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The Synthesis of Novel 7-(Substituted benzyl)-4,5-dihydro[1,2,3]-triazolo[1,5-*a*]pyrazin-6(7*H*)-ones via Tandem Ugi–Huisgen Reactions

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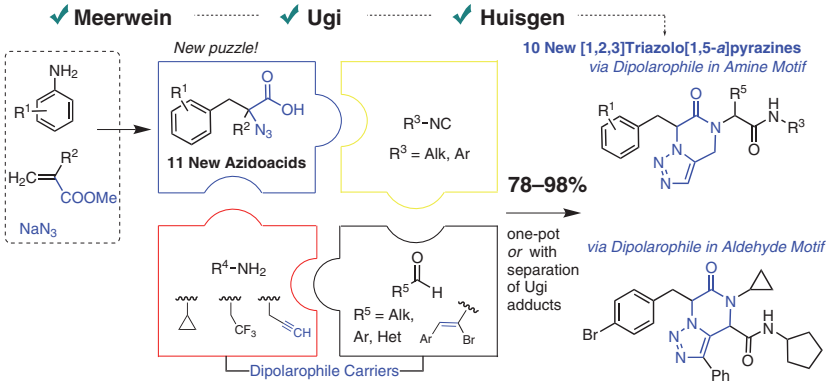

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Abstract A convenient method for the synthesis of 2-azido-3-arylpropanoic acids via the Meerwein halogenoarylation reaction of acrylic acid esters with diazonium salts, subsequent nucleophilic substitution of the halogen by an azide, and saponification is developed. The newly formed 2-azido-3-arylpropanoic acids react under the conditions of non-catalytic four-component Ugi reactions, leading to the formation of α-azidoamides in good yields. The use of propargylamine as the amine component allows the formation of Ugi adducts with azide and acetylene motifs ready for intramolecular 1,3-dipolar Huisgen cycloaddition to give the [1,2,3]triazolo[1,5-*a*]pyrazine annulated system. The Ugi reaction is found to give 2-azido-3-aryl-*N*-(2-oxo-1,2-disubstituted ethyl)-*N*-(prop-2-yn-1-yl)propanamides at room temperature without azide–alkyne cycloaddition. These dipeptides are converted into 4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-ones in near quantitative yields by heating in toluene. However, when the Ugi reaction is carried out by heating, it results in a one-pot Ugi–Huisgen tandem reaction leading to 4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-ones in excellent yields. Moreover, the possibility of the incorporation of a bromovinyl fragment (the synthetic equivalent of an acetylene fragment) via the aldehyde component of the Ugi reaction is demonstrated in an alternative preparation of the [1,2,3]triazolo[1,5-*a*]pyrazine system.

Key words azides, 1,2,3-triazoles, [1,2,3]triazolo[1,5-*a*]pyrazines, Ugi reaction, Huisgen cycloaddition, one-pot, Meerwein reaction

During the last decade, our laboratory has focused on the design and synthesis of new 1,2,3-triazoles in an effort to discover compounds with biological activities.[1] Among these studies, condensed triazole systems occupy a special place because such compounds have shown good antiproliferative activity and are promising for further anticancer research.[2] To expand the research field of condensed 1,2,3-triazole derivatives, 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines deserve attention.[3] [1,2,3]Triazolo[1,5-*a*]pyrazines have been shown to act as modulators of sigma receptors,[4] β-secretase inhibitors (BACE 1) for Alzheimer's disease therapy,[5] Cyp8b1 inhibitors for the treatment of diabetes and cardiodiabetic diseases,[6] and as antiviral agents[7] for the treatment of hepatitis B viral infection[8] (Figure 1). In addition, compounds of this class were found to possess antitumor activity.[9] Therefore, the development of suitable methods to obtain 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines is an important area of research.

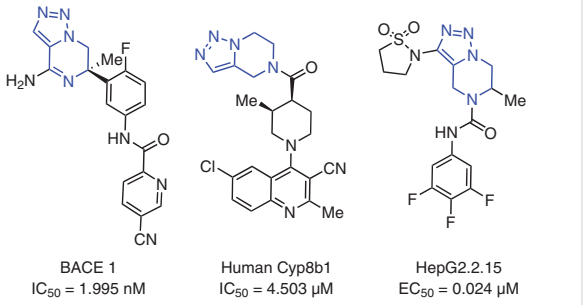
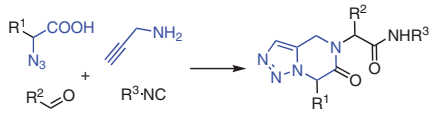


Figure 1 Chemical structures of bioactive [1,2,3]triazolo[1,5-*a*]pyrazines

A general approach to the simultaneous formation of 1,2,3-triazole and pyrazine rings is the 1,3-dipolar cyclization of α-azido-*N*-(prop-2-ynyl)amides. A previously described two-step approach to obtain [1,2,3]triazolo[1,5-*a*]pyrazines proceeded via a sequential Ugi reaction involving an α-azidoacetic acid or an α-azidophenylacetic acid and propargylamine, followed by a Huisgen cyclization

(Scheme 1).[10] Recently, a one-step method was developed for the preparation of 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]-pyrazines in an Ugi reaction using superparamagnetic copper-modified iron oxide and 2-aminobenzamide as the catalyst.[11] However, the reaction was studied only on an unsubstituted azidoacetic acid (Scheme 1). Our attention was drawn to derivatives of 2-azido-3-arylpropanoic acids as analogues of azidated phenylalanine, with 3-phenyl-2-azidopropanoic acid having already been used for the synthesis of peptidomimetics with 1,2,3-triazole rings instead of amide fragments.[12] In addition, the 3-aryl-2-(1*H*-1,2,3-triazol-1-yl)-propanoic acid motif is present in compounds used in cancer diagnostics[13] and therapy.[14] Some 3-aryl-2-(1*H*-1,2,3-triazol-1-yl)propanoic acid derivatives have been discovered to be inhibitors of histone deacetylase 8[15] and are being investigated as antidiabetic agents.[16] It should be noted that 3-phenyl-2-azidopropanoic acid and similar compounds are synthetically available via diazo transfer reactions from the corresponding natural α-amino acids.[17] However, when the α-amino acids are not readily available synthetically, the preparation of α-azido acids is limited.



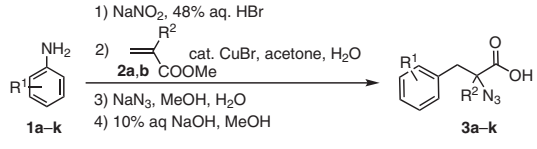
Previous work:
[ref. 10] R^1 = H, Ph; 2 examples. (1) MeOH, 24–48 h, rt; (2) PhH, reflux, 4–18 h.
[ref. 11] R^1 = H; 10 examples. [Cu@ABA-Fe_3O_4-@SiO_2], H_2O, RT, 12 h.

This work:
R^1 = $ArCH_2$, 10 examples. (1) MeOH, 20–30 min, rt; (2) PhMe, reflux, 24 h.

Scheme 1 Previously used and proposed methods for obtaining [1,2,3]triazolo[1,5-*a*]pyrazines via the Ugi reaction

In the present work, we have developed a convenient method for the synthesis of 2-azido-3-arylpropanoic acids based on the Meerwein arylation and have utilized the obtained adducts in a tandem Ugi–Huisgen sequence for the synthesis of new 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines.

Reactions of acrylic acid esters with diazonium salts under Meerwein arylation conditions is a convenient route to a variety of alkyl 3-aryl-2-bromopropanoates. Such esters have already been used for the incorporation of substituted benzyl motifs into thiazoles, quinoxalines, 1,4-thiazines, and thiomorpholines,[18] and for the preparation of alkyl 2-(1,2,3-triazol-1-yl)-3-arylpropanoates.[19] We have investigated this approach for the formation of a combinatorial library of 2-azido-3-arylpropanoic acids. CuBr-catalyzed arylation of acrylic acid esters **2a**,**b** with diazonium salts obtained from readily available anilines **1a–k** gave methyl 3-aryl-2-bromopropanoates. Subsequent nucleophilic substitution of bromine with sodium azide and saponification of the ester group under mild conditions produced novel 2-azido-3-arylpropionic acids **3a–k** in good overall yields (Scheme 2). The 2-azido-3-arylpropionic acids **3a–k** were produced pure without the need for chromatographic purification. Remarkably, substitution of the bromine by the azide and hydrolysis of the ester group proceeded quantitatively without side reactions such as nucleophilic elimination leading to cinnamic acids. Using this method, a diverse combinatorial library of 2-azido-3-arylpropionic acids could be obtained in gram quantities, with both donor and acceptor substituents on the aromatic core, thereby expanding the possibilities for studying their chemical properties.



1a–k

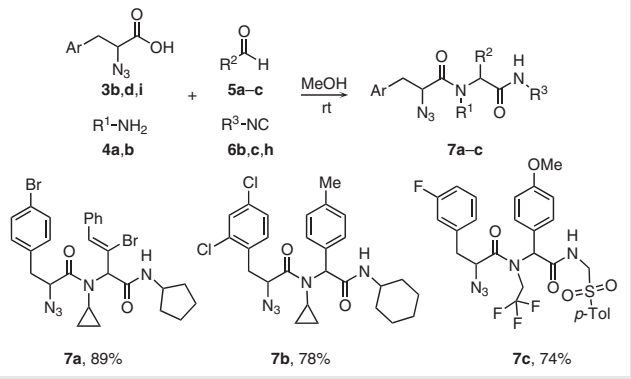
R^1 = 3-Me (**1a**)
R^1 = 4-Br (**1b**)
R^1 = 4-F (**1c**)
R^1 = 3-F (**1d**)
R^1 = 2-F (**1e**)
R^1 = 4-NO_2 (**1f**)
R^1 = 2-Cl (**1g**)
R^1 = 3,4-Cl_2 (**1h**)
R^1 = 2,4-Cl_2 (**1i**)
R^1 = 3-NO_2 (**1j**)
R^1 = 3-CF_3 (**1k**)

3a–k

R^1 = 3-Me, R^2 = H (**3a**)
R^1 = 4-Br, R^2 = H (**3b**)
R^1 = 4-F, R^2 = H (**3c**)
R^1 = 3-F, R^2 = H (**3d**)
R^1 = 2-F, R^2 = H (**3e**)
R^1 = 4-NO_2, R^2 = H (**3f**)
R^1 = 2-Cl, R^2 = H (**3g**)
R^1 = 3,4-Cl_2,, R^2 = H (**3h**)
R^1 = 2,4-Cl_2, R^2 = H (**3i**)
R^1 = 3-NO_2, R^2 = Me (**3j**)
R^1 = 3-CF_3, R^2 = Me (**3k**)

Scheme 2 Synthesis of 2-azido-3-arylpropanoic acids **3a–k**

The synthesized 2-azido-3-arylpropionic acids **3** were studied in a non-catalytic four-component Ugi reaction. It is well-known that the four-component Ugi reaction represents one of the most powerful tools for the rapid and direct synthesis of linear dipeptides.[20] The growing interest in peptidomimetics as pharmacological agents has promoted active research and applications of the Ugi reaction. Due to the high flexibility of the Ugi reaction, a wide range of linear bis-amides and pseudo-peptides (linear or cyclic) with different functional groups can be obtained. A variety of heterocyclic compounds with different biological activities can also be synthesized by various post-modifications.[21] For example, in 2019, the anticancer drug ivosidenib was approved in the United States, which was the first drug produced using the Ugi reaction.[22] Moreover, Ugi adducts are convenient precursors for further heterocyclization to obtain a wide range of heterocyclic derivatives with different ring sizes, as discussed in recent reviews.[23] It should be noted that for a long time the main limitation in the application of the Ugi reaction was the problematic odors associated with the preparation and purification of the starting isonitriles. Recently, however, a practical flash chromatography protocol has been proposed that enables the preparation of highly pure isonitriles in short times.[24]



Scheme 3 Synthesis of Ugi adducts **7a–c**

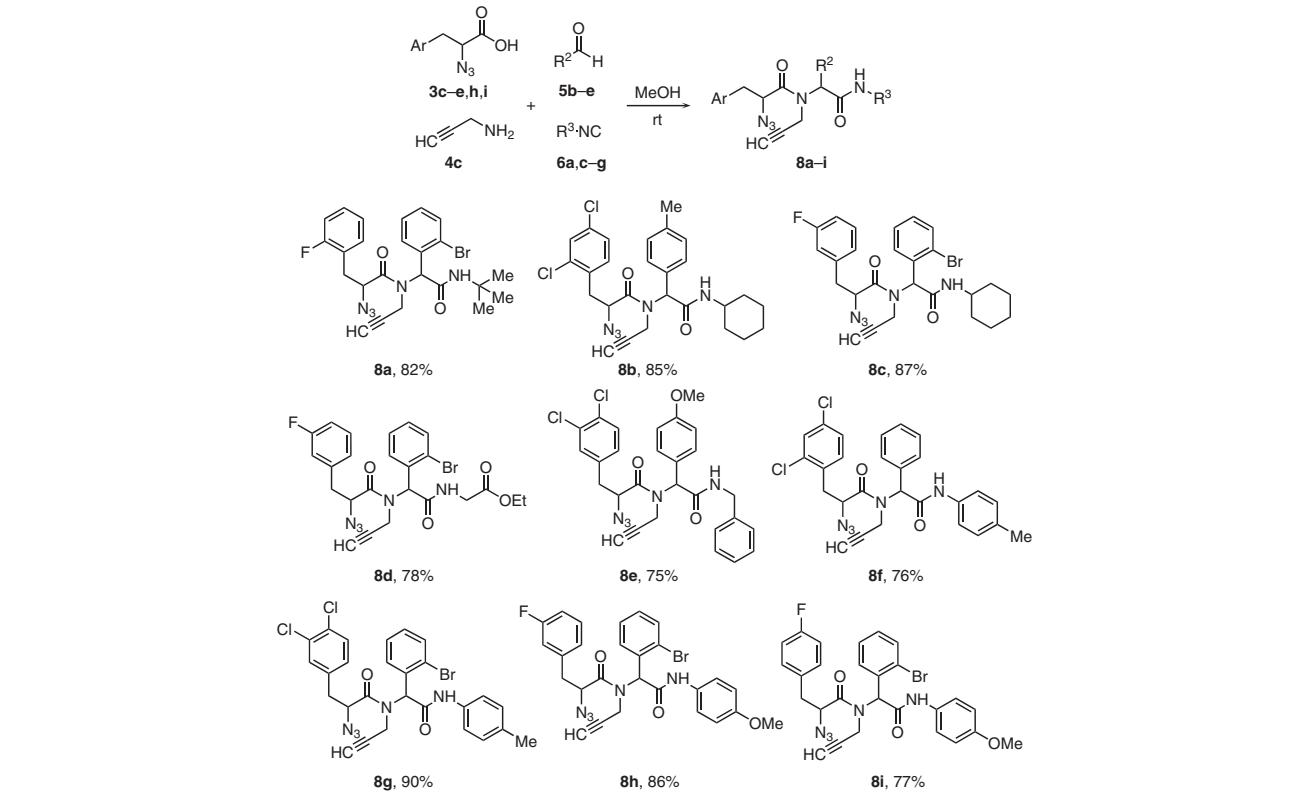
Firstly, 2-azido-3-arylpropionic acids **3a–k** were tested in the Ugi reaction with cyclopropylamine (**4a**) and 2,2,2-trifluoroethylamine (**4b**). The target Ugi adducts **7a–c** were obtained by mixing the components in methanol at room temperature for 20–30 minutes (Scheme 3). The reaction was monitored by TLC for the disappearance of the starting azido acid. Compounds **7a–c** did not require further purification and were separated from the reaction mixture by filtration as individual white crystalline substances.

LC-MS analysis data confirmed that compounds **7a–c** were indeed pure, individual reaction products, indicating excellent selectivity. The presence of a highly reactive azide group in the obtained adducts **7a–c** makes them suitable building blocks for the modification of peptide molecules.

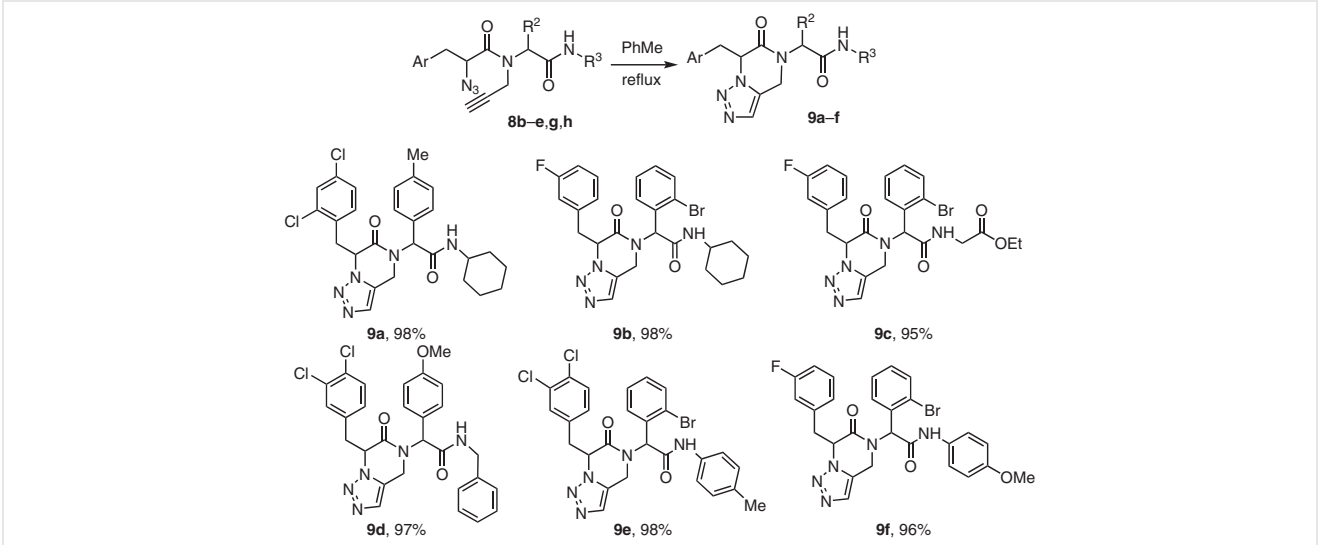
To allow intramolecular cyclization to form a cyclic [1,2,3]triazolo[1,5-*a*]pyrazine system, propargylamine (**4c**) was introduced into the Ugi reaction, and a series of compounds (**8a–i**) was obtained (Scheme 4). In this case, the reaction took place at room temperature, and the target products precipitated from the reaction medium in the form of a white precipitate. With the participation of alkyl isonitriles, the reaction proceeded within 10–30 minutes, whilst the introduction of aryl isonitriles into the reaction prolonged the reaction time to 40–60 minutes.

The Ugi linear adducts **8** contain azido groups and dipolarophiles, which allowed them to be 'cross-linked' by Huisgen 1,3-dipolar cycloadditions. Refluxing the selected compounds **8** in toluene for 24 hours led to the formation of 4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-ones **9a–f** in close to quantitative yields (Scheme 5).

Considering that there are rotamers present in compounds **8** (see the Supporting Information), which complicate the signal assignments in the ^{1}H NMR spectra, ^{13}C NMR spectra were used to monitor the progress of the cycloaddition based on the acetylene signals appearing in the region



Scheme 4 Synthesis of Ugi adducts **8a–i**



Scheme 5 Synthesis of 4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-ones **9a–f**

of the spectrum highlighted within the red frame in Figure 2. The ^{13}C NMR spectrum of the non-cyclic Ugi adduct **8c** is shown in Figure 2A, whilst that of the corresponding Huisgen cyclization product **9b** is displayed in Figure 2B. The ^{13}C NMR spectrum of compound **8c** exhibits characteristic signals at 79.24 (C_{sp}) and 74.70 (CH_{sp}) ppm, indicating the presence of a propargyl fragment, while no such peaks were observed in the ^{13}C NMR spectrum of the dry residue after refluxing in toluene (compound **9b**). The target products **9a–f** were obtained from the reaction medium by evaporation of toluene under reduced pressure, and they did not require any further purification. Thus, the Huisgen cyclization of compounds **8a–i** occurs quantitatively without the formation of side products. It is known that similar cyclizations of NH-unsubstituted 2-azido-*N*-(prop-2-ynyl)propanamides are accompanied by the formation of intermolecular interaction products, and the formation of the targeted 4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-ones is achieved under high pressure in the presence of microwave irradiation.[25] Apparently, intermolecular conjugation leading to the formation of oligomeric products is unfavorable due to steric factors.

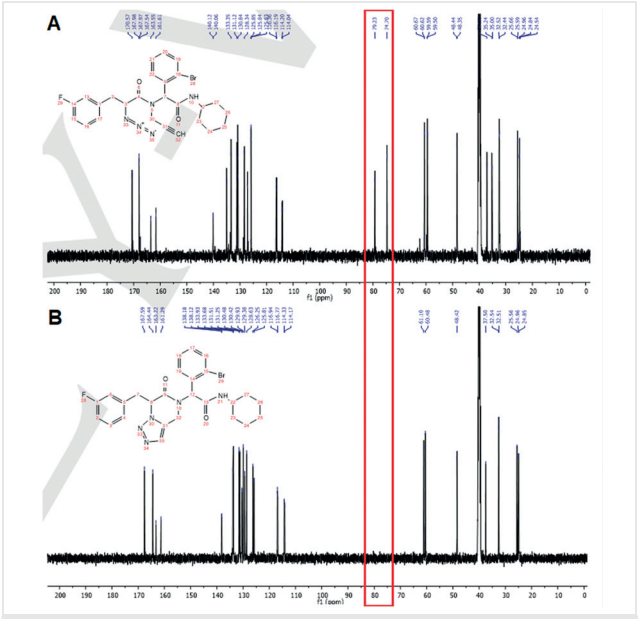
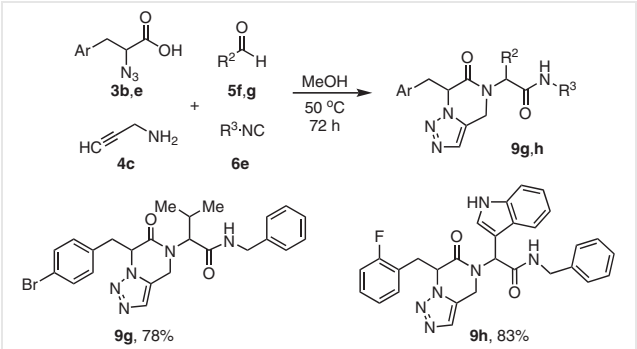


Figure 2 ^{13}C NMR spectra of compounds **8c** (A) and **9b** (B)

Next, the one-pot tandem Ugi–Huisgen reaction was studied. After increasing the temperature of the Ugi reaction to 50 °C and extending the reaction time to 72 hours, cyclic [1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one adducts **9** were obtained as individual products (Scheme 6). This synthetic approach minimizes losses during isolation of the intermediate and is effective when the linear Ugi adducts are markedly soluble in methanol, making their isolation difficult.



Scheme 6 The one-pot tandem Ugi–Huisgen reaction

The [1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-ones **9g**,**h** obtained by the one-pot method were further purified by recrystallization from dichloromethane/hexane (3:1). It should be noted that different types of crystals were formed depending on the crystallization rate, which affects the physicochemical properties of the substance. Thus, rapid crystallization (1 day) of product **9g** resulted in the formation of crystals with mp = 238–240 °C, whilst slow crystallization over 10 days led to the formation of crystals with mp = 181–183 °C. X-ray diffraction analyses were performed on both crystal types.[26] The two diastereomers of **9g** [**9g** (A) and **9g** (B)] crystallize in the centrosymmetric space groups *C*2/*c* and *Pbcn*, respectively, each with one molecule in the asymmetric unit (Figure 3).

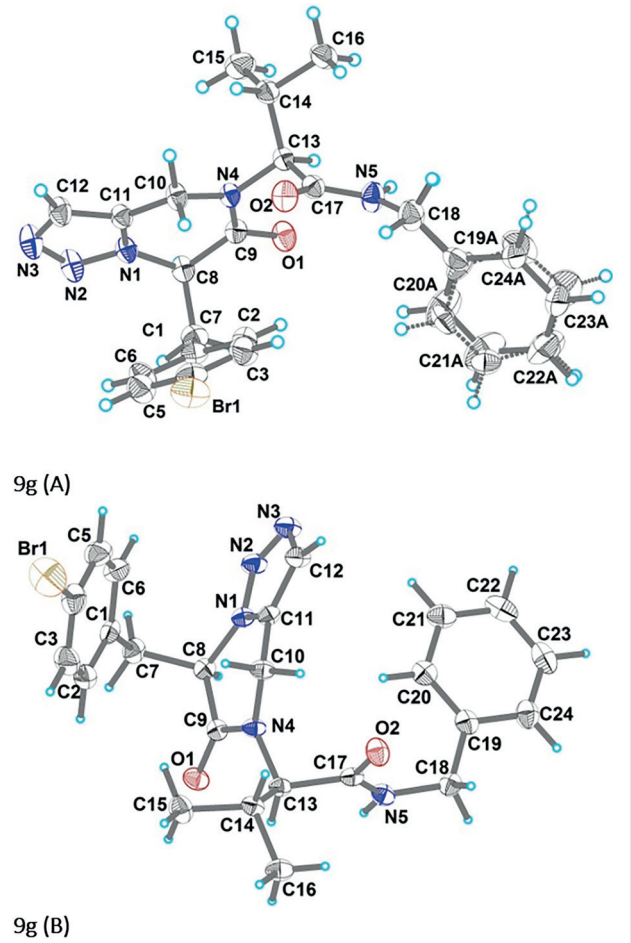
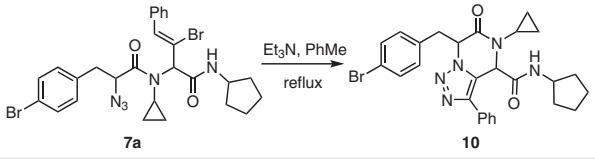


Figure 3 The molecular structures of **9g** (A) and **9g** (B) (derived from single-crystal XRD experiments) with displacement ellipsoids drawn at the 50% probability level. One of the two disordered positions of the phenyl ring in **9g** is shown in dashed mode.

The molecules exhibit some differences in their geometries; for example, the corresponding N4–C13–C17–N5 torsion angles are 127.1(2)° in **9g** (A) and –90.9(2)° in **9g** (B). The 4-bromophenyl group is aligned with the adjacent 4,5-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one, and the angle between the planes is 46.5(2)° in **9g** (A) and 42.7(2)° in **9g** (B). In **9g** (B), the second phenyl ring is almost perpendicular to the triazole ring [the angle between these planes is 78.92(2)°], while in **9g** (A) a close arrangement of the phenyl substituents causes the disorder of one of them at two positions with an occupancy ratio of 0.59(2):0.41(2).

X-ray structural analysis data showed that the 4 optical isomers of compound **9g** separated into two pairs of enantiomers during crystallization. A pair of (*R*,*S*)- and (*S*,*R*)-isomers [**9g** (**A**)] crystallized first, and after a lengthy period of time (approximately 2 weeks), a pair of (*R*,*R*)- and (*S*,*S*)-isomers [**9g** (**B**)] crystallized. The significant difference in crystallization times of the different optical isomers is a convenient and effective technique in separating the diastereomeric mixture of products **9** into separate optical isomers.

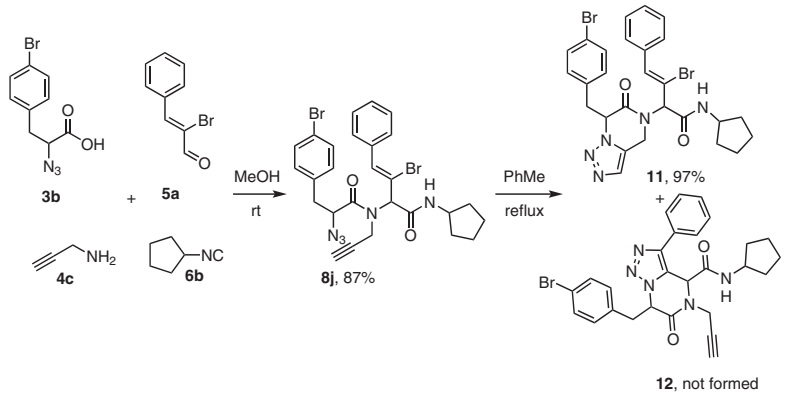
The dipolarophilic group for the Huisgen-1,3-dipolar cycloaddition to construct the [1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one system could also be involved in the Ugi reaction via the aldehyde moiety. First, 3-phenylpropiolaldehyde was tested in the Ugi reaction with 2-azido-3-arylpropionic acids. However, we were unable to obtain any linear Ugi adducts, probably due to the instability of the intermediate Schiff bases formed during the Ugi reaction with 2-azido-3-arylpropionic acids. However, this synthetic route could be successfully carried out with the synthetic precursor (*Z*)-2-bromo-3-phenylacrylaldehyde. Thus, the Ugi product **7a**, on refluxing in toluene with one equivalent of triethylamine, undergoes a Huisgen cyclization to give polysubstituted [1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one **10** in a high yield (Scheme 7).



Scheme 7 Synthesis of [1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one **10**

Finally, we decided to test the chemoselectivity of the 1,3-dipolar Huisgen cycloaddition in the presence of the two dipolarophiles we had studied in the Ugi reaction. For this purpose, adduct **8j** was prepared. A thermally initiated cycloaddition was performed and it was found that in our case only the propargyl fragment was involved in the 1,3-dipolar cycloaddition. Compound **11** was the only product produced from the reaction mixture. The possible alternative product **12** or its intermediate were not observed (Scheme 8).

In conclusion, we have developed an efficient method for obtaining 2-azido-3-arylpropionic acids using Meerwein bromoarylation products. It was found that 2-azido-3-aryl-



Scheme 8 Synthesis of [1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-one **11**

propionic acids could be used in a multicomponent Ugi reaction to obtain new polysubstituted dipeptides. In the Huisgen reaction, these compounds form a triazole ring from which 2-(7-aryl-6-oxo-6,7-dihydro[1,2,3]triazolo[1,5-*a*]-pyrazin-5(4*H*)-yl)acetamides are formed. A convenient one-pot method was also proposed and developed for the tandem Ugi–Huisgen reaction. Thus, the sequential combination of the Ugi reaction and Huisgen cyclization is a convenient synthetic approach for the preparation of a broad range of 7-(substituted benzyl)-4,5-dihydro[1,2,3]triazolo-[1,5-*a*]pyrazin-6(7*H*)-ones, starting from 2-azido-3-arylpropionic acids, without the use of metal catalysts, specific equipment and chromatographic purification of the target products, which is in good agreement with modern concepts of organic synthesis. The method is generally applicable to a wide range of starting substrates and allows the introduction of pharmacophoric fragments of natural amino acid residues into the target molecule, for example, the compounds we obtained containing glycine (**9c**), valine (**9g**) and tryptophan (**9h**) residues. The obtained compounds are of significant interest as potential biologically active compounds. In addition, the products obtained with 2-bromobenzaldehyde may serve as suitable precursors for further intramolecular cross-couplings, giving rise to new polycyclic systems.

^{1}H and ^{13}C NMR spectra were recorded on Varian Unity Plus 400 (400 and 101 MHz, respectively), Bruker 170 Avance 500 (500 and 126 MHz, respectively), and Agilent 600 MHz Premium COMPACT (600 and 151 MHz, respectively) spectrometers in DMSO-d_6, using TMS or the residual solvent peaks (2.50 ppm for ^{1}H nuclei and 39.5 ppm for ^{13}C nuclei) as internal references. Mass spectral analyses were performed using an Agilent 1100 series LC/MSD in API-ES/APCI mode (200 eV). Elemental analysis was accomplished using a Carlo Erba 1106 instrument. Melting points were determined on a Boetius melting point apparatus. The starting anilines **1**, amines **4**, aldehydes **5** and toluenesulfonylmethyl isocyanide (**6h**) were commercially available and ware used without further purification.

2-Azido-3-arylpropanoic Acids 3a–k; General Procedure

Aniline **1** (0.25 mol) was dissolved in an excess of 48% bromic acid (62.3 mL, 0.55 mol). The obtained mixture was cooled to 0 °C and a solution of sodium nitrite (17.25 g, 0.25 mol) in water (10 mL) was added. The resulting diazonium bromide solution was added dropwise to a mixture of methyl acrylate **2** (0.25 mol), acetone (250 mL), water (15 mL), and copper(I) bromide (2.5 g) with stirring. After 40 min, the reaction mixture was poured into water. The liquid products were extracted with DCM and the solvent evaporated in vacuo. The crude methyl 2-bromo-3-aryl propanoates were purified by vacuum distillation at 1 mm Hg. The obtained methyl 2-bromo-3-arylpropanoate (0.1 mol) was dissolved in MeOH (50 mL) and a solution of NaN_3 (6.5 g) in H_2O (15 mL) was added. The resulting mixture was then heated under reflux for 3–4 h with vigorous stirring. The methanol was evaporated in vacuo and the residue was poured into water (20 mL). Extraction with DCM (3 × 20 mL) and evaporation of the combined organic layers in vacuo gave the corresponding methyl 2-azido-3-arylpropanoate residue. This was dissolved in MeOH (225 mL) at 0 °C and a solution of NaOH (4 g) in water (50 mL) was added with vigorous stirring. The mixture was then allowed to stand overnight. The methanol was evaporated in vacuo without heating and the acidic sodium salt solution was washed with DCM and TBME. HCl was added to adjust the pH to 2, and the obtained 2-azido-3-arylpropanoic acid was extracted with DCM. The DCM was removed in vacuo to afford pure acid **3**. The products were used in further reactions without any additional purification.

2-Azido-3-(*m*-tolyl)propanoic Acid (3a)

Yield: 9.94 g (46%); white solid; mp 56–57 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.44 (s, 1 H, COOH), 7.19 (t, *J* = 7.5 Hz, 1 H, CH_{Ar}-5), 7.11–7.03 (m, 3 H, CH_{Ar}-2,4,6), 4.33 (dd, *J* = 8.9, 4.9 Hz, 1 H, CH), 3.07 (dd, *J* = 14.1, 5.0 Hz, 1 H, CH_2), 2.88 (dd, *J* = 14.1, 8.9 Hz, 1 H, CH_2), 2.28 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.75 (COOH), 137.86 (C_{Ar}-3), 137.07 (C_{Ar}-1), 130.30 (CH_{Ar}-2), 128.70 (CH_{Ar}-5), 127.88 (CH_{Ar}-4), 126.70 (CH_{Ar}-6), 62.77 (CH), 37.11 (CH_2), 21.45 (CH_3).

MS (APCI): *m*/*z* = 206 $[M + H]^+$.

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.51; H, 5.39; N, 20.47.

2-Azido-3-(4-bromophenyl)propanoic Acid (3b)

Yield: 14.58 g (54%); white solid; mp 78–79 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.34 (s, 1 H, COOH), 7.46 (d, J = 7.7 Hz, 2 H, CH_{Ar}-3,5), 7.19 (d, J = 7.7 Hz, 2 H, CH_{Ar}-2,6), 4.38 (dd, J = 8.8, 5.1 Hz, 1 H, CH), 3.03 (dd, J = 14.1, 5.3 Hz, 1 H, CH_2), 2.86 (dd, J = 14.2, 8.4 Hz, 1 H, CH_2).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.49 (COOH), 136.62 (C_{Ar}-1), 131.94 (2 C, CH_{Ar}-3,5), 131.62 (2 C, CH_{Ar}-2,6), 120.44 (C_{Ar}-4), 62.40 (CH), 36.41 (CH_2).

MS (APCI): m/z = 270, 272 $[M + H]^+$.

Anal. Calcd for $C_9H_8BrN_3O_2$: C, 40.02; H, 2.99; N, 15.56. Found: C, 40.00; H, 3.01; N, 15.55.

2-Azido-3-(4-fluorophenyl)propanoic Acid (3c)

Yield: 11.91 g (57%); white solid; mp 172–174 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.40–7.21 (m, 2 H, CH_{Ar}-3,5), 7.09 (t, J = 8.7 Hz, 2 H, CH_{Ar}-2,6), 4.06 (dd, J = 9.2, 4.6 Hz, 1 H, CH), 3.08 (dd, J = 14.3, 4.6 Hz, 1 H, CH_2), 2.85 (dd, J = 14.2, 9.2 Hz, 1 H, CH_2).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 172.15 (COOH), 161.53 (d, $J_{C–F}$ = 242.0 Hz, C_{Ar}-4), 134.44 (d, $J_{C–F}$ = 2.9 Hz, C_{Ar}-1), 131.45 (d, $J_{C–F}$ = 8.1 Hz, 2 C, CH_{Ar}-2,6), 115.39 (d, $J_{C–F}$ = 21.1 Hz, 2 C, CH_{Ar}-3,5), 64.13 (CH), 36.83 (CH_2).

MS (APCI): m/z = 210 $[M + H]^+$.

Anal. Calcd for $C_9H_8FN_3O_2$: C, 51.68; H, 3.86; N, 20.09. Found: C, 51.65; H, 3.89; N, 20.10.

2-Azido-3-(3-fluorophenyl)propanoic Acid (3d)

Yield: 10.66 g (51%); colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.33–7.22 (m, 1 H, CH_{Ar}-2), 7.13–6.95 (m, 3 H, CH_{Ar}-4,5,6), 4.40 (dd, J = 8.6, 4.7 Hz, 1 H, CH), 3.09 (dd, J = 14.2, 4.9 Hz, 1 H, CH_2), 2.91 (dd, J = 14.1, 8.9 Hz, 1 H, CH_2).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.51 (COOH), 162.53 (d, $^1J_{C–F}$ = 243.3 Hz, C_{Ar}-3), 140.03 (d, $^3J_{C–F}$ = 7.5 Hz, C_{Ar}-1), 130.55 (d, $^3J_{C–F}$ = 8.4 Hz, CH_{Ar}-5), 125.79 (d, $^4J_{C–F}$ = 2.8 Hz, CH_{Ar}-6), 116.35 (d, $^2J_{C–F}$ = 21.5 Hz, CH_{Ar}-2), 113.98 (d, $^2J_{C–F}$ = 20.9 Hz, CH_{Ar}-4), 62.40 (CH), 36.70 (CH_2).

MS (APCI): m/z = 210 $[M + H]^+$.

Anal. Calcd for $C_9H_8FN_3O_2$: C, 51.68; H, 3.86; N, 20.09. Found: C, 51.70; H, 3.84; N, 20.10.

2-Azido-3-(2-fluorophenyl)propanoic Acid (3e)

Yield: 9.82 g (47%); colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.48 (s, 1 H, COOH), 7.34–7.25 (m, 2 H, CH_{Ar}-4,6), 7.18–7.08 (m, 2 H, CH_{Ar}-3,5), 4.30 (dd, J = 9.3, 4.9 Hz, 1 H, CH), 3.13 (dd, J = 14.3, 4.9 Hz, 1 H, CH_2), 2.93 (dd, J = 14.2, 9.4 Hz, 1 H, CH_2).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.48 (COOH), 161.19 (d, $^1J_{C–F}$ = 244.2 Hz, C_{Ar}-2), 132.07 (d, $^3J_{C–F}$ = 4.3 Hz, CH_{Ar}-6), 129.48 (d, $^3J_{C–F}$ = 8.1 Hz, CH_{Ar}-4), 124.81 (d, $^4J_{C–F}$ = 3.5 Hz, CH_{Ar}-5), 124.00 (d, $^2J_{C–F}$ = 15.4 Hz, C_{Ar}-1), 115.62 (d, $^2J_{C–F}$ = 21.9 Hz, CH_{Ar}-3), 61.71 (CH), 30.46 (CH_2).

MS (APCI): m/z = 210 $[M + H]^+$.

Anal. Calcd for $C_9H_8FN_3O_2$: C, 51.68; H, 3.86; N, 20.09. Found: C, 51.67; H, 3.85; N, 20.07.

2-Azido-3-(4-nitrophenyl)propanoic Acid (3f)

Yield: 10.86 g (46%); white solid; mp 90–91 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.55 (s, 1 H, COOH), 8.17 (d, J = 8.2 Hz, 2 H, CH_{Ar}-3,5), 7.56 (d, J = 8.2 Hz, 2 H, CH_{Ar}-2,6), 4.58 (dd, J = 8.9, 4.8 Hz, 1 H, CH), 3.24 (dd, J = 14.3, 5.4 Hz, 1 H, CH_2), 3.07 (dd, J = 14.1, 9.0 Hz, 1 H, CH_2).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 171.40 (COOH), 146.98 (C_{Ar}-4), 145.58 (C_{Ar}-1), 131.08 (2 C, CH_{Ar}-2,6), 123.83 (2 C, CH_{Ar}-3,5), 62.09 (CH), 36.69 (CH_2).

MS (APCI): m/z = 237 $[M + H]^+$.

Anal. Calcd for $C_9H_8N_4O_4$: C, 45.77; H, 3.41; N, 23.72. Found: C, 45.79; H, 3.39; N, 23.71.

2-Azido-3-(2-chlorophenyl)propanoic Acid (3g)

Yield: 10.82 g (48%); white solid; mp 53–54 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.55 (s, 1 H, COOH), 7.45–7.42 (m, 1 H, CH_{Ar}-3), 7.41–7.35 (m, 1 H, CH_{Ar}-5), 7.34–7.23 (m, 2 H, CH_{Ar}-4,6), 4.36 (dd, J = 9.6, 4.8 Hz, 1 H, CH), 3.28 (dd, J = 14.3, 4.6 Hz, 1 H, CH_2), 3.02 (dd, J = 14.2, 9.9 Hz, 1 H, CH_2).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 171.47 (COOH), 134.77 (C_{Ar}-1), 133.81 (C_{Ar}-2), 132.07 (CH_{Ar}-6), 129.77 (CH_{Ar}-3), 129.25 (CH_{Ar}-4), 127.66 (CH_{Ar}-5), 61.38 (CH), 34.85 (CH_2).

MS (APCI): m/z = 226 $[M + H]^+$.

Anal. Calcd for $C_9H_8ClN_3O_2$: C, 47.91; H, 3.57; N, 18.62. Found: C, 47.89; H, 3.58; N, 18.60.

2-Azido-3-(3,4-dichlorophenyl)propanoic Acid (3h)

Yield: 14.04 g (54%); white solid; mp 85–86 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.19 (s, 1 H, COOH), 7.59–7.43 (m, 2 H, CH_{Ar}-2,5), 7.23 (dt, J = 6.7, 3.3 Hz, 1 H, CH_{Ar}-6), 4.47 (dd, J = 8.7, 4.9 Hz, 1 H, CH), 3.06 (dd, J = 14.2, 5.0 Hz, 1 H, CH_2), 2.90 (dd, J = 14.2, 8.7 Hz, 1 H, CH_2).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.39 (COOH), 138.52 (C_{Ar}-1), 131.70 (CH_{Ar}-2), 131.24 (C_{Ar}-3), 130.82 (CH_{Ar}-5), 130.18 (CH_{Ar}-6), 129.91 (C_{Ar}-4), 62.16 (CH), 35.96 (CH_2).

MS (APCI): m/z = 260, 262 $[M + H]^+$.

Anal. Calcd for $C_9H_7Cl_2N_3O_2$: C, 41.56; H, 2.71; N, 16.16. Found: C, 41.55; H, 2.69; N, 16.17.

2-Azido-3-(2,4-dichlorophenyl)propanoic Acid (3i)

Yield: 15.34 g (59%); white solid; mp 94–95 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.56 (s, 1 H, CH_{Ar}-3), 7.37 (m, 2 H, CH_{Ar}-5,6), 4.36 (dd, J = 9.6, 4.9 Hz, 1 H, CH), 3.21 (dd, J = 14.3, 5.0 Hz, 1 H, CH_2), 2.97 (dd, J = 14.4, 9.6 Hz, 1 H, CH_2).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.37 (COOH), 134.83 (C_{Ar}-2), 134.06 (C_{Ar}-1), 133.38 (CH_{Ar}-6), 132.95 (C_{Ar}-4), 129.22 (CH_{Ar}-3), 127.84 (CH_{Ar}-5), 61.20 (CH), 34.28 (CH_2).

MS (APCI): m/z = 260, 262 $[M + H]^+$.

Anal. Calcd for $C_9H_7Cl_2N_3O_2$: C, 41.56; H, 2.71; N, 16.16. Found: C, 41.57; H, 2.73; N, 16.13.

2-Azido-2-methyl-3-(3-nitrophenyl)propanoic Acid (3j)

Yield: 9.75 g (39%); white solid; mp 114–116 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.09 (d, J = 9.3 Hz, 1 H, CH_{Ar}-4), 8.04 (s, 1 H, CH_{Ar}-2), 7.64 (d, J = 7.7 Hz, 1 H, CH_{Ar}-6), 7.56 (t, J = 7.9 Hz, 1 H, CH_{Ar}-5), 3.17 (d, J = 13.5 Hz, 1 H, CH_2), 3.04 (d, J = 13.8 Hz, 1 H, CH_2), 1.41 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 173.38 (COOH), 147.97 (C_{Ar}-3), 138.38 (C_{Ar}-1), 137.68 (CH_{Ar}-6), 129.97 (CH_{Ar}-5), 125.22 (CH_{Ar}-2), 122.48 (CH_{Ar}-4), 67.01 (C), 42.46 (CH_2), 22.71 (CH_3).

MS (APCI): m/z = 251 $[M + H]^+$.

Anal. Calcd for $C_{10}H_{10}N_4O_4$: C, 48.00; H, 4.03; N, 22.39. Found: C, 47.98; H, 4.04; N, 22.40.

2-Azido-2-methyl-3-(3-(trifluoromethyl)phenyl)propanoic Acid (3k)

Yield: 10.10 g (37%); colorless oil.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.59 (s, 1 H, COOH), 7.62–7.57 (m, 1 H, CH_{Ar}-5), 7.55 (s, 1 H, CH_{Ar}-2), 7.54–7.51 (m, 2 H, CH_{Ar}-4,6), 3.17 (d, J = 13.5 Hz, 1 H, CH_2), 3.03 (d, J = 13.5 Hz, 1 H, CH_2), 1.42 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 173.44 (COOH), 137.46 (C_{Ar}-1), 134.87 (CH_{Ar}-5), 129.43 (CH_{Ar}-6), 129.38 (q, $^2J_{C–F}$ = 31.4 Hz, C_{Ar}-3), 127.11 (q, $^3J_{C–F}$ = 3.9 Hz, CH_{Ar}-2), 124.65 (q, $^1J_{C–F}$ = 272.2 Hz, CF_3), 124.12 (q, $^3J_{C–F}$ = 3.9 Hz, CH_{Ar}-4), 67.01 (C), 42.80 (CH_2), 22.67 (CH_3).

MS (APCI): m/z = 274 $[M + H]^+$.

Anal. Calcd for $C_{11}H_{10}F_3N_3O_2$: C, 48.36; H, 3.69; N, 15.38. Found: C, 48.37; H, 3.70; N, 15.36.

Ugi Adducts 7a–c and 8a–j; General Procedure

A solution of 2-azido-3-arylpropionic acid **3** (2 mmol), amine **4** (2 mmol), aldehyde **5** (2 mmol), and isonitrile **6** (2 mmol) in methanol (5 mL) was stirred for 20–30 min at room temperature to form a precipitate. The precipitate was then filtered off and washed with a small amount of methanol and dried in vacuo.

2-(2-Azido-3-(4-bromophenyl)-*N*-cyclopropylpropanamido)-3-bromo-*N*-cyclopentyl-4-phenylbut-3-enamide (7a)

Yield: 1.09 g (89%); white solid; mp 173–175 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.43 (d, J = 7.1 Hz, 1 H, NH), 7.52 (br s, 1 H), 7.50 (br s, 2 H), 7.48 (br s, 1 H), 7.45–7.33 (m, 3 H), 7.29 (d, J = 7.8 Hz, 2 H), 6.79 (s, 1 H), 5.42 (s, 1 H), 4.86 (t, J = 7.6 Hz, 1 H), 4.03 (q, J = 6.6 Hz, 1 H), 3.12 (d, J = 7.6 Hz, 2 H), 2.54 (d, J = 1.7 Hz, 1 H), 1.82 (dq, J = 12.7, 6.5 Hz, 2 H), 1.70–1.55 (m, 2 H), 1.51 (s, 3 H), 1.47–1.34 (m, 2 H), 0.94 (s, 1 H), 0.81–0.58 (m, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.41, 166.08, 135.48, 134.76, 132.34, 131.51 (2 C), 131.46 (2C), 128.53 (3C), 128.41 (2C), 120.76, 120.19, 68.91, 58.63, 50.84, 36.17, 32.29, 31.57, 27.15, 23.38, 23.36, 9.54, 9.09.

MS (APCI): m/z = 614, 616 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{29}Br_2N_5O_2$: C, 52.70; H, 4.75; N, 11.38. Found: C, 52.69; H, 4.72; N, 11.40.

2-Azido-*N*-(2-(cyclohexylamino)-2-oxo-1-(*p*-tolyl)ethyl)-*N*-cyclopropyl-3-(2,4-dichlorophenyl)propanamide (7b)

Yield: 0.82 g (78%); white solid; mp 190–193 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.81 (d, J = 8.2 Hz, 1 H), 7.65 (s, 1 H), 7.44 (t, J = 6.4 Hz, 2 H), 7.08 (d, J = 7.6 Hz, 2 H, Tol), 6.73 (d, J = 7.4 Hz, 2 H, Tol), 5.56 (s, 1 H), 4.89 (t, J = 7.8 Hz, 1 H), 3.58 (q, J = 9.4 Hz, 1 H), 3.29–3.23 (m, 3 H), 2.26 (s, 3 H, Me), 1.80–1.47 (m, 6 H), 1.33–1.00 (m, 6 H), 0.76 (dq, J = 11.1, 5.7 Hz, 1 H), 0.58 (dt, J = 10.1, 5.4 Hz, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.26 (CON), 168.25 (CON), 137.13, 134.97, 133.72, 133.43, 133.25, 133.17, 129.58 (2 C, Tol), 129.40, 129.01 (2 C, Tol), 128.19, 63.67, 56.91, 48.40, 35.12, 32.72, 32.52, 28.67, 25.63, 25.00, 24.92, 21.09, 11.12, 9.35.

MS (APCI): m/z = 528, 530 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{31}Cl_2N_5O_2$: C, 61.36; H, 5.91; N, 13.25. Found: C, 61.38; H, 5.88; N, 13.24.

2-Azido-3-(3-fluorophenyl)-*N*-(1-(4-methoxyphenyl)-2-oxo-2-((tosylmethyl)amino)ethyl)-*N*-(2,2,2-trifluoroethyl)propanamide (7c)

Yield: 0.92 g (74%); white solid; mp 184–186 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.39 and 9.06 (s, 1 H, NH), 7.78–6.77 (m, 12 H), 5.86–5.59 (m, 1 H), 5.12–4.83 (m, 1 H), 4.79–4.44 (m, 1 H), 4.42–3.89 (m, 3 H), 3.78 and 3.75 (s, 3 H, MeO), 3.19–2.96 (m, 1 H), 2.90–2.59 (m, 1 H), 2.39 and 2.37 (s, 3 H, Me).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.96, 159.99, 145.28, 134.98, 131.97, 130.28, 130.07, 128.82, 125.88, 116.29, 114.78, 114.35, 114.16, 63.29, 62.64, 60.24, 60.14, 55.70, 36.35, 21.54.

MS (APCI): m/z = 622 $[M + H]^+$.

Anal. Calcd for $C_{28}H_{27}F_4N_5O_5S$: C, 54.10; H, 4.38; N, 11.27. Found: C, 54.08; H, 4.41; N, 11.25.

2-Azido-*N*-(1-(2-bromophenyl)-2-(*tert*-butylamino)-2-oxoethyl)-3-(2-fluorophenyl)-*N*-(prop-2-yn-1-yl)propanamide (8a)

Yield: 0.84 g (82%); white solid; mp 146–148 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.13 (s, 1 H, NH), 7.61 (d, J = 7.8 Hz, 1 H), 7.47–7.38 (m, 2 H), 7.37–7.27 (m, 3 H), 7.22–7.08 (m, 2 H), 6.07 (s, 1 H, CH), 4.54–4.25 (m, 2 H, CH_2N), 4.03–3.80 (m, 1 H, CH), 3.38–3.28 (m, 1 H, CH_2), 3.16 (dd, J = 14.3, 10.1 Hz, 1 H, CH_2), 2.92 (s, 1 H, C_{sp}H), 1.27 (s, 9 H, 3 × Me).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 169.69 (CON), 168.05 (CON), 160.92 (d, $^1J_{C–F}$ = 244.4 Hz, C_{Ar}-2), 134.86, 132.92, 131.59 (d, $^3J_{C–F}$ = 4.1 Hz, CH_{Ar}-6), 130.47, 130.27, 129.11 (d, $^3J_{C–F}$ = 7.9 Hz, C_{Ar}-4), 127.82, 126.83, 124.42 (d, $^4J_{C–F}$ = 2.6 Hz, CH_{Ar}-5), 123.52 (d, $^2J_{C–F}$ = 15.5 Hz, C_{Ar}-1), 115.27 (d, $^2J_{C–F}$ = 21.9 Hz, CH_{Ar}-3), 78.61 (C_{sp}), 74.17 (CH_{sp}), 60.41 (CH), 58.31 (CH), 50.61 (CHN), 34.75 (CH_2N), 30.26 (CH_2), 28.31 (3 × Me).

MS (APCI): m/z = 514, 516 $[M + H]^+$.

Anal. Calcd for $C_{24}H_{25}BrFN_5O_2$: C, 56.04; H, 4.90; N, 13.61. Found: C, 56.03; H, 4.91; N, 13.59.

2-Azido-*N*-(2-(cyclohexylamino)-2-oxo-1-(*p*-tolyl)ethyl)-3-(2,4-dichlorophenyl)-*N*-(prop-2-yn-1-yl)propanamide (8b)

Yield: 0.89 g (85%); white solid; mp 161–163 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.22–8.16 (m, 1 H, NH), 7.58–7.54 (m, 1 H, Ar), 7.45–7.40 (m, 1 H, Ar), 7.23–7.17 (m, Ar), 7.14 (d, J = 7.6 Hz, 2 H, Tol), 6.99 (d, J = 7.8 Hz, 2 H, Tol), 6.03 (s, 1 H), 4.60–4.39 (m, 1 H), 4.21 (m, 1 H), 4.05–3.95 (m, 1 H), 3.59 (d, J = 10.0 Hz, 1 H), 3.30 (d, J = 7.0 Hz, 2 H), 3.17–2.69 (m, 1 H), 2.29 (s, 3 H, Me), 1.89–1.47 (m, 5 H, cyclohex), 1.38–0.95 (m, 5 H, cyclohex).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 169.95, 168.05, 137.84, 135.10, 133.38, 133.29, 133.17, 132.54, 129.73, 129.49 (2 C, Tol), 129.29 (2 C, Tol), 129.09, 128.86, 127.92, 80.01, 79.68, 79.42, 79.16, 74.84, 59.94, 57.76, 48.23, 35.04, 34.35, 32.63, 32.52, 25.63, 24.92, 21.19.

MS (APCI): m/z = 526, 528 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{29}Cl_2N_5O_2$: C, 61.60; H, 5.55; N, 13.30. Found: C, 61.62; H, 5.54; N, 13.28.

2-Azido-*N*-(1-(2-bromophenyl)-2-(cyclohexylamino)-2-oxoethyl)-3-(3-fluorophenyl)-*N*-(prop-2-yn-1-yl)propanamide (8c)

Yield: 0.94 g (87%); white solid; mp 173–175 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.29 (d, J = 7.7 Hz, 1 H, NH), 7.59 (d, J = 7.8 Hz, 1 H, Ar), 7.36 (m, 2 H, Ar), 7.27 (m, 2 H, Ar), 7.18–7.09 (m, 2 H, Ar), 7.09–7.00 (m, 1 H, Ar), 6.07 (s, 1 H), 4.67–4.43 (m, 2 H, CH_2N), 4.05–3.90 (m, 1 H), 3.58 (s, 1 H), 3.40 (dd, J = 14.2, 4.1 Hz, 1 H), 3.02 (dd, J = 14.3, 10.3 Hz, 1 H), 2.93 (s, 1 H), 1.87–1.40 (m, 5 H, cyclohex), 1.11 (m, 5 H, cyclohex).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 170.58 (CON), 167.98 (CON), 162.58 (d, $^1J_{C–F}$ = 243.4 Hz, C_{Ar}-3), 140.09 (d, $^3J_{C–F}$ = 7.6 Hz, C_{Ar}-1), 135.03 (Ar), 133.36 (Ar), 131.13 (Ar), 130.85 (Ar), 130.77 (d, $^3J_{C–F}$ = 8.4 Hz, CH_{Ar}-5), 128.35 (Ar), 127.18 (Ar), 125.84 (C_{Ar-F}-6), 116.28 (d, $^2J_{C–F}$ = 21.1 Hz, CH_{Ar}-4), 114.13 (d, $^2J_{C–F}$ = 20.6 Hz, CH_{Ar}-2), 79.24 (C_{sp}), 74.71 (C_{sp}), 60.63 (CH), 59.51 (CH), 48.36 (CH_2N), 37.12 (CHNHcyclohex), 35.25 (CH_2), 32.53 (cyclohex), 32.45 (cyclohex), 25.59 (cyclohex), 24.98 (cyclohex), 24.85 (cyclohex).

MS (APCI): m/z = 540, 542 [M + H]$^+$.

Anal. Calcd for $C_{26}H_{27}BrFN_5O_2$: C, 57.78; H, 5.04; N, 12.96. Found: C, 57.76; H, 5.05; N, 12.94.

Ethyl (2-(2-Azido-3-(3-fluorophenyl)-*N*-(prop-2-yn-1-yl)propanamido)-2-(2-bromophenyl)acetyl)glycinate (8d)

Yield: 0.85 g (78%); white solid; mp 148–150 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.93 (t, J = 5.9 Hz, 1 H, NH), 7.65 (d, J = 8.0 Hz, 1 H), 7.38–7.31 (m, 2 H), 7.49–7.40 (m, 2 H), 7.23–7.12 (m, 2 H), 7.09 (t, J = 9.0 Hz, 1 H), 6.24 (s, 1 H, CH), 4.70–4.54 (m, 2 H, CH_2N), 4.11 (q, J = 7.1 Hz, 2 H, CH_2Me), 4.02–3.86 (m, 2 H, CH_2COOEt), 3.82–3.79 (m, CH), 3.44 (dd, J = 14.5, 3.9 Hz, 1 H, CH_2), 3.05 (dd, J = 14.6, 10.8 Hz, 1 H, CH_2), 2.97 (s, 1 H, C_{sp}H), 1.20 (t, J = 7.1 Hz, 3 H, Me).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 170.34, 169.46, 169.21, 162.15 (d, $^1J_{C–F}$ = 243.5 Hz, C_{Ar}-3), 139.66 (d, $^3J_{C–F}$ = 8.5 Hz, C_{Ar}-1), 133.99, 132.82, 131.54, 130.58, 130.33 (d, $^3J_{C–F}$ = 8.3 Hz, CH_{Ar}-5), 127.78, 126.75, 125.38 (C_{Ar-F}-6), 115.81 (d, $^2J_{C–F}$ = 21.1 Hz, CH_{Ar}-4), 113.69 (d, $^2J_{C–F}$ = 21.0 Hz, CH_{Ar}-2), 78.64 (C_{sp}), 74.34 (CH_{sp}), 60.56, 60.26, 59.06, 40.91, 36.72 (CH_2N), 34.78 (CH_2), 14.07 (Me).

MS (APCI): m/z = 544, 546 [M + H]$^+$.

Anal. Calcd for $C_{24}H_{23}BrFN_5O_4$: C, 52.95; H, 4.26; N, 12.87. Found: C, 52.93; H, 4.27; N, 12.85.

2-Azido-*N*-(2-(benzylamino)-1-(4-methoxyphenyl)-2-oxoethyl)-3-(3,4-dichlorophenyl)-*N*-(prop-2-yn-1-yl)propanamide (8e)

Yield: 0.83 g (75%); white solid; mp 131–133 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.76 (s, 1 H, NH), 7.56–6.87 (m, 12 H), 6.02 (s, 1 H), 4.56–4.02 (m, 4 H), 3.72 (s, 3 H, OMe), 3.55–2.68 (m, 4 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 170.50, 169.49, 159.69, 139.44, 138.11, 131.69, 131.46, 131.04 (2 C), 130.34, 130.16, 128.71 (2 C), 128.06, 127.74 (2 C), 127.30, 126.98, 114.37 (2 C), 80.38 (C_{sp}), 74.88 (C_{sp}), 60.05, 59.06, 55.63, 42.63, 36.26, 35.02.

MS (APCI): m/z = 550, 552 [M + H]$^+$.

Anal. Calcd for $C_{28}H_{25}Cl_2N_5O_3$: C, 61.10; H, 4.58; N, 12.72. Found: C, 61.12; H, 4.60; N, 12.70.

2-Azido-3-(2,4-dichlorophenyl)-*N*-(2-oxo-1-phenyl-2-(*p*-tolylamino)ethyl)-*N*-(prop-2-yn-1-yl)propanamide (8f)

Yield: 0.79 g (76%); white solid; mp 163–165 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.30 (s, 1 H, NH), 7.62 (s, 1 H), 7.54–7.12 (m, 11 H), 6.21 (s, 1 H), 4.61 (t, J = 7.5 Hz, 1 H), 4.39–4.34 (m, 1 H, CH_2), 4.03–3.98 (m, 1 H, CH_2), 3.29–2.80 (m, 3 H), 2.25 (s, 3 H, Me).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 169.86 (CON), 167.32 (CON), 136.02, 134.64, 134.26, 132.93, 132.88, 132.72, 123.68, 129.18 (4 C), 128.91, 128.74 (2 C), 128.54, 127.52, 119.34 (2 C), 79.32 (CH_{sp}), 74.56 (CH_{sp}), 60.95 (CH), 57.42 (CH), 34.78 (CH_2N), 33.90 (CH_2), 20.45 (Me).

MS (APCI): m/z = 520, 522 [M + H]$^+$.

Anal. Calcd for $C_{27}H_{23}Cl_2N_5O_2$: C, 62.32; H, 4.45; N, 13.46. Found: C, 62.34; H, 4.42; N, 13.44.

2-Azido-*N*-(1-(2-bromophenyl)-2-oxo-2-(*p*-tolylamino)ethyl)-3-(3,4-dichlorophenyl)-*N*-(prop-2-yn-1-yl)propanamide (8g)

Yield: 1.08 g (90%); white solid; mp 168–170 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.36 (s, 1 H, NH), 7.73–7.30 (m, 9 H), 7.12 (d, J = 8.1 Hz, 2 H), 6.26 (s, 1 H), 4.72–4.52 (m, 2 H, CH_2N), 4.06–3.95 (m, 1 H, CH), 3.40 (dd, J = 14.2, 5.3 Hz, 1 H, CH_2), 3.11 (dd, J = 14.0, 9.4 Hz, 1 H, CH_2), 2.92 (s, 1 H, C_{sp}H), 2.25 (s, 3 H, Me).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 169.88 (CON), 167.28 (CON), 137.76, 136.02, 133.81, 133.11, 132.76, 131.26, 130.95, 130.72, 130.65, 130.48, 129.85, 129.62, 129.21 (2 C), 128.14, 126.76, 119.33 (2 C), 78.64 (C_{sp}), 74.39 (CH_{sp}), 61.19 (CH), 58.79 (CH), 35.90 (CH_2N), 34.83 (CH_2), 20.44 (Me).

MS (APCI): m/z = 598, 600, 602 [M + H]$^+$.

Anal. Calcd for $C_{27}H_{22}BrCl_2N_5O_2$: C, 54.11; H, 3.70; N, 11.69. Found: C, 54.09; H, 3.72; N, 11.70.

2-Azido-*N*-(1-(2-bromophenyl)-2-((4-methoxyphenyl)amino)-2-oxoethyl)-3-(3-fluorophenyl)-*N*-(prop-2-yn-1-yl)propanamide (8h)

Yield: 0.97 g (86%); white solid; mp 172–174 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.33 (s, 1 H, NH), 7.67 (d, J = 7.9 Hz, 1 H), 7.51 (d, J = 8.6 Hz, 2 H), 7.46–7.30 (m, 4 H), 7.24–7.15 (m, 2 H), 7.13–7.06 (m, 1 H), 6.89 (d, J = 8.7 Hz, 2 H), 6.28 (s, 1 H, CH), 4.67–4.61 (m, 2 H, CH_2N), 4.05–3.99 (m, 1 H, CH), 3.72 (s, 3 H, OMe), 3.45 (dd, J = 14.1, 4.4 Hz, 1 H, CH_2), 3.08 (dd, J = 14.2, 10.0 Hz, 1 H, CH_2), 2.95 (s, 1 H, C_{sp}H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 170.38 (CON), 167.03 (CON), 162.22 (d, $^1J_{C–F}$ = 228.4 Hz, C_{Ar}-3), 161.19, 155.58, 139.57 (d, $^3J_{C–F}$ = 7.6 Hz, C_{Ar}-1), 133.98, 133.10, 131.65, 130.68, 130.34 (d, $^3J_{C–F}$ = 8.5 Hz, CH_{Ar}-5), 128.15, 126.77, 125.44 (d, $^4J_{C–F}$ = 2.0 Hz, CH_{Ar}-6), 120.85 (2 C), 115.87 (d, $^2J_{C–F}$ = 21.3 Hz, CH_{Ar}-4), 114.00 (2 C), 113.72 (d, $^2J_{C–F}$ = 19.6 Hz, CH_{Ar}-2), 78.67 (CH_{sp}), 74.41 (CH_{sp}), 61.09 (CH), 59.10 (CH), 55.21 (OMe), 36.68 (CH_2N), 34.85 (CH_2).

MS (APCI): m/z = 564, 566 [M + H]$^+$.

Anal. Calcd for $C_{27}H_{23}BrFN_5O_3$: C, 57.46; H, 4.11; N, 12.41. Found: C, 57.47; H, 4.09; N, 12.40.

2-Azido-*N*-(1-(2-bromophenyl)-2-((4-methoxyphenyl)amino)-2-oxoethyl)-3-(4-fluorophenyl)-*N*-(prop-2-yn-1-yl)propanamide (8i)

Yield: 0.87 g (77%); white solid; mp 185–187 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.33 (s, 1 H, NH), 7.66 (d, J = 7.8 Hz, 1 H), 7.50 (d, J = 8.8 Hz, 2 H), 7.44–7.29 (m, 5 H), 7.15 (t, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.8 Hz, 2 H), 6.27 (s, 1 H, CH), 4.66–4.51 (m, 2 H, CH_2N), 4.02–3.98 (m, 1 H, CH), 3.71 (s, 3 H, Me), 3.40 (dd, J = 14.1, 3.7 Hz, 1 H, CH_2), 3.03 (dd, J = 13.9, 10.3 Hz, 1 H, CH_2), 2.98 (s, 1 H, C_{sp}H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 170.92 (CON), 167.46 (CON), 161.69 (d, $^{1}J_{C-F}$ = 241.8 Hz, C_{Ar}-4), 155.99, 134.43, 133.52, 133.30, 132.09, 131.54 (d, $^{3}J_{C-F}$ = 8.0 Hz, 2 C, CH_{Ar}-2,6), 131.09 (d, $^{4}J_{C-F}$ = 2.8 Hz, C_{Ar}-1), 128.57, 127.21, 121.26 (2 C), 115.62 (d, $^{2}J_{C-F}$ = 21.0 Hz, 2 C, CH_{Ar}-3,5), 114.42 (2 C), 79.12 (C_{sp}), 74.86 (CH_{sp}), 61.50 (CH), 59.84 (CH), 55.64 (Me), 36.65 (CH_2N), 35.29 (CH_2).

MS (APCI): *m*/*z* = 564, 566 [M + H]$^+$.

Anal. Calcd for $C_{27}H_{23}BrFN_5O_3$: C, 57.46; H, 4.11; N, 12.41. Found: C, 57.47; H, 4.09; N, 12.42.

2-(2-Azido-3-(4-bromophenyl)-*N*-(prop-2-yn-1-yl)propanamido)-3-bromo-*N*-cyclopentyl-4-phenylbut-3-enamide (8j)

Yield: 1.07 g (87%); white solid; mp 138–140 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.61–8.56 (m, 1 H, NH), 7.64–6.96 (m, 10 H), 5.92–5.80 (m, 1 H), 4.64–3.90 (m, 4 H), 3.56–3.37 (m, 1 H), 3.24–3.11 (m, 1 H), 3.02 (dd, *J* = 16.2, 8.2 Hz, 1 H), 1.93–1.72 (m, 2 H, cyclopent), 1.69–1.28 (m, 6 H, cyclopent).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 135.16, 131.97, 131.81, 129.27, 128.80, 127.95, 121.17, 72.96, 66.33, 64.80, 59.36, 55.72, 51.18, 32.65, 23.85.

MS (APCI): *m*/*z* = 612, 614, 616 [M + H]$^+$.

Anal. Calcd for $C_{27}H_{27}Br_2N_5O_2$: C, 52.87; H, 4.44; N, 11.42. Found: C, 52.89; H, 4.43; N, 11.40.

4,5-Dihydro[1,2,3]triazolo[1,5-*a*]pyrazine-6(7*H*)-ones 9a–f and 11; General Procedure

Compound **8** (1 mmol) was dissolved by heating in dry toluene (4 mL). The reaction mixture was refluxed for 24 h, then cooled and evaporated under reduced pressure to give the target products **9**.

***N*-Cyclohexyl-2-(7-(2,4-dichlorobenzyl)-6-oxo-6,7-dihydro[1,2,3]-triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-2-(*p*-tolyl)acetamide (9a)**

Yield: 0.51 g (98%); white solid; mp 201–203 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.31 (d, *J* = 7.6 Hz, 1 H, NH), 7.51 (s, 1 H, CH_{Ar}), 7.48 (d, *J* = 2.1 Hz, 1 H, CH_{Ar}), 7.22–7.15 (m, 3 H, CH_{Tol} + CH_{Tr}), 7.07 (d, *J* = 7.8 Hz, 2 H, Tol), 6.98 (d, *J* = 8.3 Hz, 1 H, CH_{Ar}), 6.17 (s, 1 H, CH), 5.61 (t, *J* = 6.4 Hz, 1 H, CH), 4.54 (d, *J* = 16.6 Hz, 1 H, CH_2), 4.09 (d, *J* = 16.6 Hz, 1 H, CH_2), 3.63 (tdt, *J* = 11.1, 7.6, 3.9 Hz, 1 H, cyclohex), 3.57–3.41 (m, 2 H, CH_2), 2.26 (s, 3 H, Me), 1.85–1.46 (m, 5 H, cyclohex), 1.38–0.97 (m, 5 H, cyclohex).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 167.83 (CON), 165.25 (CON), 138.18 (Tr-4), 135.05 (C_{Ar}-2), 133.51 (CH_{Ar}-6), 133.06 (C_{Ar}-1), 132.53 (C_{Ar}-4), 132.00 (C_{Tol}-1), 129.90 (2 C, CH_{Tol}), 129.57 (C_{Tol}-4), 129.50 (CH_{Ar}-3), 129.06 (CH_{Ar}-5), 129.03 (2 C, CH_{Tol}), 127.61 (Tr-5), 59.75 (CH), 59.55 (CH), 48.25 (CH_2N), 38.73 (CHNHcyclohex), 35.83 (CH_2), 32.64 (2 C, CH_2 cyclohex), 25.61 (cyclohex), 24.98 (cyclohex), 24.87 (cyclohex), 21.11 (CH_3).

MS (APCI): *m*/*z* = 526, 528 [M + H]$^+$.

Anal. Calcd for $C_{27}H_{29}Cl_2N_5O_2$: C, 61.60; H, 5.55; N, 13.30. Found: C, 61.57; H, 5.50; N, 13.33.

2-(2-Bromophenyl)-*N*-cyclohexyl-2-(7-(3-fluorobenzyl)-6-oxo-6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)acetamide (9b)

Yield: 0.53 g (98%); white solid; mp 228–230 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.34 (d, *J* = 8.1 Hz, 1 H, NH), 7.72–6.93 (m, 7 H), 6.64–6.60 (m, 2 H), 6.08 (s, 1 H), 5.74–5.58 (m, 1 H), 4.50 (d, *J* = 16.0 Hz, 1 H), 3.63 (t, *J* = 6.8 Hz, 1 H, cyclohex), 3.52–3.38 (m, 3 H), 1.76–1.43 (m, 5 H, cyclohex), 1.26–0.91 (m, 5 H, cyclohex).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 167.59 (CON), 164.44 (CON), 162.25 (d, $^{1}J_{C-F}$ = 243.1 Hz, C_{Ar}-3), 138.15 (d, $^{3}J_{C-F}$ = 7.5 Hz, C_{Ar}-1), 133.93, 133.68, 131.51, 131.25, 130.45 (d, $^{3}J_{C-F}$ = 8.3 Hz, CH_{Ar}-5), 129.93, 129.38, 128.63, 126.25 (C_{Ar}-6), 125.81, 116.85 (d, $^{2}J_{C-F}$ = 20.9 Hz, CH_{Ar}-4), 114.25 (d, $^{2}J_{C-F}$ = 20.7 Hz, CH_{Ar}-2), 61.10 (CH), 60.48 (CH), 48.42 (CH_2N), 37.50, 32.54 (CH_2 cyclohex), 32.51 (CH_2 cyclohex), 25.56 (CH_2 cyclohex), 24.96 (CH_2 cyclohex), 24.85 (CH_2 cyclohex).

MS (APCI): *m*/*z* = 540, 542 [M + H]$^+$.

Anal. Calcd for $C_{26}H_{27}BrFN_5O_2$: C, 57.78; H, 5.04; N, 12.96. Found: C, 57.80; H, 5.00; N, 12.93.

Ethyl (2-(2-Bromophenyl)-2-(7-(3-fluorobenzyl)-6-oxo-6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)acetyl)glycinate (9c)

Yield: 0.52 g (95%); white solid; mp 187–189 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.06 (t, *J* = 5.9 Hz, 1 H, NH), 7.68 (d, *J* = 7.9 Hz, 1 H), 7.56–7.41 (m, 3 H), 7.36 (dd, *J* = 9.0, 4.7 Hz, 1 H), 7.16–7.12 (m, 1 H), 7.03–6.91 (m, 1 H), 6.63–6.59 (m, 2 H), 6.34 (s, 1 H, CH), 5.74 (t, *J* = 4.7 Hz, 1 H, CH), 4.28–4.07 (m, 3 H), 4.01 (dd, *J* = 17.1, 5.9 Hz, 1 H, CH_2), 3.91–3.71 (m, 2 H), 3.50 (d, *J* = 5.0 Hz, 2 H, CH_2), 1.21 (t, *J* = 7.1 Hz, 3 H, $OCH_2C\underline{H}_3$).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 169.44 (COO), 168.54 (CON), 164.72 (CON), 161.52 (d, $^{1}J_{C-F}$ = 259.3 Hz, C_{Ar}-3), 137.12 (d, $^{3}J_{C-F}$ = 7.7 Hz, C_{Ar}-1), 133.42, 132.94, 131.55, 130.92, 130.09 (d, $^{3}J_{C-F}$ = 8.4 Hz, CH_{Ar}-5), 129.10, 128.82, 128.01, 125.34 (d, $^{4}J_{C-F}$ = 1.9 Hz, C_{Ar}-6), 124.85, 116.17 (d, $^{2}J_{C-F}$ = 21.4 Hz, CH_{Ar}-4), 113.88 (d, $^{2}J_{C-F}$ = 21.7 Hz, CH_{Ar}-2), 60.58, 60.39, 59.77, 40.84, 38.51, 38.09, 14.09 ($OCH_2\underline{C}H_3$).

MS (APCI): *m*/*z* = 544, 546 [M + H]$^+$.

Anal. Calcd for $C_{24}H_{23}BrFN_5O_4$: C, 52.95; H, 4.26; N, 12.87. Found: C, 52.97; H, 4.27; N, 12.85.

***N*-Benzyl-2-(7-(3,4-dichlorobenzyl)-6-oxo-6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-2-(4-methoxyphenyl)acetamide (9d)**

Yield: 0.53 g (97%); white solid; mp 105–107 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.84 (br s, 1 H, NH), 7.57–7.49 (m, 1 H), 7.43–7.07 (m, 7 H), 7.04–6.65 (m, 4 H), 6.48 (d, *J* = 8.2 Hz, 1 H), 6.18 (s, 1 H, CH), 5.76–5.75 (m, 1 H), 4.66 (d, *J* = 16.4 Hz, 1 H), 4.30–4.24 (m, 2 H), 3.73 (s, 3 H, OMe), 3.30 (br s, 2 H, CH_2Ph), 3.05–3.01 (m, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 168.95 (CON), 164.22 (CON), 159.79, 139.38, 136.08, 131.81, 131.55, 131.32, 131.06 (2 C), 130.60, 129.87, 129.68, 129.54, 128.75 (2 C), 127.81, 127.74, 127.34, 125.97, 114.69, 114.48, 59.99 (CH), 59.27 (CH), 55.66 (CH_2N), 42.68 (CH_2Ph), 38.28 (OCH_3), 31.44 (CH_2).

MS (APCI): *m*/*z* = 550, 552 [M + H]$^+$.

Anal. Calcd for $C_{28}H_{25}Cl_2N_5O_3$: C, 61.10; H, 4.58; N, 12.72. Found: C, 61.09; H, 4.59; N, 12.70.

2-(2-Bromophenyl)-2-(7-(3,4-dichlorobenzyl)-6-oxo-6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-*N*-(*p*-tolyl)acetamide (9e)

Yield: 0.59 g (98%); white solid; mp 244–245 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.46 (s, 1 H, NH), 7.75–7.68 (m, 1 H), 7.59–7.27 (m, 7 H), 7.14 (br s, 2 H), 7.05 (br s, 1 H), 6.77 (br s, 1 H), 6.37 (s, 1 H, CH), 5.80 (br s, 1 H, CH), 4.30 (d, *J* = 16.5 Hz, 1 H, CH_2), 3.88 (d, *J* = 16.5 Hz, 1 H, CH_2), 3.60–3.41 (m, 2 H, CH_2), 2.27 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.66 (CON), 164.71 (CON), 136.07, 135.69, 133.64, 132.86, 132.76, 131.52, 131.11, 130.88, 130.24, 129.84, 129.64, 129.37, 129.20 (2 C), 128.86, 128.45, 125.14, 119.37, 119.30 (2 C), 61.64, 59.56, 38.92, 37.34, 20.46 (CH_3).

MS (APCI): *m*/*z* = 598, 600, 602 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{22}BrCl_2N_5O_2$: C, 54.11; H, 3.70; N, 11.69. Found: C, 54.13; H, 3.73; N, 11.65.

2-(2-Bromophenyl)-2-(7-(3-fluorobenzyl)-6-oxo-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-*N*-(4-methoxyphenyl)acetamide (9f)

Yield: 0.54 g (96%); white solid; mp 221–222 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.43 (s, 1 H, NH), 7.71 (d, *J* = 7.7 Hz, 1 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 7.50 (s, 1 H), 7.44 (d, *J* = 7.2 Hz, 1 H), 7.38–7.31 (m, 2 H), 7.14 (d, *J* = 6.7 Hz, 1 H), 6.99 (s, 1 H), 6.92 (d, *J* = 8.4 Hz, 2 H), 6.62 (br s, 2 H), 6.37 (s, 1 H, CH), 5.78 (br s, 1 H, CH), 4.17 (d, *J* = 16.2 Hz, 1 H, CH_2), 3.88 (d, *J* = 16.2 Hz, 1 H, CH_2), 3.74 (s, 3 H, OMe), 3.54 (br s, 2 H, CH_2).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.33 (CON), 165.03 (CON), 161.93 (d, $^1J_{C–F}$ = 244.2 Hz, C_{Ar}-3), 155.61, 137.10 (d, $^3J_{C–F}$ = 8.0 Hz, C_{Ar}-1), 133.65, 132.97, 131.72, 131.05, 130.80, 130.05 (d, $^3J_{C–F}$ = 8.3 Hz, CH_{Ar}-5), 129.17, 128.88, 128.42, 125.34 (d, $^4J_{C–F}$ = 2.4 Hz, C_{Ar}-6), 124.99, 120.79 (2 C), 116.25 (d, $^2J_{C–F}$ = 21.1 Hz, CH_{Ar}-4), 114.00 (2 C), 113.92 (d, $^2J_{C–F}$ = 20.9 Hz, CH_{Ar}-2), 61.56, 59.81, 55.23, 38.71, 38.09.

MS (APCI): *m*/*z* = 564, 566 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{23}BrFN_5O_3$: C, 57.46; H, 4.11; N, 12.41. Found: C, 57.55; H, 4.08; N, 12.39.

(*Z*)-3-Bromo-2-(7-(4-bromobenzyl)-6-oxo-6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-*N*-cyclopentyl-4-phenylbut-3-enamide (11)

Yield: 0.59 g (97%); white solid; mp 216–220 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.75, 8.63 (2 d, *J* = 6.7 Hz, 1 H, NH), 7.72–7.54 (m, 3 H), 7.44–7.39 (m, 3 H), 7.30 (t, *J* = 7.9 Hz, 2 H), 7.00 (d, *J* = 2.7 Hz, 1 H), 6.69–6.65 (m, 2 H), 5.96 (d, *J* = 7.5 Hz, 1 H), 5.83–5.73 (m, 1 H), 5.02, 4.51 (2 d, *J* = 16.4 Hz, 1 H), 4.17–3.84 (m, 2 H), 3.50–3.25 (m, 2 H), 1.96–1.76 (m, 2 H, cyclopent), 1.70–1.37 (m, 6 H, cyclopent).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.70 (CON), 165.20 (CON), 131.51, 131.30 (2C), 131.21, 129.26, 129.12, 128.91 (2C), 128.86 (2C), 128.44 (2C), 128.38 (2C), 120.48, 119.42, 64.22, 59.97, 50.80, 40.07, 38.13, 32.18, 31.89, 23.48, 23.34.

MS (APCI): *m*/*z* = 612, 614, 616 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{27}Br_2N_5O_2$: C, 52.87; H, 4.44; N, 11.42. Found: C, 52.88; H, 4.46; N, 11.40.

4,5-Dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-6(7*H*)-ones 9g and 9h; General Procedure

A solution of 2-azidopropionic acid **3** (2 mmol), amine **4c** (2 mmol), aldehyde **5** (2 mmol) and isonitrile **6** (2 mmol) in methanol (5 mL) was stirred at room temperature for 30 min. The temperature was then raised to 50 °C and stirring was continued for 72 h. Upon completion of the reaction, the methanol was evaporated and the residue was recrystallized from dichloromethane/hexane (3:1).

***N*-Benzyl-2-(7-(4-bromobenzyl)-6-oxo-6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-3-methylbutanamide (9g)**

Yield: 0.78 g (78%); white solid; mp 239–241 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.85 (t, *J* = 5.8 Hz, 1 H, NH), 7.56 (s, 1 H), 7.29–7.16 (m, 5 H), 7.11 (d, *J* = 8.1 Hz, 2 H, Ar), 6.54 (d, *J* = 8.0 Hz, 2 H, Ar), 5.65 (t, *J* = 4.5 Hz, 1 H, CH), 4.71 (d, *J* = 11.1 Hz, 1 H), 4.50 (d, *J* = 17.1 Hz, 1 H), 4.33 (dd, *J* = 15.1, 6.2 Hz, 1 H, CH_2), 4.21 (dd, *J* = 15.1, 5.8 Hz, 1 H, CH_2), 3.73 (d, *J* = 17.0 Hz, 1 H), 3.47–3.35 (m, 2 H), 2.11 (dp, *J* = 12.8, 6.5 Hz, 1 H, $CHMe_2$), 0.81 (d, *J* = 6.5 Hz, 3 H, Me), 0.61 (d, *J* = 6.6 Hz, 3 H, Me).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 168.46 (CON), 165.22 (CON), 139.60, 134.08, 131.62 (2 C), 131.53 (2 C), 129.70, 129.33, 128.72 (2 C), 127.73 (2 C), 127.29, 120.88, 61.92, 60.22, 42.58, 38.53, 37.58, 26.24, 19.43 (Me), 18.93 (Me).

MS (APCI): *m*/*z* = 496, 498 $[M + H]^+$.

Anal. Calcd for $C_{24}H_{26}BrN_5O_2$: C, 58.07; H, 5.28; N, 14.11. Found: C, 58.09; H, 5.26; N, 14.10.

***N*-Benzyl-2-(7-(2-fluorobenzyl)-6-oxo-6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-2-(1*H*-indol-3-yl)acetamide (9h)**

Yield: 0.84 g (83%); white solid; mp 252–254 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.27 (s, 1 H, NH_{Ind}), 8.86 (t, *J* = 6.2 Hz, 1 H, NH), 7.37 (s, 2 H), 7.33–7.16 (m, 8 H), 7.07 (t, *J* = 7.7 Hz, 1 H), 7.01–6.81 (m, 4 H), 6.55 (s, 1 H, CH), 5.68–5.65 (m, 1 H, CH), 4.36 (d, *J* = 5.8 Hz, 2 H, CH_2), 4.28–4.17 (m, 2 H), 3.52–3.35 (m, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 169.21 (CON), 165.16 (CON), 161.17 (d, $^1J_{C–F}$ = 245.3 Hz, C_{Ar}-2), 139.62, 136.72, 131.99 (d, $^3J_{C–F}$ = 3.9 Hz, CH_{Ar}-6), 129.70 (d, $^3J_{C–F}$ = 8.2 Hz, C_{Ar}-4), 129.58, 129.24, 128.66 (2 C, Ph), 127.82 (2 C, Ph), 127.26, 126.89, 126.74, 124.69 (d, $^4J_{C–F}$ = 3.4 Hz, CH_{Ar}-5), 122.25, 122.08 (d, $^2J_{C–F}$ = 15.7 Hz, C_{Ar}-1), 119.85, 118.49, 115.53 (d, $^2J_{C–F}$ = 21.8 Hz, CH_{Ar}-3), 112.33, 107.47, 60.01 (CH), 53.75 (CH), 42.71 (CH_2N), 38.11 (CH_2Ph), 32.42 (CH_2).

MS (APCI): *m*/*z* = 509 $[M + H]^+$.

Anal. Calcd for $C_{29}H_{25}FN_6O_2$: C, 68.49; H, 4.96; N, 16.53. Found: C, 68.50; H, 4.97; N, 16.51.

7-(4-Bromobenzyl)-*N*-cyclopentyl-5-cyclopropyl-6-oxo-3-phenyl-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazine-4-carboxamide (10)

Compound **7a** (2 mmol) was dissolved by heating in dry toluene (8 mL) and then triethylamine (2 mmol) was added to the solution. The reaction mixture was refluxed for 24 h and then cooled, evaporated under reduced pressure, and washed with water to give the target product **10**.

Yield: 0.98 g (92%); white solid; mp 223–224 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.26–8.14 (m, 1 H, NH), 7.80–7.62 (m, 3 H), 7.50–7.35 (m, 5 H), 7.21 (d, *J* = 7.5 Hz, 2 H), 4.82–4.66 (m, 1 H), 4.01–3.81 (m, 1 H), 3.08 (dd, *J* = 14.3, 4.3 Hz, 1 H), 2.90–2.71 (m, 1 H), 2.54–2.51 (m, 1 H), 1.68 (br s, 1 H), 1.55–1.27 (m, 3 H), 1.26–1.07 (m, 3 H), 0.88–0.61 (m, 3 H), 0.54–0.37 (m, 1 H), 0.12 (br s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 171.89 (CON), 166.31 (CON), 152.68, 137.41, 134.79, 132.54, 132.04 (2 C), 131.53 (2 C), 130.86, 130.65 (2 C), 128.83 (2 C), 120.25, 82.80, 63.08, 51.99, 35.70, 31.52, 31.19, 24.61, 23.84, 23.59, 6.71 (cyclopropyl), 6.37 (cyclopropyl).

MS (APCI): *m*/*z* = 534, 536 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{28}BrN_5O_2$: C, 60.68; H, 5.28; N, 13.10. Found: C, 60.70; H, 5.25; N, 13.09.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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(26) Single-crystal X-ray diffraction data for compound **9g** (A) (CCDC 2194707): $C_{24}H_{26}BrN_5O_2$, monoclinic crystal system, space group *C*2/*c*, *Z* = 8, unit cell dimensions: *a* = 20.3612(6), *b* = 21.6139(7), *c* = 10.6307(3) Å, *β* = 93.042(2)°, *V* = 4671.8(2) Å^3 at 150 K; ρ_{calcd} = 1.412 g/cm^3, $R[F^2 > 2\sigma(F^2)]$ = 0.0369 for 4035 reflections, $wR(F^2)$ = 0.1051 for all 4511 reflections. Diffraction data were collected on a Gemini+ diffractometer with Cu Kα radiation (λ = 1.54184 Å) and an Atlas CCD detector. Single-crystal X-ray diffraction data for compound **9g** (B) (CCDC 2194708): $C_{24}H_{26}BrN_5O_2$, orthorhombic crystal system, space group *Pbcn*, *Z* = 8, unit cell dimensions: *a* = 27.1556(6), *b* = 10.9436(2), *c* = 15.6823(3) Å, *V* = 4660.43(17) Å^3 at 150 K; ρ_{calcd} = 1.415 g/cm^3, $R[F^2 > 2\sigma(F^2)]$ = 0.0395 for 3695 reflections, $wR(F^2)$ = 0.1060 for all 4561 reflections. Diffraction data were collected on a Gemini+ diffractometer with Cu Kα radiation (λ = 1.54184 Å) and an Atlas CCD detector. CCDC 2194707 and 2194708 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures