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Synthesis of diverse 2, 5 Dihydropyrroles *via* K_2CO_3 mediated intramolecular carbocyclization of Ugi-MCR precursors

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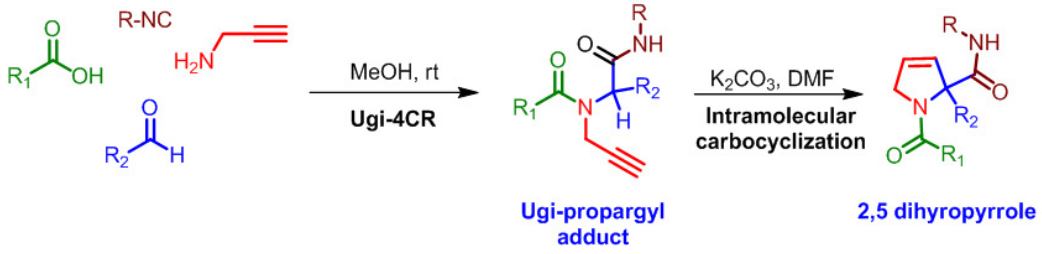
Abstract: An efficient synthetic protocol for the synthesis of highly substituted 2, 5 dihydropyrrole has been developed. The protocol involves K_2CO_3 mediated carbanion-yne intramolecular cyclization of Ugi-propargyl adducts to afford the 2, 5 dihydropyrrole derivatives in good to excellent yield. Moreover, the nature of the substituents at the benzaldehyde (R_2) of the Ugi-propargyl adduct has a crucial effect on the yield of the cyclized product.



Keywords: Multicomponent reaction, Ugi reaction, Propargylamine, Dihydropyrrole, *endo-dig* cyclization

Among the five-membered nitrogen heterocycles, the 2, 5-dihydropyrroles are privileged structural core present in vast array of natural products[1] and biologically relevant compounds (Figure 1). These compounds have been shown to exhibit a broad range of biological activities, including anti-tumor, anti-inflammatory, antioxidant, antibiotic activities, thrombine inhibitor, MAO inhibitors and NMDA receptor agonists.[2] Also, dihydropyrroles are extensively used as powerful versatile intermediates for the synthesis of pyrrolidines and pyrroles.[3] Due to the immense significance of these 2, 5-dihydropyrroles, the development

of simple and efficient synthetic protocols for the preparation of these 2, 5-dihydropyrroles skeleton is always an attractive research topic in the field of heterocyclic chemistry. To date, many synthetic methods have been developed for the construction of 2, 5-dihydropyrroles,[4] including cycloaddition, metal-catalyzed reaction, aza-cope-Mannich, tandem Wittig–Horner/intramolecular Michael reaction followed by a retro Diels–Alder cleavage and ring-closure metathesis of N-allyl- β-amino-α-methylene esters.

In the recent decades, intramolecular carbocyclization reaction with alkynes containing nucleophilic center in close proximity to the inactivated alkyne bond has been utilized extensively for the construction of variety of biologically interesting carbo- and hetero-cycles.[5] Although these reactions are gaining importance because of its efficiency, selectivity as well as mild reaction conditions for cyclization, however they lack the feature of molecular diversity within the same molecular framework.

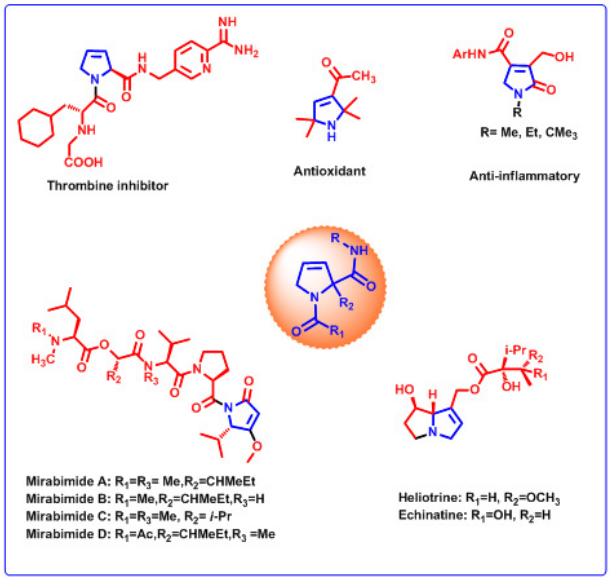
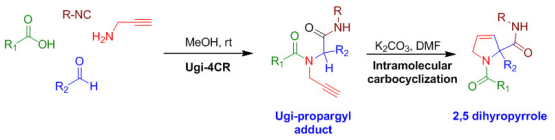


Figure 1: Some natural products and biologically active compounds having "2, 5 dihydropyrrole" scaffolds**.**

In contrast, multicomponent reactions followed by its post modification appeared as a powerful strategy for the rapid construction of structurally diverse, complex and biologically relevant molecules in an atom and step-economical manner.[6] In this regard, Ugi reaction coupled with post transformation has been extensively studied with great zeal because of their operational simplicity, diversity of bond-forming processes, inherent atom economy and high levels of chemo-, regio-, and stereo selectivities and consequently, represents veritable gold mines for the creation of wide range of heterocyclic scaffolds with amplified molecular diversity.[7] Recently, metal catalyzed post cyclization of Ugi-alkyne adduct have been widely used for the generation of variety of heterocycles.[8] Meanwhile, Polindara-García and Miranda developed ^{t}BuOK promoted alkyne-allene isomerization of Ugi-propargyl adduct and an in situ formal 5-endo cycloisomerization that occurs in a regioselective manner at the allenamide C-γ into 2,3-dihydropyrroles.[9] More recently, we have also reported the facile and efficient metal free synthesis of highly diverse 1, 4-benzoxazepine-5(2H)-ones *via* base mediated *7-exo-dig* intramolecular cyclization of Ugi-Propargyl precursors.[10] Based on the above observation, we anticipated that use of mild base may lead to the creation of biologically important 2, 5 dihydropyrrole by direct *5-endo-dig* carbanion–yne intramolecular cyclization. With this in mind and as a part of our ongoing interest in the development of new strategies for the synthesis of biologically relevant compounds utilizing isocyanide-based multicomponent reactions[11] herein, we report a facile and efficient protocol for the synthesis of 2, 5 dihydropyrrole by K_2CO_3 mediated *5-endo-dig* carbanion–yne intramolecular cyclization of Ugi-4-CR/Propargyl adduct (Scheme-1).

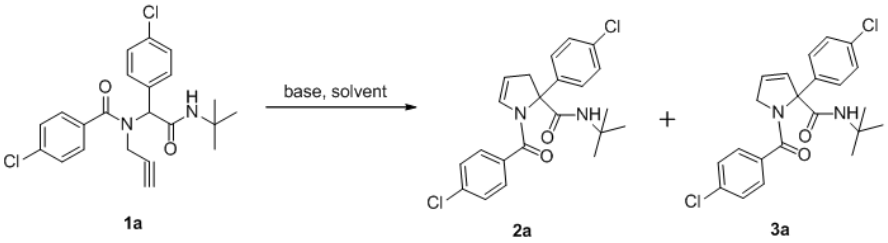
Scheme-1 General strategy for the synthesis of 2, 5 dihydropyrrole



To study the intramolecular carbocyclization, a series of Ugi-propargyl adduct were used as precursor, which were easily prepared by using various acids, aldehydes, propargylamine as the amine input and isocyanides(Scheme 1).

In the initial phase of investigation, Ugi-propargyl precursor **1a** was used as a model substrate to optimize the *5-endo-dig* carbanion–yne intramolecular cyclization reaction conditions including bases, solvents and reaction temperatures (Table 1). Indeed, it is well documented in literature that propargyl amides undergo isomerization to allenamides under stronge basic condition, we imagined that use of mild base may obstruct the formation of allenamide and leads to the formation of cyclized product **3a** exclusively. Accordingly, to test the proposed intramolecular cyclization, we carried out cyclization reaction of Ugi precursor **1a** in the presence of a series of mild bases as Et_3N, DBU, K_2CO_3, K_3PO_4, Cs_2CO_3 and KOH (strong base) using DMF as a solvent at

Table 1: Optimization of reaction conditions for the synthesis of 2, 5dihydropyrroles[a]

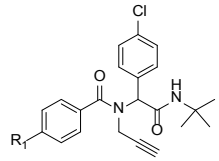
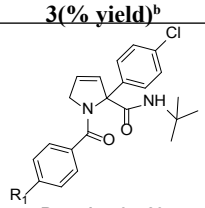
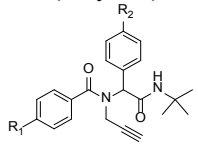
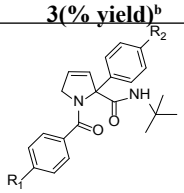
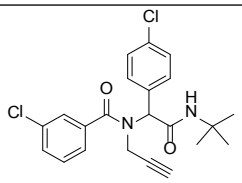
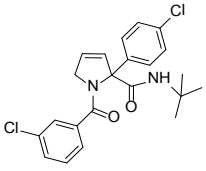
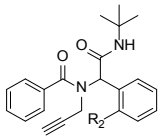
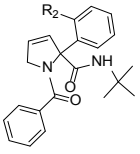
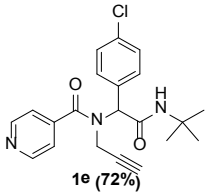
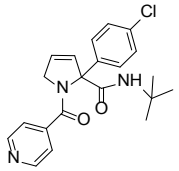
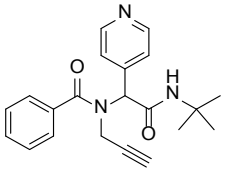
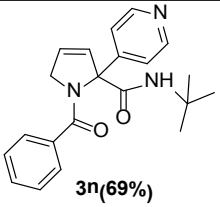
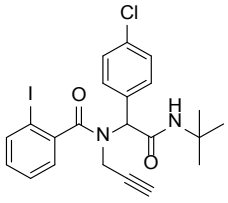
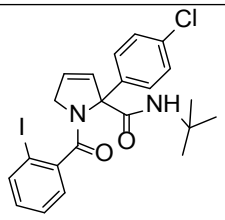
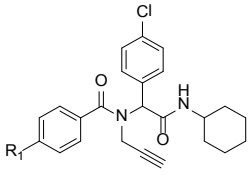
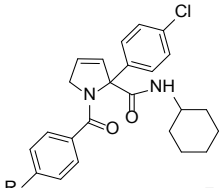
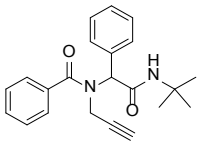
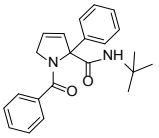
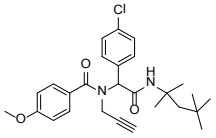
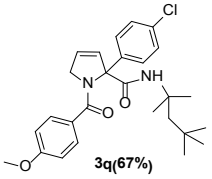


Entry	Base	Solvent	Time	Temp (°C)	Yield[b] (%) 2a/3a
1	Et_3N	DMF	5 h	90	Nr[c]
2	DBU	DMF	5 h	90	Nr
3	Cs_2CO_3	DMF	2.5 h	90	18/62
4	K_3PO_4	DMF	1h	90	12/74
5	**K_2CO_3**	**DMF**	**50 min**	**90**	**10/80**
6	KOH	DMF	2 h	90	Cm[d]
7	K_2CO_3	EtOH	3h	90	-/45
8	K_2CO_3	CH_3CN	3h	80	trace/56
9	K_2CO_3	THF	3h	80	Nr
10	K_2CO_3	DMSO	1 h	90	15/72
11	K_2CO_3	Dioxane	3h	90	Nr
12	K_2CO_3	Toluene	3h	90	Nr
13	K_2CO_3	DMF	18 h	50	trace/68
14	K_2CO_3	DMF	50 min	110	28/65
15	K_2CO_3[e]	DMF	2 h	90	15/72

[a]Reaction conditions: substrate 1 (0.5 mmol), base (2 equiv.), solvent (2.5 mL), [b]Isolated yield, [c]No reaction, [d]Complex mixture, [e]base (1.5 equiv.)

90°C (Table-1,entries 1-6). Among the bases used, organic bases Et_3N and DBU (Table-1, entries 1 & 2) completely failed to promote the cyclization reaction in forward direction, whereas use of inorganic mild bases as K_2CO_3, K_3PO_4, Cs_2CO_3 afforded desired product **3a** as major product along with minor product **2a**. Among inorganic bases used, K_2CO_3 proved to be effective as base provided the cyclized product **3a** in highly efficient manner with 80 % yield (Table-1, entry 5). Use of strong base KOH resulted in the formation of complex mixtures of undistinguishable compounds from which the desired compound could not be isolated. With K_2CO_3 as effective base in hand, other parameters such as temperature and solvent were investigated. The choice of solvent had a profound effect on the reaction, switching the solvent from DMF to DMSO at 90 ºC furnished **3a** in a slightly lower yield (Table-1, entry 10), whereas carrying out the reaction in EtOH and CH_3CN provided **3a** in significantly lower

Table 2: Substrate Scope for the synthesis of 2,5 –Dihydropyrroles[a]

Ugi adduct 1 (% yield)[b]	Cyclized product 3(% yield)[b]	Ugi adduct 1(% yield)[b]	Cyclized product 3(% yield)[b]
 R_1 = Cl, 1a (84%) R_1 = OMe, 1b (77%) R_1= H, 1c (76%)	 R_1 = Cl, 3a (80%) R_1 = OMe, 3b (74%) R_1 = H, 3c (79%)	 R_1= H, R_2= CH_3, 1h (74%) R_1= H, R_2= Br, 1i (70%) R_1= H, R_2=CF_3, 1j (80%) R_1= OMe, R_2=NO_2, 1k (78%)	 R_1=H, R_2= CH_3, 3h (0 %) R_1=H, R_2= Br, 3i (76%) R_1=H, R_2= CF_3, 3j (86%) R_1=OMe, R_2= NO_2, 3k (92%)
 1d (82%)	 3d (84%)	 R_2= Br, 1l (72%) R_2= NO_2, 1m(69%)	 R_2= Br, 3l (0%) R_2= NO_2,3m(0%)
 1e (72%)	 3e (80%)	 1n(78%)	 3n(69%)
 1f (78%)	 3f (66%)	 R_1= OMe, 1o(80%) R_1= H, 1p(82%)	 R_1= OMe, 3o(76%) R_1= H, 3p(70%)
 1g (86%)	 3g (69%)	 1q (80%)	 3q(67%)

[a]Reaction conditions: substrate 1 (0.5 mmol), base (2 equiv.), DMF (2.5 mL) at 90 °C. [b]Isolated yield.

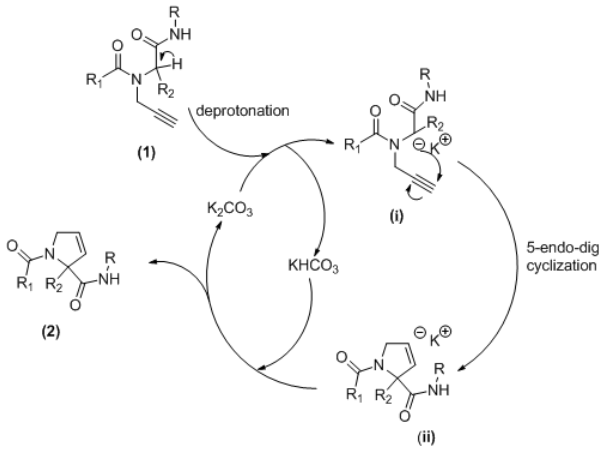
yields (Table-1, entries 7 and 8). Conversely, the use of less polar solvents such as THF, dioxane and toluene completely failed to afford the title compound. This noticeably, suggested that solvent polarity had a marked influence on reaction. Moreover, increase of the temperature and decrease of concentration both have detrimental effect on yield of desired product.

To evaluate the scope and limitations of our optimized protocol (Table-1, entry 5), different Ugi-propargyl adducts were synthesized in good to excellent yields, and subjected to the carbocyclization reaction utilizing optimized conditions to afford the desired cyclised products **3(a-q)**[12] (Table 2).

The protocol was effective with benzoic acids (R_1) having either electron-withdrawing or electron donating groups. Furthermore, the presence of substituents at the ortho-, meta- and para- positions also had no noticeable effect on the yields of the cyclized product and all the products were obtained in good yields (Table-2). We then investigated the scope of substituted benzaldehydes (R_2) and results revealed the strong influence of steric and electronic properties of substituents on the cyclization step and on the yield of the product as well. Generally, reaction with electron-withdrawing *p*-chloro and *p*-bromo- substituents at R_2 provided product in very good yields whereas, excellent yields were obtained in the case of strongly electron withdrawing *p*-trifluoromethyl group **(3j),** and a *p*-nitro group **(3k).** However, Ugi adducts with electron donating substituents at R_2 completely failed to give desired product **(3h)**. In contrast, reaction also went smoothly with heteroaromatic substituted system. It is noteworthy to mention that trace-10% of 2, 3 dihydropyrrole was also formed along with 2, 5 dihydropyrroles in case of aldehydes having halogen substituents whereas, 2, 5 dihydropyrrole was the sole product in case of electron withdrawing CF_3 **(3j)** and NO_2 **(3k)** substituents. When *o*-bromo and *o*-nitro were explored, the reactions did not yield any desired product. This fact may be attributed to steric hindrance which led to the obstruction in anion generation, thereby failed to give desired product. In case of isocyanides, tert-butyl and cyclohexyl isocyanides both provided the product in good yields. The Ugi precursor containing 1, 1, 3, 3-Tetramethylbutyl isocyanide also underwent cyclization smoothly to afford the corresponding product **(3q)** but in relatively low yield. The structure of the products **3(a-q)** were deduced from their IR, HRMS, ^{1}H NMR and ^{13}C NMR spectra.

On the basis of the results presented above, we postulated the following possible mechanism for the formation of these 2, 5 dihydropyrroles, as shown in Scheme 2.

Scheme-2. Possible mechanism for *5-endo-dig* cyclization reaction of Ugi-propargyl adduct-1



Abstraction of an acidic proton by potassium carbonate results in generation of carbanion (i). The anion thus formed undergoes *5-endo-dig* carbocyclization reaction with the pendant alkyne group to give intermediate (ii). Subsequent protonation of (ii) by the conjugate acid $KHCO_3$, leads to the formation of desired 2, 5 dihydropyrrole derivatives.

In summary, we have developed an efficient two step protocol for the synthesis of highly diverse 2, 5 dihydropyrroles. The reaction

sequence involves Ugi-4CR followed by K_2CO_3 mediated intramolecular carbocyclizationto afford the desired product in good to excellent yields. The strategy allows synthesis of biologically important highly functionalized 2, 5 dihydropyrroles in a straightforward and atom-economical manner.

Conclusions

In summary, we have developed an efficient two step protocol for the synthesis of highly diverse 2, 5 dihydropyrroles. The reaction sequence involves Ugi-4CR followed by K_2CO_3 mediated intramolecular carbocyclization, in good to excellent yields. The strategy allows synthesis of biologically important highly functionalized 2, 5 dihydropyrroles in a straightforward and atom-economical manner.

Experimental

General procedure for the preparation of Ugi-propargyl adduct 1

A solution of benzaldehyde (1.0 mmol), benzoic acid (1.0 mmol), propargylamine (1.0mmol), isocyanide (1.0 mmol) in MeOH (3mL) was stirred at rt for 24 hrs. The progress of the reaction was monitored on TLC (30 % Hexane / EtOAc). After completion of reaction, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel (eluent: hexane/ EtOAc) to afforded Ugi-Propargyl precursors **1(a-q).**

N-(2-(tert-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-4-chloro-N-(prop-2-yn-1-yl) benzamide (1a)

White solid; Yield 84%; IR (KBr) ν_{max}: 3423, 3304, 1722, 1626, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.56(d, 2H, *J* = 8.1 Hz), 7.41-7.35(m, 6H), 5.79(s, 1H), 4.20 (dd, 1H, *J* = 2.4 Hz, *J* = 18.5 Hz), 4.02 (dd, 1H, *J* = 2.0 Hz, *J* = 18.5 Hz), 2.02 (t, 1H, *J* = 2.3 Hz), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.3, 167.9, 136.6, 134.6, 133.4, 132.9, 131.1, 129.0, 128.8, 128.6, 79.3, 72.3, 62.0, 51.9, 38.1, 28.5; ESI-MS: (m/z) = 418 $[M + H]^+$

N-(2-(tert-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-N-(prop-2-yn-1-yl) benzamide (1c)

White solid; Yield 76% ; IR (KBr) ν_{max}: 3443, 3304, 3024, 1722, 1629, 1516 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.59(d, 2H, *J* = 6.0 Hz), 7.46-7.35(m, 7H), 5.92(s, 1H), 5.78 (br s, 1H), 4.22 (dd, 1H, *J*= 2.4 Hz, *J* =18.3 Hz), 4.04 (dd, 1H, *J* = 2.3 Hz, *J*=18.3 Hz), 2.05(t, 1H *J*=2.2 Hz), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.3, 168.1, 135.1, 134.7, 133.3, 131.1, 130.4, 128.9, 128.6, 127.1, 79.5, 72.2, 62.1, 51.9, 38.2, 28.6; ESI-MS: (m/z) = 383 $[M + H]^+$.

N-(2-(tert-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-3-chloro-N-(prop-2-yn-1-yl) benzamide (1d)

White solid; Yield 82%; IR (KBr) ν_{max}: 3423, 3304, 1722, 1626, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.59 (br s, 1H), 7.49-7.42(m, 3H), 7.38-7.34(m, 4H), 5.76(s, 1H), 4.20(dd, 1H, *J* = 2.4 Hz, *J* =18.4 Hz), 4.03(d, 1H, *J* = 19.1 Hz), 2.04 (t, 1H, *J* = 2.4 Hz), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.8, 167.8, 136.7, 134.8, 134.5, 132.9, 131.1, 130.5, 129.8, 129.0, 127.2, 125.1, 79.2, 72.3, 61.8, 51.9, 38.0, 28.5; ESI-MS: (m/z) = 418 $[M + H]^+$.

N-(2-(tert-butylamino)-2-oxo-1-phenylethyl)-N-(prop-2-yn-1-yl)benzamide (1g)

White solid; Yield 86% ; IR (KBr) ν_{max}: 3439, 3027, 1742, 1634, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.58 (br s, 2H), 7.47-7.37(m, 7H), 5.88(s, 1H), 4.19(dd, 1H, *J*= 2.4 Hz, *J*=18.2 Hz), 4.03 (dd, 1H, *J*= 1.9 Hz, *J*=18.2 Hz), 1.99 (s, 1H) 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.2, 168.3, 135.2, 134.6, 130.2, 129.6, 128.7,

128.5, 128.4, 126.9, 79.6, 71.7, 62.6, 51.7, 38.2, 28.5; ESI-MS: (m/z) = 349 $[M + H]^+$.

2-(4-chlorophenyl)-1-(4-methoxybenzoyl)-N-(2,4,4-trimethylpentan-2-yl)-2,5-dihydro-1H-pyrrole-2-carboxamide (1q)

White solid; Yield 80%; IR (KBr) ν_{max} : 3421, 3307, 1637, 1516, 1216, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, 2H, *J* =8.5 Hz), 7.43(d, 2H, *J* =7.5 Hz), 7.35 (d, 2H, *J* =8.4 Hz), 6.93(d, 2H, *J* =8.7 Hz), 6.12 (brs, 1H), 5.66 (s, 1H), 4.24 (dd, 1H, *J* = 2.1, *J* = 18.3 Hz), 4.08 (dd, 1H, *J* = 2.3, *J* = 18.4 Hz), 3.83 (s, 3H), 2.10 (t,1H, *J*=2.2Hz), 1.77-1.66(m, 2H), 1.45 (d, 6H, *J* =3.7 Hz), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ =172.0, 167.8, 161.4, 134.4, 133.4, 130.9, 129.3, 128.8, 126.9, 113.7, 79.5, 72.5, 63.6, 55.8, 55.3, 52.2, 38.5, 31.5, 31.4, 28.8, 28.4; ESI-MS: (m/z) = 470 $[M + H]^+$.

General procedure for the preparation of 2, 5 dihydropyrroles 3(a-q).

To a solution of **1** (0.5 mmol) in DMF (2.5 mL) was added K_2CO_3 (2.0 equiv.) and the reaction mixture was heated at 90 °C for 50 min – 1.5 h. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure and partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3 times), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude thus obtained was purified by flash column chromatography to afford desired product.

N-(tert-butyl)-1-(4-chlorobenzoyl)-2-(4-chlorophenyl)-2,5-dihydro-1H-pyrrole-2-carboxamide (3a)

White solid; Yield 80 %; IR (KBr) ν_{max} : 3421, 3307, 2401, 1637, 1517, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.88 (s, 1H), 7.44-7.32(m, 6H), 7.22 (d, 2H, *J* = 8.5 Hz), 5.99-5.97 (m, 1H), 5.80-5.77 (m, 1H), 4.46-4.42 (m, 1H), 4.32-4.27 (m, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.7, 169.6, 137.8, 136.2, 135.1, 134.3, 133.5, 128.9, 128.7, 127.4, 127.1, 121.8, 81.3, 58.4, 51.5, 28.5; HRMS (ESI TOF (+)) calcd for $[C_{22}H_{22}Cl_2N_2O_2 + H^+]$ 417.1131 found 417.1131.

N-(tert-butyl)-2-(4-chlorophenyl)-1-(4-methoxybenzoyl)-2,5-dihydro-1H-pyrrole-2-carboxamide (3b)

White solid; Yield 74%; IR (KBr) ν_{max} : 3427, 3019, 2930, 1663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.14 (s, 1H), 7.42 (d, 2H, *J* = 8.5 Hz), 7.33 (d, 2H, *J* = 8.5 Hz), 7.22 (d, 2H, *J* = 8.5 Hz), 6.95(d, 2H, *J* = 8.6 Hz), 5.98-5.96 (m, 1H), 5.79-5.77 (m, 1H), 4.56 (dt, 1H, *J* = 2.1 Hz, *J*= 15.1 Hz), 4.39-4.35(m, 1H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ =170.5, 169.9, 160.8, 138.3, 134.2, 133.1, 128.9, 128.5, 127.9, 126.9, 121.8, 113.8, 81.3, 58.4, 55.3, 51.3, 28.5; HRMS (ESI TOF (+)) calcd for $[C_{23}H_{25}ClN_2O_3 + H^+]$ 413.1626 found 413.1626.

1-benzoyl-N-(tert-butyl)-2-(4-chlorophenyl)-2,5-dihydro-1H-pyrrole-2-carboxamide (3c)

White solid, Yield 79 %; IR (KBr) ν_{max}; 3421, 3307, 3018, 1637, 1216, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ =8.12(s, 1H), 7.46-7.39(m, 6H), 7.35(d, 2H, *J* =8.6 Hz), 7.25(d, 2H, *J* =8.6 Hz), 5.99-5.97(m, 1H), 5.78-5.75(m, 1H), 4.48 (dt, 1H, *J* = 2.1 Hz, *J*= 15.0 Hz), 4.33(dt, 1H, *J* = 2.5 Hz, *J* = 15.3 Hz), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ =170.8, 169.9, 138.1, 136.8, 134.3, 133.3, 130.0, 128.7, 127.0, 125.8, 121.7, 81.2, 58.4, 51.4, 28.5; HRMS (ESI) calcd for$[C_{22}H_{23}ClN_2O_2 + H^+]$ 383.1521 found 383.1521.

N-(tert-butyl)-1-(3-chlorobenzoyl)-2-(4-chlorophenyl)-2,5-dihydro-1H-pyrrole-2-carboxamide (3d)

White solid, Yield 84 %; IR (KBr) ν_{max}; 3441, 3020, 1661, 1215, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.89(s, 1H), 7.45-7.37(m, 3H), 7.36-7.29 (m, 3H), 7.24-7.22 (m, 2H), 6.00-5.97(m, 1H), 5.80-5.78(m, 1H), 4.47 (dt,

1H, *J* = 1.9 Hz, *J*= 14.9 Hz), 4.32(dt, 1H, *J* = 1.9 Hz, *J* = 14.9 Hz), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.5, 169.1, 138.4, 137.7, 134.8, 134.2, 133.5, 130.1, 128.7, 127.1, 126.1, 123.9, 121.8, 81.3, 58.3, 51.5, 28.5; HRMS (ESI) calcd for[$C_{22}H_{22}Cl_2N_2O_2$ + H^+] 417.1131 found 417.1136.

N-(tert-butyl)-2-(4-chlorophenyl)-1-isonicotinoyl-2,5-dihydro-1H-pyrrole-2-carboxamide (3e)

White solid; Yield 80%; IR (KBr) ν_{max}: 3422, 3016, 1665, 1549, 1216, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.75-8.74(m, 2H), 7.69(m, 1H), 7.37-7.34(m, 2H), 7.31-7.29(m, 2H), 7.26-7.24(m, 2H), 6.01(dt, 1H, *J* = 2.2 Hz, *J*= 6.3 Hz), 5.82 (dt, 1H, *J* = 1.9 Hz, *J*= 6.3 Hz), 4.43(dt, 1H, *J* = 2.1 Hz, *J*= 14.7 Hz), 4.28(dt, 1H, *J* = 2.1 Hz, *J*= 14.7 Hz), 1.39 (s, 9H);^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.1, 168.1, 150.5, 143.9, 137.5, 134.1, 133.7, 128.8, 127.2, 121.9, 120.0, 81.3, 58.1, 51.6, 28.5; HRMS (ESI) calcd for[$C_{21}H_{22}ClN_3O_2$ + H^+] 384.1473 found 384.1473

N-(tert-butyl)-2-(4-chlorophenyl)-1-(2-iodobenzoyl)-2,5-dihydro-1H-pyrrole-2-carboxamide (3f)

White solid; Yield 66 %; IR (KBr) ν_{max}: 3462, 3018, 1669, 1564, 1216, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.44(m, 1H), 7.85(d, 1H, *J* =7.9 Hz), 7.46-7.42(m, 1H), 7.36-7.24(m, 4H), 7.16-7.09(m, 2H), 6.00(d, 1H, *J* = 6.2 Hz), 5.77(d, 1H, *J* =6.2 Hz), 4.31-4.09(m, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.6, 169.4, 142.6, 139.5, 134.4, 133.5, 130.6, 128.7, 126.9, 125.9, 121.5, 80.9, 57.8, 51.6, 28.7: HRMS (ESI) calcd for[$C_{22}H_{22}ClIN_2O_2$ + H^+] 508.0414found 508.0416.

1-benzoyl-N-(tert-butyl)-2-phenyl-2,5-dihydro-1H-pyrrole-2-carboxamide (3g)

White solid; Yield 69 %; IR (KBr) ν_{max}: 3420, 3307, 3019, 1637, 1216, 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20(s, 1H), 7.44(s, 4H), 7.39-7.26(m, 5H), 6.01(d, 1H, *J* = 3.7 Hz), 5.74(d, 1H, *J* = 4.9 Hz), 4.48(d, 1H, *J* = 14.9 Hz), 4.32(d, 1H, *J* = 14.8 Hz), 1.40(s, 9H),^{13}C NMR (75 MHz, $CDCl_3$) δ =170.8, 170.4, 139.5, 137.2, 134.7, 129.9, 128.7, 128.5, 127.6, 125.9, 125.5, 121.3, 81.8, 58.6, 51.3, 28.6; HRMS (ESI) calcd for[$C_{22}H_{24}N_2O_2$ + H^+] 349.1911 found 349.1911.

1-benzoyl-2-(4-bromophenyl)-N-(tert-butyl)-2,5-dihydro-1H-pyrrole-2-carboxamide (3i)

White solid; Yield 76%; IR (KBr) ν_{max}; 3682, 3426, 3020, 1663, 1215, 1021 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.15 (s, 1H), 7.50-7.47 (m, 2H), 7.46-7.43 (m, 3H), 7.42-7.40 (m, 2H), 7.18-7.16 (m, 2H), 5.98 (dt, 1H, *J* = 2.2 Hz, *J*= 6.3 Hz), 5.78 (dt, 1H, *J* = 1.9 Hz, *J* = 6.2 Hz), 4.49 (dt, 1H, *J* = 2.1 Hz, *J*= 15.0 Hz), 4.32 (dt, 1H, *J* = 2.1 Hz, *J*= 15.0 Hz), 1.39 (s, 9H);^{13}C NMR (100 MHz, $CDCl_3$) δ =170.8, 169.8, 138.6, 136.8, 134.2, 131.6, 129.9, 128.6, 127.3, 125.7, 121.8, 121.5, 81.3, 58.4, 51.4, 28.5; HRMS (ESI) calcd for[$C_{22}H_{23}BrN_2O_2$ + H^+] 427.1016 found 427.1016.

1-benzoyl-N-(tert-butyl)-2-(4-(trifluoromethyl)phenyl)-2,5-dihydro-1H-pyrrole-2-carboxamide (3j)

White solid; Yield 86%; IR (KBr) ν_{max}: 3428, 3019, 1664, 1625, 1216, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ =8.15 (s, 1H), 7.64 (d, 2H, *J* =8.3 Hz), 7.47-7.40 (m, 7H), 6.00 (dt, *J* = 2.2 Hz, *J*= 6.4 Hz, 1H), 5.81 (dt, *J* = 2.0 Hz, *J*= 6.4 Hz, 1H), 4.53 (dt, *J* = 2.0 Hz, *J*= 15.1 Hz, 1H), 4.36(dt, *J* = 2.1 Hz, *J*= 15.1 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.9, 169.7, 143.5, 136.7, 134.2, 130.2, 128.8, 125.9, 125.8, 125.6, 125.5, 122.1, 81.5, 58.5, 51.5, 28.6; HRMS (ESI) calcd for[$C_{23}H_{23}F_3N_2O_2$ + H^+] 417.1784 found 417.1790.

N-(tert-butyl)-1-(4-methoxybenzoyl)-2-(4-nitrophenyl)-2,5-dihydro-1H-pyrrole-2-carboxamide (3k)

White solid; Yield 92%; IR (KBr) ν_{max}; 3681,

3408, 3021, 1619, 1215, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 1H), 7.41(d, 2H, *J* =8.5 Hz), 7.33(d, 2H, *J* =8.5 Hz), 7.22(d, 2H, *J* =8.6 Hz), 6.95(d, 2H, *J* =8.6 Hz), 5.98(dt, 1H, *J* = 2.1 Hz, *J* = 6.3 Hz), 5.79-5.76(m, 1H), 4.54(dt, 1H, *J* = 2.1 Hz, *J* = 15.0 Hz), 4.39-4.35(m, 1H), 3.84(s, 3H), 1.39 (s, 9H);^{13}C NMR (100 MHz, $CDCl_3$) δ =170.6, 170.0, 160.9, 138.3, 134.4, 129.1, 128.6, 127.0, 121.8, 113.9, 81.4, 58.4, 55.4, 51.4, 29.6; HRMS (ESI) calcd for[$C_{23}H_{25}N_3O_5 + H^+$] 424.1867 found 424.1869.

1-benzoyl-N-(tert-butyl)-2-(pyridin-4-yl)-2,5-dihydro-1H-pyrrole-2-carboxamide (3n)

White solid; Yield 69%; IR (KBr) ν_{max}; 3672, 3462, 3036, 1666, 1215, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.61 (s, 2H), 8.07(s, 1H), 7.48-7.44 (m, 5H), 7.21-7.20 (m, 2H), 5.78-5.96 (m, 1H), 5.84-5.81(m, 1H), 4.54(dt, 1H, *J* = 2.1 Hz, *J*= 15.1 Hz), 4.37 (dt, 1H, *J* = 1.96 Hz, *J*= 15.1 Hz), 1.39 (s, 9H);^{13}C NMR (100 MHz, $CDCl_3$) δ =170.8, 168.9, 149.8, 148.4, 136.4, 133.5, 130.2, 128.7, 125.8, 122.8, 120.5, 80.9, 58.5, 51.5, 28.5; HRMS (ESI) calcd for[$C_{21}H_{23}N_3O_2 + H^+$] 350.1863 found 350.1866.

2-(4-chlorophenyl)-N-cyclohexyl-1-(4-methoxybenzoyl)-2,5-dihydro-1H-pyrrole-2-carboxamide (3o)

White solid; Yield 76%; IR (KBr) ν_{max}; 3682, 3451, 3066, 1664, 1220, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.08 (s, 1H), 7.41(d, 2H, *J* = 8.5 Hz), 7.32(d, 2H, *J* =8.5 Hz), 7.22(d, 2H, *J* =8.6 Hz), 6.94(d, 2H, *J* = 8.6 Hz), 6.01(dt, 1H, *J* = 2.1 Hz, *J* = 6.3 Hz), 5.80-5.78(m, 1H), 4.54(dt, 1H, *J* = 2.1 Hz, *J* = 15.0 Hz), 4.39(d, 1H, *J* = 14.9 Hz), 3.89-3.84(m, 4H), 1.98-1.95(m, 1H), 1.87-1.83(m, 1H), 1.69-1.61(m, 3H), 1.56-1.52(m, 1H), 1.47-1.31(m, 3H), 1.24-1.20(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ =170.7, 170.0, 160.9, 138.2, 134.2, 133.3, 129.0, 128.6, 128.0, 127.2, 122.0, 113.9, 80.8, 58.4, 55.4, 48.3, 32.5, 32.4, 29.7, 25.5, 24.4; HRMS (ESI) calcd for[$C_{25}H_{27}ClN_2O_3 + H^+$] 439.1783 found 439.1786.

1-benzoyl-2-(4-chlorophenyl)-N-cyclohexyl-2,5-dihydro-1H-pyrrole-2-carboxamide (3p)

White solid; Yield 70 %; IR (KBr) ν_{max}; 3425, 3017, 1657, 1216, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.12(d, 1H, *J* = 7.9 Hz), 7.45-7.40(m, 5H), 7.35(d, 2H, *J* = 8.5 Hz), 7.25(d, 2H, *J* =8.5 Hz), 6.02(dt, 1H, *J* = 1.9 Hz, *J* = 6.1 Hz), 5.79-5.77(m, 1H), 4.47(dt, 1H, *J* = 2.0 Hz, *J* = 15.0 Hz), 4.33-4.28(m, 1H), 3.93-3.84(m, 1H), 1.99-1.85(m, 2H), 1.69-1.62(m, 1H), 1.44-1.33(m, 2H), 1.30-1.17(m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ =170.9, 169.9, 138.0, 136.9, 134.2, 133.5, 130.1, 128.7, 127.2, 125.8, 121.9, 80.7, 58.5, 48.3, 32.6, 32.4, 25.6, 24.5, 24.4; HRMS (ESI) calcd for[$C_{24}H_{25}ClN_2O_2 + H^+$] 409.1677 found 409.1677.

2-(4-chlorophenyl)-1-(4-methoxybenzoyl)-N-(2, 4, 4-trimethylpentan-2-yl)-2,5-dihydro-1H-pyrrole-2-carboxamide (3q)

White solid; Yield 67%; IR (KBr) ν_{max} : 3423, 3304, 1722, 1626 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.18 (s, 1H), 7.39-7.31(m, 4H), 7.22-7.19(m, 2H), 6.95(d, 2H, *J* = 7.9 Hz), 5.99 (d, 1H, *J* = 5.6 Hz), 5.78 (d, 1H, *J* = 5.1 Hz), 4.51(m, 2H), 3.85(s, 3H), 2.23(d, 1H, *J* = 19.6 Hz), 1.57(s, 3H), 1.41-1.36(m, 4H), 0.98(s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ =170.5, 169.9, 160.8, 138.3, 134.5, 133.2, 129.0, 128.6, 127.9, 126.9, 121.5, 113.8, 81.4, 58.4, 55.3, 55.2, 50.9, 31.5, 31.3, 29.2, 28.8; HRMS (ESI TOF (+)) calcd for [$C_{27}H_{33}ClN_2O_3 + H^+$] 468.2180 found 468.2182.

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