



Highly efficient azido-Ugi multicomponent reactions for the synthesis of bioactive tetrazoles bearing sulfonamide scaffolds

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ABSTRACT

Recent studies revealed that the contribution of the different bioactive scaffolds in one structure creates modern drugs/compounds with unique synergistic biological properties. In this regard, thanks to the interesting biological and medicinal properties of sulfonamide and tetrazole skeletons, this study describes the engagement of sulfonamides in the Ugi tetrazole reaction to access a library of tetrazole bearing sulfonamide. This four-component reaction was performed in a one-pot among available starting material, i.e., an isocyanide, a sulfonamide, an aldehyde and sodium azide in MeOH at 45 °C using ZnCl₂ as a catalyst, for the synthesis of very versatile products with high atom economy and yields. The key point in this strategy is the formation of an intermediate Schiff base and its activation in the azido-Ugi reaction by a Lewis acid catalyst. Importantly, all products are purified through the group-assisted purification (GAP) chemistry, which can avoid traditional purification such as recrystallization and chromatography methods. Also, the docking study between the synthesized compounds and human serum albumin (HSA) was stimulated to theoretically rationalize their biological activity and potential binding interactions.

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1. Introduction

Tetrazoles have been known as an important class of unsaturated five-membered aromatic heterocycles with four nitrogen atoms in the ring [1]. They are significant synthetic scaffolds finding broad applications in numerous fields such as medicinal chemistry, biochemistry, pharmacology [2], organometallic [3], coordination chemistry [4], organocatalysis [5,6], and materials chemistry (photography, and imaging chemicals) [7–9]. Also, tetrazoles are investigated as rocket propellant components and environmentally friendly fuel in a gas generator [10–12]. However, the most important and useful application of tetrazoles with many future outlooks is their utility in medicinal chemistry [13,14]. Moreover, sulfonamide-based scaffolds are another core part of many clinical drugs, which have a wide range of applications in medicine, pharmacology, and pharmaceuticals such as antiviral, anti-inflammatory, antibacterial, antifungal, anti-cancer, anti-epileptic

drug, anticonvulsant, receptor tyrosine kinase inhibitors, and antitumor [15–17]. During recent years studies discovered that the contribution of the different bioactive scaffolds in one structure creates modern drugs/compounds with unique synergistic biological properties. In this regard, due to the interesting biological and medicinal properties of sulfonamide and tetrazole skeletons, they have created modern drugs and bioactive compounds with unique synergistic biological properties when these structures are assembled in one molecule [18]. Recently, these compounds have potentially been employed as diuretic agents azosemide (a drugs loop diuretic used to treat hypertension, edema, and ascites) [19], experimental drugs on 1,3-dehydroquinone dehydratase [1], propionates antimicrobial [20], PTP1B inhibitors [21] and inhibitor of death-associated protein kinase 3 (DAPK3) (Fig. 1) [22]. The synthesis of these types of tetrazole bearing sulfonamide structures is rarely reported in the literature; thus, this is a pristine and very attractive field for synthesizing and studying innovative biological properties of this class of structures.

According to the applications of tetrazole and sulfonamide, the synthesis of conjugated structure has concerned a significant interest. In this regard, the application of multicomponent reaction

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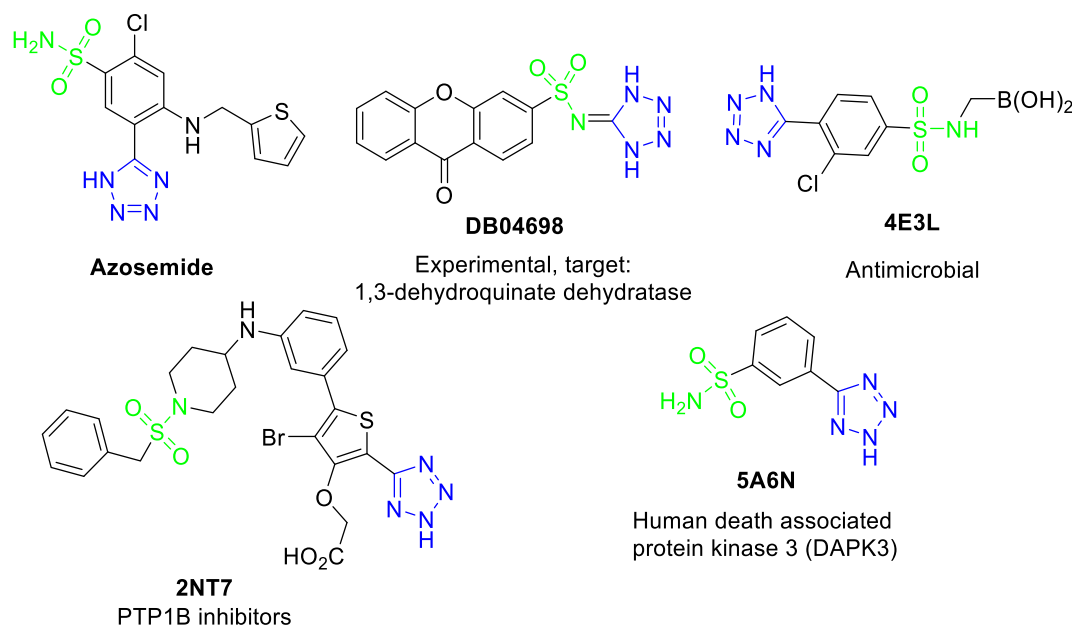


Fig. 1. Representative natural products and bioactive compounds.

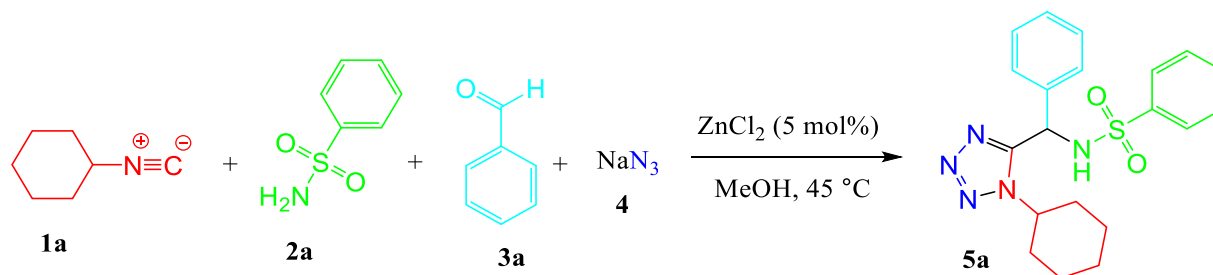
(MCRs) is known and they are a very efficient approach for the synthesis of numerous kinds of complex molecules [23–25]. It is well established that MCRs chemistry has several advantages over sequential step-by-step chemistry. They show a high grade of variety due to the nature of the starting materials as well as they are one-pot, mild, high atom economy and avoid purification of all intermediate products [26–28]. The Ugi four-component reactions (U-4CR) is a well-known MCR since it has a very powerful tool and efficient for making peptides and peptide mimics [29–31]. In the classical Ugi reaction, the replacement of carboxylic acids with other compounds such as azide, carbonic acid, and phenol opens up a new avenue for the synthesis of diverse U-4CR products (tetrazole, pseudo-peptide, etc.). Furthermore, in classical U-4CR, a wide diversity of primary amines can be successfully employed [32,33]. However, NH_3 already gives poor to no yield or hydroxylamine, *N*-acylated hydrazine, *N*-sulfonated hydrazine gives mixed or poor yields [34–38]. Usually, these types of processes require an activating agent to successfully advance the reaction. Various synthetic approaches have been developed for this transformation. Most of them are performed through activation of the amine by different Lewis acids. Recently, Dömling reported an efficient method for the synthesis of tetrazoles using catalytic amounts of ZnCl_2 in methanol [39]. These features make U-4CR as a potent tool to be utilized in designing and constructing tetrazole bearing sulfonamides through selecting appropriate starting compounds like azide and sulfonamide. In our continuing interest in sulfonamide chemistry and designing new MCRs for the synthesis of heterocycles [40–48], we have previously reported a two-step protocol for the synthesis of 1,5-disubstituted tetrazoles containing β -sulfonamide via an isocyanide-based multicomponent reaction (I-MCRs) [49]. But we report here our findings of the first successful use of sulfonamide in the azido-Ugi reaction (AU-4CR) to yield a tetrazole bearing sulfonamide in a one-pot protocol, performing among an isocyanide **1a**, a sulfonamide **2a**, an aldehyde **3a**, and sodium azide **4a** in MeOH using ZnCl_2 as a catalyst at 45 °C (Scheme 1). In this method, sulfonamide (as an inactive amine) was purposefully used instead of ordinary amine. It is noteworthy that this synthesis procedure was also designed to follow the GAP chemistry, which can avoid traditional purification such as recrystallization and chromatography

methods [50,51].

2. Results and discussion

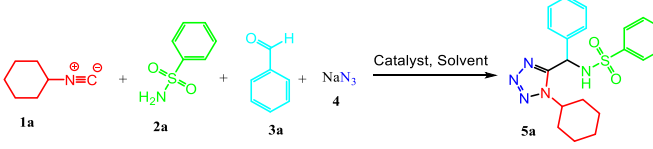
Initially, we evaluated the four-component reaction of cyclohexyl isocyanide **1a**, benzenesulfonamide **2a**, benzaldehyde **3a** and sodium azide **4a**. The reaction mixture containing a 1:1:1:1 mixture of **1a**, **2a**, **3a** and **4a** was investigated in various conditions and obtained results are summarized in Table 1. The optimization process indicated that the reaction did not occur in MeOH under catalyst-free conditions even by raising temperature (Table 1, Entries 1 and 2). Also, the reaction did not proceed in the presence of acid catalysts ($\text{PTSA} \cdot \text{H}_2\text{O}$ and HCl) in MeOH after 24 h (Table 1, Entries 3 and 4). In continuation, a 5 mol% of various Lewis acid catalysts such as FeCl_3 , InCl_3 , SnCl_2 and ZnCl_2 were examined that only the reaction was occurred in the presence of ZnCl_2 and the product **5a** was obtained in an acceptable yield (Table 1, Entry 9). The reaction was investigated in various solvents such as CH_3CN , EtOH, toluene, water and under the neat conditions at 60 °C (Table 1, Entries 10–14). Among all the solvents, methanol was found to be an optimum medium in terms of yield and reaction efficiency. We proceeded further to optimize the increasing temperature. Subsequently, by increasing temperature from 25 °C to 45 °C the yield of product **5a** was improved over 72% after 6 h, (Table 1, Entry 16). On the other hand, the reaction under reflux conditions was tested and no significant change was observed in the reaction yield (Table 1, Entry 17). For the effectiveness of the Zn catalyst, a variety of Zn salts including $\text{Zn}(\text{OAc})_2$, $\text{Zn}(\text{OTf})_2$, and $\text{Zn}(\text{NO}_3)_2$ were also investigated. A comparatively high yield was obtained in the presence of $\text{Zn}(\text{NO}_3)_2$ at 45 °C in methanol (Table 1, Entry 18–20). However, since ZnCl_2 is safer and more economical than $\text{Zn}(\text{NO}_3)_2$, it was considered as a suitable catalyst for the synthesis of tetrazoles. It is worth mentioning that product **5a** was isolated via GAP chemistry, which can avoid traditional purification such as recrystallization and chromatography methods [50,52,53].

Upon optimization of the reaction conditions, we investigated the scope and limitations of the four-component reaction synthesis of tetrazole bearing sulfonamide **5**. These reactions were extended to various isocyanides **1**, sulfonamides **2**, and aldehydes **3** (Scheme



Scheme 1. The model reaction for the synthesis of tetrazole bearing sulfonamide.

Table 1
Optimization of the second step reaction conditions^a.



Entry	Catalyst (mol%)	Solvent	T (°C)	Time (h)	Yield ^b (%)
1	—	MeOH	25	24	0
2	—	MeOH	reflux	24	0
3	HCl (5)	MeOH	25	24	0
4	PTSA.H ₂ O (5)	MeOH	25	24	0
5	FeCl ₃ (5)	MeOH	25	24	Trace
6	AlCl ₃ (5)	MeOH	25	24	Trace
7	InCl ₃ (5)	MeOH	25	24	23
8	SnCl ₂ (5)	MeOH	25	24	17
9	ZnCl ₂ (5)	MeOH	25	24	40
10	ZnCl ₂ (5)	EtOH	25	24	25
11	ZnCl ₂ (5)	MeCN	25	24	15
12	ZnCl ₂ (5)	Toluene	25	24	10
13	ZnCl ₂ (5)	H ₂ O	25	24	—
14	ZnCl ₂ (5)	—	60	24	25
15	ZnCl ₂ (5)	MeOH	45	24	73
16	ZnCl ₂ (5)	MeOH	45	6	72
17	ZnCl ₂ (5)	MeOH	reflux	6	70
18	Zn(OAc) ₂ (5)	MeOH	45	6	25
19	Zn(OTf) ₂ (5)	MeOH	45	6	65
20	Zn(NO ₃) ₂ (5)	MeOH	45	6	71

^a Conditions: The one-pot four-component domino reaction: **1a** (0.25 mmol), **2a** (0.25 mmol), **3a** (0.25 mmol), **4a** (0.25 mmol), 2 mL solvent. ^b Isolated yields.

2), the results are summarized in Scheme 3. The aromatic aldehydes with substituent electron-withdrawing groups and halogens (NO₂, F, Cl and Br) and electron-donating groups (Me, OMe) were investigated for preparing the desired product (Scheme 3). In this strategy, increasing the electron-withdrawing effect of substituents on the benzaldehyde leads to an increase in the yield of the final products. But, the electron-donating effect of substituents on the benzaldehyde leads to a drastic reduction in the yield of the final products. To further explore the versatility of this protocol, the feasibility of variation of aldehyde to aliphatic aldehydes was investigated (Scheme 2), which they well tolerated under the reaction conditions and afforded the desired products in satisfactory yields (Scheme 3). Interestingly, placing the substituent electron donor groups in the sulfonamide **2** increases afforded the desired yields for products [54]. A different trend was observed for the isocyanides, whereas the yields obtained of products for the cyclohexyl isocyanide **1a** were excellent, but relatively lower yields were obtained using *tert*-butyl isocyanide **1b**.

For example, the structure of compound **5g** confirming by their analytical and spectral data was considered in this section. The

mass spectra of **5g** displayed the molecular ion peak at 412 for M⁺ consistent with the molecular structure. The IR spectrum of **5g** displayed characteristic absorption bands at 3332, 1598, 1327, and 1158 cm⁻¹ due to NH, N=N and SO₂ stretching vibrations, respectively. The ¹H NMR spectrum of **5g** consisted of signals for the cyclohexyl ring (δ = 1.13–1.88 ppm, 10H) and signals with multiple splitting for NH–CH (δ = 4.90–4.61 ppm, 1H); the two singlet peaks (δ = 2.29, and δ = 6.16 ppm) for the –CH₃ and CH_{Bn} groups, respectively; the peaks for aromatic protons (δ = 7.17–7.53, 9H) and a signal for the NH group (δ = 9.19 ppm, bs, 1H). The ¹³C NMR spectrum of **5g** revealed characteristic signals at 57.2 and 51.2 ppm due to the presence of C–N_{cyclohexyl} and C_{Bn}, respectively.

Finally, the structure of **5g** was unambiguously verified by single-crystal X-ray analysis, displaying in Fig. 2 (Detailed information can be seen in the Supporting Information).

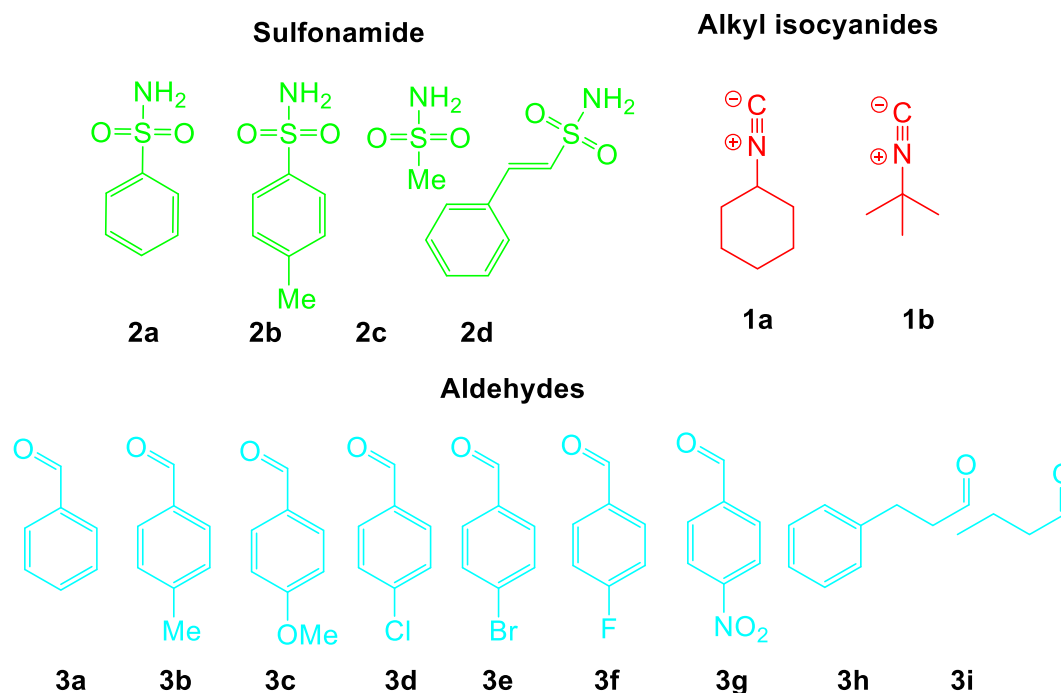
The proposed mechanism for the formation of **5** is shown in Scheme 4 [55]. The first reaction is the condensation of sulfonamide **2** with aldehyde **3** in the presence of ZnCl₂ for the formation of a Schiff base **7** that is a key intermediate in all Ugi-type multicomponent reactions. Upon Schiff base **7** activation by Lewis acid (ZnCl₂), the isocyanide attacks the activated Schiff base **8** (imine) to form the intermediate nitrilium ion **9**, the process is then followed in the presence of azide ion [39]. Finally, the Ugi tetrazole product **5** is prepared by an irreversible sigmatropic rearrangement.

3. Molecular docking

Molecular docking is a technique that calculates the binding of a molecule with a specific direction to another (macro)molecule, arranging a stable complex [56]. This simulation is essentially used to estimate either interaction or binding between a ligand and targeted protein [57,58]. In human plasma, HSA is the most significant carrier of endogenous and exogenous molecules. Therefore, molecular docking was performed on the synthesized compounds (**5a–p**) with HSA to theoretically rationalize their biological activity and potential binding interactions. Docking results in binding with HAS protein were summarized in Table S1. The synthesized compounds **5a–p** have a MolDock Score from –86.63 to 108.52. Among the tested compounds, compound **5l** that binds with Lys 439 amino acid residue showed a higher MolDock Score (108.52) and hydrogen bonding (–8.96), Fig. 3. Results revealed that the tetrazole, sulfonamide and also polar groups like nitroxide effectively enhanced the binding ability of ligand with protein. The findings of the docking study may develop the theoretical understanding of the pharmacokinetic properties of tetrazole bearing sulfonamide scaffolds and also their possible clinical application as an effective therapeutic agent.

4. Conclusions

In summary, an efficient synthesis of tetrazole bearing



Scheme 2. The variety of reactants.

sulfonamide *via* a AU-4CR has been developed in this work. The AU-4CR carried out among the isocyanide, sulfonamide, aldehyde, and sodium azide in MeOH using ZnCl_2 as a catalyst at 45 °C, for producing high diversity of tetrazoles. In this protocol, the bottleneck is Schiff base (as a key intermediate) formation, which is formed by the catalytic participation of Lewis acid (ZnCl_2) and subsequently activates it to continue the reaction. This reaction is done in a one-pot with high atom economy and available starting material for the synthesis of products with very versatile and high yielding products. All products are purified through GAP chemistry. Besides, the docking investigation revealed the binding ability of the synthesized compounds with HAS protein.

5. Experimental section

5.1. Materials and methods

All commercially available chemicals and reagents were purchased from Merck Co. and used without further purification. Melting points were measured with an Electrothermal 9200 apparatus. Fourier-transform infrared (FT-IR) spectra were recorded on a THERMO NICOLET spectrophotometer in cm^{-1} . ^1H NMR spectra were recorded on a Bruker DRX-500 and BRUKER DRX-300 AVANCE spectrometer at 500 and 300.13 MHz. ^{13}C NMR spectra were recorded on Bruker DRX-500 and DRX-300 Avance spectrometers at 125 and 75.47 MHz. NMR spectra were obtained in CDCl_3 and $\text{DMSO}-d_6$. Mass spectra of the products were obtained with an HP (Agilent technologies) 5937 Mass Selective Detector. Elemental analyses were performed on an elementaranalyse system GmbH VarioEL CHN mode.

5.2. Molecular docking

The docking study between the synthesized compounds and HSA were stimulated using the Molegro Virtual Docker version 2013. The three-dimensional (3D) crystal structure of HSA (PDB ID

code: 1A06) has been downloaded from Protein Data Bank (PDB) online. Afterward, structures of synthesized compounds **5a–p** were drawn in ChemBioDraw Ultra 14.0, copied to ChemBio3D Ultra 14.0, and minimized their energy then saved as Mol2 format. The possible binding sites of HSA were determined based on the established grid-based cavity prediction algorithm. According to the searching algorithm of MolDock Optimizer and energetic evaluation of the complex with MolDock, the finest binding pose of the formed complex between HAS and compounds was achieved.

5.3. Representative synthesis of (*E*)-2-phenylethene-1-sulfonamide (**2d**)

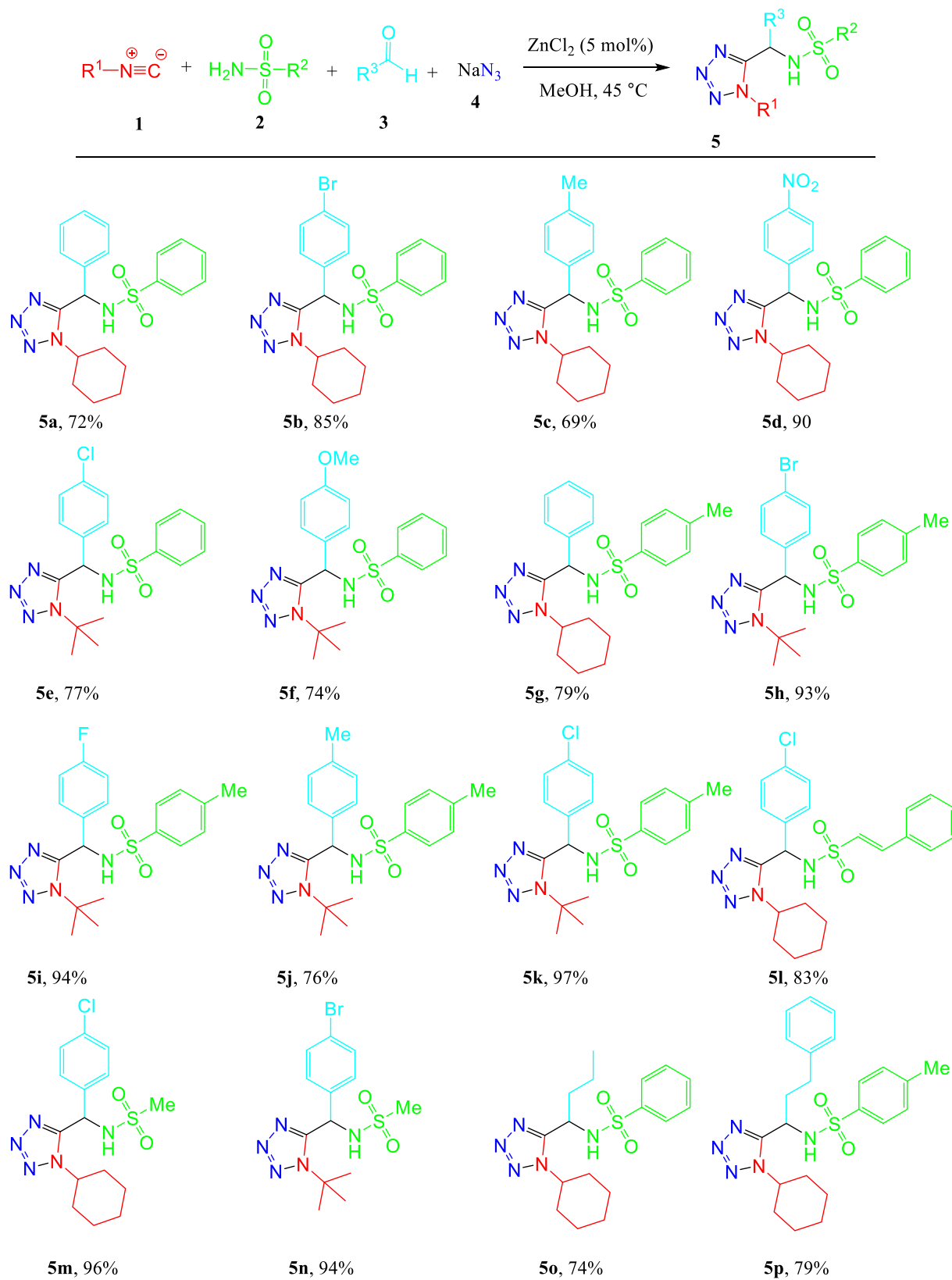
The (*E*)-2-phenylethene-1-sulfonyl chloride **12** was synthesized according to the reported methods [59]. Then, to of this synthesized compound **12** (1 mmol 202.6 mg), 1.2 mmol (20.0 mg) of ammonia was added. Afterward, the mixture was stirred for 4 h at 40 °C. Upon the completion of the reaction (monitored by TLC), the solid precipitate was filtered and washed with water (2 mL $\times$ 2) and dried to yield the pure product **2d** 179.3 mg, yield 98% [60].

5.4. Representative synthesis of *N*-((1-cyclohexyl-1H-tetrazol-5-yl)(phenyl)methyl)benzenesulfonamide (**5a**)

A mixture of cyclohexyl isocyanide **1a** (0.25 mmol, 27.2 mg), benzenesulfonamide **2a** (0.25 mmol, 39.2 mg), benzaldehyde **3a** (0.25 mmol, 26.5 mg), NaN_3 **4** (0.25 mmol, 16.2 mg) and ZnCl_2 (0.005 mmol, 1.6 mg) in MeOH (2 mL) was stirred for 6 h at 45 °C. Upon the completion of the reaction (monitored by TLC), the solid precipitate was filtered and washed with methanol (2 mL $\times$ 2) and dried to yield the pure product **5a** 71.4 mg, yield 72%.

5.4.1. *N*-((1-Cyclohexyl-1H-tetrazol-5-yl)(phenyl)methyl)benzenesulfonamide (**5a**)

White powder (71 mg, 72%); mp 297–299 °C. δ_{H} (DMSO, 300 MHz): 1.23–1.72 (m, 10H, $\text{H}_{\text{cyclohexyl}}$), 4.69 (bs, 1H, NHCH), 6.03

Scheme 3. Substrate Scope ^a.

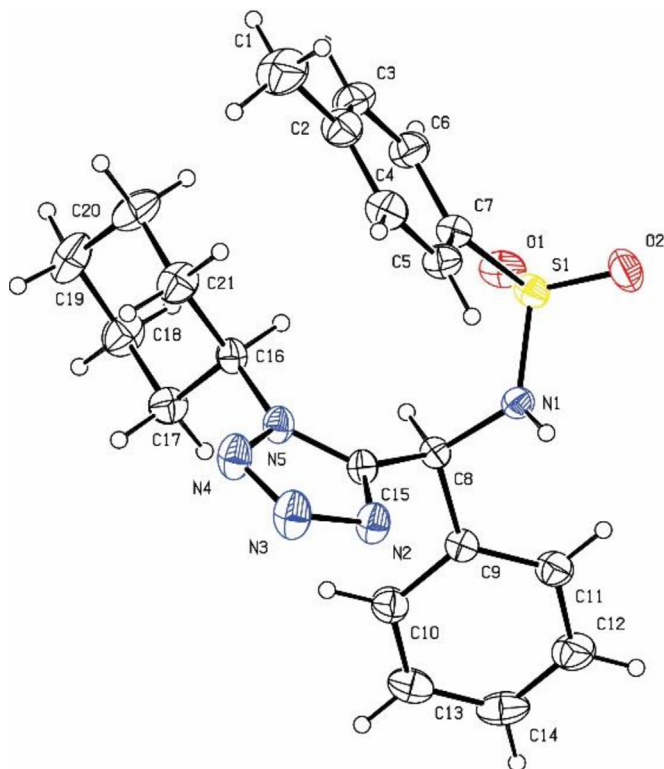


Fig. 2. X-ray crystal structure of compound **5g** (CCDC code. 2053125).

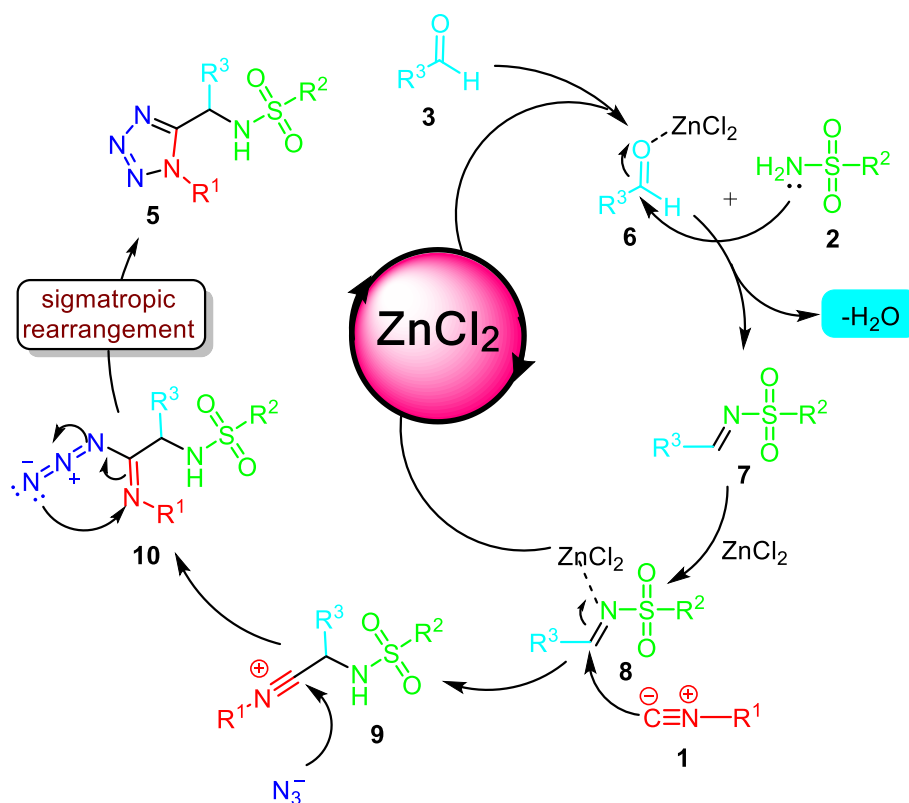
(s, 1H, CH_{Bn}), 7.13–7.29 (m, 7H, H_{Ar}), 7.57 (d, 2H, *J*=9 Hz, H_{Ar}), 7.84 (bs, 1H, NH). ¹³C NMR δ (75 MHz, DMSO) 156.31, 142.79, 137.95, 134.66, 132.42, 128.62, 127.93, 126.65, 124.36, 57.24 (NCH), 54.93 (CH_{Bn}), 33.72, 25.05, 24.92, 21.96. ν_{max} (ATR), 3468 (NH), 2933 (CH), 1558 (N=N), 1279, 1148 (SO₂) cm⁻¹. Found: C, 60.40; H, 5.80; N, 17.60. C₂₀H₂₃N₅O₂S requires C, 60.43; H, 5.83; N, 17.62%. *m/z* (EI, 70 eV) 397 (M⁺, 4.19), 313 (20.51), 246 (14.50), 236 (62.11), 112 (17.95), 84 (89.85), 57 (100).

5.4.2. *N*-((4-Bromophenyl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl) benzenesulfonamide (**5b**)

White powder (111 mg, 85%); mp 151–150 °C. δ_H (DMSO, 300 MHz): 1.20–1.45 (m, 3H, H_{cyclohexyl}), 1.65–1.86 (m, 6H, H_{cyclohexyl}), 1.94–1.98 (m, 1H, H_{cyclohexyl}), 4.62 (m, 1H, NHCH), 6.23 (s, 1H, CH_{Bn}), 7.25 (d, 2H, *J*=6 Hz, H_{Ar}), 7.37–7.41 (m, 4H, H_{Ar}), 7.48–7.53 (m, 1H, H_{Ar}), 7.62 (d, 2H, *J*=6 Hz, H_{Ar}), 9.30 (bs, 1H, NH). ¹³C NMR δ (75 MHz, DMSO) 153.87, 141.15, 136.10, 132.78, 131.48, 130.39, 129.32, 126.77, 121.83, 57.30 (NCH), 50.62 (CH_{Bn}), 32.94, 32.63, 25.12, 24.92. ν_{max} (ATR), 3248 (NH), 2952 (CH), 1590 (N=N), 1156, 1335 (SO₂) cm⁻¹. Found: C, 50.39; H, 4.63; N, 14.67. C₂₀H₂₂BrN₅O₂S requires C, 50.42; H, 4.65; N, 14.70%. *m/z* (EI, 70 eV) 477 (M⁺ [⁷⁹Br], 2.71), 475 (M⁺ [⁸¹Br], 2.04), 411 (12.67), 330 (9.81), 228 (28.89), 199 (100), 141 (26.47), 77 (67.01).

5.4.3. *N*-((1-Cyclohexyl-1H-tetrazol-5-yl)(*p*-tolyl)methyl) benzenesulfonamide (**5c**)

White powder (80 mg, 69%); mp 269–270 °C. δ_H (DMSO, 300 MHz): 1.24–1.73 (m, 10H, H_{cyclohexyl}), 2.23 (s, 3H, CH₃), 4.73 (bs, 1H, NHCH), 5.98 (s, 1H, CH_{Bn}), 7.04–7.34 (m, 6H, H_{Ar}), 7.59–7.87 (m, 3H, H_{Ar}), 9.24 (bs, 1H, NH). ¹³C NMR δ (75 MHz, DMSO) 155.96, 145.03, 136.98, 132.14, 129.41, 128.99, 128.56, 127.52, 126.47, 126.04, 56.88 (NCH), 52.38 (CH_{Bn}), 33.04, 32.28, 25.10, 21.07. ν_{max} (ATR),



Scheme 4. The plausible mechanism of compound **5**.

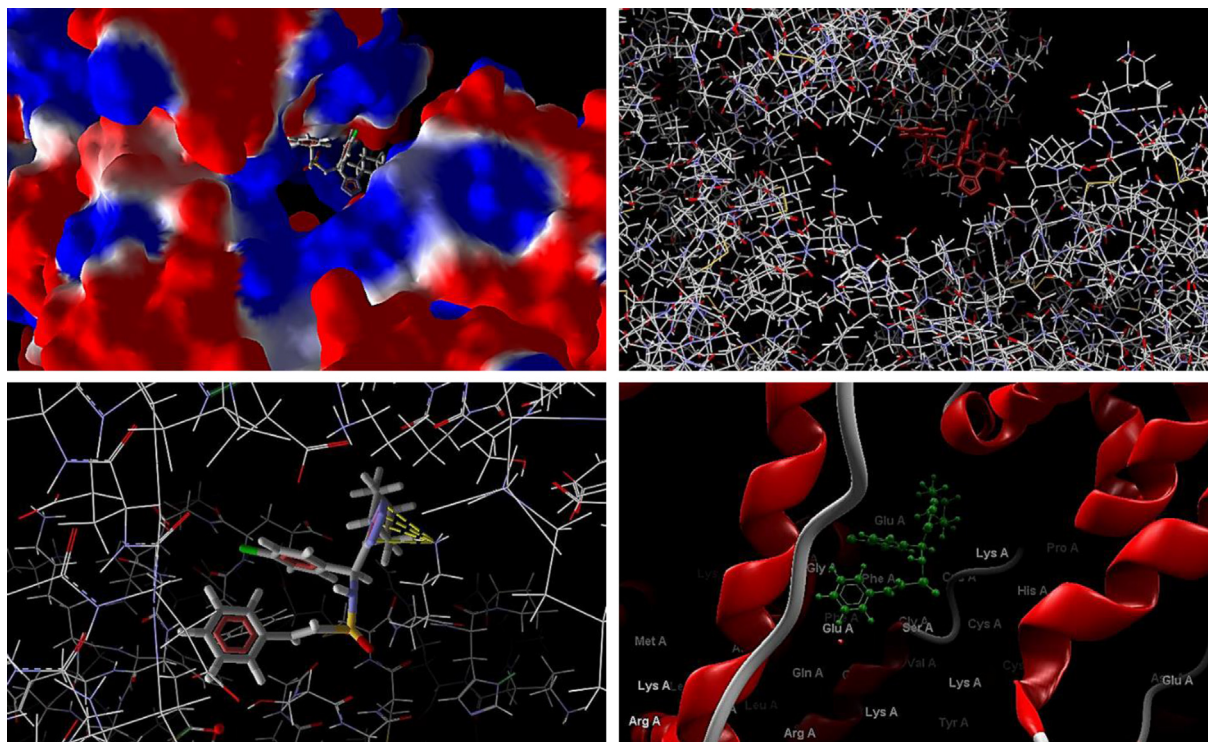


Fig. 3. Binding modes for compounds **5l** in different views. Hydrogen bonds are displayed by yellow dashes.

3310 (NH), 2922 (CH), 1560 (N=N), 1147, 1335 (SO₂) cm⁻¹. Found: C, 61.25; H, 6.09; N, 17.98. C₂₁H₂₅N₅O₂S requires C, 61.29; H, 6.12; N, 17.02%. m/z (EI, 70 eV) 411 (M⁺, 0.99), 347 (15.53), 266 (12.64), 213 (100), 155 (13.03), 106 (25.55), 91 (33.14), 77 (16.01), 55 (19.03).

5.4.4. *N*-((1-Cyclohexyl-1H-tetrazol-5-yl)(4-nitrophenyl)methyl)benzenesulfonamide (**5d**)

White powder (99 mg, 90%); mp 247–248 °C. δ_H (DMSO, 300 MHz): 1.20–1.45 (m, 3H, H_{cyclohexyl}), 1.54–1.86 (m, 7H, H_{cyclohexyl}), 4.72–4.78 (bs, 1H, NHCH), 6.23 (s, 1H, CH_{Bn}), 7.02 (d, *J* = 9 Hz, 2H, H_{Ar}), 7.31–7.41 (m, 4H, H_{Ar}), 9.97 (d, *J* = 9 Hz, 2H, H_{Ar}), 9.30 (bs, 1H, NH). ¹³C NMR δ (75 MHz, DMSO) 151.31, 141.83, 139.33, 137.39, 133.16, 132.15, 131.02, 129.30, 127.33, 57.36 (NCH), 50.49 (CH_{Bn}), 30.45, 24.91, 21.97, 20.99. ν_{max} (ATR), 3279 (NH), 3062 (CH), 1554 (N₂), 1268, 1148 (SO₂) cm⁻¹. Found: C, 54.25; H, 5.00; N, 18.96. C₂₀H₂₂N₆O₄S requires C, 54.29; H, 5.01; N, 18.99%. m/z (EI, 70 eV) 442 (M⁺, 6.87), 368 (85.08), 313 (68.25), 236 (100), 109 (44.07), 83 (74.36), 57 (96.17).

5.4.5. *N*-((1-(*Tert*-butyl)-1H-tetrazol-5-yl)(4-chlorophenyl)methyl)benzenesulfonamide (**5e**)

White powder (78 mg, 77%); mp 249–250 °C. δ_H (DMSO, 300 MHz): 1.64 (s, 9H, H_{tert-Bu}), 6.15 (s, 1H, CH_{Bn}), 7.25 (bs, 4H, H_{Ar}), 7.37 (t, 2H, *J* = 6 Hz, H_{Ar}), 7.50 (t, 1H, *J* = 6 Hz, H_{Ar}), 7.57 (d, 1H, *J* = 6 Hz, H_{Ar}), 9.34 (bs, 1H, NH). ¹³C NMR δ (75 MHz, DMSO) 153.72, 141.46, 133.39, 132.77, 130.49, 129.18, 128.73, 126.79, 62.48 (C_{tert-Bu}), 52.44 (CH_{Bn}), 29.74 (CH₃). ν_{max} (ATR), 3290 (NH), 2998 (CH), 1593 (N=N), 1270, 1143 (SO₂) cm⁻¹. Found: C, 53.22; H, 4.94; N, 17.22. C₁₈H₂₀ClN₅O₂S requires C, 53.26; H, 4.97; N, 17.25%. m/z (EI, 70 eV) 408 (M⁺ [³⁷Cl], 0.29), 406 (M⁺ [³⁵Cl], 0.55), 341 (20.05), 280 (100), 180 (50.97), 141 (66.85), 77 (68.06), 41 (47.09).

5.4.6. *N*-((1-(*Tert*-butyl)-1H-tetrazol-5-yl)(4-methoxyphenyl)methyl)benzenesulfonamide (**5f**)

White powder (74 mg, 74%); mp 255–256 °C. δ_H (DMSO,

300 MHz): 1.43 (s, 9H, H_{tert-Bu}), 3.66 (s, 3H, -OCH₃), 5.94 (s, 1H, CH_{Bn}), 6.69–6.85 (m, 1H, H_{Ar}), 7.06–7.17 (m, 2H, H_{Ar}), 7.37–7.45 (m, 6H, H_{Ar}), 7.83 (bs, 1H, NH). ¹³C NMR δ (126 MHz, DMSO) 150.86, 144.26, 139.34, 135.76, 132.81, 129.16, 128.01, 125.33, 63.44 (C_{tert-Bu}), 57.19 (-OCH₃), 50.30 (CH_{Bn}), 29.87 (CH₃). ν_{max} (ATR), 3330 (NH), 3057 (CH), 1591 (N=N), 1143, 1270 (SO₂) cm⁻¹. Found: C, 56.80; H, 5.75; N, 17.40. C₁₉H₂₃N₅O₃S requires C, 56.84; H, 5.77; N, 17.44%. m/z (EI, 70 eV) 401 (M⁺ 0.98), 368 (3.79), 285 (68.37), 236 (11.26), 131 (100), 104 (13.99), 77 (22.50), 57 (15.59).

5.4.7. *N*-((1-Cyclohexyl-1H-tetrazol-5-yl)(phenyl)methyl)-4-methylbenzenesulfonamide (**5g**)

White powder (81 mg, 79%); mp 171–170 °C; N, 16.98. δ_H (DMSO, 300 MHz): 1.13–1.39 (m, 3H, H_{cyclohexyl}), 1.52–1.88 (m, 7H, H_{cyclohexyl}), 2.29 (s, 3H, CH₃), 4.90–4.61 (m, 1H, NHCH), 6.16 (s, 1H, CH_{Bn}), 7.17–7.31 (m, 7H, H_{Ar}), 7.53 (d, 2H, *J* = 9 Hz, H_{Ar}), 9.19 (bs, 1H, NH). ¹³C NMR δ (75 MHz, DMSO) 154.26, 143.06, 138.38, 136.77, 129.67, 128.72, 128.50, 128.05, 126.85, 57.21 (NCH), 51.28 (CH_{Bn}), 32.79, 32.69, 25.04, 24.91, 21.35. ν_{max} (ATR), 3332 (NH), 2937 (CH), 1598 (N=N), 1327, 1158 (SO₂) cm⁻¹. Found: C, 61.26; H, 6.09; N, 16.98. C₂₁H₂₅N₅O₂S requires C, 61.29; H, 6.12; N, 17.02%. m/z (EI, 70 eV) 412 (M⁺, 0.99), 347 (15.53), 266 (12.64), 213 (100), 155 (13.03), 106 (25.55), 91 (33.14), 77 (16.01), 55 (19.03).

5.4.8. *N*-((4-Bromophenyl)(1-(*tert*-butyl)-1H-tetrazol-5-yl)methyl)-4-methylbenzenesulfonamide (**5h**)

White powder (170 mg, 93%); mp 245–246 °C. δ_H (DMSO, 300 MHz): 1.16 (s, 9H, H_{tert-Bu}), 2.32 (s, 3H, CH₃), 6.09 (s, 1H, CH_{Bn}), 7.16 (d, 4H, *J* = 9 Hz, H_{Ar}), 7.37–7.45 (m, 4H, H_{Ar}), 9.21 (bs, 1H, NH). ¹³C NMR δ (75 MHz, DMSO) 153.72, 142.79, 139.21, 135.99, 131.57, 130.79, 129.53, 126.85, 121.90, 62.50 (C_{tert-Bu}), 52.38 (CH_{Bn}), 29.74 (CH₃), 21.40 (CH₃). ν_{max} (ATR), 3335 (NH), 2926 (CH), 1597 (N=N), 1146, 1278 (SO₂) cm⁻¹. Found: C, 49.11; H, 4.75; N, 15.06. C₁₉H₂₂BrN₅O₂S requires C, 49.14; H, 4.78; N, 15.08%. m/z (EI, 70 eV) 465 (M⁺ [⁷⁹Br], 0.04), 463 (M⁺ [⁸¹Br], 0.03), 401 (7.86), 343 (21.79),

224 (13.99), 184 (32.31), 155 (57.43), 91 (100), 57 (49.38).

5.4.9. *N*-((1-(*Tert*-butyl)-1*H*-tetrazol-5-yl)(4-fluorophenyl)methyl)-4-methylbenzenesulfonamide (5i**)**

White powder (95 mg, 94%); mp 208–209 °C. δ_{H} (DMSO, 500 MHz): 1.59 (s, 9H, $\text{H}_{\text{tert-Bu}}$), 2.27 (s, 3H, CH_3), 6.07 (s, 1H, CH_{Bn}), 6.98–7.01 (m, 2H, H_{Ar}), 7.10 (d, 2H, $J = 5$ Hz, H_{Ar}), 7.27 (bs, 2H, H_{Ar}), 7.42 (d, 2H, $J = 5$ Hz, H_{Ar}), 9.18 (bs, 1H, NH). ^{13}C NMR δ (75 MHz, DMSO) 163.51, 160.28 (C–F, $J_1 = 242.3$ Hz), 155.66, 141.59, 135.34 (C_{Ar}), 130.43, 130.33 (C–C–F, $J_3 = 7.5$ Hz), 129.17, 128.85, 126.72, 126.16, 126.11 (C–C–C–F, $J_4 = 3.8$ Hz), 115.40, 115.13 (C–C–F, $J_4 = 20.2$ Hz), 62.22 ($\text{C}_{\text{tert-Bu}}$), 53.24 (CH_{Bn}), 29.80 (CH_3), 21.28 (CH_3). ν_{max} (ATR), 3477 (NH), 2909 (CH), 1525 (N=N), 1278, 1122 (C=C) cm^{-1} . Found: C, 56.53; H, 5.47; N, 17.32. $\text{C}_{19}\text{H}_{22}\text{FN}_5\text{O}_2\text{S}$ requires C, 56.56; H, 5.50; N, 17.36%. m/z (EI, 70 eV) 403 (M^+ , 2.01), 339 (6.05), 313 (5.95), 278 (28.13), 155 (59.57), 121 (69.76), 91 (100), 57 (61.50).

5.4.10. *N*-((1-(*Tert*-butyl)-1*H*-tetrazol-5-yl)(*p*-tolyl)methyl)-4-methylbenzenesulfonamide (5j**)**

White powder (78 mg, 76%); mp 239–240 °C. δ_{H} (DMSO, 500 MHz): 2.31 (s, 9H, $\text{H}_{\text{tert-Bu}}$), 2.50 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 5.90 (s, 1H, CH_{Bn}), 7.07 (d, 4H, $J = 5$ Hz, H_{Ar}), 7.60 (d, 4H, $J = 10$ Hz, H_{Ar}), 9.44 (bs, 1H, NH). ^{13}C NMR δ (125 MHz, DMSO) 159.71, 145.95, 142.65, 138.72, 135.07, 130.15, 128.36, 125.64, 123.27 63.44 ($\text{C}_{\text{tert-Bu}}$), 56.56 (CH_{Bn}), 26.65 (CH_3), 21.03 (CH_3). ν_{max} (ATR), 3416 (NH), 2924 (CH), 1521 (N=N), 1270, 1116 (SO_2) cm^{-1} . Found: C, 60.10; H, 6.28; N, 17.50. $\text{C}_{20}\text{H}_{25}\text{N}_5\text{O}_2\text{S}$ requires C, 60.13; H, 6.31; N, 17.53%. m/z (EI, 70 eV) 399 (M^+ , 1.81), 361 (1.56), 327 (3.63), 383 (13.63), 171 (15.45), 91 (75.45), 57 (56.36), 48 (100).

5.4.11. *N*-((1-(*Tert*-butyl)-1*H*-tetrazol-5-yl)(4-chlorophenyl)methyl)-4-methylbenzenesulfonamide (5k**)**

Yellow powder (102 mg, 97%); mp 251–252 °C. δ_{H} (DMSO, 500 MHz): 1.64 (s, 9H, $\text{H}_{\text{tert-Bu}}$), 2.30 (s, 3H, CH_3), 6.10 (s, 1H, CH_{Bn}), 7.15 (d, 2H, $J = 10$ Hz, H_{Ar}), 7.19–7.27 (m, 4H, H_{Ar}), 7.43 (d, 2H, $J = 10$ Hz, H_{Ar}), 9.18 (bs, 1H, NH). ^{13}C NMR δ (125 MHz, DMSO) 161.38, 153.80, 147.55, 142.99, 133.09, 130.02, 129.07, 128.20, 126.47, 62.02 ($\text{C}_{\text{tert-Bu}}$), 52.26 (CH_{Bn}), 29.35 (CH_3), 20.66 (CH_3). ν_{max} (ATR), 3421 (NH), 2931 (CH), 1591 (N=N), 1275, 1105 (C=C) cm^{-1} . Found: C, 54.30; H, 5.25; N, 16.63. $\text{C}_{19}\text{H}_{22}\text{ClN}_5\text{O}_2\text{S}$ requires C, 54.34; H, 5.28; N, 16.68%. m/z (EI, 70 eV) 421 (M^+ [^{37}Cl], 0.92), 419 (M^+ [^{35}Cl], 2.72), 313 (6.27), 265 (3.99), 239 (8.16), 123 (8.29), 97 (23.84), 69 (48.13), 57 (83.00), 43 (100).

5.4.12. (*E*)-*N*-((4-chlorophenyl)(1-cyclohexyl-1*H*-tetrazol-5-yl)methyl)-2-phenylethene-1-sulfonamide (5l**)**

Yellow powder (95 mg, 83%); mp 295–296 °C. δ_{H} (DMSO, 300 MHz): 1.13–1.39 (m, 3H, $\text{H}_{\text{cyclohexyl}}$), 1.52–1.88 (m, 7H, $\text{H}_{\text{cyclohexyl}}$), 2.29 (s, 3H, CH_3), 4.90–4.61 (m, 1H, NHCH), 6.16 (s, 1H, CH_{Bn}), 7.17–7.31 (m, 7H, H_{Ar}), 7.53 (d, 2H, $J = 9$ Hz, H_{Ar}), 9.19 (bs, 1H, NH). ^{13}C NMR δ (75 MHz, DMSO) 155.12, 144.23, 139.60, 133.29, 130.49, 130.37, 129.25, 128.78, 126.59, 120.50, 57.43 (NCH), 50.84 (CH_{Bn}), 32.93, 32.68, 25.04, 24.88. ν_{max} (ATR), 3330 (NH), 2937 (CH), 1597 (N=N), 1276, 1143 (SO_2) cm^{-1} . Found: C, 57.66; H, 5.25; N, 15.26. $\text{C}_{22}\text{H}_{24}\text{ClN}_5\text{O}_2\text{S}$ requires C, 57.70; H, 5.28; N, 15.29%. m/z (EI, 70 eV) 459 (M^+ [^{37}Cl], 1.48), 457 (M^+ [^{35}Cl], 3.01), 340 (1.99), 235 (16.00), 188 (18.46), 149 (28.11), 105 (100), 77 (23.42), 57 (9.25).

5.4.13. *N*-((4-Chlorophenyl)(1-cyclohexyl-1*H*-tetrazol-5-yl)methyl)methanesulfonamide (5m**)**

White powder (95 mg, 96%); mp 205–206 °C. δ_{H} (DMSO, 500 MHz): 1.21–1.41 (m, 3H, $\text{H}_{\text{cyclohexyl}}$), 1.65–1.84 (m, 6H, $\text{H}_{\text{cyclohexyl}}$), 2.02 (s, 1H, $\text{H}_{\text{cyclohexyl}}$), 2.79 (s, 3H, $-\text{SO}_2\text{CH}_3$), 4.59–4.61 (m, 1H, NHCH), 6.28 (s, 1H, CH_{Bn}), 7.50 (d, 2H, $J = 3$ Hz, H_{Ar}), 7.57 (d, 2H, $J = 3$ Hz, H_{Ar}), 8.73 (bs, 1H, NH). ^{13}C NMR δ (125 MHz, DMSO) 153.80,

145.58, 138.98, 133.44, 128.52, 62.73 (NCH), 57.53 (CH_{Bn}), 42.08 (SO_2CH_3) 34.50, 32.18, 27.62, 24.32. ν_{max} (ATR), 3331 (NH), 2939 (CH), 1598 (N=N), 1276, 1143 (SO_2) cm^{-1} . Found: C, 48.68; H, 5.43; N, 18.90. $\text{C}_{15}\text{H}_{20}\text{ClN}_5\text{O}_2\text{S}$ requires C, 48.71; H, 5.45; N, 18.94%. m/z (EI, 70 eV) 371 (M^+ [^{37}Cl], 0.02), 369 (M^+ [^{35}Cl], 0.05), 260 (100), 232 (24.33), 204 (21.03), 124 (53.68), 109 (30.97), 91 (25.06), 65 (4.59).

5.4.14. *N*-((4-Bromophenyl)(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)methyl)methanesulfonamide (5n**)**

Yellow powder (100 mg, 94%); mp 222–223 °C. δ_{H} (DMSO, 500 MHz): 1.66 (s, 9H, $\text{H}_{\text{tert-Bu}}$), 2.76 (s, 3H, CH_3), 6.22 (s, 1H, CH_{Bn}), 7.44 (d, 2H, $J = 3$ Hz, H_{Ar}), 7.62 (d, 2H, $J = 3$ Hz, H_{Ar}), 8.67 (bs, 1H, NH). ^{13}C NMR δ (125 MHz, DMSO) 154.35, 136.37, 131.83, 130.67, 122.02, 62.01 ($\text{C}_{\text{tert-Bu}}$), 51.91 (CH_{Bn}), 41.69 (SO_2CH_3), 29.23 (CH_3). ν_{max} (ATR), 3307 (NH), 2985 (CH), 1597 (N=N), 1158, 1327 (SO_2) cm^{-1} . Found: C, 40.17; H, 4.64; N, 18.01. $\text{C}_{13}\text{H}_{18}\text{BrN}_5\text{O}_2\text{S}$ requires C, 40.21; H, 4.67; N, 18.04%. m/z (EI, 70 eV) 390 (M^+ [^{79}Br], 1.97), 388 (M^+ [^{81}Br], 1.38), 334 (11.23), 308 (28.50), 252 (53.75), 226 (76.21), 184 (100), 117 (17.15), 57 (47.10).

5.4.15. *N*-(1-(1-Cyclohexyl-1*H*-tetrazol-5-yl)butyl)benzenesulfonamide (5o**)**

White powder (67 mg, 74%); mp 203–205 °C. ν_{max} (ATR), 3338 (NH), 2982 (CH), 1584 (N=N), 1155, 1330 (SO_2) cm^{-1} . δ_{H} (DMSO, 300 MHz): 0.80 (t, 3H, $J = 6$ Hz, CH_3), 1.06–1.13 (m, 2H, CH_2), 1.21–1.26 (m, 1H, $\text{H}_{\text{cyclohexyl}}$), 1.38–1.41 (m, 1H, $\text{H}_{\text{cyclohexyl}}$), 1.65–1.84 (m, 7H, $\text{H}_{\text{cyclohexyl}}$), 1.99–2.02 (m, 1H, $\text{H}_{\text{cyclohexyl}}$), 2.27–2.30 (m, 2H, CH_2), 4.57–4.67 (m, 1H, NHCH), 5.15 (t, 1H, $J = 6$ Hz, CHNSO_2), 7.49–7.57 (m, 3H, H_{Ar}), 7–89 (d, 2H, $J = 3$ Hz, H_{Ar}), 8.45 (bs, 1H, NH). ^{13}C NMR δ (75 MHz, DMSO) 158.28, 149.16, 129.87, 128.41, 125.98, 57.85 (NCH), 50.42 (CHNSO_2), 37.25, 33.32, 26.87, 25.61, 14.61, 10.76. Found: C, 56.14; H, 6.90; N, 19.23. $\text{C}_{17}\text{H}_{25}\text{N}_5\text{O}_2\text{S}$ requires C, 56.18; H, 6.93; N, 19.27%. m/z (EI, 70 eV) 363 (M^+ , 1.78), 231 (18.75), 171 (20.33), 155 (35.45), 91 (100), 65 (36.36).

5.4.16. *N*-(1-(1-Cyclohexyl-1*H*-tetrazol-5-yl)-3-phenylpropyl)-4-methylbenzenesulfonamide (5p**)**

White powder (87 mg, 79%); mp 226–228 °C. ν_{max} (ATR), 3345 (NH), 2994 (CH), 1590 (N=N), 1150, 1327 (SO_2) cm^{-1} . δ_{H} (DMSO, 300 MHz): 1.17–1.39 (m, 3H, $\text{H}_{\text{cyclohexyl}}$), 1.56–1.67 (m, 4H, $\text{H}_{\text{cyclohexyl}}$), 1.74–1.88 (m, 3H, $\text{H}_{\text{cyclohexyl}}$), 2.07–2.13 (m, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.63 (t, 2H, $J = 6$ Hz, CH_2), 4.50–4.59 (m, 1H, NHCH), 4.83 (t, 1H, $J = 6$ Hz, CHNSO_2), 7.17–7.31 (m, 5H, H_{Ar}), 7.54 (d, 2H, $J = 9$ Hz, H_{Ar}), 7.73 (d, 2H, $J = 9$ Hz, H_{Ar}), 8.82 (bs, 1H, NH). ^{13}C NMR δ (75 MHz, DMSO) 156.66, 146.01, 142.79, 139.56, 128.88, 127.15, 125.88, 123.10, 61.42 (NCH), 50.42 (CHNSO_2), 34.93, 31.43, 29.82, 25.89, 24.00, 21.32. Found: C, 62.80; H, 6.61; N, 15.90. $\text{C}_{23}\text{H}_{29}\text{N}_5\text{O}_2\text{S}$ requires C, 62.85; H, 6.65; N, 15.93%. m/z (EI, 70 eV) 439 (M^+ , 1.73), 309 (1.30), 171 (35.65), 155 (33.04), 109 (25.86), 91 (100), 65 (37.39).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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