N-(1-(4-((1-Phenyl-3,4-dihydro-1H-pyrido[3,4-b] indol-2(9H)-yl)methyl)-1H-1,2,3-triazol-1-yl) propan-2-yl) isoquinoline-5-sulfonamide (***A1B6***)* Light yellow solid, yield: 72%, a diastereomeric mixture (1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 1H, one isomer), 9.20 (s, 1H, another isomer), 8.62 (d, $J = 6.0$ Hz, 1H, one isomer), 8.59 (d, $J = 6.0$ Hz, 1H, another isomer), 8.41 (d, $J = 7.5$ Hz,

1H, one isomer), 8.38 (d, $J = 7.5$ Hz, 1H, another isomer), 8.28 (d, $J = 3.0$ Hz, 1H, one isomer), 8.27 (d, $J = 3.0$ Hz, 1H, another isomer), 8.12 (d, $J = 8.0$ Hz, 1H, one isomer), 8.05 (d, J = 8.0 Hz, 1H, another isomer), 7.65 (t, $J = 8.0$ Hz, 1H, one isomer), 7.60 (t, $J = 8.0$ Hz, 1H, another isomer), 7.50 (m, 2 × 2H), 7.36–7.31 (m, 2 × 6H), 7.19 (s, 1H, one isomer), 7.17 (s, 1H, another isomer), 7.12–7.09 (m, 2 × 2H), 5.67 (m, 2 × 1H), 4.69–4.62 (m, 2 × 1H), 4.38–4.24 (m, 2 × 2H), 3.83–3.73 (m, 2 × 1H), 3.65–3.60 (m, 2 × 1H), 3.21–3.18 (m, 2 × 1H), 2.91–2.88 (m, 1H), 2.82–2.79 (m, 1H), 2.75–2.73 (m, 1H), 1.05 (d, $J = 7.0$ Hz, 3H, one isomer), 0.99 (d, $J = 7.0$ Hz, 3H, another isomer). Some signals could not be separated. ESI-MS: m/z $[M + H]^+$ 578.3.

*(S)-N-(1-(4-((3,4-Dihydro-1H-pyrido[3,4-b]indol-2 (9H)-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl) isoquinoline-5-sulfonamide (***A1B7***)* Light yellow solid, yield: 40%. Mp: 125–127 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.66 (s, 1H), 8.56 (d, $J = 6.0$ Hz, 1H), 8.40 (d, $J = 7.0$ Hz, 1H), 8.31 (d, $J = 5.5$ Hz, 1H), 8.15 (d, $J = 8.0$ Hz, 1H), 7.66 (t, $J = 8.0$ Hz, 1H), 7.57 (s, 1H), 7.42 (d, $J = 7.5$ Hz, 1H), 7.30–7.27 (m, 1H), 7.10 (t, $J = 7.5$ Hz, 1H), 7.06 (t, $J = 7.5$ Hz, 1H), 4.34 (dd, $J = 14$, 4.0 Hz, 1H), 4.28 (dd, $J = 14$, 6.5 Hz, 1H), 3.84–3.80 (m, 2H), 3.75–3.70 (m, 1H), 3.60 (s, 2H), 2.94 (m, 2H), 2.80 (m, 2H), 0.95 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 145.1, 136.1, 134.7, 133.7, 133.2, 130.9, 128.9, 127.0, 126.0, 124.8, 121.4, 119.3, 118.0, 117.2, 110.9, 107.5, 54.8, 52.1, 51.3, 49.9, 49.5, 21.1, 18.7. ESI-MS: m/z $[M + H]^+$ 502.3.

*(S)-N-(1-(4-((4,5-Dihydrothieno[2,3-c] pyridin-6(7H)-yl) methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl) isoquinoline-5-sulfonamide (***A1B8***)* Light yellow solid, yield: 72%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.68 (d, $J = 6.0$ Hz, 1H), 8.43 (d, $J = 7.5$ Hz, 1H), 8.32 (d, $J = 5.5$ Hz, 1H), 8.21 (d, $J = 8.0$ Hz, 1H), 7.71–7.68 (m, 1H), 7.48 (s, 1H), 7.07 (d, $J = 4.5$ Hz, 1H), 6.76 (d, $J = 4.5$ Hz, 1H), 5.60–5.89 (m, 1H), 4.37 (dd, $J = 14$, 4.5 Hz, 1H), 4.30 (dd, $J = 14$, 5.5 Hz, 1H), 3.82–3.77 (m, 3H), 3.71 (s, 2H), 2.82 (t, $J = 5.5$ Hz, 2H), 2.73 (t, $J = 5.5$ Hz, 2H), 1.02 (d, $J = 6.5$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 469.2.

*(S)-N-(1-(4-((4-Phenylpiperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)isoquinoline-5-sulfonamide (***A1B9***)* Light yellow solid, yield: 55%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.68 (d, $J = 6.5$ Hz, 1H), 8.44 (d, $J = 7.0$ Hz, 1H), 8.33 (d, $J = 6.0$ Hz, 1H), 8.22 (d, $J = 8.5$ Hz, 1H), 7.72–7.69 (m, 1H), 7.51 (s, 1H), 7.25–7.23 (m, 2H), 6.91–6.89 (m, 2H), 6.86–6.83 (m, 1H), 4.40 (dd, $J = 14$, 4.5 Hz, 1H), 4.33 (dd, $J = 14$, 5.5 Hz, 1H), 3.83–3.77 (m, 1H), 3.66 (d, $J = 14$ Hz, 1H), 3.63 (d, $J = 14$ Hz, 1H), 3.18 (t, $J = 6.0$ Hz, 4H), 2.67 (t, $J = 6.0$ Hz, 4H), 1.01 (d, $J = 7.0$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 492.3.

*(S)-N-(1-(4-((4-(2-Fluorophenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)isoquinoline-5-sulfonamide (***A1B10***)* Yellow oil, yield: 46%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.69 (d, $J = 6.0$ Hz, 1H), 8.44 (d, $J = 7.5$ Hz, 1H), 8.33 (d, $J = 6.0$ Hz, 1H), 8.22 (d, $J = 8.0$ Hz, 1H), 7.72–6.91 (m, 1H), 7.48 (s, 1H), 7.04–6.98 (m, 2H), 6.94–6.92 (m, 2H), 5.53 (m, 1H), 4.40 (dd, $J = 14$, 4.5 Hz, 1H), 4.34 (dd, $J = 14$, 6.0 Hz, 1H), 3.83–3.82 (m,1H), 3.70–3.63 (m, 2H), 3.11 (s, 4H), 2.69 (s, 4H), 1.02 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6 (d, $J = 244.6$ Hz), 153.3, 145.3, 139.8 (d, $J = 8.0$ Hz), 134.6, 133.8, 133.2, 132.9, 131.0, 129.0, 125.9, 124.7, 124.5 (d, $J = 3.5$ Hz), 122.7 (d, $J = 7.4$ Hz), 119.0, 117.1, 116.1 (d, $J = 20.5$ Hz), 54.9, 52.9, 52.8, 50.0, 49.9, 19.0. ESI-MS: m/z $[M + H]^+$ 510.3.

*(S)-N-(1-(4-((4-(4-Fluorophenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)isoquinoline-5-sulfonamide (***A1B11***)* Yellow oil, yield: 58%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.59 (d, $J = 6.0$ Hz, 1H), 8.41–8.38 (m, 2H), 8.18 (d, $J = 8.0$ Hz, 1H), 7.80 (s, 1H), 7.67 (t, $J = 8.0$ Hz, 1H), 7.01–6.96 (m, 2H), 6.91–6.88 (m, 2H), 4.42–4.41 (m, 2H), 3.84 (d, $J = 14$ Hz, 1H), 3.78 (m, 1H), 3.74 (d, $J = 14$ Hz, 1H), 3.14 (t, $J = 5.0$ Hz, 4H), 2.86 (t, $J = 5.0$ Hz, 4H), 1.01 (d, $J = 6.5$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 510.3.

*(S)-N-(1-(4-((4-(4-Methoxyphenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)isoquinoline-5-sulfonamide (***A1B12***)* Yellow solid, yield: 74%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 6.68 (d, $J = 5.5$ Hz, 1H), 8.43 (d, $J = 7.0$ Hz, 1H), 8.21 (d, $J = 9.0$ Hz, 1H), 7.72–7.69 (m, 1H), 7.50 (s, 1H), 6.87 (d, $J = 9.0$ Hz, 2H), 6.82 (d, $J = 9.0$ Hz, 2H), 5.89 (m, 1H), 4.38 (dd, $J = 14$, 4.0 Hz, 1H), 4.32 (dd, $J = 14$, 5.5 Hz, 1H), 3.81–3.80 (m, 1H), 3.76 (s, 3H), 3.67 (d, $J = 8.5$ Hz, 1H), 3.63 (d, $J = 8.5$ Hz, 1H), 3.09 (t, $J = 5.0$ Hz, 4H), 2.67 (t, $J = 5.0$ Hz, 4H), 1.03 (d, $J = 6.5$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 522.3.

*(S)-N-(1-(4-((4-(4-Nitrophenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)isoquinoline-5-sulfonamide (***A1B13***)* Yellow solid, yield: 47%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.68 (d, $J = 6.0$ Hz, 1H), 8.43 (d, $J = 7.5$ Hz, 1H), 8.33 (d, $J = 6.0$ Hz, 1H), 8.22 (d, $J = 8.5$ Hz, 1H), 8.09 (d, $J = 9.0$ Hz, 2H), 7,72–7.69 (m, 1H), 7.56 (s, 1H), 6.79 (d, $J = 9.5$ Hz, 2H), 5.72 (m, 1H), 4.41 (dd, $J = 14$, 4.5 Hz, 1H), 4.34 (dd, $J = 14$, 6.0 Hz, 1H), 3.80 (m, 1H), 3.69 (d, $J = 14$ Hz, 1H), 3.65 (d, $J = 14$ Hz,

1H), 3.43 (t, $J = 5.0$ Hz, 4H), 2.68 (t, $J = 5.0$ Hz, 4H), 1.01 (d, $J = 6.5$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 537.3.

*(S)-N-(1-(4-((4-(4-(Trifluoromethyl)phenyl)piperazin-1-yl) methyl)-1H-1,2,3-triazol-1-yl) propan-2-yl)isoquinoline-5-sulfonamide (***A1B14***)* Light yellow solid, yield: 80%. Mp: 102–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.67 (d, $J = 6.0$ Hz, 1H), 8.44 (d, $J = 7.2$ Hz, 1H), 8.34 (d, $J = 6.0$ Hz, 1H), 8.22 (d, $J = 8.0$ Hz, 1H), 7.72–7.68 (d, $J = 7.2$ Hz, 1H), 7.55 (s, 1H), 7.46 (d, $J = 8.8$ Hz, 2H), 6.89 (d, $J = 8.8$ Hz, 2H), 5.90 (m, 1H), 4.41 (dd, $J = 14$, 4.4 Hz, 1H), 4.34 (dd, $J = 14$, 5.6 Hz, 1H), 4.14–4.09 (m, 2H), 3.27 (t, $J = 4.8$ Hz, 4H), 2.67 (t, $J = 4.8$ Hz, 4H), 1.01 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 153.1, 145.0, 143.5, 134.8, 133.7, 133.1, 131.0, 129.0, 126.4, 126.3, 124.6 ($J = 269$ Hz), 124.5, 120.6 (q, $J = 32.5$ Hz), 117.2, 114.6, 55.0, 52.8, 52.5, 49.9, 47.7, 18.9. ESI-MS: m/z $[M + H]^+$ 560.3.

*(S)-N-(1-(4-((4-(Naphthalen-1-yl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)isoquinoline-5-sulfonamide (***A1B15***)* Light yellow solid, yield: 68%. Mp: 115–117 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.70 (d, $J = 6.0$ Hz, 1H), 8.45 (d, $J = 7.0$ Hz, 1H), 8.34 (d, $J = 6.0$ Hz, 1H), 8.21 (d, $J = 8.0$ Hz, 1H), 8.17–8.16 (m, 1H), 7.82–7.80 (m, 1H), 7.72–7.69 (m, 1H), 7.55–5.53 (m, 2H), 7.46–7.44 (m, 2H), 7.38 (t, $J = 8.0$ Hz, 1H), 7.06 (d, $J = 7.5$ Hz, 1H), 5.60 (m, 1H), 4.41 (dd, $J = 14$, 4.5 Hz, 1H), 4.34 (dd, $J = 14$, 5.5 Hz, 1H), 3.83–3.80 (m, 1H), 3.75 (d, $J = 14$ Hz, 1H), 3.72 (d, $J = 14$ Hz, 1H), 3.14 (s, 4H), 2.81 (s, 4H), 1.03 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 149.1, 145.1, 142.9, 134.8, 134.7, 133.7, 133.6, 133.1, 131.0, 129.0, 128.7, 128.4, 126.0, 125.9, 125.4, 125.0, 123.7, 123.4, 117.3, 114.7, 54.9, 53.2, 52.8, 52.3, 50.0, 19.0. ESI-MS: m/z $[M + H]^+$ 542.4.

*(S)-N-(1-(4-((4-(Naphthalen-2-yl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)isoquinoline-5-sulfonamide (***A1B16***)* Light yellow solid, yield: 57%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.60 (d, $J = 6.5$ Hz, 1H), 8.40 (d, $J = 6.5$ Hz, 1H), 8.38 (d, $J = 6.5$ Hz, 1H), 8.16 (d, $J = 6.5$ Hz, 1H), 7.78 (s, 1H), 7.69–7.67 (m, 2H), 7.65–7.64 (m, 2H), 7.37 (t, $J = 7.5$ Hz, 1H), 7.28 (d, $J = 7.5$ Hz, 1H), 7.19 (dd, $J = 9.0$, 2.5 Hz, 1H), 7.07 (d, $J = 2.5$ Hz, 1H), 6.19 (m, 1H), 4.42 (dd, $J = 14$, 4.5 Hz, 1H), 4.37 (dd, $J = 14$, 6.5 Hz, 1H), 3.80 (d, $J = 17.5$ Hz, 1H), 3.77–3.73 (m, 2H), 3.31 (t, $J = 5.0$ Hz, 4H), 2.85 (t, $J = 5.0$ Hz, 4H), 0.97 (d, $J = 6.5$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 542.3.

*(S)-N-(1-(4-((4-(4-Bromonaphthalen-1-yl)piperazin-1-yl) methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)isoquinoline-5-sulfonamide (***A1B17***)* Light yellow solid, yield: 52%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.70 (d, $J = 6.0$ Hz, 1H), 8.45 (d, $J = 7.5$ Hz, 1H), 8.33 (d, $J = 6.0$ Hz, 1H), 8.23–8.18 (m, 3H), 7.72–7.66 (m, 2H), 7.58–7.55 (m, 1H), 7.52–7.51 (m, 1H), 7.48–7.44 (m, 1H), 6.92 (d, $J = 8.0$ Hz, 1H), 5.47 (m, 1H), 4.41 (dd, $J = 14$, 4.5 Hz, 1H), 4.33 (dd, $J = 14$, 5.5 Hz, 1H), 3.82–3.81 (m, 1H), 3.76–3.72 (m, 2H), 3.11 (m, 4H), 2.80 (m, 4H), 1.02 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 149.4, 145.2, 134.7, 133.7, 133.2, 132.8, 131.0, 130.1, 129.7, 129.0, 127.7, 127.3, 126.2, 126.0, 124.7, 123.9, 117.4, 117.2, 115.5, 114.7, 54.9, 53.2, 52.9, 52.5, 50.0, 19.0. ESI-MS: m/z $[M + H]^+$ 620.2.

*(S)-N-(1-(4-((4-(6-Bromonaphthalen-2-yl)piperazin-1-yl) methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)isoquinoline-5-sulfonamide (***A1B18***)* Light yellow solid, yield: 55%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.69 (d, $J = 5.5$ Hz, 1H), 8.43 (d, $J = 7.5$ Hz, 1H), 8.36 (d, $J = 6.0$ Hz, 1H), 8.21 (d, $J = 8.0$ Hz, 1H), 7.85 (s, 1H), 7.71–7.68 (m, 2H), 7.61 (d, $J = 9.0$ Hz, 1H), 7.52 (d, $J = 9.0$ Hz, 1H), 7.44 (dd, $J = 9.0$, 2.0 Hz, 1H), 7.23 (dd, $J = 9.0$, 2.0 Hz, 1H), 7.04 (s, 1H), 4.41 (d, $J = 14$ Hz, 1H), 4.37 (d, $J = 14$ Hz, 1H), 3.82–3.80 (m, 2H), 3.72–3.70 (m, 1H), 3.50 (t, $J = 5.0$ Hz, 4H), 2.81 (t, $J = 5.0$ Hz, 4H), 1.04 (d, $J = 7.0$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 620.0.

*(S)-N-(1-(4-((Diethylamino)methyl)-1H-1,2,3-triazol-1-yl) propan-2-yl)benzenesulfonamide (***A2B1***)* Yellow oil, yield: 73%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.80 (m, 2H), 7.60 (s, 1H), 7.55–7.52 (m, 1H), 7.48–7.45 (m, 2H), 4.41–4.35 (m, 2H), 3.78–3.76 (m, 3H), 2.57 (q, $J = 7.0$ Hz, 4H), 1.08 (t, $J = 7.0$ Hz, 6H), 1.02 (d, $J = 7.0$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 352.2.

*(S)-N-(1-(4-((4-Methylpiperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)benzenesulfonamide (***A2B2***)* Yellow oil, yield: 68%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.81 (m, 2H), 7.56–7.54 (m, 2H), 7.50–7.46 (m, 2H), 4.42 (dd, $J = 14$, 5.0 Hz, 1H), 4.36 (dd, $J = 14$, 5.5 Hz, 1H), 3.75–3.72 (m, 1H), 3.66 (m, 2H), 2.54–2.47 (m, 8H), 2.27 (s, 3H), 1.02 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 140.5, 132.7, 129.2, 126.9, 124.5, 54.9, 54.6, 52.7, 51.8, 49.8, 45.5, 18.5. ESI-MS: m/z $[M + H]^+$ 379.3.

*(S)-N-(1-(4-(Piperidin-1-ylmethyl)-1H-1,2,3-triazol-1-yl) propan-2-yl)benzenesulfonamide (***A2B3***)* Light yellow solid, yield: 59%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.81 (m, 2H), 7.64 (s, 1H), 7.56–7.53 (m, 1H), 7.50–7.46 (m, 2H), 4.41 (dd, $J = 14$, 5.0 Hz, 1H), 4.37 (dd, $J = 14$, 6.0 Hz, 1H), 3.78–3.75 (m, 1H), 3.70 (d, $J = 14$ Hz, 1H), 3.64 (d, $J = 14$ Hz, 1H), 2.51 (t, $J = 5.5$ Hz, 4H), 1.59

(t, $J = 5.5$ Hz, 4H), 1.02 (d, $J = 7.0$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 364.3.

*(S)-N-(1-(4-(Morpholinomethyl)-1H-1,2,3-triazol-1-yl) propan-2-yl)benzenesulfonamide (***A2B4***)* Light yellow solid, yield: 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80–7.79 (m, 2H), 7.57 (s, 1H), 7.56–7.52 (m, 1H), 7.49–7.45 (m, 2H), 5.85 (m, 1H), 4.41 (dd, $J = 14$, 5.0 Hz, 1H), 4.36 (dd, $J = 14$, 6.0 Hz, 1H), 3.76–3.72 (m, 1H), 3.66 (t, $J = 4.5$ Hz, 4H), 3.63–3.57 (m, 2H), 2.47 (t, $J = 4.5$ Hz, 4H), 1.02 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 140.4, 132.8, 129.2, 126.8, 124.4, 66.8, 54.9, 53.4, 53.2, 49.8, 18.6. ESI-MS: m/z $[M + H]^+$ 366.2.

*(S)-N-(1-(4-((Benzyl(methyl)amino)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)benzenesulfonamide (***A2B5***)* Light yellow solid, yield: 72%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.81 (m, 2H), 7.53–7.50 (m, 2H), 7.48–7.45 (m, 2H), 7.33–7.30 (m, 4H), 7.25 (m, 1H), 4.40 (dd, $J = 14$, 6.0 Hz, 1H), 4.35 (dd, $J = 14$, 5.5 Hz, 1H), 3.79–3.75 (m, 1H), 3.69 (d, $J = 14.5$ Hz, 1H), 3.65 (d, $J = 14.5$ Hz, 1H), 3.55 (s, 2H), 2.22 (s, 3H), 1.05 (d, $J = 7.0$ Hz, 1H). ESI-MS: m/z $[M + H]^+$ 400.3.

*N-(1-,(4-((1-Phenyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl) benzenesulfonamide (***A2B6***)* Light yellow solid, yield: 48%. A diastereomeric mixture (1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.78 (m, 2 × 2H), 7.52–7.49 (m, 2 × 2H), 7.46–7.42 (m, 2 × 6H), 7.40–7.33 (m, 2 × 4H), 7.30–7.29 (m, 2 × 1H), 7.17–7.16 (m, 2 × 1H), 7.10–7.07 (m, 2 × 2H), 5.08 (m, 1H, one isomer), 4.94 (m, 1H, another isomer), 4.73 (s, 2H), 4.40–4.37 (m, 2 × 1H), 4.34–4.29 (m, 2 × 1H), 3.87–3.83 (m, 2 × 1H), 3.77–3.69 (m, 2 × 2H), 3.30–3.27 (m, 2 × 1H), 2.97–2.91 (m, 2 × 1H), 2.84–2.74 (m, 2 × 2H), 1.05 (d, $J = 7.0$ Hz, 3H, one isomer), 1.03 (d, $J = 7.0$ Hz, 3H, another isomer). ESI-MS: m/z $[M + H]^+$ 527.3.

*(S)-N-(1-(4-((3,4-Dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl) benzenesulfonamide (***A2B7***)* Light yellow solid, yield: 45%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.82 (d, $J = 7.0$ Hz, 2H), 7.57–7.54 (m, 2H), 7.49–7.46 (m, 2H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.28 (d, $J = 8.0$ Hz, 1H), 7.13–7.10 (m, 1H), 7.08–7.05 (m, 1H), 5.34 (m, 1H), 4.41 (dd, $J = 14$, 4.5 Hz, 1H), 4.32 (dd, $J = 14$, 5.5 Hz, 1H), 3.91 (s, 2H), 3.73 (m, 1H), 3.68 (d, $J = 15$ Hz, 1H), 3.63 (d, $J = 15$ Hz, 1H), 2.97 (t, $J = 5.5$ Hz, 2H), 2.82 (t, $J = 5.5$ Hz, 2H), 1.01 (d, $J = 6.5$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 451.2.

*(S)-N-(1-(4-((4,5-Dihydrothieno[2,3-c]pyridin-6(7H)-yl) methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl) benzenesulfonamide (***A2B8***)* Light yellow solid, yield: 45%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, $J = 8.0$ Hz, 2H), 7.58–7.54 (m, 2H), 7.49–7.46 (m, 2H), 7.08 (d, $J = 4.0$ Hz, 1H), 6.76 (d, $J = 4.0$ Hz, 1H), 5.52 (m, 1H), 4.40–4.34 (m, 2H), 3.85 (s, 2H), 3.76–3.73 (m, 3H), 2.84 (t, $J = 6.0$ Hz, 2H), 2.74 (t, $J = 6.0$ Hz, 2H), 1.04 (d, $J = 6.5$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 418.2.

*(S)-N-(1-(4-((4-Phenylpiperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)benzenesulfonamide (***A2B9***)* Light yellow solid, yield: 58%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.82 (m, 2H), 7.61–7.56 (m, 2H), 7.52–7.48 (m, 2H), 7.24–7.23 (m, 2H), 6.92–6.90 (m, 2H), 6.86–6.83 (m, 1H), 4.43 (dd, $J = 14$, 4.5 Hz, 1H), 4.37 (dd, $J = 14$, 5.5 Hz, 1H), 3.78–3.77 (m, 1H), 3.72 (d, $J = 14$ Hz, 1H), 3.70 (d, $J = 14$ Hz, 1H), 3.19 (t, $J = 6.0$ Hz, 4H), 2.67 (t, $J = 6.0$ Hz, 4H), 1.05 (d, $J = 7.0$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 441.3.

*(S)-N-(1-(4-((4-(2-Fluorophenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)benzenesulfonamide (***A2B10***)* Light yellow solid, yield: 61%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.83 (m, 2H), 7.72 (s, 1H), 7.57–7.54 (m, 1H), 7.50–7.47 (m, 2H), 7.05–6.98 (m, 2H), 6.94–6.91 (m, 2H), 5.76 (m, 1H), 4.44–4.42 (m, 2H), 3.84–3.72 (m, 3H), 3.16 (t, $J = 5.0$ Hz, 4H), 2.80 (t, $J = 5.0$ Hz, 4H), 1.06 (d, $J = 7.0$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 459.2.

*(S)-N-(1-(4-((4-(4-Fluorophenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)benzenesulfonamide (***A2B11***)* Light yellow solid, yield: 59%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.83 (m, 2H), 7.59–7.58 (m, 2H), 7.52–7.50 (m, 2H), 6.94–6.92 (m, 2H), 6.87–6.85 (m, 2H), 5.20 (m, 1H), 4.44 (dd, $J = 14$, 5.0 Hz, 1H), 4.37 (dd, $J = 14$, 5.5 Hz, 1H), 3.77 (m, 1H), 3.74 (d, $J = 14$ Hz, 1H), 3.71 (d, $J = 14$ Hz, 1H), 3.12 (t, $J = 5.0$ Hz, 4H), 2.68 (t, $J = 5.0$ Hz, 4H), 1.06 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2 (d, $J = 241.1$ Hz), 147.9, 140.2, 132.9, 129.3, 126.9, 124.4, 117.9 (d, $J = 7.4$ Hz), 115.5 (d, $J = 21.9$ Hz), 54.9, 53.1, 52.8, 50.0, 49.7, 18.8. ESI-MS: m/z $[M + H]^+$ 459.2.

*(S)-N-(1-(4-((4-(4-Methoxyphenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)benzenesulfonamide (***A2B12***)* Off-white solid, yield: 65%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.84 (m, 2H), 7.58–7.56 (m, 2H), 7.52–7.49 (m, 2H), 6.88 (d, $J = 9.0$ Hz, 2H), 6.82 (d, $J = 9.0$ Hz, 2H), 5.09 (m, 1H), 4.43 (dd, $J = 14$, 4.5 Hz, 1H), 4.37 (dd, $J = 14$, 5.5 Hz, 1H), 3.76–3.74 (m, 3H), 3.11 (t, $J = 5.0$ Hz,

4H), 2.70 (t, $J = 5.0$ Hz, 4H), 1.07 (d, $J = 7.0$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 471.3.

*(S)-N-(1-(4-((4-(4-Nitrophenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)benzenesulfonamide(***A2B13***)* Yellow solid, yield: 48%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, $J = 9.0$ Hz, 2H), 7.84 (d, $J = 7.0$ Hz, 2H), 7.61 (s, 1H), 7.60–7.58 (m, 1H), 7.53–7.50 (m, 2H), 6.80 (d, $J = 9.0$ Hz, 2H), 4.90 (d, $J = 7.0$ Hz, 1H), 4.47 (dd, $J = 14, 4.5$ Hz, 1H), 4.37 (dd, $J = 14, 5.5$ Hz, 1H), 3.81–3.76 (m, 1H), 3.75–3.71 (m, 2H), 3.43 (t, $J = 5.0$ Hz, 4H), 2.67 (t, $J = 5.0$ Hz, 4H), 1.06 (d, $J = 7.0$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 486.3.

*(S)-N-(1-(4-((4-(4-(Trifluoromethyl)phenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl) benzenesulfonamide (***A2B14***)* Light yellow solid, yield: 82%. Mp: 167–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, $J = 7.6$ Hz, 2H), 7.59–7.57 (m, 2H), 7.53–7.45 (m, 4H), 6.89 (d, $J = 8.4$ Hz, 2H), 5.15 (d, $J = 7.2$ Hz, 1H), 4.45 (dd, $J = 14, 4.8$ Hz, 1H), 4.37 (dd, $J = 14, 5.6$ Hz, 1H), 3.79–3.76 (m, 1H), 3.72–3.68 (m, 2H), 3.28 (t, $J = 4.4$ Hz, 4H), 2.66 (t, $J = 4.4$ Hz, 4H), 1.06 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 144.1, 140.3, 132.9, 129.3, 126.8, 126.4, 124.7 (q, $J = 269$ Hz), 124.3, 120.4 (q, $J = 35.4$ Hz), 114.5, 54.9, 53.1, 52.5, 49.8, 47.8, 18.7. ESI-MS: m/z $[M + H]^+$ 509.3.

*(S)-N-(1-(4-((4-(Naphthalen-1-yl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)benzenesulfonamide (***A2B15***)* Light yellow solid, yield: 75%. Mp: 174–176 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19–8.17 (m, 1H), 7.85 (d, $J = 7.5$ Hz, 2H), 7.82–7.80 (m, 1H), 7.60 (s, 1H), 7.58–7.56 (m, 1H), 7.55–7.49 (m, 3H), 7.46–7.45 (m, 2H), 7.40–7.37 (m, 1H), 7.07 (d, $J = 7.5$ Hz, 1H), 5.07 (m, 1H), 4.45 (dd, $J = 14, 4.5$ Hz, 1H), 4.38 (dd, $J = 14.0, 5.5$ Hz, 1H), 3.81–3.78 (m, 3H), 3.15 (s, 4H), 2.82 (s, 4H), 1.08 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 143.9, 140.3, 134.7, 132.8, 129.3, 128.8, 128.4, 126.9, 125.8, 125.4, 124.5, 123.6, 123.5, 114.7, 54.9, 53.4, 53.2, 52.6, 49.7, 18.8. ESI-MS: m/z $[M + H]^+$ 491.3.

*(S)-N-(1-(4-((4-(Naphthalen-2-yl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)benzenesulfonamide (***A2B16***)* Light yellow solid, yield: 52%. Mp: 112–114 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.84 (m, 2H), 7.72–7.66 (m, 3H), 7.59–7.56 (m, 2H), 7.52–7.49 (m, 2H), 7.40–7.37 (m, 1H), 7.29–7.28 (m, 1H), 7.25–7.23 (m, 1H), 7.10 (m, 1H), 5.13 (d, $J = 7.0$ Hz, 1H), 4.44 (dd, $J = 14, 4.5$ Hz, 1H), 4.38 (dd, $J = 14, 5.5$ Hz, 1H), 3.81–3.73 (m, 3H), 3.31 (t, $J = 4.5$ Hz, 4H), 2.74 (t, $J = 4.5$ Hz, 4H), 1.06 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 140.4, 134.5, 132.8, 129.2, 128.7, 128.6, 127.4, 126.8, 126.7, 126.3, 124.7, 123.5, 123.4, 119.4, 110.4, 55.0, 53.0, 52.7, 49.8, 49.2, 18.7. ESI-MS: m/z $[M + H]^+$ 491.3.

*(S)-N-(1-(4-((4-(4-Bromonaphthalen-1-yl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl) benzenesulfonamide (***A2B17***)* Light yellow solid, yield: 66%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21–8.19 (m, 2H), 7.85–7.84 (m, 2H), 7.66 (d, $J = 8.0$ Hz, 1H), 7.61 (s, 1H), 7.57–7.54 (m, 2H), 7.52–7.49 (m, 3H), 3.92 (d, $J = 8.0$ Hz, 1H), 5.24 (m, 1H), 4.45 (dd, $J = 14, 4.5$ Hz, 1H), 4.39 (dd, $J = 14, 5.5$ Hz, 1H), 3.82–3.76 (m, 3H), 3.11 (t, $J = 4.5$ Hz, 4H), 2.81 (t, $J = 4.5$ Hz, 4H), 1.07 (d, $J = 7.0$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 569.2.

*(S)-N-(1-(4-((4-(6-Bromonaphthalen-2-yl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl) benzenesulfonamide (***A2B18***)* Light yellow solid, yield: 52%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.83 (m, 3H), 7.62–7.57 (m, 3H), 7.54–7.49 (m, 3H), 7.44 (dd, $J = 9.0, 2.0$ Hz, 1H), 7.24 (d, $J = 2.0$ Hz, 1H), 7.04 (m, 1H), 4.46 (dd, $J = 14, 4.5$ Hz, 1H), 4.38 (dd, $J = 14, 5.5$ Hz, 1H), 3.78–3.72 (m, 3H), 3.30 (t, $J = 4.5$ Hz, 4H), 2.73 (t, $J = 4.5$ Hz, 4H), 1.04 (d, $J = 6.5$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 569.2.

*(S)-N-(1-(4-((4-(4-Nitrophenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)methanesulfonamide(***A3B13***)* Yellow solid, yield: 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, $J = 9.6$ Hz, 2H), 7.68 (s, 1H), 6.80 (d, $J = 9.6$ Hz, 2H), 4.97 (d, $J = 8.0$ Hz, 1H), 4.53 (dd, $J = 14, 4.8$ Hz, 1H), 4.41 (dd, $J = 14, 6.4$ Hz, 1H), 4.01–3.98 (m, 1H), 3.76 (s, 2H), 3.42 (t, $J = 4.8$ Hz, 4H), 2.87 (s, 3H), 2.68 (t, $J = 4.8$ Hz, 4H), 1.32 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 144.0, 138.4, 126.0, 124.4, 112.7, 55.2, 53.0, 52.3, 50.1, 46.9, 41.6, 19.5. ESI-MS: m/z $[M + H]^+$ 424.2.

*(S)-N-(1-(4-((4-(4-(Trifluoromethyl)phenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl) methanesulfonamide (***A3B14***)* Light yellow solid, yield: 49%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.46 (d, $J = 8.4$ Hz, 2H), 6.90 (d, $J = 8.4$ Hz, 2H), 4.91 (d, $J = 8.0$ Hz, 1H), 4.53 (dd, $J = 14, 4.4$ Hz, 1H), 4.41 (dd, $J = 14, 6.4$ Hz, 1H), 4.01–3.98 (m, 1H), 3.74 (s, 2H), 3.28 (t, $J = 4.8$ Hz, 4H), 2.86 (s, 3H), 2.67 (t, $J = 4.8$ Hz, 4H), 1.31 (d, $J = 6.8$ Hz, 3H). ESI-MS: m/z $[M + H]^+$ 447.2.

*(S)-N-(1-(4-((4-(Naphthalen-1-yl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)methanesulfonamide (***A3B15***)* Light yellow solid, yield: 67%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, $J = 6.0, 3.0$ Hz, 1H), 7.81 (dd, $J = 6.0, 3.0$ Hz, 1H), 7.68 (s, 1H), 7.54 (d, $J = 8.0$ Hz, 1H), 7.47–7.44 (m, 2H), 7.40–7.37 (m, 1H), 7.07 (d, $J = 7.0$ Hz, 1H), 4.86 (m, 1H), 4.54 (dd, $J = 14, 4.5$ Hz, 1H), 4.42 (dd,

J = 14, 6.5 Hz, 1H), 4.03–4.01 (m, 1H), 3.85 (s, 2H), 3.15 (t, J = 4.5 Hz, 4H), 2.86 (t, J = 4.5 Hz, 4H), 1.93 (s, 3H), 1.32 (d, J = 7.0 Hz, 3H). ESI-MS: m/z $[M + H]^+$ 429.3.

*(S)-N-(1-(4-((4-(Naphthalen-2-yl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)methanesulfonamide (***A3B16***)* Light yellow solid, yield: 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.72–7.66 (m, 3H), 7.41–7.37 (m, 1H), 7.31–7.22 (m, 2H), 7.10 (s, 1H), 5.32–5.30 (m, 1H), 4.53 (dd, J = 14, 4.4 Hz, 1H), 4.43 (dd, J = 14, 6.8 Hz, 1H), 4.02–3.99 (m, 1H), 3.88 (d, J = 14.8 Hz, 1H), 3.84 (d, J = 14.8 Hz, 1H), 3.34 (t, J = 4.8 Hz, 4H), 2.84 (t, J = 4.8 Hz, 4H), 2.29 (s, 3H), 1.30 (d, J = 6.8 Hz, 3H). ESI-MS: m/z $[M + H]^+$ 429.2.

*(S)-N-(1-(4-((4-(4-Bromonaphthalen-1-yl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)methanesulfonamide (***A3B17***)* Light yellow solid, yield: 46%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21–8.18 (m, 2H), 7.73 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.58–7.55 (m, 1H), 7.53–7.50 (m, 1H), 6.92 (d, J = 8.0 Hz, 1H), 4.53 (dd, J = 14, 4.5 Hz, 1H), 4.43 (dd, J = 14, 7.0 Hz, 1H), 4.00 (m, 1H), 3.86 (d, J = 14.0 Hz, 1H), 3.83 (d, J = 14 Hz, 1H), 3.12 (t, J = 4.5 Hz, 4H), 2.25 (t, J = 4.5 Hz, 4H), 2.84 (s, 3H), 1.31 (d, J = 7.0 Hz, 3H). ESI-MS : m/z $[M + H]^+$ 507.2.

*(S)-N-(1-(4-((4-(6-Bromonaphthalen-2-yl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)methanesulfonamide (***A3B18***)* Light yellow solid, yield: 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.71 (s, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.26–7.24 (m, 1H), 7.05 (s, 1H), 4.86 (d, J = 8.0 Hz, 1H), 4.54 (dd, J = 14, 4.4 Hz, 1H), 4.42 (dd, J = 14, 6.0 Hz, 1H), 4.04–3.98 (m, 1H), 3.86–3.78 (m, 2H), 3.32 (m, 4H), 2.87 (s, 3H), 2.78 (m, 4H), 1.30 (d, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 133.0, 129.6, 129.5, 129.4, 128.4, 127.9, 124.8, 122.3, 120.1, 112.6, 110.2, 55.3, 53.0, 52.7, 50.0, 48.8, 41.7, 19.5. ESI-MS: m/z $[M + H]^+$ 507.2.

*(S)-N-(1-(4-((Diethylamino)methyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropan-2-yl)methanesulfonamide (***A4B1***)* Light yellow solid, yield: 49%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.35–7.32 (m, 2H), 7.28–7.23 (m, 3H), 4.55 (dd, J = 14, 4.5 Hz, 1H), 4.50 (dd, J = 14, 5.5 Hz, 1H), 4.07–4.02 (m, 1H), 3.89 (d, J = 14.5 Hz, 1H), 3.86 (d, J = 14.5 Hz, 1H), 2.93 (dd, J = 14, 5.5 Hz, 1H), 2.71 (dd, J = 14, 9.0 Hz, 1H), 2.68–2.63 (m, 4H), 2.34 (s, 3H), 1.13 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 136.8, 129.6, 128.9, 127.3, 125.0, 56.2, 54.1, 47.3, 46.5, 40.7, 39.2, 11.2. ESI-MS: m/z $[M + H]^+$ 366.3.

*(S)-N-(1-(4-((4-Methylpiperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropan-2-yl)methanesulfonamide (***A4B2***)* Yellow oil, yield: 50%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.35–7.32 (m, 2H), 7.29–7.25 (m, 3H), 6.17 (m, 1H), 4.56 (dd, J = 14 Hz, 4.5 Hz, 1H), 4.52 (dd, J = 14, 5.0 Hz, 1H), 4.00 (m, 1H), 3.82 (d, J = 14 Hz, 1H), 3.79 (d, J = 14 Hz, 1H), 2.97 (dd, J = 14 Hz, 1H), 2.78–2.71 (m, 9H), 2.38 (s, 3H), 2.33 (s, 3H). ESI-MS: m/z $[M+H]^+$ 393.5.

*(S)-N-(1-Phenyl-3-(4-(piperidin-1-ylmethyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)methanesulfonamide (***A4B3***)* Light yellow solid, yield: 88%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.34–7.31 (m, 2H), 7.28–7.23 (m, 3H), 4.55 (dd, J = 14, 4.5 Hz, 1H), 4.48 (dd, J = 14, 5.5 Hz, 1H), 4.04–4.02 (m, 1H), 3.65 (d, J = 14 Hz, 1H), 3.61 (d, J = 14 Hz, 1H), 2.95 (dd, J = 14, 5.5 Hz, 1H), 2.75 (dd, J = 14, 9.0 Hz, 1H), 2.46 (s, 4H), 2.32 (s, 3H), 1.57 (t, J = 5.5 Hz, 4H), 1.42 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 136.9, 129.6, 129.0, 127.3, 124.5, 56.2, 54.2, 54.1, 53.8, 40.6, 39.3, 25.8, 24.1. ESI-MS: m/z $[M + H]^+$ 378.3.

*(S)-N-(1-(4-(Morpholinomethyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropan-2-yl)methanesulfonamide (***A4B4***)* White solid, yield: 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.34–7.31 (m, 2H), 7.28–7.24 (m, 3H), 5.59–5.55 (m, 1H), 4.56 (dd, J = 14, 4.5 Hz, 1H), 4.49 (dd, J = 14, 5.5 Hz, 1H), 4.02 (d, J = 4.0 Hz, 1H), 3.69–3.62 (m, 6H), 2.98 (dd, J = 14, 5.5 Hz, 1H), 2.80 (dd, J = 14, 4.5 Hz, 1H), 2.51 (t, J = 5.0 Hz, 4H), 2.29 (s, 3H). ESI-MS: m/z $[M + H]^+$ 380.3.

*(S)-N-(1-(4-((Benzyl(methyl)amino)methyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropan-2-yl)methanesulfonamide (***A4B5***)* White solid, yield: 60%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.35–7.30 (m, 6H), 7.28–7.25 (m, 2H), 7.23–7.21 (m, 2H), 5.17 (m, 1H), 4.55 (dd, J = 14, 4.5 Hz, 1H), 4.47 (dd, J = 14, 5.5 Hz, 1H), 4.05 (m, 1H), 3.75 (d, J = 14 Hz, 1H), 3.71 (d, J = 14 Hz, 1H), 3.58 (s, 2H), 2.95 (dd, J = 14, 6.0 Hz, 1H), 2.77 (dd, J = 14, 8.5 Hz, 1H), 2.36 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 138.5, 136.8, 129.6, 129.0, 128.9, 128.3, 127.4, 127.1, 124.4, 61.4, 56.2, 54.1, 51.9, 42.0, 40.7, 39.3. ESI-MS: m/z $[M + H]^+$ 414.2.

*N-(1-Phenyl-3-(4-((1-phenyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)methyl)-1H-1,2,3-triazol-1-yl) propan-2-yl) methanesulfonamide (***A4B6***)* Light yellow solid, yield: 49%. A diastereomeric mixture (1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.49 (m, 2 × 2H), 7.43–7.41 (m, 2 × 2H), 7.37–7.31 (m, 2 × 6H), 7.28–7.25 (m, 2 × 1H), 7.22–7.20 (m, 2 × 2H), 7.16–7.15 (m, 2 × 1H), 7.10–7.07 (m, 2 × 2H), 5.21 (d, J = 7.5 Hz, 1H, one isomer), 5.13 (d, J = 7.5 Hz, 1H, another isomer), 4.75 (s, 2 × 1H), 4.53–4.49 (m, 2 × 1H),

4.44–4.39 (m, 2 × 1H), 4.04 (m, 2 × 1H), 3.91–3.87 (m, 2 × 1H), 3.77–3.73 (m, 2 × 1H), 3.32–3.29 (m, 2 × 1H), 2.95–2.90 (m, 2 × 2H), 2.81–2.74 (m, 2 × 3H), 2.32 (s, 3H, one isomer), 2.31 (s, 3H, another isomer). Some signals could not be separated. ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 140.8, 136.5, 136.3, 134.6, 129.5, 129.2, 129.0, 128.8, 128.2, 127.4, 127.1, 124.4, 121.5, 119.3, 118.3, 110.8, 108.7, 63.5, 63.3, 56.1, 53.9, 48.8, 40.7, 39.3, 21.2. ESI-MS: m/z $[M + H]^+$ 541.3.

*(S)-N-(1-(4-((3,4-Dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)methyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropan-2-yl) methanesulfonamide (***A4B7***)* Light yellow solid, yield: 55%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.54 (s, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.31–7.26 (m, 4H), 7.20–7.19 (m, 2H), 7.13–7.10 (m, 1H), 7.08–7.05 (m, 1H), 5.70 (m, 1H), 4.45 (dd, J = 14, 4.5 Hz, 1H), 4.37 (dd, J = 14, 6.0 Hz, 1H), 3.96 (m, 1H), 3.88 (s, 2H), 3.58 (d, J = 14.5 Hz, 1H), 3.52 (d, J = 14.5 Hz, 1H), 2.96–2.89 (m, 3H), 2.84–2.78 (m, 3H), 2.32 (s, 3H). ESI-MS: m/z $[M + H]^+$ 465.2.

*(S)-N-(1-(4-((4,5-Dihydrothieno[2,3-c]pyridin-6(7H)-yl) methyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropan-2-yl) methanesulfonamide (***A4B8***)* Light yellow solid, yield: 68%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.35–7.32 (m, 2H), 7.28–7.27 (m, 1H), 7.24–7.22 (m, 2H), 7.08 (d, J = 5.0 Hz, 1H), 6.76 (d, J = 5.0 Hz, 1H), 5.15 (d, J = 8.0 Hz, 1H), 4.55 (dd, J = 14, 4.5 Hz, 1H), 4.46 (dd, J = 14, 5.5 Hz, 1H), 4.07–4.03 (m, 1H), 3.91 (d, J = 15 Hz, 1H), 3.88 (d, J = 15 Hz, 1H), 3.76 (s, 2H), 2.96 (dd, J = 14, 6.0 Hz, 1H), 2.86 (t, J = 6.0 Hz, 2H), 2.80 (dd, J = 14, 6.0 Hz, 1H), 2.75 (t, J = 6.0 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 137.0, 133.3, 132.2, 129.6, 128.9, 127.3, 126.9, 125.0, 122.6, 56.5, 54.2, 51.9, 51.7, 50.0, 40.6, 39.3, 25.2. ESI-MS: m/z $[M + H]^+$ 432.2.

*(S)-N-(1-Phenyl-3-(4-((4-phenylpiperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)methanesulfonamide (***A4B9***)* Light yellow solid, yield: 51%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.35–7.32 (m, 2H), 7.29–7.26 (m, 1H), 7.25–7.23 (m, 4H), 6.92–6.90 (m, 2H), 6.86–6.83 (m, 1H), 5.22 (d, J = 7.5 Hz, 1H), 4.57 (dd, J = 14, 5.0 Hz, 1H), 4.49 (dd, J = 14, 5.5 Hz, 1H), 4.05 (m, 1H), 3.77 (d, J = 14 Hz, 1H), 3.74 (d, J = 14 Hz, 1H), 3.20 (t, J = 5.0 Hz, 4H), 2.98 (dd, J = 14, 6.0 Hz, 1H), 2.78 (dd, J = 14, 9.0 Hz, 1H), 2.70 (t, J = 5.0 Hz, 4H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 144.2, 136.8, 129.6, 129.1, 129.0, 127.4, 124.8, 119.8, 116.1, 56.3, 54.2, 53.1, 52.9, 49.0, 40.6, 39.2. ESI-MS: m/z $[M + H]^+$ 455.4.

*(S)-N-(1-(4-((4-(2-Fluorophenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropan-2-yl)methanesulfonamide (***A4B10***)* Light yellow solid, yield: 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.35–7.32 (m, 2H), 7.29–7.27 (m,1H), 7.25–7.23 (m, 2H), 7.05–7.01 (m, 2H), 6.95–6.90 (m, 2H), 5.20 (d, J = 8.0 Hz, 1H), 4.57 (dd, J = 14, 4.5 Hz, 1H), 4.50 (dd, J = 14, 5.5 Hz, 1H), 4.06–4.04 (m, 1H), 3.80 (d, J = 14 Hz, 1H), 3.77 (d, J = 14 Hz, 1H), 3.12 (t, J = 4.5 Hz, 4H), 2.98 (dd, J = 14, 6.0 Hz, 1H), 2.79–2.74 (m, 5H), 2.36 (s, 3H). ESI-MS: m/z $[M + H]^+$ 473.3.

*(S)-N-(1-(4-((4-(4-Fluorophenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropan-2-yl) methanesulfolinebreak namide (***A4B11***)* Light yellow solid, yield: 42%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.35–7.32 (m, 2H), 7.28–7.24 (m, 3H), 6.96–6.92 (m, 2H), 6.86–6.84 (m, 2H), 5.25 (m, 1H), 4.57 (dd, J = 14, 4.5 Hz, 1H), 4.50 (dd, J = 14, 6.0 Hz, 1H), 4.03 (m, 1H), 3.78 (d, J = 14 Hz, 1H), 3.75 (d, J = 14 Hz, 1H), 3.12 (t, J = 5.0 Hz, 4H), 2.98 (dd, J = 14, 6.0 Hz, 1H), 2.79 (dd, J = 14, 9 Hz, 1H), 2.71 (t, J = 5.0 Hz, 4H), 2.35 (s, 3H). ESI-MS: m/z $[M + H]^+$ 473.3.

*(S)-N-(1-(4-((4-(4-Methoxyphenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropan-2-yl) methanesulfolinebreak namide (***A4B12***)* Off-white solid, yield: 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.35–7.32 (m, 2H), 7.29–7.27 (m, 1H), 7.25–7.24 (m, 2H), 6.88 (d, J = 9.0 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 5.21 (d, J = 7.5 Hz, 1H), 4.56 (dd, J = 14, 4.5 Hz, 1H), 4.90 (dd, J = 14, 5.5 Hz, 1H), 4.06–4.05 (m, 1H), 3.81–3.77 (m, 2H), 3.76 (s, 3H), 3.10 (s, 4H), 2.97 (dd, J = 14, 5.5 Hz, 1H), 2.80 (dd, J = 14, 8.5 Hz, 1H), 2.72 (s, 4H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 145.5, 143.9, 136.9, 129.6, 129.0, 127.3, 124.9, 118.2, 114.4, 56.3, 55.6, 54.2, 53.0, 52.9, 50.4, 40.7, 39.3. ESI-MS: m/z $[M + H]^+$ 485.3.

*(S)-N-(1-(4-((4-(4-Nitrophenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropan-2-yl)methanesulfonamide (***A4B13***)* Light yellow solid, yield: 79%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 9.0 Hz, 2H), 7.64 (s, 1H), 7.36–7.33 (m, 2H), 7.30–7.29 (m, 1H), 7.24–7.23 (m, 2H), 6.80 (d, J = 9.0 Hz, 2H), 4.88 (d, J = 8.5 Hz, 1H), 4.59 (dd, J = 14, 5.5 Hz, 1H), 4.49 (dd, J = 14, 6.0 Hz, 1H), 4.07–4.03 (m, 1H), 3.78 (d, J = 14.5 Hz, 1H), 3.75 (d, J = 14.5 Hz, 1H), 3.43 (t, J = 5.0 Hz, 4H), 3.01 (dd, J = 14, 5.5 Hz, 1H), 2.77 (dd, J = 14, 9.0 Hz, 1H), 2.36 (s, 3H). ESI-MS: m/z $[M + H]^+$ 500.3.

(S)-N-(1-Phenyl-3-(4-((4-(4-(trifluoromethyl)phenyl) piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)

*methanesulfonamide (***A4B14***)* Light yellow solid, yield: 78%. Mp: 194–196 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.46 (d, J = 8.8 Hz, 2H), 7.34–7.29 (m, 2H), 7.28–7.24 (m, 3H), 6.90 (d, J = 8.8 Hz, 2H), 5.22 (d, J = 8.4 Hz, 1H), 4.58 (dd, J = 14, 4.4 Hz, 1H), 4.50 (dd, J = 14, 5.6 Hz, 1H), 4.08–4.02 (m, 1H), 3.77 (d, J = 14.4 Hz, 1H), 3.73 (d, J = 14.4 Hz, 1H), 3.28 (t, J = 4.8 Hz, 4H), 3.00 (dd, J = 14, 5.6 Hz, 1H), 2.80 (dd, J = 14, 8.8 Hz, 1H), 2.68 (t, J = 4.8 Hz, 4H), 2.34 (s, 3H). ^{13}C NMR (125 Hz, $CDCl_3$) δ 153.2, 144.2, 136.9, 129.6, 129.0, 127.4, 126.4, 124.8 (q, J = 269 Hz), 124.7, 120.4 (q, J = 32.5 Hz), 114.5, 56.4, 54.3, 53.0, 52.5, 47.8, 40.7, 39.2. ESI-MS: m/z $[M + H]^+$ 523.3.

*(S)-N-(1-(4-((4-(Naphthalen-1-yl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropan-2-yl) methanesulfolinebreak namide (***A4B15***)* Light yellow solid, yield: 81%. Mp: 96–98 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19–8.17 (m, 1H), 7.82–7.80 (m, 1H), 7.67 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.46–7.44 (m, 2H), 7.40–7.33 (m, 3H), 7.29 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 7.5 Hz, 2H), 7.08 (d, J = 7.0 Hz, 1H), 4.97 (m, 1H), 4.59 (dd, J = 14, 4.5 Hz, 1H), 4.50 (dd, J = 14, 5.5 Hz, 1H), 4.01–4.07 (m, 1H), 3.89–3.83 (m, 2H), 3.16 (s, 4H), 2.99 (dd, J = 14, 5.5 Hz, 1H), 2.85 (s, 4H), 2.77 (dd, J = 14, 8.5 Hz, 1H), 1.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 143.7, 136.9, 134.7, 129.6, 129.0, 128.8, 128.4, 127.4, 125.8, 125.4, 125.1, 123.6, 123.5, 114.7, 56.4, 54.2, 53.3, 53.0, 52.5, 40.7, 39.3. ESI-MS: m/z $[M + H]^+$ 505.3.

*(S)-N-(1-(4-((4-(Naphthalen-2-yl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropan-2-yl)methanesulfonamide (***A4B16***)* Off-white solid, yield: 48%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.57 (s, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.29–7.27 (m, 1H), 7.24– 7.20 (m, 1H), 7.16–7.14 (m, 2H), 6.91 (d, J = 8.5 Hz, 1H), 6.83 (s, 1H), 5.25 (d, J = 8.5 Hz, 1H), 4.55–4.49 (m, 3H), 4.41 (dd, J = 14, 5.0 Hz, 1H), 3.99 (m, 1H), 2.92 (dd, J = 17.5, 5.0 Hz, 1H), 2.76 (dd, J = 17.5, 9.0 Hz, 1H), 2.28 (s, 3H). ESI-MS: m/z $[M + H]^+$ 505.3.

*(S)-N-(1-(4-((4-(4-Bromonaphthalen-1-yl)piperazin-1-yl) methyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropan-2-yl) methanesulfonamide (***A4B17***)* Light yellow solid, yield: 42%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21–8.19 (m, 2H), 7.69–7.66 (m, 2H), 7.58–7.55 (m, 1H), 7.52–7.49 (m, 1H), 7.36–7.32 (m, 3H), 7.28 (d, J = 7.5 Hz, 1H), 7.25–7.23 (m, 2H), 6.93 (d, J = 8.0 Hz, 1H), 5.11 (m, 1H), 4.59 (dd, J = 14, 5.0 Hz, 1H), 4.51 (dd, J = 14, 5.5 Hz, 1H), 4.07 (m, 1H), 3.85–3.84 (m, 2H), 3.11 (t, J = 4.5 Hz, 4H), 2.99 (dd, J = 14, 6.0 Hz, 1H), 2.82 (t, J = 4.5 Hz, 4H), 2.80 (dd, J = 14, 9.0 Hz, 1H), 2.37 (s, 3H). ESI-MS: m/z $[M + H]^+$ 583.2.

*(S)-N-(1-(4-((4-(6-Bromonaphthalen-2-yl)piperazin-1-yl) methyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropan-2-yl)methanesulfonamide (***A4B18***)* Light yellow solid, yield: 51%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.68 (s, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.44 (dd, J = 9.0, 6.5 Hz, 1H), 7.36–7.33 (m, 2H), 7.30–7.24 (m, 4H), 7.05 (s, 1H), 5.12 (d, J = 8.5 Hz, 1H), 4.59 (dd, J = 14, 4.5 Hz, 1H), 4.51 (dd, J = 14, 5.0 Hz, 1H), 4.06–4.05 (m, 1H), 3.81 (d, J = 14 Hz, 1H), 3.78 (d, J = 14 Hz, 1H), 3.31 (t, J = 5.0 Hz, 4H), 2.30 (dd, J = 14, 5.5 Hz, 1H), 2.79–2.76 (m, 5H), 1.81 (s, 3H). ESI-MS: m/z $[M + H]^+$ 583.2.

Cytotoxic activity

All cell lines (HL60, HepG2, A549, PC3, SGC7901) were obtained from Shanghai Institute of Cell Biology, Chinese Academy of Sciences (Shanghai, China), and cultured in proper medium in a humidified atmosphere containing 5% CO_2. The cytotoxic activity was measured using the MTT assay. 20 μL MTT at 5 mg/mL in PBS was added per well after cells were treated with drug for 72 h, and the cells were incubated for another 4 h at 37 °C. After the medium was discarded, 100 μL DMSO was added. The optical density (OD) of the resultant solution was measured at a wavelength of 570 nm with a microplate reader (Bio-Tek Instruments, Winooski, VT). In all of these experiments, three replicate wells were used to determine each point. Taxol was used as a positive control and tested in the same manner.

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