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Stereoselective synthesis of bio-hybrid amphiphiles of coumarin derivatives by Ugi–Mannich triazole randomization using copper catalyzed alkyne azide click chemistry

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ABSTRACT

An efficient synthesis of ester-triazole-amide amphiphiles of coumarin derivatives by triazole randomization based on click approach is described. Twenty-five small peptide azides were synthesized using Ugi or alternate Mannich-type multi-component reactions. The new azides were then used for the triazole randomization of alkyne functionalized coumarin ester under CuAAC conditions. Sixty-five new peptide bio-hybrids are obtained in near quantitative yield with high regio and stereoselectivity.

Click chemistry represents an ideal set of near perfect reactions.[1] In recent years, click chemistry has emerged as a fast and powerful approach to the synthesis of novel compounds with desired properties. Among the various click reactions capable of producing wide range of functional organic molecules, the copper catalyzed [3+2] azide and alkyne cycloaddition (CuAAC) resulting in the formation of 1,2,3-triazoles has drawn considerable attention as an archetypical example of click chemistry.[2] CuAAC is particularly useful for the synthesis of a variety of molecules ranging from enzyme inhibitors to molecular materials.[3] 1,2,3-Triazoles are important class of target molecules due to their interesting biological properties such as anti-allergic,[4] anti-bacterial,[5] and anti-HIV activity.[6] Some of these classes of drug molecules are now available in the market or in the final stage of clinical trials (Fig. 1).[7] Additionally, due to the resemblance in physiochemical properties such as planarity, dipole moment, Cα distance and H-bond acceptor properties (of the lone pairs in nitrogen atoms), 1,2,3-triazoles are considered as peptide bond isosteres.[8] In addition to this, 1,2,3-triazole ring is highly chemically stable under hydrolytic as well as reductive and oxidative conditions. Consequently, amide-to-triazole substitutions are now common in drug-like molecules whose amide bonds are known to be crucial for biological activity.[9] A recent trend in this field is the synthesis

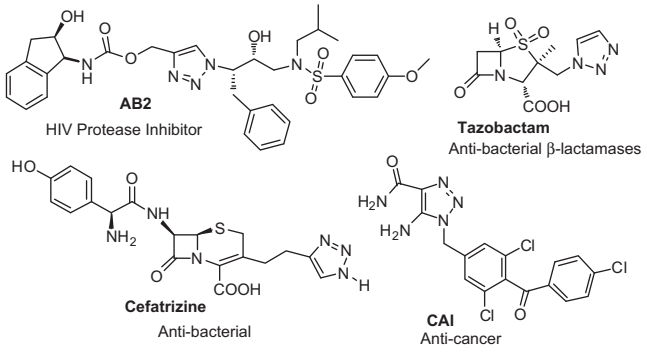

Figure 1. Representative drug examples of 1,2,3-triazole derivatives.

of 'bio-hybrid' amphiphiles consists of both amide and triazole functionality, which are highly useful in materials development.[10]

Coumarin and its derivatives are one of the important classes of compounds possessing diverse range of pharmacological and therapeutic properties. Several therapeutically active compounds containing coumarin derivatives have been reported, such as anti-bacterials,[11a] anti-fungals,[11b] anti-coagulants[11c] and anti-HIV agents.[11d] The pharmacological, biochemical and therapeutic properties of coumarin derivatives are strongly depend on the nature as well as position of the structural substituents.[12] For example, 3-phenyl coumarin based compounds containing

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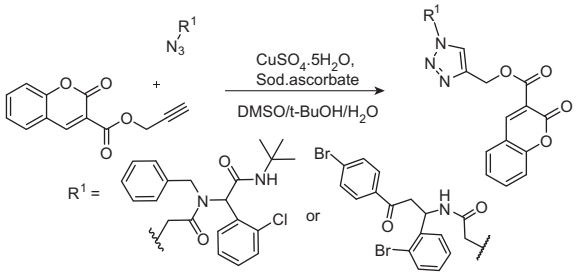
carbamate groups are relatively efficient for inhibiting the cell cycle arrest activity of the HIV-1Vpr.[11d] (HIV-1Vpr is an accessory protein that has been shown to have multiple roles in the human immunodeficiency virus-1 (HIV-1) pathogenesis). Here also, the presence of the amide functionality in the 3-substituted coumarin scaffold was reported to be critical for the activity against the viral protein.

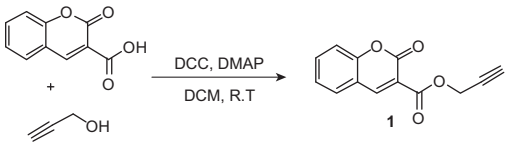
In our previous papers, we reported the synthesis of small peptide like β-acetamido carbonyl compounds which are amenable to further end group transformation to produce highly functionalized scaffolds.[13] We envisaged that, the combination of our β-N-substituted carbonyl compounds chemistry with click chemistry could be interesting for the access of new scaffolds useful for medicinal chemistry research. Herein we report a concise procedure for the synthesis of a series of bio-hybrid amphiphiles of coumarin by randomization of terminal alkyne functionalized coumarin esters with a series of small peptide like functional azides using CuAAC reaction (Scheme 1).

Synthesis of alkyne **1** was carried out by esterification of commercially available coumarin-3-carboxylic acid with propargyl alcohol under alkaline condition (Scheme 2). The carboxylic acid was efficiently esterified by stirring with propargyl alcohol in the presence of *N*,*N*-dicyclohexyl cabodiimide (1.1 equiv), and 4-dimethylaminopyridine (0.1 equiv) in dichloromethane.[14]

We then synthesized two series of terminal azides. The type 1 azides, based on Mannich-type β-amido ketone derivatives were

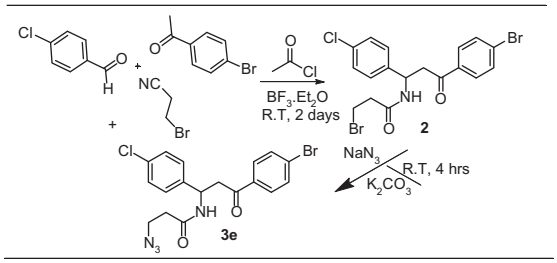


Scheme 1. Triazole randomization of coumarin ester with small peptide azides.



Scheme 2. Esterification of coumarin-3-carboxylic acid with propargyl alcohol

Table 1
List of type 1 azides prepared from Mannich-type β-amido ketone derivatives



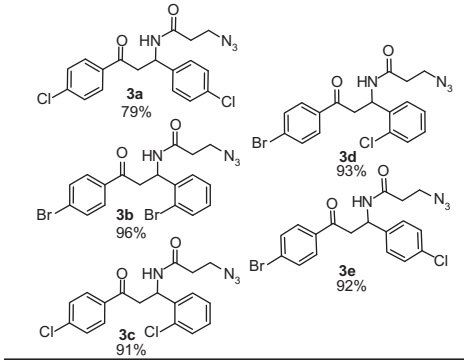
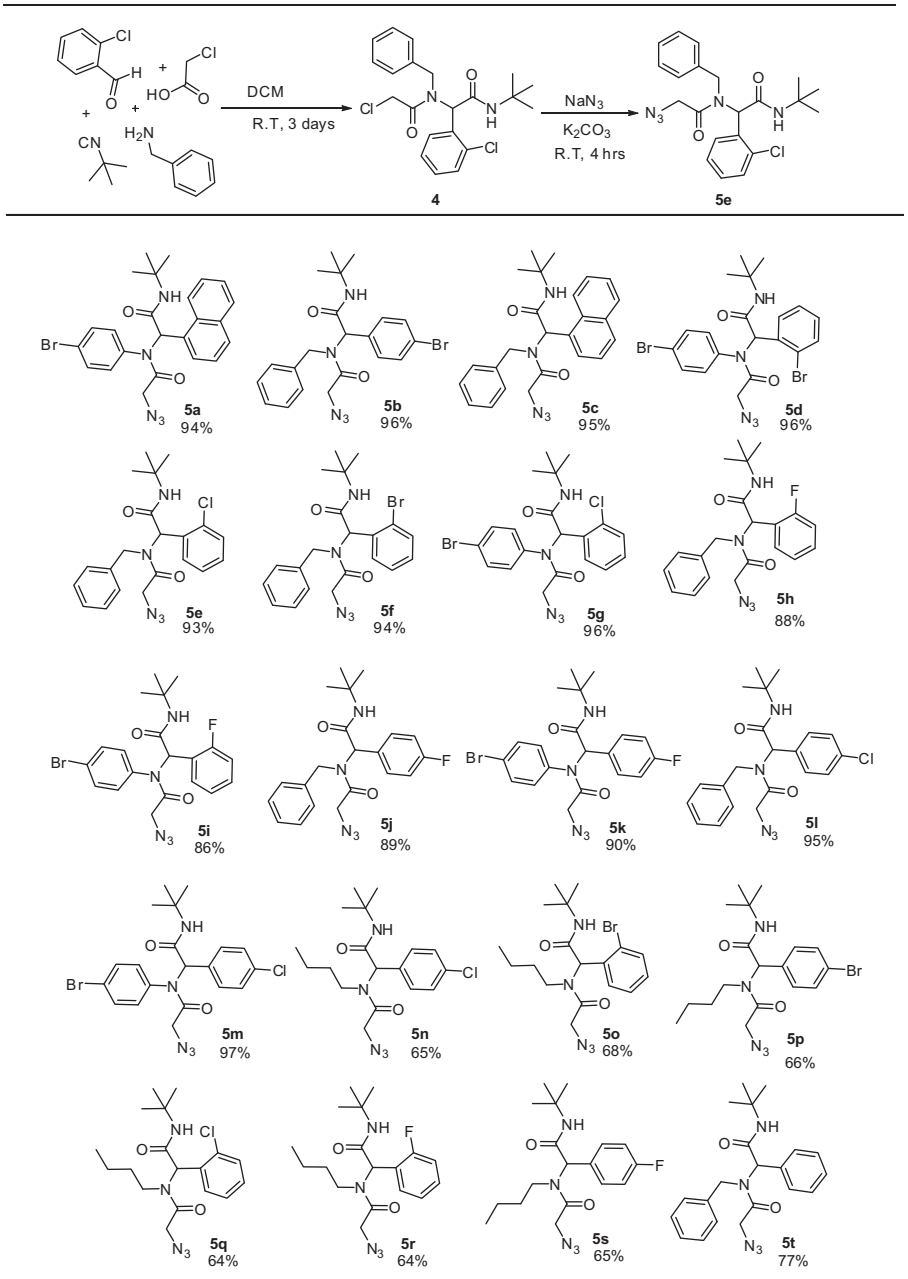


Table 2
List of type 2 azides prepared from Ugi-type α-amino acyl amide derivatives

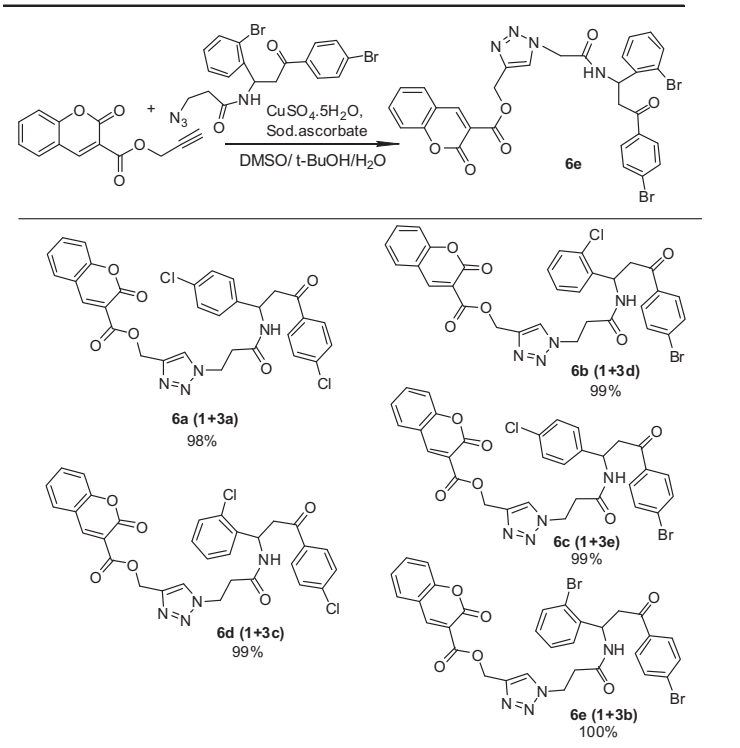


synthesized by a two stage process. The first stage involved the synthesis of the bromo derivative **2** based on a solvent less three component coupling reaction between an aldehyde, ketone and 3-bromopropionitrile in the presence of acetyl chloride and catalytic amount of boron trifluoride etherate at room temperature.[13] The aqueous workup of the reaction mixture followed by solvent wash afforded the bromo derivative **2** in pure form for the use in the second step. The same protocol was adopted for the synthesis of five such bromo-β-amido ketones with different substitution patterns. The bromo derivatives were then quantitatively converted to corresponding keto-amide azides by treating with sodium azide in presence of potassium carbonate in DMF at room temperature (Table 1).[15]

The type 2 azides based on Ugi-type α-amino acyl amides listed in Table 2 were synthesized by the post reaction modification of the Ugi reaction product **4** by azide functionalization. The Ugi-4 component reaction[16] between chloroacetic acid, an aromatic aldehyde, an amine source and *tert*-butyl isocyanide in dichloromethane afforded the Ugi type small peptide chloride **4**.[17] Following the same procedure, we have synthesized twenty Ugi derived chlorides (see Supplementary data) with different substitution patterns. The Ugi type chlorides were then quantitatively converted to the corresponding Ugi derived azides by treating with sodium azide in presence of potassium carbonate in DMF at room temperature (Table 2).[18]

With alkyne and azides in hand, we tested the feasibility of randomizing coumarin using CuAAC reaction. As shown in Scheme 1, in a typical CuAAC reaction of alkyne **1** and a type 1 azide(keto-amide azide) **3d** in a solvent mixture of *t*-BuOH, H_2O and DMSO (4:2:1) in the presence of copper sulphate

Table 3
List of products obtained from the click reactions of coumarin **1** with Mannich type β-amido ketone azides



and sodium ascorbate at room temperature afforded the ester-triazole-ketoamide amphiphile **6b** in 99% yield.[19] Good conversions and yields were observed in all the five reactions (Table 3). The 1,4-disubstituted 1,2,3-triazoles **6a–e** were easily isolated by aqueous workup and identified by spectral methods. In a similar manner, we have conducted the CuAAC reactions of akyne 1 and Ugi-type α-amino acyl amide azides (type 2). Type 2 azides also afforded the 1,4-disusbstituted triazoles **7a–t** in near quantitative yield (Table 4). Among the twenty click products obtained from the reactions of type 2 azides, the formation of the fluorinated analogues **7h–m** proceed with 100% yield in many cases. On the other hand, the CuAAC reactions of Ugi-type azides bearing substituents other than fluorine did not show any significant change in yield with respect to the nature of the substituents present in them. Fluorinated analogues of small peptide like molecules are important class of drug-like molecules due to the ability of fluorine to increase the intrinsic activity, the chemical and metabolic stability, and the bioavailability required for drug action.[20] A wide range of pharmaceuticals across therapeutic categories contain fluoro groups, including anti-depressants, anti-inflammatory agents, anti-malarial drugs, anti-psychotics, anti-viral agents, steroids, and anaesthetics.[21]

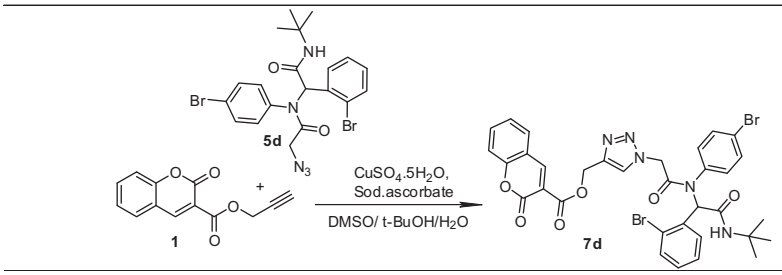
It is reported that, the regio and stereo control in CuAAC reaction is strongly depends on the nature of the catalysts and reagents employed.[22a] Copper (I) salts are known to afford exclusively 1,4-adducts, while catalysts like cyclopentadienyl ruthenium (II) promotes 1,5-adduct formation. In order to suggest the regio and stereo selectivity in triazole formation, we have compared the spectral data of our compounds with literature values. The ^{1}H NMR spectra shows a similar signal corresponds to the triazole proton of the *anti* 1,4-regio isomer. More over the presence of electron withdrawing groups present in the alkyne or azide moieties are known to influence the polarization of the azide group and allows the orientation of the cycloaddition to proceed in the *anti*-selective manner.[22b] In the present study, the observed *anti*-diastereoselectivity may be due to the polarizing effect exerted by electron withdrawing keto-amide functionality present in the azide side chain (For a proposed mechanism, see Scheme 4 given in Supplementary data).

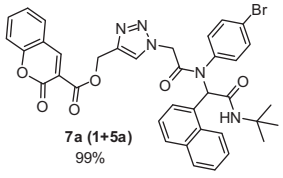
For generalizing the protocol, we have prepared three more coumarin derived alkynes **8**, **9** and **10** shown in Scheme 3 and conducted the click reactions with type 1 and type 2 azides. All the reactions afforded the corresponding click products in near quantitative yield (For details, see Tables 5–10 given in Supplementary data).

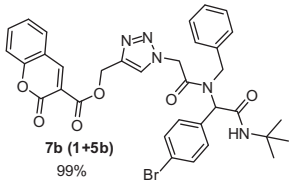
Drug-likeness of molecules are mainly depends on their molecular size, liphophilicity (log*P*), polarity (accessed by the polar surface area, tPSA), and the presence of optimal number of rotatable bonds.[23a] Drug like molecules usually have log*P* values in between −0.4 and 5.6.[23b] Compounds with molecular weight between 160 and 480 with tPSA between 75 and 150 Å^2 are considered as orally bioavailable.[23c] Some of the molecules with higher molecular weight (>500) and log*P* (>7) are identified as prodrugs.[24] In order to give an indication about the drug-likeness of our compounds, we have calculated the values of log*P* and tPSA using Molinspiration Property Calculation Service (www.molinspiration.com). Most of the compounds have log*P* value in between 4.2 and 5.63 with tPSA between 126.73 and 129.97 Å^2 (see Table 11 given in Supplementary data).

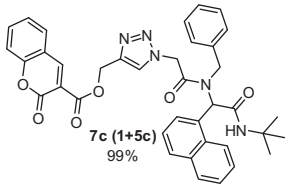
In summary, we have developed a convenient and near perfect CuAAC process for the regio and stereo controlled synthesis of ester-triazole-amide amphiphiles of coumarin. Primary success of the process reveals the possibility of developing large number library of structurally complex and diversely substituted extended peptide like scaffolds of coumarin for screening purpose.

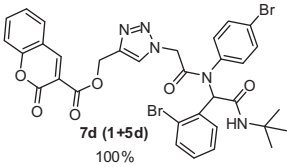
Table 4
List of products obtained from click reaction of alkyne **1** with Ugi-type α-amino acyl amide azides




7a (1+5a)
99%


7b (1+5b)
99%


7c (1+5c)
99%


7d (1+5d)
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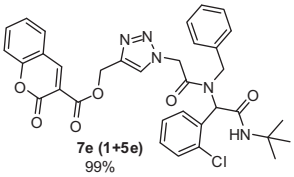
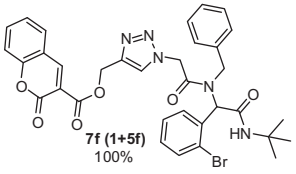
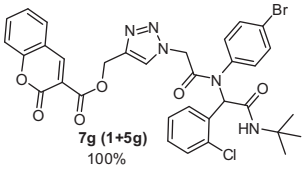
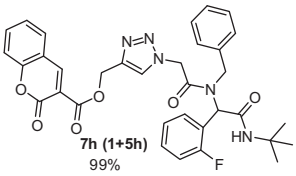
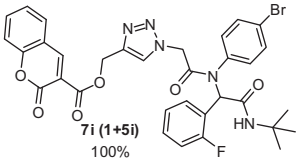
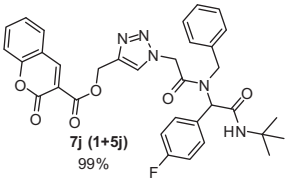

7e (1+5e)
99%

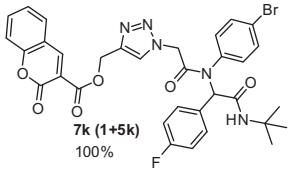

7f (1+5f)
100%

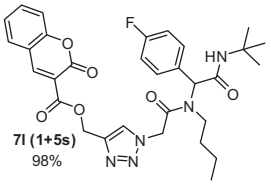

7g (1+5g)
100%

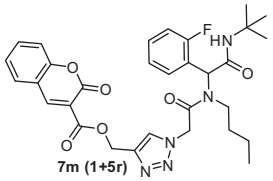

7h (1+5h)
99%

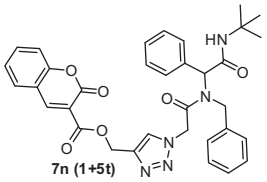

7i (1+5i)
100%


7j (1+5j)
99%


7k (1+5k)
100%


7l (1+5s)
98%


7m (1+5r)
98%


7n (1+5t)
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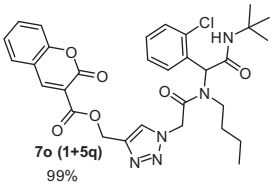
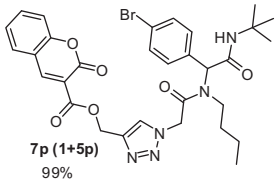
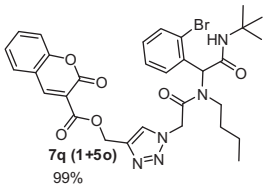

7o (1+5q)
99%


7p (1+5p)
99%


7q (1+5o)
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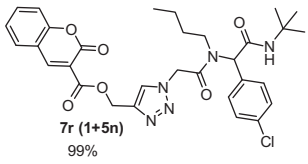
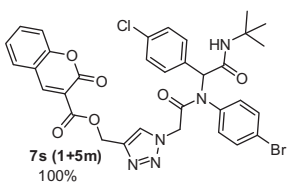

7r (1+5n)
99%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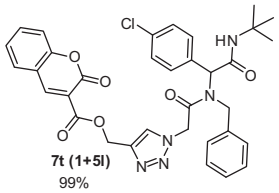
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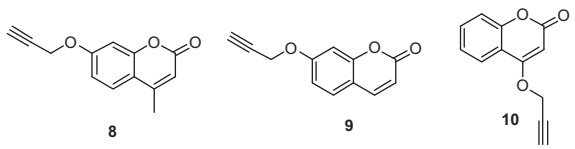

Scheme 3. Structure of alkynes **8**, **9** and **10** used for the click reactions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.01.111.

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14. *Typical experimental procedure for the synthesis of prop-2-yn-1-yl 2-oxo-2H-chromene-3-carboxylate* ***1***: A solution of Coumarin-3-carboxylic acid (1.9 g, 0.01 mol), Propargyl alcohol (0.56 ml, 0.01 mol), *N,N*-dicyclohexyl cabodiimide (2.3 g, 011 mol), and 4-dimethylaminopyridine (0.122 g, 0.001 mol) in dichloromethane was stirred at room temperature for 6 h. After 6 h, the precipitated *N,N*-dicyclohexylurea was filtered off and the filtrate was washed with water, 5% acetic acid, and again with water. It was then dried over magnesium sulphate and the solvent was evaporated. The residue obtained was washed with petroleum ether to afford the ester **1** (2.4 g, 96%). FT-IR, KBr, γ_{max}: 3229.2, 3057.6, 2929.3, 2851.2, 2118.4, 1749.9, 1713.4, 1615.1, 1563.9, 1370.2, 1240.0, 1213.0, 1035.6, 999.9, 770.4; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.826 (s,1H), 7.971–7.963 (m, 1H), 7.778–7.733 (m,1H), 7.459–7.400 (m, 2H), 4.942–4.937 (d, J = 2.0 Hz, 2H), 3.327 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.8, 155.8, 154.7, 134.8, 130.5, 124.9, 117.8, 116.7, 116.2, 78.2, 78.1, 52.806; MS: m/z 229.1 Calcd for $C_{13}H_8O_4$, 228.2; Found, 229.1.
15. *Typical experimental procedure for the synthesis of β-keto-amide azide* ***3e***: An equi-molar amount of β-ketoamide (1.09 g, 0.0025 mol) and sodium azide (700 mg) are taken in dimethyl acetamide (4 mL). To this, K_2CO_3 (1 g) was added and stirred at room temperature for 4 h. The reaction mixture was then diluted with water. The white precipitate obtained was filtered and washed repeatedly with water to afford the pure azide **3e** (1.06 g, 97%).
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17. *Typical experimental procedure for the synthesis of Ugi chloride* ***4i***: An equi-molar amount of 2-fluoro benzaldehyde (1.24 g, 0.01 mol) and 4-bromo aniline are taken in dichloromethane (8 mL) and stirred in room temperature for 20 min. to form the schiff-base. To this, one equivalent of *tert*-butyl isocyanide (0.83 g, 0.01 mol) and chloroacetic acid (0.95 g, 0. 01 mol) were added and stirred at room temperature. The reaction was monitored by TLC and found to complete after 48 h. The solvent was then evaporated off under vacuum. The crude product obtained was washed with petroleum ether (5×15 mL) to afford the pure Ugi chloride **4i** (4.01 g, 88%). FT-IR, KBr, γ_{max}: 3334.3, 2963.1, 1690.3, 1658.5, 1540.9, 1485.9, 1455.0, 1382.7, 1363.4, 1256.4, 1232.3, 1014.4, 759.8, 629.6; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.982 (s, 1H), 7.551–6.869 (m, 8H), 6.236 (s, 1H), 4.106–3.899 (m, 2H), 1.255 (s, 9H); MS: m/z Calcd for $C_{20}H_{21}BrClFN_2O_2$, 455.7; Found, 457.1.
18. *Typical experimental procedure for the synthesis of Ugi azide* ***5d***: An equi-molar amount of the corresponding Ugi chloride (1.29 g, 0.0025 mol) and sodium azide (700 mg) are taken in dimethyl acetamide (4 mL). To this K_2CO_3 (1 g) was added and stirred at room temperature for 4 h. The reaction mixture was then diluted with water. The white precipitate obtained was filtered and washed repeatedly with water to afford the pure azide **5d** (1.24 g, 95%). FT-IR, KBr, γ_{max}: 3349.7, 3059.5, 2965.0, 2104. 9, 1684. 5, 1658. 4, 1536. 0, 1486. 8, 1391. 3, 1267. 2, 1015. 3, 740. 5; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.089 (s, 1H), 7. 547–7.528 (d, J = 7.6 Hz, 2H), 7. 129–7.092 (m, 4H), 6. 938–6. 920 (d, J = 7.2 Hz, 2H), 6.22 (s, 1H), 3. 889–3.542 (m, 2H), 1. 265 (s, 9H); MS: m/z Calcd for $C_{20}H_{21}Br_2N_5O_2$, 523.22; Found, 524.0. *Compound* ***5e***: FT-IR, KBr, γ_{max}: 3304. 4, 3072.0, 2972.7, 2101.0, 1643.8, 1552.4, 1220.7, 1040.4, 948.8, 749.209; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.096–8.073 (d, J = 9.2 Hz, 1H), 7.373–6.843 (m, 9H), 6.341 (s, 1H), 4.902–4.577 (m, 2H), 4.206-3.914 (m, 2H) 1. 162 (s, 9H). *Compound* ***5g***: FT-IR, KBr, γ_{max}: 3392.2, 3343.9, 2965.0, 2928.4, 2103.9, 1686.4, 1655.0, 1538.9, 1485.9, 1391.4, 1257.4, 1014.4, 743.4; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.081 (s, 1H), 7.377–7.358 (d, J = 7.6 Hz, 2H), 6.950–6.931 (d, J = 7.6 Hz, 2H), 7.206–7.170 (m, 2H), 7.107–7.070 (m, 2H), 6.628 (s, 1H), 3.913–3.522 (m, 2H), 1.266 (s, 9H).
19. *General procedure for the Cu (I) 1, 3-dipolar cycloaddition reactions*: An equi-molar amount of prop-2-yn-1-yl 2-oxo-2*H*-chromene-3-carboxylate **1** (57.05 mg, 0.25 mmol) and the Ugi azide **5d** (130.8 mg, 0.25 mol) are dissolved in minimum amount of DMSO. To this, 2 ml of *t*-BuOH, 1 ml of water, $CuSO_4{\cdot}5H_2O$ (200 mg) and sodium ascorbate (150 mg) are added and stirred in room temperature for 12 h. and then poured in to cold water. The precipitated click product was filtered, washed with water and dried under vacuum to afford **7d** in pure form (180 mg, 97%). FT-IR, KBr, γ_{max}: 3312.1, 2970.8, 2933.2, 2107.8, 1773.3, 1706.7, 1671.9, 1610.3, 1565.9, 1484.9, 1391.4, 1206.3, 764.6; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.756 (s, 1H), 8.127 (S, 1H), 8.028 (s, 1H), 7.924–7.904 (d, J = 8.0 Hz 2H),7.742–7.700 (m, 1H), 7.546–7.527 (d, J = 7.6 Hz, 1H), 7.424–7.362 (m, 3H), 7.114–7.085 (m, 3H), 6.923–6.905 (d, J = 7.2 Hz, 2H), 6.260 (s, 1H), 5.332 (s, 2H), 5.169–4.312 (m, 2H), 1.252 (s, 9H); MS: m/z Calcd for $C_{33}H_{29}Br_2N_5O_6$, 751.4; Found, 752.0.
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