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

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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 cyclization with dipolarophile in amine motif.

Key words  azides, 1,2,3-triazoles, [1,2,3]triazolo[1,5-α]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. 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-α]pyrazines deserve attention. 3 [1,2,3]triazolo[1,5-α]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 (Figure 1). In addition, compounds of this class were found to possess antitumor activity. 8 Therefore, the development of suitable methods to obtain 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-α]pyrazines is an important area of research.

A general approach to the simultaneous formation of 1,2,3-triazole and pyrazine rings is the 1,3-dipolar cycloisomerization of α-azido-N-(prop-2-ynyl)amides. A previously described two-step approach to obtain [1,2,3]triazolo[1,5-α]pyrazines proceeded via a sequential Ugi reaction involving an α-azidoacetic acid or an α-azidophenylacetic acid and propargylamine, followed by a Huisgen cycloisomerization.
Recently, a one-step method was developed for the preparation of 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-α]pyrazines in an Ugi reaction using superparamagnetic copper-modified iron oxide and 2-aminobenzamide as the catalyst. 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 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-arylpropanoic 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-arylpropanoic 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.

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-α]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, and for the preparation of alkyl 2-(1,2,3-triazol-1-yl)-3-arylpropanoates. 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.
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(7H)-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 ¹H NMR spectra, ¹³C NMR spectra were used to monitor the progress of the cycloaddition based on the acetylene signals appearing in the region...
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Synthesis 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. Apparently, intermolecular conjugation leading to the formation of oligomeric products is unfavorable due to steric factors.

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

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

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 \(C2/c\) and \(Pbcn\), respectively, each with one molecule in the asymmetric unit (Figure 3).

![Figure 3](image)

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 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](image)

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-...
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-α]-pyrazin-5(4H)-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-α]pyrazin-6(7H)-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-bromo-benzaldehyde may serve as suitable precursors for further intramolecular cross-couplings, giving rise to new polycyclic systems.

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

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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-arylpropanoates 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 NaN3 (6.5 g) in H2O (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.

**1H** NMR (500 MHz, DMSO-d6): δ = 13.44 (s, 1 H, COOH), 7.19 (t, J = 7.5 Hz, 1 H, CHα-5), 7.11–7.03 (m, 3 H, CHAr-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, CHβ), 2.88 (dd, J = 14.1, 8.9 Hz, 1 H, CHβ), 2.28 (s, 3 H, CH3).

**13C** NMR (126 MHz, DMSO-d6): δ = 171.75 (COOH), 137.86 (Cα-3), 137.07 (Cα-1), 130.30 (CHAr-2), 128.70 (CHAr-5), 127.88 (CHAr-4), 126.70 (CHAr-6), 62.77 (CH3), 37.11 (CH2), 21.45 (CH3).

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


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

Yield: 14.58 g (54%); white solid; mp 78–79 °C.
2-Azido-3-(4-fluorophenyl)propanoic Acid (3d)

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

1H NMR (400 MHz, DMSO-d6): δ = 13.55 (s, 1 H, COOH), 7.45–7.42 (m, 1 H, CHAr-2), 7.34–7.31 (m, 1 H, CHAr-5), 7.3–7.27 (m, 2 H, CHAr-2,6), 4.47 (dd, J = 9.6, 4.9 Hz, 1 H, CH), 3.06 (dd, J = 14.5, 5.0 Hz, 1 H, CH2), 2.90 (dd, J = 14.2, 8.7 Hz, 1 H, CH2).

13C NMR (101 MHz, DMSO-d6): δ = 171.39 (COOH), 138.52 (CAr-1), 131.60 (CHAr-2), 131.24 (CHAr-3), 130.82 (CHAr-5), 130.18 (CHAr-6), 129.25 (CHAr-4), 127.66 (CHAr-5), 61.38 (CH), 34.85 (CH2).

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

Anal. Calcld for C8H7ClNO3: C, 41.56; H, 3.17; N, 18.60.

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

Yield: 11.54 g (46%); white solid; mp 90–91 °C.

1H NMR (500 MHz, DMSO-d6): δ = 13.55 (s, 1 H, COOH), 8.17 (d, J = 8.2 Hz, 2 H, CHAr-3,5), 7.56 (d, J = 8.2 Hz, 2 H, CHAr-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, CH2), 3.07 (dd, J = 14.1, 9.0 Hz, 1 H, CH2).

13C NMR (101 MHz, DMSO-d6): δ = 171.40 (COOH), 146.98 (CAr-4), 145.58 (CAr-1), 131.08 (2 C, CHAr-2,6), 123.83 (2 C, CHAr-3,5), 62.09 (CH), 36.69 (CH2).

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

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

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

Anal. Calcd for C_{10}H_{10}N_{4}O_{4}: C, 48.00; H, 4.03; N, 22.39. Found: C, 52.69; H, 4.72; N, 13.40.

1H 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, CHN), 4.03–3.80 (m, 1 H, CH), 3.38–3.28 (m, 1 H, CH), 3.16 (dd, J = 14.3, 10.1 Hz, 1 H, CH), 2.92 (s, 1 H, CH), 1.27 (s, 9 H, 3 × Me).

13C NMR (126 MHz, DMSO-d_{6}): δ = 169.69 (CON), 168.05 (CON), 160.92 (d, J_{C-F} = 244.4 Hz, C_{Ar-1}), 134.86, 132.92, 131.59 (d, J_{C-F} = 4.1 Hz, CH_{Ar-6}), 130.47, 130.27, 129.11 (d, J_{C-F} = 7.9 Hz, CH_{Ar-4}), 128.72, 126.83, 124.42 (d, J_{C-F} = 2.6 Hz, CH_{Ar-5}), 123.32 (d, J_{C-F} = 15.5 Hz, C_{Ar-1}), 115.27 (d, J_{C-F} = 21.9 Hz, CH_{Ar-3}), 78.61 (C_{sp2}), 74.17 (CH_{sp3}), 60.41 (CH_{sp2}), 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_{16}H_{15}BrF_{3}N_{2}O_{5}: C, 56.04; H, 4.90; N, 13.61. Found: C, 56.03; H, 4.91; N, 13.59.

2-Azido-3-(3-fluorophenyl)-N-(1-(4-methoxyphenyl)-2-oxo-2-((tosylethylamino)ethyl))-N'-(2,2,2-trifluoroethyl)propanamide (8a)

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

1H 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, CHN), 4.03–3.80 (m, 1 H, CH), 3.38–3.28 (m, 1 H, CH), 3.16 (dd, J = 14.3, 10.1 Hz, 1 H, CH), 2.92 (s, 1 H, CH), 1.27 (s, 9 H, 3 × Me).

13C NMR (126 MHz, DMSO-d_{6}): δ = 169.69 (CON), 168.05 (CON), 160.92 (d, J_{C-F} = 244.4 Hz, C_{Ar-1}), 134.86, 132.92, 131.59 (d, J_{C-F} = 4.1 Hz, CH_{Ar-6}), 130.47, 130.27, 129.11 (d, J_{C-F} = 7.9 Hz, CH_{Ar-4}), 128.72, 126.83, 124.42 (d, J_{C-F} = 2.6 Hz, CH_{Ar-5}), 123.32 (d, J_{C-F} = 15.5 Hz, C_{Ar-1}), 115.27 (d, J_{C-F} = 21.9 Hz, CH_{Ar-3}), 78.61 (C_{sp2}), 74.17 (CH_{sp3}), 60.41 (CH_{sp2}), 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_{16}H_{15}BrF_{3}N_{2}O_{5}: C, 56.04; H, 4.90; N, 13.61. Found: C, 56.03; H, 4.91; N, 13.59.

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

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

1H NMR (500 MHz, DMSO-d_{6}): δ = 8.22–8.16 (m, 1 H, Ar), 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, CH), 4.60–4.39 (m, 1 H, 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).

13C 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, 71.76, 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_{16}H_{15}BrF_{3}N_{2}O_{5}: 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: 0.84 g (97%); white solid; mp 173–175 °C.

1H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 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$_2$N), 4.05–3.90 (m, 1 H, C$_3$H$_2$), 3.80 (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).

13C NMR (126 MHz, DMSO-d$_6$): $\delta$ = 137.76, 136.02, 133.81, 133.11, 132.76, 132.16, 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 (C$_{sp}$), 65.19 (CH$_3$), 58.79 (CH$_3$), 35.90 (CH$_3$), 34.83 (CH$_3$), 20.44 (Me).

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

Anal. Calcd for C$_{27}$H$_{22}$BrCl$_2$N$_5$O$_2$: C, 54.86; H, 3.60; N, 11.69. Found: C, 54.69; H, 3.72; N, 11.70.

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.

1H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 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, 2 H, CH$_2$N), 4.06–3.95 (m, 1 H, CH$_2$), 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$_3$H$_2$), 2.25 (s, 3 H, Me).

13C NMR (126 MHz, DMSO-d$_6$): $\delta$ = 169.88 (CON), 167.28 (CON), 137.76, 136.02, 133.81, 133.11, 132.76, 132.16, 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 (C$_{sp}$), 65.19 (CH$_3$), 58.79 (CH$_3$), 35.90 (CH$_3$), 34.83 (CH$_3$), 20.44 (Me).

MS (APCI): $m/z$ = 598, 600 [M + H]$^+$. Anal. Calcd for C$_{27}$H$_{22}$BrCl$_2$N$_5$O$_2$: 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.

1H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 10.33 (s, 1 H, NH), 7.67 (d, $J$ = 7.9 Hz, 1 H, J$_{1,2}$), 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, 2 H, CH$_2$N), 4.67–4.61 (m, 2 H, CH$_2$), 4.05–3.99 (m, 1 H, CH$_2$), 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, CH$_2$).

13C NMR (126 MHz, DMSO-d$_6$): $\delta$ = 170.38 (CON), 167.03 (CON), 162.2 (d, $J_{CH,O}$ = 228.4 Hz, C$_{sp}$), 161.19, 155.58, 139.57 (d, $J_{CH,O}$ = 7.6 Hz, C$_{sp}$), 133.98, 133.10, 131.65, 130.68, 130.34 (d, $J_{CH,O}$ = 8.5 Hz, C$_{sp}$), 128.15, 126.77, 125.44 (d, $J_{CH,O}$ = 4.0 Hz, C$_{sp}$), 120.25 (s), 115.87 (d, $J_{CH,O}$ = 21.3 Hz, C$_{sp}$), 114.00 (2 C), 113.72 (d, $J_{CH,O}$ = 19.6 Hz, C$_{sp}$), 78.67 (C$_{sp}$), 74.41 (C$_{sp}$), 61.09 (CH$_3$), 59.10 (CH$_3$), 55.21 (OMe), 36.68 (CH$_3$), 34.83 (C$_{sp}$).

MS (APCI): $m/z$ = 564, 566 [M + H]$^+$. Anal. Calcd for C$_{27}$H$_{22}$BrCl$_2$N$_5$O$_2$: 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.

1H NMR (500 MHz, DMSO-d$_6$): $\delta$ = 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$_2$N), 4.66–4.51 (m, 2 H, CH$_2$N$_2$), 4.02–3.98 (m, 1 H, CH$_2$), 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$_3$H$_2$).

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

\[ \text{N-Cyclohexyl-2-(7-(4,2,3-dichlorobenzyl)-6-oxo-6,7-dihydro[1,2,3]-triazol-1,5-yl)pyrazin-5(4H)-yl)-2-(p-tolyl)acetamide (9a)} \]

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

\[ \text{1H NMR (400 MHz, DMSO-}\text{d}_6): \delta = 8.31 (s, J = 7.6 Hz, 1 H, NH), 7.51 (s, 1 H, CH\text{Ar}-2), 7.48 (s, J = 2.1 Hz, 1 H, CH\text{Ar}), 7.22–7.15 (m, 3 H, CH\text{CH}_3 + CH\text{CH}_2), 7.07 (d, J = 7.8 Hz, 2 H, Tol), 6.98 (d, J = 8.3 Hz, 1 H, CH\text{Ar}), 6.17 (s, 1 H, CH), 5.61 (t, J = 6.4 Hz, 1 H, CH), 4.09 (d, J = 16.6 Hz, 1 H, CH_2), 3.63 (dd, J \text{= 11.1, 7.6 Hz, 9 H, 1 H, cyclohexyl}), 3.75–3.41 (m, 2 H, CH_2), 2.26 (s, 3 H, Me), 1.85–1.46 (m, 5 H, cyclohexyl), 1.38–0.97 (m, 5 H, cyclohexyl).} \]

\[ \text{13C NMR (151 MHz, DMSO-}\text{d}_6): \delta = 167.83 \text{ (CON), 165.25 (CON), 138.18 (Tr-4), 135.05 (CN-2), 133.51 (CN-6), 133.06 (CN-1), 123.52 (CN\text{Ar}-4), 123.00 (CN\text{Ar}-1), 129.90 (2 C, CH\text{CH}_3), 129.57 (CN\text{Ar}-4), 129.50 (CH\text{CH}_3-3), 129.06 (CH\text{CH}_2-5), 129.03 (2 C, CH\text{CH}_3), 127.61 (Tr-5), 59.75 (CH\text{N}), 48.25 (CH\text{N}), 38.73 (CH\text{N}), 35.83 (CH\text{N}), 32.64 (2 C, CH\text{Cyclohexyl), 25.61 (cyclohexyl), 24.98 (cyclohexyl), 24.87 (cyclohexyl), 21.11 (CH\text{Ar}-5), MS (APCI): m/z = 550, 552 [M + H]^+}. \]

\[ \text{Anal. Calcld for C_{36}H_{29}Cl_{13}N_3O_2: C, 61.90; H, 5.58; N, 13.30. Found: C, 61.57; H, 5.50; N, 13.33.} \]

\[ \text{2-(Bromomethyl)-N-cyclohexyl-2-(7-(3-fluorobenzyl)-6-oxo-6,7-dihydro[1,2,3]triazol-1,5-yl)pyrazin-5(4H)-yl)-2-(p-tolyl)acetamide (9b)} \]

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

\[ \text{1H NMR (400 MHz, DMSO-}\text{d}_6): \delta = 8.34 (d, J = 8.1 Hz, 1 H, NH), 7.72–6.93 (m, 7 H), 6.64–6.60 (m, 2 H), 6.08 (s, 1 H), 5.74–5.58 (m, 1 H), 4.50 (d, J = 16.0 Hz, 1 H), 3.63 (t, J = 6.8 Hz, 1 H, cyclohexyl), 3.52–3.38 (m, 3 H), 1.76–1.43 (m, 5 H, cyclohexyl), 1.26–0.91 (m, 5 H, cyclohexyl).} \]

\[ \text{13C NMR (126 MHz, DMSO-}\text{d}_6): \delta = 167.59 \text{ (CON), 164.44 (CON), 162.25 (d, J_{\text{CH-F}} = 243.1 Hz, CH\text{Ar}-3), 138.15 (d, J_{\text{CH-F}} = 7.5 Hz, CH\text{Ar}-1), 133.93, 133.68, 131.51, 131.25, 130.45 (d, J_{\text{CH-F}} = 8.3 Hz, CH\text{CH}_2-5), 129.93, 129.38, 128.63, 126.25 (CN\text{Ar}-6), 128.61, 116.85 (d, J_{\text{CH-F}} = 20.9 Hz, CH\text{Ar}-4), 114.25 (d, J_{\text{CH-F}} = 20.7 Hz, CH\text{Ar}-2), 61.10 (CH), 60.48 (CH_2), 48.42 (CH\text{N}), 37.50, 32.54 (CH\text{Cyclohexyl), 32.51 (CH\text{Cyclohexyl), 25.56 (CH\text{Cyclohexyl), 24.96 (CH\text{Cyclohexyl), 24.85 (CH\text{Cyclohexyl).}} \]

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

\[ \text{Anal. Calcld for C_{36}H_{23}BrFN_5O_3: C, 52.87; H, 4.43; N, 12.41. Found: C, 52.87; H, 4.43; N, 12.40.} \]
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**Synthesis**

**Paper**

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

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

13C NMR (126 MHz, DMSO-d6): 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 (CH3).

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


1H NMR (400 MHz, DMSO-d6): 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, CH), 4.50 (d, J = 17.1 Hz, 1 H), 4.33 (dd, J = 15.1, 6.2 Hz, 1 H, CH2), 4.21 (dd, J = 15.1, 5.8 Hz, 1 H, CH3), 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, CHMe2), 0.81 (d, J = 6.5 Hz, 3 H, Me), 0.61 (d, J = 6.6 Hz, 3 H, Me).

13C NMR (126 MHz, DMSO-d6): 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]+.


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

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

1H NMR (400 MHz, DMSO-d6): δ = 11.27 (s, 1 H, NHInd), 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, CH2), 4.28–4.17 (m, 2 H), 3.52–3.35 (m, 2 H).

13C NMR (126 MHz, DMSO-d6): δ = 169.21 (CON), 165.16 (CON), 161.17 (d, J = 245.3 Hz, C≡N–2), 139.62, 136.72, 131.99 (d, J = 3.9 Hz, CH–C≡N–4), 129.70 (d, J = 8.2 Hz, CH2–4), 129.58, 129.24, 128.66 (2 C, Ph), 127.82 (2 C, Ph), 127.26, 128.69, 124.69 (d, J = 3.4 Hz, CH2–C≡N–4), 122.25, 122.08 (d, J = 15.7 Hz, CAr–1), 119.85, 118.49, 115.53 (d, J = 21.8 Hz, CH2–C≡N–2), 112.33, 107.47, 60.01 (CH), 53.75 (CH), 42.71 (CH2N), 38.11 (CH2Ph), 32.42 (CH2).

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


**4,5-Dihydro[1,2,3]triazolo[1,5-a]pyrazine-6(7H)-ones 9g and 9i:**

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(4H)-yl)-3-methylbutanamide (9g)

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

Conflict of Interest

The authors declare no conflict of interest.
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Supporting Information
Supporting information for this article is available online at https://doi.org/10.1055/s-0042-1751382.

References
(20) Fouad, M. A.; Abdel-Hamid, H.; Ayoub, M. S. RSC Adv. 2020, 10, 42644.
(26) Single-crystal X-ray diffraction data for compound 9g (A) (CCDC 2194707): C24H26BrN5O2, monoclinic crystal system, space group C2/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) Å3 at 150 K; R(calcd) = 1.412 g/cm3, R2([F2] > 2σ(F2)) = 0.0395 for 3695 reflections, wR(F2) = 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): C24H26BrN5O2, orthorhombic crystal system, space group Pbcn, Z = 8, unit cell dimensions: a = 27.1556(6), b = 10.9436(2), c = 15.6823(7) Å, V = 4671.8(2) Å3 at 150 K; R(calcd) = 1.415 g/cm³, R2([F2] > 2σ(F2)) = 0.0395 for 3695 reflections, wR(F2) = 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.