Synthesis of Novel Tetrazole Containing Quinoline and 2,3,4,9-Tetrahydro-1*H*-β-Carboline Derivatives

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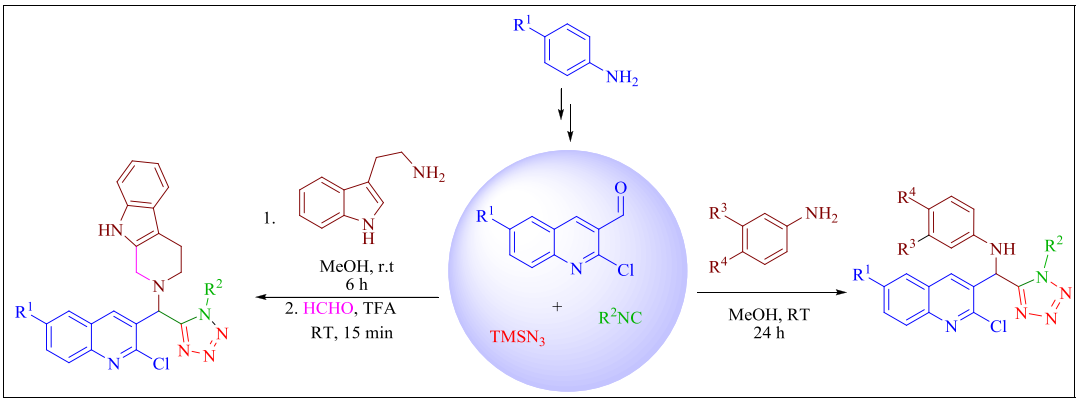

This presentation describes the successful synthesis of novel tetrazole-based quinoline and tetrahydro-1*H*-β-carboline derivatives via one-pot multicomponent reactions in moderate to good yields. These reactions have presumably proceeded through Ugi-azide or Ugi-azide/Pictet–Spengler processes, respectively.

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INTRODUCTION

Multi-component reactions (MCRs) are processes in which at least three different simple substrates react in one-pot to give the target materials [1]. These reactions, which have gained significant attention during the past years, do not occur through a single-step procedure, but rather via several sequential steps involving cascades or domino reactions [2]. Simplicity, greater efficiency, and atom economy with generation of molecular complexity and diversity in one-pot transformations are some advantages of these reactions [3]. These reactions are highlighted as diversity-oriented syntheses and can be extended to combinatorial strategies [4].

The isocyanide-based multicomponent reactions (IMCRs) [5] have emerged as efficient and powerful tools for the synthesis of highly complex natural and diverse drug-like compounds. The most popular IMCR is probably the Ugi reaction, in which a carboxylic acid, a primary amine, an aldehyde, and an isocyanide react in a one-pot manner to afford an *N*-substituted acyl aminoamide containing four independently varying groups in one reaction [6]. The Ugi-azide reaction, a variant of the Ugi multicomponent process, in which the carboxylic acid is replaced by hydrazoic acid or trimethylsilyl azide ($TMSN_3$) has been utilized for preparation of novel biologically promising 1,5-disubstituted-1*H*-tetrazole (1,5-DS-1*H*-T) [7].

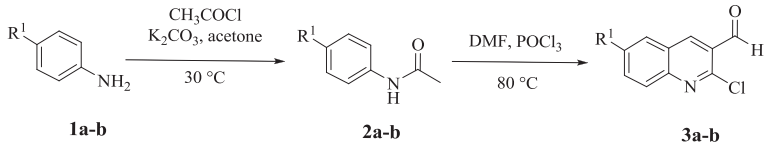
Quinoline-containing compounds have been extensively used in medicinal chemistry because of various biological activities such as anti-inflammatory [8], antimalarial [9], anticancer [10], analgesic [11], and antifungal [12]. In addition, quinoline-containing compounds have been extensively used in medicinal chemistry because of the presence of this core structure in a number of commercial drugs including quinine [13], chloroquine [14], mefloquine [15], and amodiaquine [16].

The known properties of privileged tetrazole heterocycles [17] present in many important biological compounds and drugs such as losartan and valsartan, the two widely used angiotensin receptor blockers [18] and *in clinical* phase drug BMS-317180 as a potent orally available ligand of the growth hormone secretagogue [19] along with the documented above-mentioned properties of quinoline-containing compounds and our own interest in IMCRs [20] prompted us to undertake a study on the synthesis of novel 1,5-DS-1*H*-T based quinoline and tetrahydro-1*H*-β-carboline derivatives via one-pot multicomponent reactions.

RESULTS AND DISCUSSION

In this work, we describe the one-pot synthesis of tetrazole-based quinolines, which have the 1,5-DS-1*H*-T ring system based on the Ugi-azide method. For this, 2-chloroquinoline-3-carbaldehydes **3a–b** were initially synthesized using the previously reported procedure starting from amines **1a–b** (Scheme 1) [21]. Reaction of

Scheme 1. Synthesis of aldehydes **3a–b**.



a combination of aldehydes **1a–b**, various amines **4a–f**, isocyanides **5a–b,** and $TMSN_3$ using the Ugi standard conditions in MeOH afforded DS-1*H*-T **6a–k** in moderate to excellent yields (Scheme 2, Table 1). The structure of **6a–k** was confirmed from analytical data.

In the next step, we decided to use the Pictet–Spengler reaction [22] method for the construction of tetrahydro-β-carboline (THBC), which is abundantly found in the plant and animal kingdom, and many exhibit potent biological activities [23]. Therefore, the described Ugi-azide procedure was carried out with aldehydes **1a–b**, isocyanides **5a–b**, $TMSN_3$, and tryptamine followed by addition of formaldehyde and trifluoroacetic acid (Table 2). To our delight, the novel quinoline-based 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carbolines **7a–d** were obtained within 15 min in moderate to good yields (Table 2). As was expected, the cyclization of the presumably generated **7a–d** (Fig. 1) under the Pictet–Spengler condition has proceeded successfully to the corresponding tetrazole-based 2,3,4,9-tetrahydro-1*H*-β-carboline scaffolds.

In conclusion, one-pot, four and five component reactions respectively for the synthesis of quinoline-1,5-DS-1*H*-T or quinoline-2,3,4,9-tetrahydro-1*H*-β-carboline-1,5-DS-1*H*-T derivatives were described. Overall, a number of the desired products were obtained in moderate to good yields based on the Ugi-azide or Ugi-azide/Pictet–Spengler processes. These new structures broaden the quinoline and tetrahydro-1*H*-β-carboline scaffolds, and many of them may represent interesting pharmacophores.

EXPERIMENTAL

All commercially available chemicals and reagents were purchased from Merck Chemical Company and used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer, in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a B400 Bruker Avance III 400-MHz spectrometer at 400 (^1H) and 100 MHz (^{13}C) using $CDCl_3$ as solvent and with the residual solvent signal as internal reference ($CDCl_3$, 7.24 and 77.0 ppm). Mass spectra of the products were obtained with an HP (Agilent technologies) 5937 Mass Selective Detector. Elemental analyses were carried out by a CHN-Rapid Heraeus elemental analyzer (Wellesley, MA).

Representative procedure for the synthesis of 6a–k. To a stirring solution of 2-chloroquinoline-3-carbaldehyde (1.0 mmol) in MeOH (5 mL) was added amine (1.0 mmol), and the mixture was stirred for 10 min. Isocyanide (1.0 mmol) and TMIS (0.115 g, 1.0 mmol) were then added and the mixture stirred for 24 h at room temperature. After completion as indicated by TLC, the solid product was filtered and washed with MeOH and EtOH. Recrystallization of the solid from EtOH finally afforded the products **6a–k**.

N-((2-chloroquinolin-3-yl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)aniline (6a). White solid Yield: 79%; mp 229–231°C; IR (KBr) 3292 (NH), 1599, 1389, 1293 cm^{-1}; ^1H NMR (500 MHz, DMSO): δ 1.21–2.02 (10H, m, $5CH_2$ of cyclohexyl), 4.29–4.49 (1H, m, CH of cyclohexyl), 5.33 (1H, d, *J* 8.2 Hz, C<u>H</u>NH), 6.31 (1H, d, *J* 8.2 Hz, CHN<u>H</u>), 6.72 (2H, d, *J* 7.8 Hz, Ar), 6.78 (1H, t, *J* 7.4 Hz, Ar), 7.17 (2H, t, *J* 7.7 Hz, Ar), 7.51 (1H, t, *J* 7.5 Hz, Ar), 7.72 (1H, t, *J* 8.1 Hz, Ar), 7.77 (1H, d, *J* 8.7 Hz, Ar), 8.00 (1H, d, *J* 8.4 Hz, Ar), 8.51 (1H, s, Ar); ^{13}C NMR (125 MHz, DMSO): δ 24.7 (CH_2), 25.1(CH_2), 25.2 (CH_2), 32.9 (CH_2), 33.1 (CH_2) 49.6 (<u>C</u>HNH), 58.6 (CH of cyclohexyl), 113.8 (2C), 119.6, 127.3, 127.5, 128.1, 128.2, 129.2, 129.6 (2C), 131.1, 138.3, 144.9, 147.4, 148.6, 153.6 (C—Ar); ms: *m/z* (%) 418 (77, M^+ [^{35}Cl]), 420 (26, M^+ [^{37}Cl]), 336 (6), 267 (100), 244 (7), 231 (59), 216 (14). *Anal*. Calcd for $C_{22}H_{17}ClN_2O$: C, 65.94; H, 5.53; N, 20.06%. Found: C, 65.86; H, 5.75; N, 19.96%.

Scheme 2. Synthesis of tetrazole-based quinolones **6a–k**.

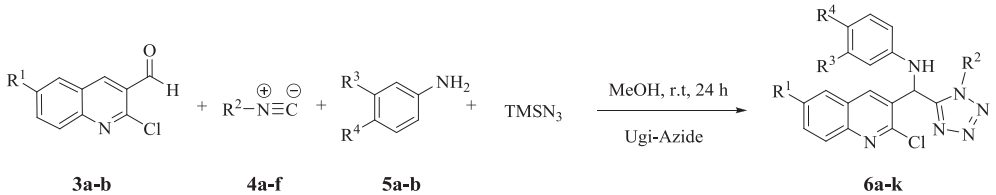
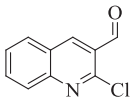
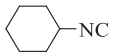
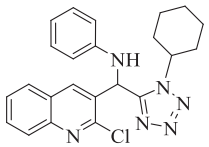
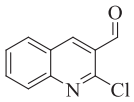
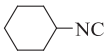
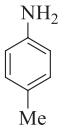
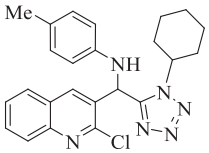
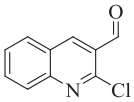
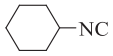
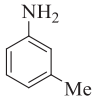
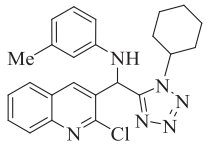
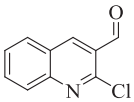
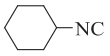
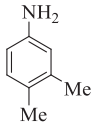
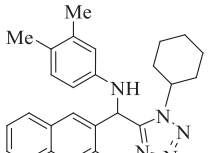
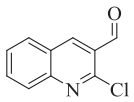
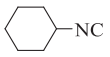
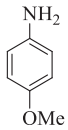
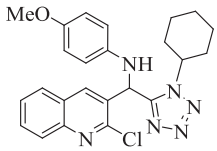
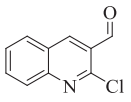
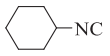
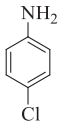
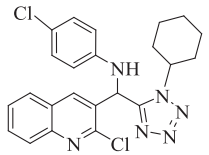
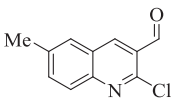
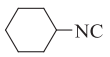
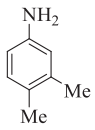
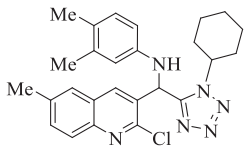
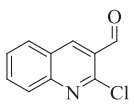
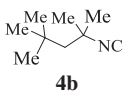
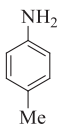
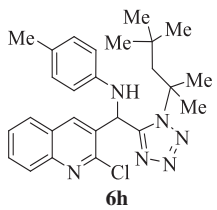


Table 1

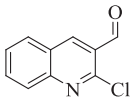
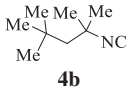
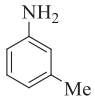
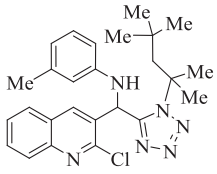
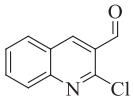
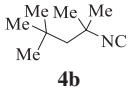
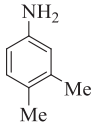
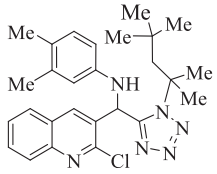
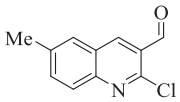
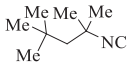
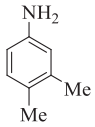
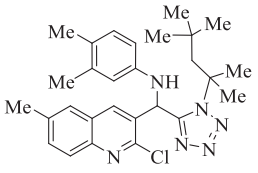
Synthesis of tetrazole-based quinolones **6a–k**.

Entry	Quinolines	Isocyanide	Amine	Product	Yield (%)[a]
1	 **3a**	 **4a**	 **5a**	 **6a**	79
2	 **3a**	 **4a**	 **5b**	 **6b**	65
3	 **3a**	 **4a**	 **5c**	 **6c**	72
4	 **3a**	 **4a**	 **5d**	 **6d**	74
5	 **3a**	 **4a**	 **5e**	 **6e**	85
6	 **3a**	 **4a**	 **5f**	 **6f**	70
7	 **3b**	 **4a**	 **5d**	 **6g**	76
8	 **3a**	 **4b**	 **5b**	 **6h**	68

(*Continued*)

Table 1

(*Continued*)

Entry	Quinolines	Isocyanide	Amine	Product	Yield (%)[a]
9	 **3a**	 **4b**	 **5c**	 **6i**	78
10	 **3a**	 **4b**	 **5d**	 **6j**	76
11	 **3b**	 **4b**	 **5d**	 **6k**	76z

[a]Isolated yields.

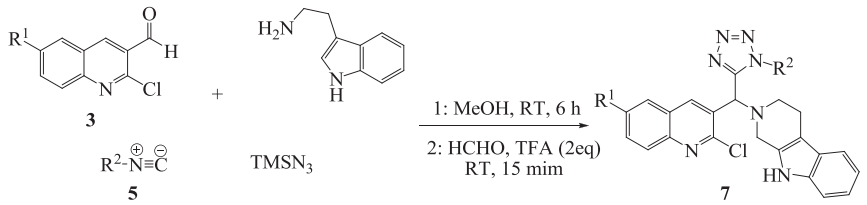
N-((2-chloroquinolin-3-yl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)-4-methylaniline (6b). White solid; Yield: 65%; mp 251–253°C; IR (KBr) 3299 (NH), 1617, 1387, 1293 cm^{-1}; ^1H NMR (500 MHz, DMSO): δ 1.20–2.05 (10H, m, $5CH_2$ of cyclohexyl), 2.11 (3H, s, Me), 4.58–4.66 (1H, m, CH of cyclohexyl), 6.43 (1H, d, *J* 8.6 Hz, CHNH), 6.71 (2H, d, *J* 8.3 Hz, Ar), 6.86 (1H, d, *J* 8.6 Hz, CHNH), 6.92 (2H, d, *J* 8.2 Hz, Ar), 7.65 (1H, t, *J* 7.4 Hz, Ar), 7.82 (1H, t, *J* 7.4 Hz, Ar), 7.99 (1H, d, *J* 8.4 Hz, Ar), 8.04 (1H, d, *J* 8.0 Hz, Ar), 8.54 (1H, s, Ar); ^{13}C NMR (125 MHz, DMSO): δ 20.0 (Me), 24.4 (CH_2), 24.6 ($2CH_2$), 32.4 (CH_2), 32.6 (CH_2), 49.1 (CHNH), 57.4 (CH of cyclohexyl), 113.7 (2C), 126.6, 126.8, 127.5, 127.7, 128.1, 129.6 (2C), 130.1, 131.1, 137.7, 143.6, 146.5, 149.1, 153.7 (C—Ar); ms: *m/z* (%) 432 (100, M^+ [^{35}Cl]), 434 (33, M^+ [^{37}Cl]), 281 (100), 245 (43), 216 (7), 152 (8), 128 (11). *Anal*. Calcd for $C_{24}H_{25}ClN_6$: C, 66.58; H, 5.82; N, 19.41%. Found: C, 66.60; H, 5.66; N, 19.53%.

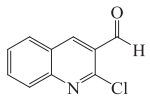
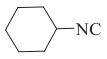
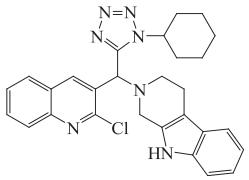
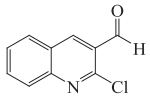
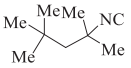
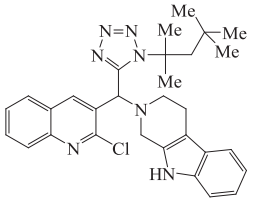
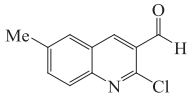
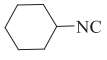
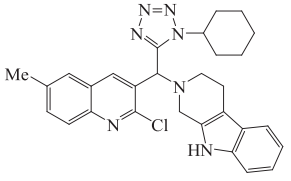
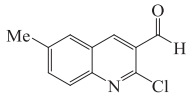
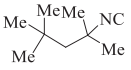
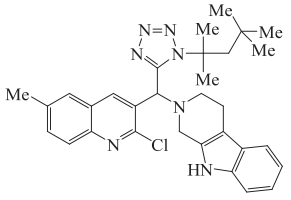
N-((2-chloroquinolin-3-yl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)-3-methylaniline (6c). White solid; Yield: 72%; mp 234–236°C; IR (KBr) 3294 (NH), 1601, 1389, 1305, cm^{-1}; ^1H NMR (500 MHz, DMSO): δ 1.18–2.02 (10H, m, $5CH_2$ of cyclohexyl), 2.16 (3H, s, Me), 4.58–4.66 (1H, m, CH of cyclohexyl), 6.46 (1H, br s, CHNH), 6.49 (1H, s, Ar), 6.58 (1H, d, *J* 7.9 Hz, Ar), 6.65 (1H, s, Ar), 6.97–7.02 (2H, m, CHNH, Ar), 7.65 (1H, t, *J* 7.5 Hz, Ar), 7.83 (1H, t, *J* 7.6 Hz, Ar), 8.00 (1H, d, *J* 8.4 Hz, Ar), 8.06 (1H, d, *J* 8.1 Hz, Ar), 8.55 (1H, s, Ar); ^{13}C NMR (125 MHz, DMSO): δ 21.3 (Me), 24.4 (CH_2), 24.6 ($2CH_2$), 32.4 (CH_2), 32.7 (CH_2), 48.8 (CHNH), 57.4 (CH of cyclohexyl), 110.6, 114.1, 118.9, 126.8, 127.5, 127.8, 128.2, 129.0, 130.2, 131.1, 137.6, 138.3, 146.0, 146.5, 149.1, 153.7 (C—Ar); ms: *m/z* (%) 432 (76, M^+ [^{35}Cl]), 434 (25, M^+ [^{37}Cl]), 281 (100), 245 (79), 216 (12), 152 (17), 128 (19). *Anal*. Calcd for $C_{24}H_{25}ClN_6$: C, 66.58; H, 5.82; N, 19.41%. Found: C, 66.60; H, 5.66; N, 19.53%.

N-((2-chloroquinolin-3-yl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)-3,4-dimethylaniline (6d). White solid; Yield: 74%; mp 243–245°C; IR (KBr) 3305 (NH), 1616, 1388, 1312 cm^{-1}; ^1H NMR (500 MHz, DMSO): δ 1.20–2.01 (10H, m, $5CH_2$ of cyclohexyl), 2.02 and 2.07 (6H, 2s, $2Me_2$), 4.59–4.67 (1H, m, CH of cyclohexyl), 6.44 (1H, d, *J* 8.7 Hz, CHNH), 6.53 (1H, d, *J* 7.8 Hz, Ar), 6.66 (1H, s, Ar), 6.82 (1H, d, *J* 8.4 Hz, Ar), 6.85 (1H, d, *J* 8.3 Hz, CHNH), 7.64 (1H, t, *J* 7.5 Hz, Ar), 7.82 (1H, t, *J* 7.6 Hz, Ar), 7.99 (1H, d, *J* 8.4 Hz, Ar), 8.04 (1H, d, *J* 8.1 Hz, Ar), 8.56 (1H, s, Ar); ^{13}C NMR (125 MHz, DMSO): δ 18.4 (Me), 19.7 (Me), 24.5 (CH_2), 24.7 ($2CH_2$), 32.5 (CH_2), 32.7 (CH_2), 49.0 (CHNH), 57.3 (CH of cyclohexyl), 110.9, 115.2, 125.6, 126.8, 127.5, 127.7, 128.1, 130.1, 130.3, 131.1, 136.7, 137.7, 143.9, 146.5, 149.2, 153.8 (C—Ar); ms: *m/z* (%) 446 (74, M^+ [^{35}Cl]), 448 (24, M^+ [^{37}Cl]), 295 (100), 259 (65), 244 (16), 216 (10), 203 (7). *Anal*. Calcd for $C_{25}H_{27}ClN_6$: C, 67.18; H, 6.09; N, 18.80%. Found: C, 67.02; H, 6.25; N, 18.86%.

Table 2

Synthesis of quinoline-based tetrazoles **7a–d**.



Aldehyde	Isocyanide	Product	Yield (%)
 **3a**	 **4a**	 **7a**	68
 **3a**	 **4b**	 **7b**	70
 **3b**	 **4a**	 **7c**	72
 **3b**	 **4b**	 **7d**	79

N-((2-chloroquinolin-3-yl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)-4-methoxyaniline (6e). White solid; Yield: 85%; mp 220–223°C; IR (KBr) 3293 (NH), 1597, 1399, 1339 cm^{-1}; ^1H NMR (500 MHz, DMSO): δ 1.18–2.06 (10H, m, $5CH_2$ of cyclohexyl), 3.60 (3H, s, OMe), 4.60–4.68 (1H, m, CH of cyclohexyl), 6.40 (1H, d, *J* 8.8 Hz, CHNH), 6.67–6.80 (5H, m, CHNH, Ar), 7.66 (1H, t, *J* 7.4 Hz, Ar), 7.83 (1H, t, *J* 7.3 Hz, Ar), 7.99 (1H, d, *J* 8.4 Hz, Ar), 8.05 (1H, d, *J* 8.0 Hz, Ar), 8.58 (1H, s, Ar); ^{13}C NMR (125 MHz, DMSO): δ 24.5 (CH_2), 24.7 ($2CH_2$), 32.5 (CH_2), 32.7 (CH_2), 49.7 (CHNH), 55.1 (OMe), 57.4 (CH of cyclohexyl), 114.7 (2C), 115.0 (2C), 126.8, 127.6, 127.8, 128.1, 130.3, 131.1, 137.8, 139.9, 146.5, 149.2, 152.2, 153.8 (C—Ar); ms: *m/z* (%) 448 (60, M^+ [^{35}Cl]), 450 (20, M^+ [^{37}Cl]), 344 (5), 296 (100), 281 (39), 261 (8), 229 (7). *Anal*. Calcd for $C_{24}H_{25}ClN_6O$: C, 64.21; H, 5.61; N, 18.72%. Found: C, 64.27; H, 5.73; N, 18.64%.

4-chloro-N-((2-chloroquinolin-3-yl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)aniline (6f). White solid; Yield: 70%; mp 227–230°C; IR (KBr) 3331 (NH), 1596, 1404, 1291 cm^{-1}; ^1H NMR (500 MHz, DMSO): δ 1.20–2.00 (10H, m, $5CH_2$ of cyclohexyl), 4.60–4.68 (1H, m, CH of cyclohexyl), 6.50 (1H, d, *J* 8.2 Hz, CHNH), 6.81 (2H, d, *J* 8.7 Hz, Ar), 7.15 (2H, d, *J*

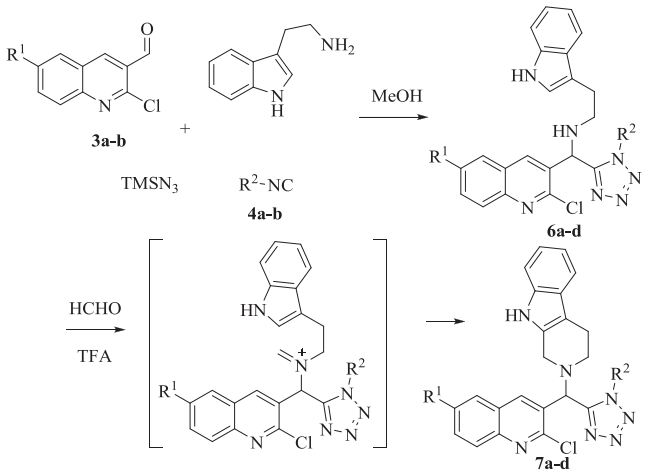


Figure 1. Proposed mechanism for the formation of tetrazole-based 2,3,4,9-tetrahydro-1*H*-β-carboline **7a–d**.

8.7 Hz, Ar), 7.26 (1H, d, *J* 8.2 Hz, CHNH), 7.65 (1H, t, *J* 7.4 Hz, Ar), 7.83 (1H, t, *J* 7.4 Hz, Ar), 7.99 (1H, d, *J* 8.4 Hz, Ar), 8.06 (1H, d, *J* 7.9 Hz, Ar), 8.49 (1H, s, Ar); ^{13}C NMR (125 MHz, DMSO): δ 24.4 (CH_2), 24.6 ($2CH_2$), 32.4 (CH_2), 32.7 (CH_2), 48.8 (CHNH), 57.3 (CH of cyclohexyl), 114.9 (2C), 121.4, 126.8, 127.5, 127.8, 128.2, 128.9 (2C), 129.6, 131.2, 137.5, 144.9, 146.6, 149.1, 153.4 (C—Ar); ms: *m/z* (%) 452 (39, M^+ [^{35}Cl]), 454 (26, M^+ [^{37}Cl]), 344 (11), 326 (5), 314 (5), 301 (100), 265 (30). *Anal*. Calcd for $C_{23}H_{22}Cl_2N_6$: C, 60.93; H, 4.89; N, 18.54%. Found: C, 61.05; H, 4.73; N, 18.62%.

N-((2-chloro-6-methylquinolin-3-yl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)-3,4-dimethylaniline (6g). White solid; Yield: 76%, mp 198–200°C; IR (KBr) 3301 (NH), 1590, 1342, 1261 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 1.21–2.01 (10H, m, $5CH_2$ of cyclohexyl), 2.02 and 2.07 (6H, 2s, $2Me_2$), 2.45 (3H, s, Me), 4.60–4.67 (1H, m, CH of cyclohexyl), 6.41 (1H, d, *J* 8.8 Hz, CHNH), 6.51 (1H, d, *J* 7.8 Hz, Ar), 6.64 (1H, s, Ar), 6.80 (1H, d, *J* 9.1 Hz, Ar), 6.84 (1H, d, *J* 8.2 Hz, CHNH), 7.64 (1H, d, *J* 8.5 Hz, Ar), 7.78 (1H, s, Ar), 7.87 (1H, d, *J* 8.5 Hz, Ar), 8.42 (1H, s, Ar); ^{13}C NMR (125 MHz, DMSO): δ 18.4 (Me), 19.7 (Me), 21.0 (Me), 24.5 (CH_2), 24.7 ($2CH_2$), 32.5 (CH_2), 32.7 (CH_2), 48.9 (CHNH), 57.4 (CH of cyclohexyl), 110.9, 115.2, 125.5, 126.7, 126.8, 127.2, 130.0, 130.1, 133.2, 136.7, 137.0, 137.5, 144.0, 145.1, 148.2, 153.8 (C—Ar); ms: *m/z* (%) 460 (45, M^+ [^{35}Cl]), 462 (15, M^+ [^{37}Cl]), 364 (7), 309 (100), 295 (11), 273 (71), 258 (19). *Anal*. Calcd for $C_{26}H_{29}ClN_6$: C, 67.74; H, 6.34; N, 18.23%. Found: C, 67.66; H, 6.12; N, 18.21%.

N-((2-chloroquinolin-3-yl)(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)methyl)-4-methylaniline (6h). White solid; Yield: 68%, mp 196–198°C; IR (KBr) 3309 (NH), 1615, 1392, 1327 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 0.77 (9H, s, CMe_3), 1.85 and 1.88 (6H, 2s, CMe_2), 2.02 (1H, d, *J* 14.9 Hz, CCHC), 2.09 (3H, s, Me), 2.26 (1H, d, *J* 14.9 Hz, CCHC), 6.43 (1H, d, *J* 9.4 Hz, CHNH), 6.65 (2H, d, *J* 8.2 Hz, Ar), 6.92 (2H, d, *J* 8.2 Hz, Ar), 7.11 (1H, d, *J* 9.4 Hz, CHNH), 7.64 (1H, t, *J* 7.6 Hz, Ar), 7.82 (1H, t, *J* 7.6 Hz, Ar), 8.00 (2H, t, *J* 7.3 Hz, Ar), 8.55 (1H, s, Ar); ^{13}C NMR (125 MHz, DMSO): δ 20.0 (Me), 28.8 (CMe_2), 29.3 (CMe_2), 30.4 (CMe_3), 31.2 (CMe_3), 50.1 (CHNH), 52.7 (CCH_2C), 66.2 (CMe_2), 113.2 (2C), 126.5, 126.8, 127.6, 127.8, 128.1, 129.8 (2C), 130.5, 131.1, 137.9, 143.0, 146.5, 149.1, 153.6 (C—Ar); ms: *m/z* (%) 462 (61, M^+ [^{35}Cl]), 464 (20, M^+ [^{37}Cl]), 350 (100), 292 (12), 281 (91), 257 (7), 245 (41). *Anal*. Calcd for $C_{26}H_{31}ClN_6$: C, 67.44; H, 6.75; N, 18.15%. Found: C, 67.48; H, 6.53; N, 18.27%.

N-((2-chloroquinolin-3-yl)(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)methyl)-3-methylaniline (6i). White solid; Yield: 78%; mp 187–189°C; IR (KBr) 3316 (NH), 1593, 1395, 1334 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 0.77 (9H, s, CMe_3), 1.84 and 1.87 (6H, 2s, CMe_2), 2.02 (1H, d, *J* 14.9 Hz, CCHC), 2.15 (3H, s, Me), 2.24 (1H, d, *J* 14.9 Hz, CCHC), 6.43–6.51 (3H, m, CHNH, Ar), 6.57 (1H, s, Ar), 6.99 (1H, t, *J* 7.7 Hz, Ar), 7.12 (1H, d, *J* 9.1 Hz, CHNH), 7.65 (1H, t, *J* 7.5 Hz, Ar), 7.83 (1H, t, *J* 7.6 Hz, Ar), 7.96 (1H, d, *J* 8.5 Hz, Ar), 8.04 (1H, d, *J* 8.1 Hz, Ar), 8.54 (1H, s, Ar); ^{13}C NMR (125 MHz, DMSO): δ 21.3 (Me), 28.7 (CMe_2), 29.4 (CMe_2), 30.5 (CMe_3), 31.2 (CMe_3), 49.9 (CHNH), 52.8 (CCH_2C), 66.3 (CMe_2), 109.9, 113.6, 118.9, 126.8, 127.6, 127.8, 128.2, 129.2, 130.6, 131.1, 137.9, 138.5, 145.4, 146.5, 149.1, 153.6 (C—Ar); ms: *m/z* (%) 462 (25, M^+ [^{35}Cl]), 464 (8, M^+ [^{37}Cl]), 448 (11), 350 (75), 296 (27), 281 (100), 257 (7). *Anal*. Calcd for $C_{26}H_{31}ClN_6$: C, 67.44; H, 6.75; N, 18.15%. Found: C, 67.48; H, 6.53; N, 18.27%.

N-((2-chloroquinolin-3-yl)(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)methyl)-3,4-dimethylaniline (6j). White solid; Yield: 76%; mp 197–199°C; IR (KBr) 3311 (NH), 1614, 1397, 1312 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 0.77 (9H, s, CMe_3), 1.84 and 1.88 (6H, 2s, CMe_2), 2.00–2.06 (7H, m, $2Me_2$, CCHC), 2.15 (1H, d, *J* 14.9 Hz, CCHC), 6.43 (2H, d, *J* 9.2 Hz, CHNH, Ar), 6.57 (1H, s, Ar), 6.84 (1H, d, *J* 8.1 Hz, Ar), 7.02 (1H, d, *J* 9.4 Hz, CHNH), 7.64 (1H, t, *J* 7.5 Hz, Ar), 7.82 (1H, t, *J* 7.6 Hz, Ar), 8.00 (2H, t, *J* 9.3 Hz, Ar), 8.55 (1H, s, Ar); ^{13}C NMR (125 MHz, DMSO): δ 18.3 (Me), 19.8 (Me), 28.7 (CMe_2), 29.4 (CMe_2), 30.5 (CMe_3), 31.2 (CMe_3), 49.9 (CHNH), 52.7 (CCH_2C), 66.2 (CMe_2), 110.1,

114.6, 125.5, 126.8, 127.6, 127.8, 128.1, 130.3, 130.7, 131.1, 136.9, 137.9, 143.4, 146.5, 149.1, 153.6 (C—Ar); ms: *m/z* (%) 476 (56, M^+ [^{35}Cl]), 478 (19, M^+ [^{37}Cl]), 364 (100), 320 (14), 306 (18), 295 (97), 259 (45). *Anal*. Calcd for $C_{27}H_{33}ClN_6$: C, 67.98; H, 6.97; N, 17.62%. Found: C, 68.16; H, 7.11; N, 17.54%.

***N-((2-chloro-6-methylquinolin-3-yl)(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)methyl)-4-methylaniline* (*6k*).** White solid; Yield: 78%; mp 222–225°C; IR (KBr) 3296 (NH), 1596, 1387, 1339 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 0.77 (9H, s, CMe_3), 1.84 and 1.88 (6H, 2s, CMe_2), 2.02 (1H, d, *J* 14.9 Hz, CCHC), 2.09 (3H, s, Me), 2.26 (1H, d, *J* 14.9 Hz, CCHC), 2.45 (3H, s, Me), 6.41 (1H, d, *J* 9.4 Hz, CHNH), 6.64 (2H, d, *J* 8.1 Hz, Ar), 6.91 (2H, d, *J* 8.0 Hz, Ar), 7.09 (1H, d, *J* 9.4 Hz, CHNH), 7.64 (1H, d, *J* 7.8 Hz, Ar), 7.75 (1H, s, Ar), 7.87 (1H, d, *J* 8.5 Hz, Ar), 8.43 (1H, s, Ar); ^{13}C NMR (125 MHz, DMSO): δ 20.0 (Me), 21.0 (Me), 28.8 (CMe_2), 29.3 (CMe_2), 30.5 (CMe_3), 31.2 (CMe_3), 50.0 (CHNH), 52.7 (CCH_2C), 66.2 (CMe_2), 113.0 (2C), 126.5, 126.8, 127.3, 127.6, 129.8 (2C), 130.4, 133.1, 137.3, 137.6, 143.1, 145.1, 148.2, 153.6 (C—Ar); ms: *m/z* (%) 476 (30, M^+ [^{35}Cl]), 478 (10, M^+ [^{37}Cl]), 462 (19), 364 (70), 350 (44), 295 (100), 281 (60). *Anal*. Calcd for $C_{27}H_{33}ClN_6$: C, 67.98; H, 6.97; N, 17.62%. Found: C, 68.16; H, 7.11; N, 17.54%.

Representative procedure for the synthesis of 7a–d. To a stirring solution of 2-chloroquinoline-3-carbaldehyde (1.0 mmol) in MeOH (5 mL) was added tryptamine (0.160 g, 1.0 mmol), isocyanide (1.0 mmol), and TMIS (0.115 g, 1.0 mmol) and the mixture stirred for 6 h at room temperature. Formaldehyde solution (0.122 cc, 37.0% in MeOH, 1.5 mmol) and TFA (0.228 g, 2.0 mmol) were then added and the mixture stirred for 15 min. After completion as indicated by TLC, the solvent was evaporated under reduced pressure. The crude was then dissolved in DCM (20 mL) and washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL) solutions, respectively. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel using a mixture of Hex-AcOEt (3:1 V/V) as eluent to afford compounds **7a–d**.

***2-((2-chloroquinolin-3-yl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido*[3–23]*indole* (*7a*).** White solid; Yield: 68%; mp 209–211°C; IR (KBr) 3280 (NH), 1619, 1392, 1330 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 1.15–1.97 (10H, m, $5CH_2$ of cyclohexyl), 2.74 (2H, br s, CH_2CH_2N), 2.97–3.05 (2H, m, CH_2CH_2N), 3.81 (2H, AB-q, *J* 13.9 Hz, CH_2N), 4.83 (1H, br s, CH of cyclohexyl), 6.13 (1H, s, CH), 6.90–7.02 (2H, m, Ar), 7.25 (1H, d, *J* 7.7 Hz, Ar), 7.36 (1H, d, *J* 7.5 Hz, Ar), 7.67 (1H, t, *J* 7.2 Hz, Ar), 7.84 (1H, t, *J* 7.3 Hz, Ar), 7.98 (1H, d, *J* 8.2 Hz, Ar), 8.21 (1H, d, *J* 7.4 Hz, Ar), 8.88 (1H, s, Ar), 10.66 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO): δ 21.4 (CH_2CH_2N), 24.4 (CH_2), 24.5 (CH_2), 24.7 (CH_2), 32.8 (CH_2), 32.9 (CH_2), 47.4 (CH_2N), 47.9 (CH_2CH_2N), 57.2 (CH of cyclohexyl), 57.7 (CH), 106.3, 110.9, 117.4, 118.4, 120.5, 126.5, 126.8, 127.4, 127.7, 128.6, 128.8, 131.4, 131.9, 135.8, 139.7, 146.5, 149.1, 152.4 (C—Ar); ms: *m/z* (%) 497 (1, M^+ [^{35}Cl]), 499 (0.33, M^+ [^{37}Cl]), 292 (22), 215 (35), 171 (100), 143 (74), 115 (20). *Anal*. Calcd for $C_{28}H_{28}ClN_7$: C, 67.53; H, 5.67; N, 19.69%. Found: C, 67.59; H, 5.75; N, 19.81%.

***2-((2-chloroquinolin-3-yl)(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido*[3–23]*indole* (*7b*).** White solid; Yield: 70%; mp 205–207°C; IR (KBr) 3278 (NH), 1619, 1399, 1325 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 0.50 (9H, s, CMe_3), 1.77–2.01 (8H, m, CMe_2, CCH_2C), 2.63 (2H, br s, CH_2CH_2N), 3.05 (1H, br s, CH_2CHN), 3.24 (1H, br s, CH_2CHN), 4.00 (2H, AB-q, *J* 13.9 Hz, CH_2N), 6.42 (1H, s, CH), 6.89–6.97 (2H, m, Ar), 7.22 (1H, d, *J* 6.7 Hz, Ar), 7.30 (1H, d, *J* 6.4 Hz, Ar), 7.67 (1H, br s, Ar), 7.85 (1H, br s, Ar), 7.99 (1H, d, *J* 7.4 Hz, Ar), 8.16 (1H, d, *J* 7.1 Hz, Ar), 8.65 (1H, s, Ar), 10.66 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO): δ 21.9 (CH_2CH_2N), 29.1 (CMe_2), 30.0 (CMe_3), 31.0 (CMe_3), 46.4 (CH_2N), 47.0 (CH_2CH_2N), 52.5 (CCH_2C), 58.8 (CH), 65.6 (CMe_2), 106.3, 110.8, 117.3, 118.3, 120.4, 126.3, 126.5, 126.9, 127.5, 127.9, 128.7, 131.7, 132.0, 135.8, 140.9, 146.4, 149.9, 152.7 (C—Ar); ms: *m/z* (%) 527 (1, M^+ [^{35}Cl]), 529 (0.33, M^+ [^{37}Cl]), 345 (5), 245 (8), 187 (49), 171 (100), 143 (83). *Anal*. Calcd for $C_{30}H_{34}ClN_7$: C, 68.23; H, 6.49; N, 18.57%. Found: C, 68.15; H, 6.61; N, 18.53%.

***2-((2-chloro-6-methylquinolin-3-yl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido*[3–23]*indole* (*7c*).** White solid; Yield: 72%; mp 196–198°C; IR (KBr) 3296 (NH), 1592, 1339, 1307 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 1.15–1.97 (10H, m, $5CH_2$ of cyclohexyl), 2.47 (3H, s, Me), 2.74 (2H, br s, CH_2CH_2N), 2.92–3.05 (2H, m, CH_2CH_2N), 3.80 (2H, AB-q, *J* 14.3 Hz, CH_2N), 4.81 (1H, br s, CH of cyclohexyl), 6.10 (1H, s, CH), 6.93 (1H, t, *J* 7.3 Hz, Ar), 7.00 (1H, t, *J* 7.3 Hz, Ar), 7.25 (1H, d, *J* 7.8 Hz, Ar), 7.36 (1H, d, *J* 7.5 Hz, Ar), 7.67 (1H, d, *J* 8.5 Hz, Ar), 7.86 (1H, d, *J* 8.5 Hz, Ar), 7.95 (1H, s, Ar), 8.74 (1H, s, Ar), 10.66 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO): δ 21.1 (Me), 21.5 (CH_2CH_2N), 24.4 (CH_2), 24.6 (CH_2), 24.7 (CH_2), 32.7 (CH_2), 32.9 (CH_2), 47.4 (CH_2N), 47.9 (CH_2CH_2N), 57.2 (CH of cyclohexyl), 57.6 (CH), 106.4, 110.9, 117.4, 118.4, 120.5, 126.5, 126.8, 127.2, 127.3, 128.7, 131.9, 133.6, 135.8, 137.5, 138.9, 145.1, 148.2, 152.5 (C—Ar); ms: *m/z* (%) 511 (1, M^+ [^{35}Cl]), 513 (0.33, M^+ [^{37}Cl]), 295 (8), 259 (8), 217 (9), 190 (17), 171 (100). *Anal*. Calcd for $C_{29}H_{30}ClN_7$: C, 68.02; H, 5.91; N, 19.15%. Found: C, 67.93; H, 6.07; N, 19.27%.

***2-((2-chloro-6-methylquinolin-3-yl)(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole* (*7d*).** White solid; Yield: 79%; mp 231–234°C; IR (KBr) 3296 (NH), 1630, 1375, 1340 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 0.50 (9H, s, CMe_3), 1.77 and 1.85 (6H, 2s, CMe_2), 1.92 (2H, AB-q, *J* 15.1 Hz, CCH_2C), 2.46 (3H, s, Me), 2.60–2.63 (2H, m, CH_2CH_2N), 3.00–3.04 (1H, m, CH_2CH_2N), 3.22–3.26 (1H, m, CH_2CH_2N), 3.99 (2H,

AB-q, *J* 14.2 Hz, CH_2N), 6.40 (1H, s, CH), 6.89 (1H, t, *J* 7.1 Hz, Ar), 6.97 (1H, t, *J* 7.2 Hz, Ar), 7.22 (1H, d, *J* 7.7 Hz, Ar), 7.30 (1H, d, *J* 7.4 Hz, Ar), 7.67 (1H, d, *J* 8.4 Hz, Ar), 7.88 (1H, d, *J* 7.7 Hz, Ar), 7.89 (1H, s, Ar), 8.53 (1H, s, Ar), 10.65 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO): δ 21.0 (Me), 21.9 ($\underline{C}H_2CH_2N$), 29.1 ($C\underline{Me}_2$), 30.0 ($C\underline{Me}_3$), 31.0 ($\underline{C}Me_3$), 46.5 (CH_2N), 47.0 ($CH_2\underline{C}H_2N$), 52.5 ($C\underline{C}H_2C$), 58.8 (CH), 65.5 ($\underline{C}Me_2$), 106.3, 110.9, 117.3, 118.3, 120.4, 126.2, 126.5, 126.7, 127.2, 127.3, 132.0, 133.8, 135.8, 137.7, 140.2, 145.1, 149.0, 152.7 (C—Ar); ms: *m/z* (%) 541 (1, M^+ [^{35}Cl]), 543 (0.33, M^+ [^{37}Cl]), 359 (5), 259 (8), 230 (9), 217 (11), 171 (100). *Anal*. Calcd for $C_{31}H_{36}ClN_7$: C, 68.68; H, 6.69; N, 18.09%. Found: C, 68.76; H, 6.53; N, 17.81%.

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