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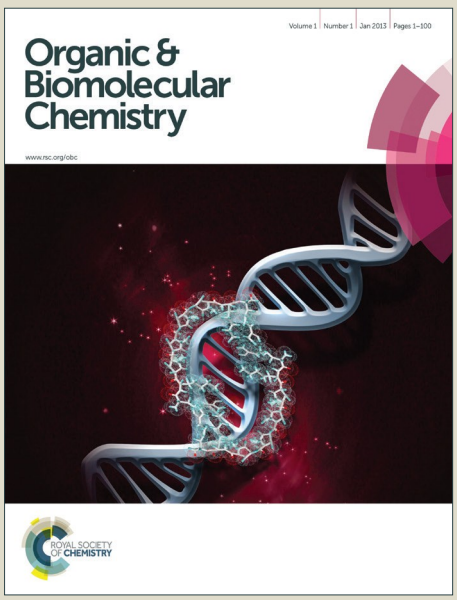

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ARTICLE

Electronically Modified Amine Substituted Alkynols for Regio-selective Synthesis of Dihydrofuran Derivatives

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An efficient and simple approach has been developed for the regio-selective synthesis of iodo-substituted dihydrofurans from amine substituted alkynols. The resulting iodo-substituted dihydrofurans have been further diversified by C-C coupling and C-N coupling reactions to afford a diverse range of substituted dihydrofuran derivatives.

Introduction

The electrophilic cyclization is one of the power tools of contemporary organic synthesis. The protocol exemplifies the compatibility of variety of functional groups and efficient synthesis of a large number of diverse cyclic compounds with interesting biological activities as well as physical properties.[1] Likewise, the synthesis of various heterocycles by electrophilic cyclization, especially with I^+ as an electrophile, has become the subject of considerable attention recently.[2] Notable features of these reactions include ease of performance, short reaction time, ease of product isolation and mainly metal free conditions. More importantly, the presence of iodine enables further functionalization of the molecule. However; in electrophilic cyclization reaction of alkynes bearing two competitive nucleophiles, several factors govern the reaction pathway. The attack of the nucleophile mainly depends on the nucleophilicity of the competing functional groups, polarization of the alkyne triple bond and the cationic nature of the intermediates; these eventually could offer simultaneous ring annulation and lead to the formation of a diverse range of fused heterocycles in few steps.[3] Although electrophilic cyclization of alkynes bearing two competing nucleophiles offers strategies in designing various heterocycles, the concept has not been the subject of extensive investigation.

We have reported recently the selective formation of pyrrole nucleus over indole by taking the advantage of two competing amine nucleophiles in the electrophilic cyclization of alkynes; this was achieved by modifying the electronic properties of one of the amine groups and hence manipulation of its nucleophilic attack.[4] The present study highlights an efficient and simple approach for the regio-selective synthesis of iodocyclized dihydrofurans from alkynes bearing two different competing nucleophiles i.e. amine and alcohol. Iodo-dihydrofurans have further been diversified by palladium/copper catalyzed C-C coupling and C-N coupling reactions to afford a diverse range of substituted dihydrofuran derivatives. The preparation of dihydrofuran moieties using this route represents a simple and efficient procedure, addressing the synthesis challenges in previously known methodology.

In the past few years there have been extensive reports on the synthesis of various kinds of furan substrates.[5] However, the synthesis of dihydrofurans by electrophilic cyclization mediated by molecular iodine has been seldom reported.[6] Dihydrofuran moiety has often been found in diverse range of molecules which include natural products, reaction intermediates, biologically active compounds and materials.[7] These five membered oxygenated heterocycles are usually prepared from oxidative coupling/ annulation of 1,3 dicarbonyl compounds with olefins in presence of excess transition metal salts as oxidants.[8] Recently, hypervalent iodine, iodobenzenediacetate was reported to promote the oxidative coupling/anulation of 1,3-cyclohexanedione with alkenes.[9] Later, Lie *et al.* developed synthetic approach for dihydrofurans and indolizines by iodine catalysed radical oxidative annulation of β-ketoester with alkenes in the presence of *tert*-butyl peroxybenzene as an oxidant.[10]

Results and Discussion

The required alkynes were prepared in high yields following our previously reported procedure, by palladium/copper catalysed Sonogashira reaction under mild reaction conditions.[4] The electrophilic cyclization of alkyne **1a** (Scheme 1) was initiated with K_2CO_3 as base and I_2 as the electrophilic source. However, the reaction failed to give the hoped-for products **2a** and/or **3a** (Scheme 1), changing the reaction conditions and

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using different bases and solvents led to same results. (Table 1) Attempts to use analogous substrates **1b** & **1c** (Scheme 1) in making **2b-2c** and **3b-3c** respectively, were not successful either. The reactions gave no traces of the desired products. (Table 1) However, protection of amine group with ester led to the formation of **5a**, which was isolated in a pure state in 47% yield (Table 1, entry 4). Inspired by the observation, a variety of solvents, bases, additive and iodine sources were used to improve the yield of reaction. Eventually, when a strong base such as KO*t*Bu was used in acetonitrile in presence of molecular iodine, a very good yield of **5a** was obtained (entry 12). The use of additive (ceric ammonium nitrate, CAN) in combination with other iodine sources could not help in this iodocyclization reaction. The product obtained in the cyclization was fully characterized by ^{1}H NMR, ^{13}C NMR and HRMS. The formation of dihydrofuran **5a** was visibly observed in the ^{1}H NMR analysis when the protons of CH_2 groups close to triple bond and hydroxyl group were shifted to downfield; (2.68 ppm (CHa_2, t) near to triple bond shifted to 3.07 ppm (CHa_2, t) and 3.78 ppm (CHb_2, t) near to oxygen shifted to 4.53 ppm (CHb_2, t). This shift was more pronounced with CHb_2 group near to oxygen than CHa_2 group near to iodine. This effect can be attributed to the higher electronegative effect of the oxygen than that of iodine.

SCHEME 1

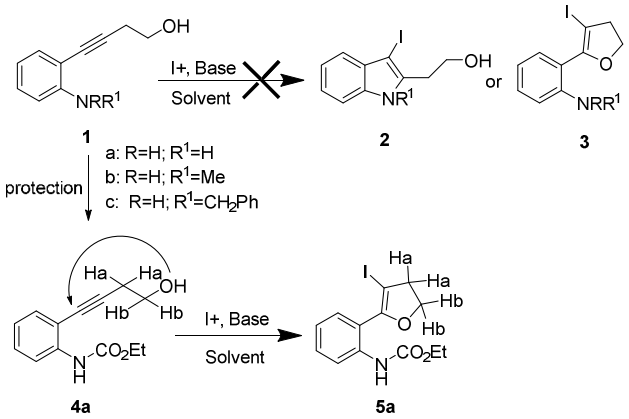


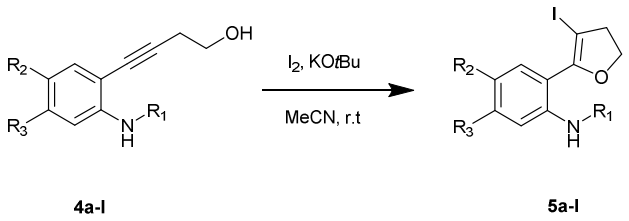
Table 1. Optimization of the reaction conditions for iodocyclization[a]

Entry	**1a/4a**	Solvent	Base (equiv)	I^+ (equiv)	Yield(%)[b] **2a/3a/5a**
1	**1a**	MeCN	K_2CO_3 (3)	I_2 (3)	-
2	**1a**	DCM	K_2CO_3 (3)	I_2 (3)	-
3	**1a**	THF	$NaHCO_3$ (3)	I_2 (3)	-
4	**4a**	MeCN	K_2CO_3 (3)	I_2 (3)	47
5	**4a**	MeCN	Cs_2CO_3 (3)	I_2 (3)	20
6	**4a**	MeCN	$NaHCO_3$ (3)	I_2 (3)	-[c]
7	**4a**	MeCN	K_2CO_3 (3)	CAN(1.1)+ I_2 (3)	-[d]
8	**4a**	MeCN	K_2CO_3 (3)	ICl (2)	-[c]
9	**4a**	DCM	-	NIS (1.1)	-[c]
10	**4a**	THF	K_2CO_3 (3)	I_2 (3)	17
11	**4a**	MeOH	K_2CO_3 (3)	I_2 (3)	trace
12	**4a**	**MeCN**	**KO*t*-Bu (3)**	**I_2 (3)**	**78**

[a]Reaction conditions: alkynol **1a/4a** (0.5 mmol), base, I^+ source, solvent (2 mL) at room temperature for 2h. [b]Yields of isolated products. [c]No desired product formed. [d]Inseparable mixture including **5a**.

Using optimized reaction conditions, the scope of the iodocyclization reaction was further extended to various amino alkynols (shown in Scheme 2). Effect of changing the substituents on the aromatic ring, position of substituents on the aromatic ring and using various groups to protect the amine functionality were explored. The methodology successfully afforded the preparation of a range of iodo-substituted dihydrofurans **5a-5m** in moderate to good yields. Though **5l** could not be isolated in pure state, we were able to detect it from the HRMS analysis (Table 2).

SCHEME 2.



The molecular structure of **5e** was confirmed by X-ray crystallography, and is shown in Figure 1. Selected bond distances and angles for **5e** are summarized in the caption to Figure 1.

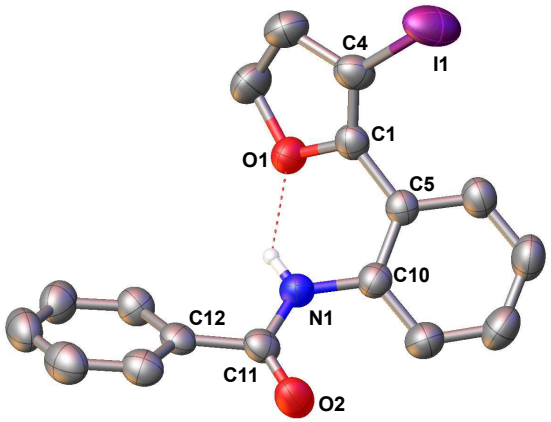
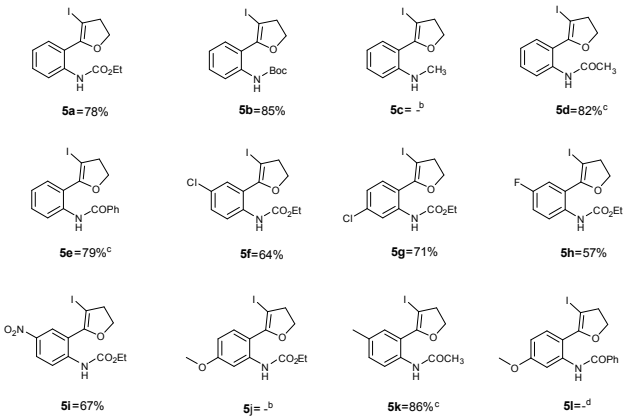


Figure 1. Molecular structure of **5e**. Ellipsoids show 50% probability levels. Hydrogen atoms have been omitted for clarity.Selected bond distances (Å) and angles (°) in 5e:N(1)–C(10) 1.414(4), N(1)–C(11) 1.350(4), C(11)–O(2) 1.221(4), C(4)–I(1)2.061(3), C(10)– N(1)–C(11)127.9(3), N(1)–C(11) –O(2) 123.7(3).

Table 2. Iododcyclization of 4a-l[a]



[a]Reaction conditions: Alkynols (1mmol), KO*t*Bu (3 equiv), I_2 (3 equiv), MeCN (4 mL) at room temperature for 2h. [b]no product observed. [c]K_2CO_3 (3 equiv) as a base was used.[d]inseparable mixture, product is confirmed by HRMS.

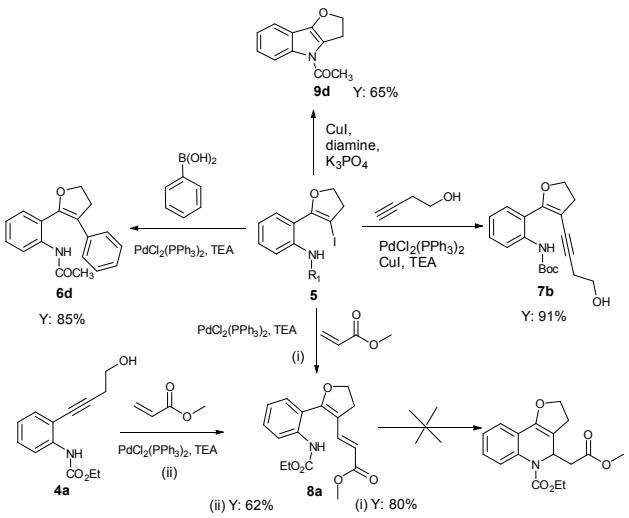
The iodocyclization reaction proceeded well with the reactants containing different protecting group (**5a, 5b, 5d, 5e**) except for the methylated amine (**5c**). The slight decrease in the product yield was observed with alkynes bearing electron withdrawing groups on the aromatic ring (**5f** to **5i**) but on the contrary to the above observation, the reaction could not proceed with electron donating substituent (**5j**). However; when the amine group was acetylated/benzoylated (**4k** and **4l**), we were able to get the product **5k** and **5l** (compound **5l** not isolated but confirmed by HRMS).

C-C and C-N coupling of iodo-dihydrofuran

With the set protocol investigated for iodocyclization of electronically modified amine substituted alkynols to various iodo-dihydrofuran substrates, we were curious to know the reactivity of iodo-dihydrofuran towards C-C and C-N bond forming reactions. In C-C coupling reactions, palladium catalysed Suzuki, Heck and Sonagashira coupling reactions were examined using corresponding coupling partners, boronic acid, methyl acrylate and propargyl alcohol respectively (Scheme 3). All the reactions were performed in the presence of catalytic amount of *bis*(triphenylphosphine)palladium(II) dichloride and quantitative yields of corresponding coupled product was observed The products obtained in coupling reactions were analysed by ^{1}H NMR, ^{13}C NMR and HRMS. Interestingly, when substrate **4a** was reacted with methyl acrylate in the presence of palladium catalyst the product obtained was identical to the product **8a** obtained in the coupling reaction of **5a** with methyl acrylate. The structure of the product **8a** was further confirmed by X-ray diffraction analysis and is shown in Figure 2. Selected bond distances and angles for **8a** are summarized in the caption to Figure 2.

Our effort to synthesize tricyclic fused heterocycles which are generally found in the major class of pharmaceutical products, biologically active compounds and materials[11] from iodo-dihydrofuran by intramolecular C-N coupling in the presence of copper iodide, diamine and potassium phosphate was fruitful and furo-indole **9d** was obtained in good yield. Unfortunately we were not successful in synthesizing dihydrofuroquinolone system by intramolecular Michael addition with various reaction conditions, which might be because of the delocalization of the double bond with the double bond of the furan ring and lone pair electrons on the oxygen atom.

SCHEME 3.



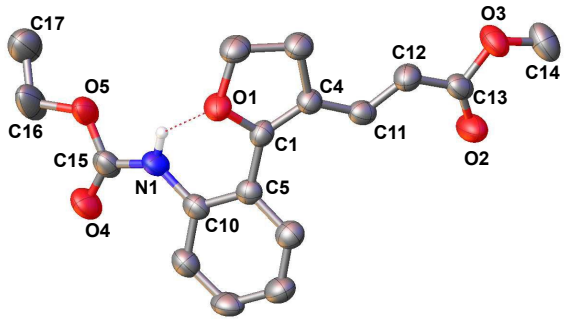


Figure 2. Molecular structure of **8a**. Ellipsoids show 50% probability levels. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (°) in 8a: N(1)–C(10) 1.400(5), N(1)–C(15) 1.356(5), C(15)–O(4) 1.194(5), C(15)–O(5)1.338(5), C(10)–N(1)–C(15)129.6(4), N(1)–C(15)–O(4)127.3(4), N(1)–C(15)–O(5) 107.6(3).

Conclusions

In summary, a regio-selective iodocyclization of amino alkynols to dihydrofurans is achieved by modifying the electronic property of amino group. The yield of regio-selective iodo-substituted dihydrofuran is optimized by the use of appropriate iodine source, base and solvent. Further, the application of regioselectively synthesized dihydrofuran embedded with an iodo handle has been exploited for the synthesis of diversely substituted dihydrofurans using well known catalytic C-C coupling and C-N coupling. To the best of our knowledge, this is the first report on the preparation of furo-indole moiety from amine substituted alkynol. Considering, the easy availability of starting materials, broad substrate scope, operationally simple methodology and importance of dihydrofuran scaffold in various range of substances, this method should find ample applications in various fields.

Experimental

All reactions were carried out in oven dried glassware under an atmosphere of dry nitrogen. Chemicals were purchased from Aldrich and used as received unless mentioned otherwise. All solvents used were dried before use. Product purification by column chromatography was accomplished using silica gel 60–120 mesh. Technical grade solvents were used for chromatography and distilled prior to use. NMR spectra were recorded in Fourier transform mode. The ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a 300 MHz, 400 MHz, and 500 MHz spectrophotometer using $CDCl_3$ and TMS as the internal standard. Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, m = multiplet, bs = broad singlet; coupling constants are reported in Hz. Low (MS) and high (HRMS) resolution mass spectra were recorded by ion trap method and mass/charge (m/z) ratios are reported as values in atomic mass units. All the melting point is uncorrected.

General procedure for the synthesis of Ethyl (2-(4-hydroxybut-1-yn-1-yl)phenyl)carbamate (4a-4l) and characterization data.

To a solution of protected 2-iodoaniline (1 mmol) in *N,N*-Dimethyformamide (3 mL) was added 3-butyn-1-ol (1.2mmol) and triethylamine (3 mmol), $PdCl_2(PPh_3)_2$ (2 mol%) and CuI (1 mol%) was added to the above solution and stirred well under nitrogen atmosphere at room temperature till the reaction was complete (approx. 6 hrs). The reaction mixture was diluted with ethyl acetate and washed with brine solution. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was purified by column chromatography over silica gel using hexane-ethyl acetate mixture (70:30).

Ethyl (2-(4-hydroxybut-1-yn-1-yl)phenyl)carbamate (4a). 216 mg, 93% Yield; brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 1H), 7.55 (s, 1H), 7.29 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.26 – 7.17 (m, 1H), 6.90 (td, *J* = 7.5, 1.1 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.78 (t, *J* = 6.4 Hz, 2H), 2.68 (t, *J* = 6.4 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 139.3, 131.6, 129.2, 122.4, 117.7, 111.7, 94.0, 77.7, 61.4, 61.0, 23.8, 14.6; HRMS (ESI) $(M+H)^+$ Calcd for $C_{13}H_{16}O_3N$ = 234.11247 , found 234.11142.

***tert*-Butyl (2-(4-hydroxybut-1-yn-1-yl)phenyl)carbamate (4b).** 253 mg, 97%Yield; brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.3 Hz, 1H), 7.38 (s, 1H), 7.34 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.31 – 7.22 (m, 1H), 6.93 (td, *J* = 7.6, 1.0 Hz, 1H), 3.86 (t, *J* = 6.3 Hz, 2H), 2.76 (t, *J* = 6.3 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 139.7, 131.6, 129.2, 122.0, 117.5, 111.4, 93.8, 80.8, 77.9, 61.1, 28.4, 23.9; HRMS (ESI) $(M+H)^+$ Calcd for $C_{15}H_{19}O_3NNa$ = 284.12571, found 284.12501.

4-(2-(Methylamino)phenyl)but-3-yn-1-ol (4c). 168 mg, 96% Yield; brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 – 7.16 (m, 2H), 6.65 – 6.55 (m, 2H), 3.81 (t, *J* = 6.2 Hz, 2H), 2.88 (s, 3H), 2.73 (t, *J* = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 132.0, 129.6, 116.3, 109.1, 107.8, 92.5, 77.4, 60.6, 30.4, 23.5; HRMS (ESI) $(M+H)^+$ Calcd for $C_{11}H_{14}ON$ = 176.10699, found 176.10713.

***N*-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)acetamide (4d).** 199 mg, 98% Yield; brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.3 Hz, 1H), 8.21 (s, 1H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.29 (dd, *J* = 12.1, 4.9 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 3.87 (t, *J* = 6.1 Hz, 2H), 2.75 (t, *J* = 6.1 Hz, 2H), 2.20 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 139.3, 131.2, 129.0, 123.3, 119.6, 112.7, 94.9, 74.8, 60.6, 23.8, 23.5; HRMS (ESI) $(M+H)^+$ Calcd for $C_{12}H_{14}O_2N$ = 204.10191, found 204.10101.

***N*-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)benzamide (4e).** 257 mg, 97% Yield; light brown solid; mp 78-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.55 (d, *J* = 8.0 Hz, 1H), 7.97 – 7.91 (m, 2H), 7.58 – 7.46 (m, 3H), 7.42 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.39 – 7.32 (m, 1H), 7.06 (td, *J* = 7.6, 1.1 Hz, 1H), 3.86 (t, *J* = 6.2 Hz, 2H), 2.79 (t, *J* = 6.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 139.1, 134.7, 132.0, 131.7, 129.3, 128.8, 127.2, 123.6, 119.3, 112.8, 95.0, 77.4, 60.9, 23.9; HRMS (ESI) $(M+H)^+$ Calcd for $C_{17}H_{16}O_2N$ = 266.11756, found 266.11672.

Ethyl (4-chloro-2-(4-hydroxybut-1-yn-1-yl)phenyl)

carbamate (4f). 262 mg, 98% Yield; brown solid; mp 66-68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.48 (s, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.24 (dd, *J* = 8.9, 2.2 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.87 (t, *J* = 6.1 Hz, 2H), 2.76 (d, *J* = 6.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 138.0, 131.1, 129.2, 127.2, 118.9, 113.2, 95.4, 76.6, 61.6, 60.9, 23.8, 14.6; HRMS (ESI) $(M+H)^+$ Calcd for $C_{13}H_{15}O_3NCl$ = 268.07350, found 268.07412.

Ethyl (5-chloro-2-(4-hydroxybut-1-yn-1-yl)phenyl) carbamate (4g). 227 mg, 85% Yield; brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.53 (s, 1H), 7.29 – 7.21 (m, 1H), 6.96 – 6.89 (m, 1H), 4.29 – 4.20 (m, 2H), 3.90 – 3.83 (m, 2H), 2.80 – 2.72 (m, 2H), 1.33 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 140.2, 135.0, 132.3, 122.5, 117.8, 110.0, 95.1, 77.0, 61.7, 60.9, 23.8, 14.5; HRMS (ESI) $(M+H)^+$ Calcd for $C_{13}H_{15}O_3NCl$ = 268.07350, found 268.07430.

Ethyl (4-fluoro-2-(4-hydroxybut-1-yn-1-yl)phenyl) Carbamate (4h). 228 mg, 91% Yield; brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.35 (s, 1H), 7.00 – 6.84(m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.77 (t, *J* = 6.2 Hz, 2H), 2.66 (t, *J* = 6.2 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 157.6 (d, *J* = 242.1 Hz), 153.6(s), 135.7 (s), 119.5 (s), 117.8 (d, *J* = 24.1 Hz), 116.2 (d, *J* = 22.2 Hz), 113.2 (s), 95.1 (s), 76.8 (s), 61.5 (s), 60.9 (s), 23.7 (s), 14.5 (s);^{19}F NMR (471 MHz, $CDCl_3$) δ -120.58. HRMS (ESI) $(M+H)^+$ Calcd for $C_{13}H_{15}O_3NF$ = 252.10305, found 252.10341.

Ethyl (2-(4-hydroxybut-1-yn-1-yl)-4-nitrophenyl) carbamate (4i). 261 mg, 94% Yield; yellow solid; mp 86-89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 9.2 Hz, 1H), 8.23 (d, *J* = 2.5 Hz, 1H), 8.15 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.91 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.92 (t, *J* = 6.2 Hz, 2H), 2.81 (t, *J* = 6.2 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 144.9, 141.9, 127.1, 124.8, 116.9, 112.0, 97.0, 75.7, 62.2, 60.7, 23.6, 14.5; HRMS (ESI) $(M+Na)^+$ Calcd for $C_{11}H_{15}O_5N_2$ = 279.09514, found 279.09370.

Ethyl (2-(4-hydroxybut-1-yn-1-yl)-5-methoxyphenyl) carbamate (4j). 210 mg, 80% Yield; brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.50 (s, 1H), 7.25 (d, *J* = 8.6 Hz, 1H), 6.52 (dd, *J* = 8.6, 2.6 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.85 (t, *J* = 6.2 Hz, 2H), 3.82 (s, 3H), 2.76 (t, *J* = 6.2 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 153.4, 140.7, 132.5, 109.2, 103.3, 102.8, 92.5, 77.6, 61.4, 61.2, 55.4, 23.9, 14.6; HRMS (ESI) $(M+H)^+$ Calcd for $C_{14}H_{18}O_4N$ = 264.12303, found 264.12242.

***N*-(2-(4-Hydroxybut-1-yn-1-yl)-4-methylphenyl) acetamide (4k).** 187 mg, 86% Yield; brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 – 8.11 (m, 2H), 7.16 (s, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 3.84 (t, *J* = 5.9 Hz, 2H), 2.72 (t, *J* = 5.9 Hz, 2H), 2.25 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 139.9, 132.1, 128.6, 124.4, 116.6, 112.5, 98.8, 76.5, 60.9, 24.8, 24.0, 21.1; HRMS (ESI) $(M+H)^+$ Calcd for $C_{13}H_{16}O_2N$ = 218.11756, found 218.11665.

***N*-(2-(4-Hydroxybut-1-yn-1-yl)-5-methoxyphenyl) benzamide (4l).** 248 mg, 84% Yield; brown solid; mp 76-78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.28 (d, *J* = 2.6 Hz, 1H), 7.98 – 7.92 (m, 2H), 7.60 – 7.47 (m, 3H), 7.32 (d, *J* = 8.6 Hz, 1H), 6.62 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.90 – 3.83 (m, 5H), 2.79 (t, *J* = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 160.3, 140.5, 134.7, 132.4, 132.1, 128.9, 127.1, 110.38, 104.7, 104.2, 93.4, 77.3, 61.1, 55.6, 23.9; HRMS (ESI) $(M+H)^+$ Calcd for $C_{18}H_{18}O_3N$ = 296.12812, found 296.12866.

General procedure for the synthesis of 4-iodo-2,3-dihydrofuran derivatives (5a-5l) and characterization data. To a solution of the alkynols (1 mmol) in MeCN (dry) (4 mL) was added KO*t*Bu (3 equiv)/ K_2CO_3 (3 equiv). To the above stirred solution powdered iodine (3 equiv) was added and the reaction was allowed to proceed under nitrogen atmosphere at room temperature until the reaction was completed. The reaction mixture was diluted with ethyl acetate and washed with saturated solution of $Na_2S_2O_3$. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was purified by column chromatography over silica gel using hexane-ethyl acetate mixture (80:20).

Ethyl (2-(3-iodo-4,5-dihydrofuran-2-yl)phenyl)carbamate (5a). 280 mg, 78% Yield; light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.3 Hz, 1H), 7.64 (s, 1H), 7.53 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.41 – 7.32 (m, 1H), 7.05 (dd, *J* = 7.7, 1.5 Hz, 1H), 4.53 (t, *J* = 9.8 Hz, 2H), 4.21 (q, *J* = 6.8 Hz, 2H), 3.08 (t, *J* = 9.8 Hz, 2H), 1.32 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 152.5, 135.7, 129.8, 129.5, 121.3, 118.8, 118.1, 69.1, 60.2, 58.4, 40.1, 13.6; HRMS (ESI) $(M+H)^+$ Calcd for $C_{13}H_{15}O_3NI$ = 360.00911, found 360.01010.

***tert*-Butyl (2-(3-iodo-4,5-dihydrofuran-2-yl)phenyl)carbamate (5b).** 329 mg, 85% Yield; light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.2 Hz, 1H), 7.51 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.45 (s, 1H), 7.37 – 7.30 (m, 1H), 7.02 (td, *J* = 7.6, 1.1 Hz, 1H), 4.53 (t, *J* = 9.5 Hz, 2H), 3.08 (t, *J* = 9.5 Hz, 2H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 152.7, 137.1, 130.9, 130.4, 122.0, 119.7, 118.9,80.5, 70.1, 59.3, 41.1, 28.4; LRMS (ESI) $(M+H)^+$ Calcd for $C_{15}H_{19}O_3NI$= 388, found 388; Anal. Calcd for $C_{15}H_{18}O_3NI$; C 46.51, H 4.65, N 3.61; found C 46.47, H 4.67, N 3.58.

***N*-(2-(3-iodo-4,5-dihydrofuran-2-yl)phenyl)acetamide (5d).** 270 mg, 82% Yield; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 – 8.19 (m, 2H), 7.57 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.42 – 7.34 (m, 1H), 7.14 – 7.07 (m, 1H), 4.55 (t, *J* = 9.5 Hz, 2H), 3.10 (t, *J* = 9.5 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 154.2, 136.4, 130.8, 130.5, 123.3, 121.5, 119.7, 70.2, 59.6, 41.3, 25.2; HRMS (ESI) $(M+H)^+$ Calcd for $C_{12}H_{13}O_2NI$ = 329.99855, found 329.99964.

***N*-(2-(3-iodo-4,5-dihydrofuran-2-yl)phenyl)benzamide (5e).** 309 mg, 79% Yield; colourless solid; mp 118-121°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.50 (d, *J* = 8.3 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.66 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.52 – 7.47 (m, 2H), 7.47 – 7.41 (m, 1H), 7.15 (td, *J* = 7.6, 1.0 Hz, 1H), 4.57 (t, *J* = 9.5 Hz, 2H), 3.10 (t, *J* = 9.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 154.0, 136.8, 135.3, 131.9, 131.0, 130.6, 128.9, 127.0, 123.4, 121.4, 119.8, 70.3, 59.8, 41.3; HRMS (ESI) $(M+H)^+$ Calcd for $C_{17}H_{15}O_2NI$ = 392.01420, found 392.01607.

Ethyl (4-chloro-2-(3-iodo-4,5-dihydrofuran-2-yl)phenyl) carbamate (5f). 252 mg, 64% Yield; light yellow oil; ^{1}H NMR

(300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 9.0 Hz, 1H), 7.62 (s, 1H), 7.54 (d, *J* = 2.9 Hz, 1H), 7.33 (dd, *J* = 9.0, 2.3 Hz, 1H), 4.57 (t, *J* = 9.5 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.11 (t, *J* = 9.5 Hz, 2H), 1.37 – 1.27 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4, 153.0, 135.4, 130.5, 130.3, 121.1, 115.9, 114.1, 70.3, 61.4, 60.5, 41.2, 14.6; HRMS (ESI) $(M+H)^+$ Calcd for $C_{13}H_{14}O_3NClI$ = 393.97014, found 393.97186.

Ethyl (5-chloro-2-(3-iodo-4,5-dihydrofuran-2-yl)phenyl) carbamate (5g). 279 mg, 71% Yield; colourless solid; mp 91-94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.67 – 7.61 (m, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 6.97 – 6.94 (m, 1H), 4.47 (t, *J* = 9.5 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.00 (t, *J* = 9.5 Hz, 2H), 1.25 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4, 153.2, 137.9, 136.4, 131.8, 122.4, 119.7, 117.2, 70.2, 61.5, 60.0, 41.1, 14.6; HRMS (ESI) $(M+H)^+$ Calcd for $C_{13}H_{14}O_3NClI$ = 393.97014, found 393.97181.

Ethyl (4-fluoro-2-(3-iodo-4,5-dihydrofuran-2-yl)phenyl)carbamate (5h). 215 mg, 57% Yield; light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.55 (s, 1H), 7.29 – 7.25 (m, 1H), 7.10 – 7.04 (m, 1H), 4.55 (t, *J* = 9.5 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.09 (t, *J* = 9.5 Hz, 2H), 1.32 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (d, *J* = 242.3 Hz), 153.6 (s), 153.1 (s), 132.9 (s), 121.8 (s), 121.0 (s), 117.4 (d, *J* = 20.3 Hz), 117.1 (d, *J* = 18.0 Hz), 70.3 (s), 61.3 (s), 60.2 (s), 41.2 (s), 14.6 (s); ^{19}F NMR (471 MHz, $CDCl_3$) δ -120.17; HRMS (ESI) $(M+H)^+$ Calcd for $C_{13}H_{14}O_3NFI$ = 377.99969, found 378.00150.

Ethyl (2-(3-iodo-4,5-dihydrofuran-2-yl)-4-nitrophenyl) carbamate (5i). 271 mg, 67% Yield; bright yellow solid; mp 116-118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 2.6 Hz, 1H), 8.41 (d, *J* = 9.3 Hz, 1H), 8.23 (dd, *J* = 9.3, 2.7 Hz, 1H), 8.04 (s, 1H), 4.61 (t, *J* = 9.6 Hz, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.14 (t, *J* = 9.6 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 152.0, 142.7, 141.8, 126.9, 125.8, 120.0, 118.9, 70.6, 62.0, 41.1, 29.7, 14.5; HRMS (ESI) $(M+H)^+$ Calcd for $C_{13}H_{14}O_5N_2I$ = 404.99419, found 404.99615.

***N*-(2-(3-iodo-4,5-dihydrofuran-2-yl)-4-methylphenyl) acetamide (5k).** 295 mg, 86% Yield; yellow solid; mp 124-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.05 (m, 2H), 7.36 (d, *J* = 1.4 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 4.53 (t, *J* = 9.5 Hz, 2H), 3.09 (t, *J* = 9.5 Hz, 2H), 2.32 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 154.3, 139.6, 136.5, 133.0, 131.1, 121.6, 119.7, 70.1, 60.5, 41.3, 25.1, 20.7; HRMS (ESI) $(M+H)^+$ Calcd for $C_{13}H_{15}O_2NI$ = 344.01420, found 344.01410.

***N*-(2-(3-iodo-4,5-dihydrofuran-2-yl)-5-methoxyphenyl) benzamide(5l).** HRMS (ESI) $(M+H)^+$ Calcd for $C_{18}H_{17}O_3N$ = 422.02476, found 422.02638.

General procedure for the synthesis of *N*-(2-(3-phenyl-4,5dihydrofuran-2-yl)phenyl)acetamide (6d) from *N*-(2-(3-iodo-4,5-dihydrofuran-2-yl)phenyl)acetamide (5d) and characterization data.

To a solution of *N*-(2-(3-iodo-4,5-dihydrofuran-2-yl)phenyl)acetamide (1 mmol) and phenyl boronic acid (1.2 mmol) in DMF:H_2O (4:1) (3 mL) was added Et_3N (3 mmol) and $PdCl_2(PPh_3)_2$ (5 mol%) under nitrogen atmosphere and stirred at 80°C till the reaction was completed. The reaction mixture was diluted with ethyl acetate and washed with brine solution. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was purified by column chromatography over silica gel using hexane-ethyl acetate mixture (60:40).

***N*-(2-(3-phenyl-4,5-dihydrofuran-2-yl)phenyl) acetamide (6d).** 237 mg, 85%Yield; brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.24 (dd, *J* = 7.4, 1.0 Hz, 1H), 5.04 (t, *J* = 8.5 Hz, 2H), 3.47 (t, *J* = 8.5 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 149.1, 139.0, 131.2, 125.0, 124.5, 123.7, 118.4, 116.8, 60.4, 30.7, 24.6; HRMS (ESI) $(M+H)^+$ Calcd for $C_{18}H_{18}O_2N$ = 280.13321, found 280.13388.

General procedure for the synthesis of *tert*-butyl (2-(3-(4-hydroxybut-1-yn-1-yl)-4,5-dihydrofuran-2-yl)phenyl)carbamate (7b) from *tert*-butyl (2-(3-iodo-4,5-dihydrofuran-2-yl)phenyl)carbamate (5b) and characterization data.

To a solution of *tert*-butyl (2-(3-iodo-4,5-dihydrofuran-2-yl)phenyl)carbamate (1 mmol) in DMF (3mL) was added 3-butyn-1-ol (1.2 mmol) and triethylamine (3 mmol). $PdCl_2(PPh_3)_2$ (2 mol%) and CuI (1 mol%) was added to the above solution and stirred well under nitrogen atmosphere at room temperature till the reaction was completed (approx. 6h). The reaction mixture was diluted with ethyl acetate and washed with brine solution. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was purified by column chromatography over silica gel using hexane-ethyl acetate mixture (50:50).

***tert*-Butyl(2-(3-(4-hydroxybut-1-yn-1-yl)-4,5-dihydrofuran-2-yl)phenyl)carbamate (7b).** 299 mg, 91% Yield; orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.2 Hz, 1H), 7.94 (s, 1H), 7.74 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.01 (td, *J* = 7.7, 1.0 Hz, 1H), 4.55 (t, *J* = 9.5 Hz, 2H), 3.71 (t, *J* = 6.2 Hz, 2H), 2.96 (t, *J* = 9.5 Hz, 2H), 2.61 (t, *J* = 6.2 Hz, 2H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 152.8, 136.6, 130.2, 129.4, 122.1, 120.2, 119.1, 95.1, 91.8, 80.4, 77.3, 69.9, 61.1, 34.3, 28.4, 24.3; HRMS (ESI) $(M+H)^+$ Calcd for $C_{19}H_{24}O_4N$ = 330.16998, found 330.16943.

General procedure for the synthesis of (*E*)-methyl 3-(2-(2-((ethoxycarbonyl)amino)phenyl)-4,5-dihydrofuran-3-yl)acrylate (8a) from ethyl (2-(4-hydroxybut-1-yn-1-yl)phenyl)carbamate (4a): To a solution of ethyl (2-(4-hydroxybut-1-yn-1-yl)phenyl) carbamate (**4a**) (1 mmol) in DMF (3mL) was added methyl acrylate (2 mmol), Et_3N (3 equiv) and $PdCl_2(PPh_3)_2$ (10 mol%) and stirred under nitrogen atmosphere at 80°C for 48h. The reaction mixture was then diluted with ethyl acetate (5 mL) and washed with brine solution. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was purified by column chromatography over silica gel using hexane and ethyl acetate mixture (70:30).

(*E*)-Methyl 3-(2-(2-((ethoxycarbonyl)amino)phenyl)-4,5-dihydrofuran-3-yl)acrylate (8a). 254 mg, 80% Yield; light

brown solid; mp 93-97 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.4 Hz, 1H), 7.67 (s, 1H), 7.54 – 7.38 (m, 2H), 7.33 – 7.26 (m, 1H), 7.11 (t, *J* = 7.5 Hz,1H), 5.65 (d, *J* = 15.4 Hz, 1H), 4.68 (t, *J* = 9.5 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 3.00 (t, *J* = 9.5 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101MHz, $CDCl_3$) δ 167.8, 159.3, 153.5, 137.9, 137.0, 131.1, 130.8, 122.9, 120.2, 118.5, 115.2, 112.9, 70.6, 61.3, 51.5, 30.1, 14.6; HRMS (ESI) $(M+Na)^+$ Calcd for $C_{17}H_{19}O_5NNa$ = 340.11554, found 340.11575.

General procedure for the synthesis of (*E*)-ethyl (2-(3-(3-oxobut-1-en-1-yl)-4,5-dihydrofuran-2-yl)phenyl)carbamate (8a) from ethyl (2-(3-iodo-4,5-dihydrofuran-2-yl)phenyl)carbamate (5a): To a solution of ethyl (2-(3-iodo-4,5-dihydrofuran-2-yl)phenyl)carbamate (1 mmol) and methyl acrylate (2 mmol) in DMF (3 mL) was added Et_3N (3 mmol) and $PdCl_2(PPh_3)_2$ (5 mol%) under nitrogen atmosphere and stirred at 80 °C until the reaction was completed (approx. 4h). The reaction mixture was diluted with ethyl acetate and washed with brine solution then with water. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was purified by column chromatography over silica gel using hexane-ethyl acetate mixture (80:20).

General procedure for the synthesis of 1-(2H-furo[3,2-*b*]indol-4(3H)-yl)ethanone from *N*-(2-(3-iodo-4,5-dihydrofuran-2-yl)phenyl)acetamide (9d) and characterization data.

To a solution of *N*-(2-(3-iodo-4,5-dihydrofuran-2-yl)phenyl)acetamide (1 mmol) in toluene (2 mL) was added CuI (10 mol%), K_3PO_4 (2 mmol), *N,N*-dimethylethylenediamine (20 mol%) and stirred under nitrogen atmosphere at 80°C until the reaction was completed (approx. 6h). The reaction mixture was diluted with ethyl acetate and washed with brine solution then with water. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was purified by column chromatography over silica gel using hexane-ethyl acetate mixture (50:50).

1-(2H-furo[3,2-b]indol-4(3H)-yl)ethanone (9d).131 mg, 65% Yield; colourless solid; mp 80-82 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.24 (dd, *J* = 7.4, 1.0 Hz, 1H), 5.04 (t, *J* = 8.5 Hz, 2H), 3.47 (t, *J* = 8.5 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 149.1, 139.0, 131.2, 125.0, 124.5, 123.7, 118.4, 116.8, 60.4, 30.7, 24.6; HRMS (ESI) $(M+H)^+$ Calcd for $C_{12}H_{12}O_2N$ = 202.08626, found 202.08686.

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