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Full Paper

Versatile Synthesis of Functionalized Tetrahydroisoquinolines by Ring Transformation of 2*H*-Pyran-2-ones

Priyanka B. Kole[A] *and Fateh V. Singh*[A,B]

[A]Chemistry Division, School of Advanced Sciences, VIT Institute, Chennai Campus, Chennai-600127, Tamil Nadu, India.
[B]Corresponding author. Email: fatehveer.singh@vit.ac.in

Functionalized tetrahydroisoquinolines are convenient precursors for the construction of numerous heterocyclic compounds of therapeutic importance. In this paper we have illustrated an efficient synthesis of highly substituted tetrahydroisoquinolines from 2*H*-pyran-2-ones via nucleophile-mediated ring transformation with *tert*-butyl-4-oxopiperidine-1-carboxylate followed by acid-mediated cleavage of the *tert*-butyloxycarbonyl group. The products were achieved smoothly in high yields with flexibility of various substituents.

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Introduction

Tetrahydroisoquinolines represent privileged heterocyclic scaffolds found in natural alkaloids endowed with a wide range of biological activities.[1] Molecules embedded with these scaffolds are established as valuable precursors for the synthesis of biologically active compounds and have gained special attention due to their diverse pharmacological properties such as antitumour,[2] antifungal,[2] antibacterial,[2] anti-inflammatory,[3] anticonvulsants, and antithrombotic properties.[3] Naturally isolated alkaloids containing tetrahydroisoquinoline entities broadly originate in several biologically active compounds (Fig. 1). Higenamine **1** extracted from the leaves of *Aristolochia brasiliences*, has been identified as an agonist for the β2-adrenergic receptor,[4,5b] antimycobacterial,[4] and anti-inflammatoric drug.[5] The complex α-substituted tetrahydroisoquinoline Noscapine **2** shows an anti-proliferative activity against human prostate cancer cells.[6] Oleracin E **3** has been developed as an antioxidant and antidepressant agent.[7] The catechol derived tetrahydroisoquinoline alkaloid Salsolinol **4** plays a vital role in pathogenic treatment associated with Parkinson's diseases.[8] In addition, carbamate-cored tetrahydroisoquinolines serve as selective ligands for the dopamine D2 receptor.[9]

Numerous synthetic approaches have been published for the synthesis of tetrahydroisoquinolines that could be integrated as privileged structural motifs in pharmaceutically applicable compounds.[10–12] The most general method for the synthesis of tetrahydroisoquinolines are associated with the metal catalyzed hydrogenation of isoquinolines.[13–15] The synthesis of similar compounds was also accomplished by Pd^{II} catalyzed reactions.[16] Furthermore, Lee and co-workers disclosed Lewis acid catalyzed cycloaddition/Michael cascade reactions of aziridines with *N,N*-dialkyl-3-vinylanilines for the synthesis of functionalized tetrahydroisoquinolines.[17]

Several one-pot sequential methods for achieving tetrahydroisoquinolines are available in the literature.[18] In 2000, Padwa and co-workers described the one-pot bicycloannulation of mono-substituted cyclic thioamides with α-bromoalkenoyl chlorides.[19] Furthermore, similar analogues were correspondingly obtained by a one-pot chemoenzymatic cascade reaction.[20] Moreover, highly substituted tetrahydroisoquinolines were also constructed through the cyclocondensation of *N*-substituted cyanacetohydrazide with dialkylbenzylcarbinols by a Ritter reaction.[21]

Although numerous methods do provide tetrahydroisoquinoline scaffolds, some of the methods require the use of costly organometallic reagents or catalysts, stringent reaction conditions, and prolonged reaction time. The existence of numerous applications and limitations of current approaches urged us to develop an easy, efficient, and metal-free approach to produce

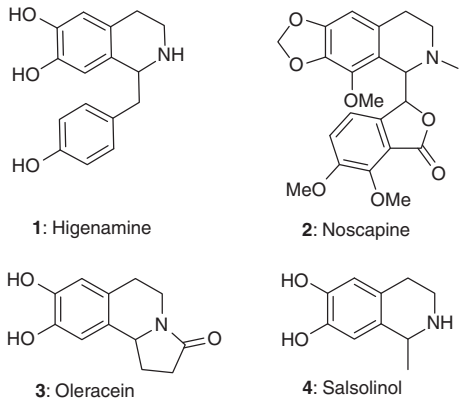
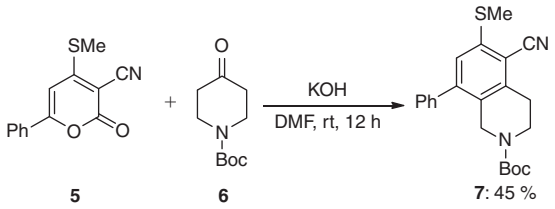


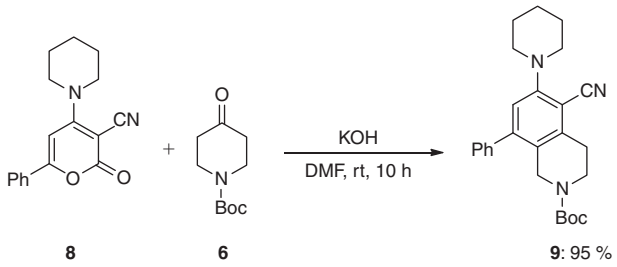
Fig. 1. Structures of naturally occurring and biologically active tetrahydroisoquinoline scaffolds.

tetrahydroisoquinolines. Herein, we report a versatile route for the synthesis of tetrahydroisoquinolines through nucleophile-mediated ring transformation of 2*H*-pyran-2-ones that could offer variability of functional groups.

2*H*-Pyran-2-ones are unsaturated cyclic esters engaged with various biological properties.[22] The ring transformations of 2*H*-pyran-2-ones are used for the construction of various functionalized arenes,[23] hetero-arenes,[24] cyclic fused systems,[25] and metallocene compounds which in turn are enriched with a wide range of biological significance.[26] The unique property of the starting substrates is the existence of three electrophilic centres within the lactone ring at the C-2, C-4, and C-6 positions, out of which the C-6 position is highly reactive and further susceptible towards nucleophiles due to broad conjugation and the availability of a nitrile group at the C-3 position in the pyran ring. During our recent study on 2*H*-pyranones, we have developed a metal-free approach for the synthesis of 2-tetralones[27] and diarylmethanes via ring transformation of 2*H*-pyran-2-ones.[28]



Scheme 1.



Scheme 2.

Results and Discussion

In 2002, the synthesis of tetrahydroisoquinolines was reported via the ring transformation of 2*H*-pyran-2-ones using 4-piperidone, 1-propyl-4-piperidone, or 1-phenethyl-4-piperidone as a source of nucleophile. But the respective tetrahydroisoquinolines were reportedly obtained in comparatively low yield up to 30–38 %.[25a] Our method to produce functionalized tetrahydroisoquinolines also depends on the ring transformation of 2*H*-pyran-2-ones and using *tert*-butyl-4-oxopiperidine-1-carboxylate as a source of nucleophile in the presence of KOH in DMF at room temperature for the duration of 10–16 h, followed by deprotection of the *tert*-butyloxycarbonyl group. In our method, we have used *tert*-butyl-4-oxopiperidine-1-carboxylate as a source of nucleophile and functionalized tetrahydroisoquinolines were achieved in high yields as compared with this earlier report. The improvements in yield may be due to the attachment of *tert*-butylpiperidine-1-carboxylate to the parent substrate 2*H*-pyran-2-ones.

The 2*H*-pyran-2-ones used as starting materials were easily obtained by the reaction of ethyl-2-cyano-3,3-bis(methylthio) acrylate with various aromatic acetophenones in DMSO at room temperature under alkaline conditions.[23a,23b,25d,25f,29] Furthermore, 6-aryl-4-amino-2*H*-pyran-2-ones were achieved by reacting 2*H*-pyran-2-ones with secondary amines in methanol at reflux for 6–8 h. The parent precursor ethyl-2-cyano-3,3-bis (methylthio)acrylate was achieved by the reaction of ethylcyanoacetate with carbon disulfide and dimethyl sulfate using freshly prepared NaOMe in absolute methanol.[23a,23b,25g,29]

Initially, the transformation reaction was examined by the treatment of 6-phenyl-4-methylsulfanyl-2-pyranone (**5**) with *tert*-butyl-4-oxopiperidine-1-carboxylate (**6**) in DMF in the presence of KOH at room temperature for 12 h (Scheme 1). Unfortunately, the latter reaction suffered from several side reactions and the desired ring transformed product **7** was only obtained in 45 % yield. Perhaps, the presence of a good leaving group at the C-4 position of the pyran ring in starting material **5** generates high molecular diversity and makes this position more liable towards nucleophilic attack leading to various undesired side products.

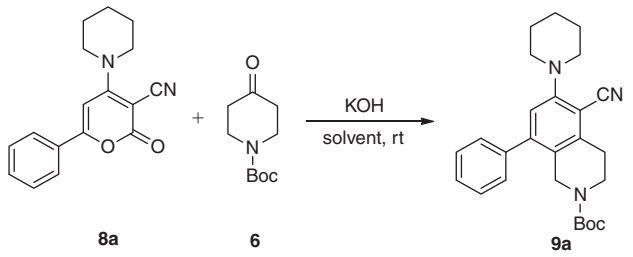
Subsequently, new substrates 6-phenyl-4-amino-2*H*-pyran-2-ones **8** were synthesized wherein the good leaving group present at the C-4 position in substrate **5** was substituted by a *tert*-amino functionality by their reaction with several secondary amines in absolute methanol at reflux.[23a,23b,25g,29] The reaction of substrate 2-oxo-6-phenyl-4-(piperidin-1-yl)-2*H*-pyran-3-carbonitrile (**8a**) was performed with *tert*-butyl-4-oxopiperidine-1-carboxylate (**6**) under the same reaction conditions and ring transformed product **9a** was perceived in much better yield (Scheme 2).

In the beginning, we made efforts to find a suitable solvent for the ring transformation of 2*H*-pyran-2-ones **8** to *N*-*tert*-butyloxycarbonyl-protected tetrahydroisoquinolines **9**. Various polar and non-polar solvents were investigated using **8a** as an ideal substrate. The reaction of substrate **8a** with 1.0 equiv. of *tert*-butyl-4-oxopiperidine-1-carboxylate (**6**) and 1.2 equiv. of KOH in more polar aprotic solvents like DMF and DMSO for 10 h gave ring transformed product **9a** in 95 and 93 % yields respectively (Table 1, entries 1 and 2). A similar reaction of **8a** in MeCN showed almost identical results and the reaction product was isolated in 90 % yield (Table 1, entry 3). The transformation reaction was also examined in DCM and $CHCl_3$ but the reaction product was observed in 60 and 68 % yields. (Table 1, entries 4 and 5). The reaction could not proceed when THF and 1,4-dioxane were used as solvents (Table 1, entries 6 and 7).

Next our efforts were directed towards the screening of base for the ring transformation of 2*H*-pyran-2-ones **8** to *N*-*tert*-butyloxycarbonyl-protected tetrahydroisoquinolines **9**. We first examined the reaction of starting precursor **8a** using 1.2 equiv. KOH as a base in DMF at room temperature and the reaction was completed in 10 h to give *N*-*tert*-butyloxycarbonyl-protected tetrahydroisoquinoline derivative **9a** in 95 % yield (Table 2, entry 1). Furthermore the same reaction was accomplished with $NaHCO_3$ and reaction product **9a** was achieved in 82 % yield (Table 2, entry 2). Later, transformation of **8a** was also verified using LiOH and $CsCO_3$ under optimized conditions and the ring transformed product **9a** was isolated in 75 and 69 % yields respectively, with a slight increase in reaction time (Table 2, entries 3 and 4).

From the above optimized study, the presence of 1.2 equiv. of KOH in the suitable solvent DMF at room temperature for 10 h were found as the best reaction conditions for the transformation of 2*H*-pyran-2-ones **8** towards the synthesis of *N*-*tert*-butyloxycarbonyl protected tetrahydroisoquinolines **9**.

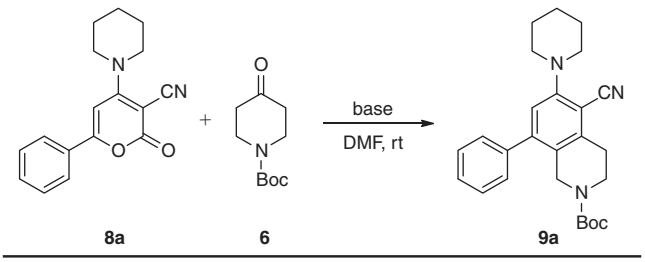
Table 1. Optimization of solvent for the transformation of 2*H*-pyran-2-one 8a to *N*-*tert*-butyloxycarbonyl-protected tetrahydroisoquinoline 9a



8a **6** **9a**

Entry	Solvent	Reaction time [h]	**9a** Yield [%]
1	DMF	10	95
2	DMSO	10	93
3	MeCN	10	90
4	DCM	12	60
5	$CHCl_3$	12	68
6	1,4-Dioxane	15	—
7	THF	15	—

Table 2. Optimization of base for the ring transformation of 2*H*-pyran-2-one 8a to *N*-*tert*-butyloxycarbonyl-protected tetrahydroisoquinoline 9a



8a **6** **9a**

Entry	Base	Reaction time [h]	**9a** Yield [%]
1	KOH	10	95
2	$NaHCO_3$	12	82
3	LiOH	14	75
4	$CsCO_3$	14	69

After finding the suitable reaction conditions, a series of *N*-*tert*-butyloxycarbonyl-protected tetrahydroisoquinolines **9a–s** were synthesised in 66–96 % yields by reacting different 2*H*-pyran-2-ones **8a–s** with *tert*-butyl-4-oxopiperidine-1-carboxylate (**6**) in DMF using KOH for 10–16 h at room temperature (Table 3, entries 1–19). Both electron-accepting and electron-donating groups were successfully tolerated on 6-aryl-4-amino-2*H*-pyran-2-ones **8**. The ring transformed products **9d–g** were obtained in comparatively lower yields with the substrates bearing electron-accepting groups **8d–g** (Table 3, entries 4–7). Whereas almost full conversion was observed of substrates **8h–l** having electron-donating groups affording products **9h–l** in good yields (Table 3, entries 8–12). Furthermore, the reaction was evaluated with bulky 6-naphthyl-2*H*-pyran-2-ones **8m–o** and the reaction products **9m–o** were successfully isolated in high yields (Table 3, entries 13–15). Likewise, the ring transformation reaction was assessed with congested substrates **8p–r** that possess an additional methyl group at C-5 of the lactone ring and fully functionalized reaction products **9p–r** were obtained in 76–85 % yields respectively (Table 3, entries 16–18). In addition, substrate 6-thienyl-2*H*-pyran-2-one (**8s**) was easily converted into the ring transformed product **9s** in 88 % yield under the optimized reaction conditions (Table 3, entry 19). Finally, all of these products were analyzed by spectroscopic techniques.

As per the reported methods,[30] the plausible reaction mechanism for the ring transformation reaction of 6-aryl-2*H*-pyran-2-ones **8** to *N*-*tert*-butyloxycarbonyl protected tetrahydroisoquinolines **9** is presented in Scheme 3. The mechanism could be initiated by the Michael attack of the anion generated on the active methylene group of *tert*-butyl-4-oxopiperidine-1-carboxylate (**6**) to the C-6 of the cyclic unsaturated ester **8** giving an intermediate **10**. Furthermore, intramolecular cyclization of **10** involves a carbonyl group of nucleophile **6** and the C-3 position of the pyran ring generating a bicyclic intermediate **11**. Finally, via simultaneous decarboxylation and dehydration of intermediate **11**, the desired ring transformed products **9** could be formed.

In order to explore the scope of this reaction, the *tert*-butyloxycarbonyl protecting group was further hydrolyzed under acidic conditions.[31] The reaction of *N*-*tert*-butyloxycarbonyl-protected tetrahydroisoquinoline derivatives **9a**,**e**,**f**,**n**,**o** with excess trifluoroacetic acid in dichloromethane at room temperature for 1 h gave tetrahydroisoquinolines **13a**,**e**,**f**,**n**,**o** in 86–94 % yields (Table 4, entries 1–5). Finally, the synthesized products were analyzed by spectroscopic techniques.

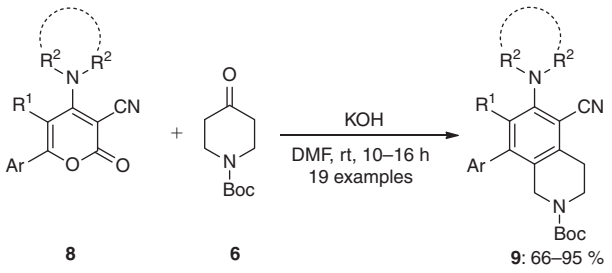
Conclusion

In conclusion, we have established an efficient and reliable synthetic method for the synthesis of fully functionalized tetrahydroisoquinolines via nucleophile-mediated ring transformation of 6-aryl-2*H*-pyranones followed by acidic hydrolysis. Our methodology is simple, economical, and does not involve the use of any toxic transition metals. This approach towards the synthesis of tetrahydroisoquinolines offers the flexibility of tolerating electron-donating as well as electron-withdrawing groups in the structural architecture of the synthesized compounds. Further investigation regarding this ring transformation methodology is currently in progress.

Experimental

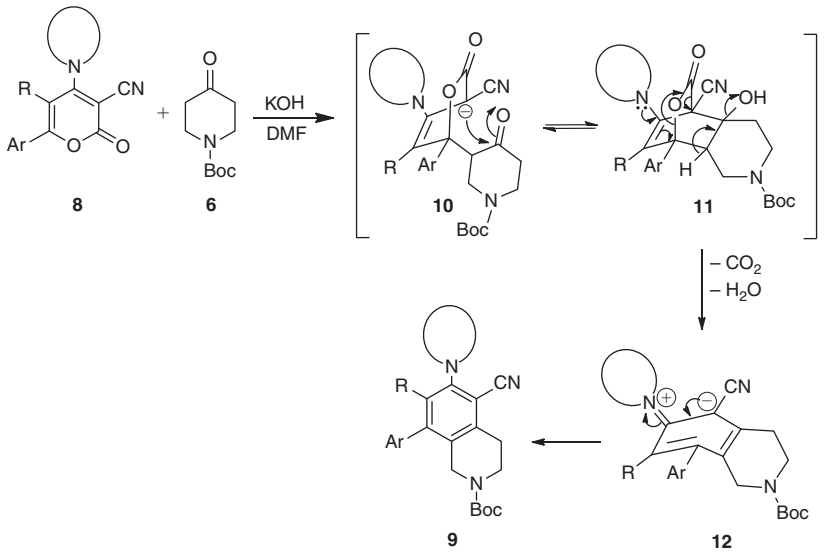
All reactions were performed in the absence of an inert atmosphere and further checked by thin-layer chromatography (TLC). The products were isolated by column chromatography using aluminium oxide (neutral, 95 %). Hexane and ethyl acetate were used as eluting solvents. All the solvents and reagents used for carrying out these experiments were purchased from Avra Synthesis Pvt Ltd and were used as obtained without purification. A REMI DDMS 2545 melting point apparatus was used to find melting points. ^{1}H NMR spectra was performed at 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz on an AV-400 Bruker spectrometer. The chemical shifts were reported in parts per million (δ) using tetramethylsilane (0 ppm for ^{1}H NMR) as an internal standard and $CDCl_3$ (77.00 ppm for ^{13}C NMR) (99.8 ATOM % D, Bio Corporals) as solvent. Signal peaks are designated as s, singlet; d, doublet; t, triplet; dd, doublet of doublet; q, quarted; br s, broad singlet; m, multiplet. A Thermo Scientific Nicolet Nexus 470FT-IR spectrometer was used to record IR data by subjecting samples to the ATR mode. Mass spectra (*m*/*z*) of the synthesized compounds were performed under electron ionization (EI). Elemental analysis

Table 3. Synthesis of *N-tert*-butyloxycarbonyl-protected tetrahydydroisoquinolines 9a–s by the ring transformation of 6-aryl-2*H*-pyran-2-ones 8a–s with *tert*-butyl-4-oxopiperidine-1-carboxylate (6) as a source of nucleophile



8 **6** **9**: 66–95 %

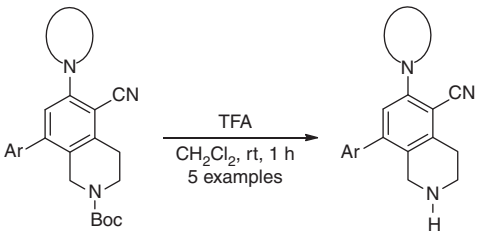
Entry	Substrate	Ar	R^1	NR^2_2	Time [h]	**9** Yield [%]
1	**8a**	C_6H_5	H	Piperidin-1-yl	10	95
2	**8b**	C_6H_5	H	*N*-Phenylpiperazin-1-yl	10	89
3	**8c**	C_6H_5	H	Diethyl amine	10	84
4	**8d**	4-ClC_6H_4	H	Piperidin-1-yl	14	74
5	**8e**	4-BrC_6H_4	H	Piperidin-1-yl	14	78
6	**8f**	2,4-Cl_2 C_6H_3	H	Piperidin-1-yl	16	66
7	**8g**	2,4-Cl_2 C_6H_3	H	Pyrrolidine	16	70
8	**8h**	3,4-OMe_2 C_6H_3	H	Piperidin-1-yl	10	90
9	**8i**	4-$OMeC_6H_4$	H	Piperidin-1-yl	10	94
10	**8j**	4-$OMeC_6H_4$	H	*N*-Phenylpiperazin-1-yl	10	88
11	**8k**	4-MeC_6H_4	H	Piperidin-1-yl	10	96
12	**8l**	4-MeC_6H_4	H	*N*-Phenylpiperazin-1-yl	10	90
13	**8m**	1-Naphthyl	H	Piperidin-1-yl	12	85
14	**8n**	1-Naphthyl	H	Morpholin-1-yl	12	80
15	**8o**	2-Naphthyl	H	Piperidin-1-yl	10	90
16	**8p**	C_6H_5	Me	Piperidin-1-yl	12	76
17	**8q**	C_6H_5	Me	*N*-Phenylpiperazin-1-yl	12	80
18	**8r**	4-$OMeC_6H_4$	Me	*N*-Phenylpiperazin-1-yl	12	85
19	**8s**	2-Thienyl	H	Piperidin-1-yl	10	88



8 **6** **10** **11** **12** **9**

Scheme 3. Plausible mechanism towards *N-tert*-butyloxycarbonyl-protected tetrahydroisoquinolines **9** via ring transformation of 6-aryl-2*H*-pyran-2-ones **8** with *tert*-butyl-4-oxopiperidine-1-carboxylate (**6**).

Table 4. Synthesis of tetrahydroisoquinolines 13a,e,f,n,o by the acid-mediated cleavage of *N-tert*-butyloxycarbonyl tetrahydroisoquinolines 9a,e,f,n,o



9 **13:** 86–94 %

Entry	Substrate	Ar	N	**13** Yield [%]
1	**9a**	C_6H_5	Piperidin-1-yl	86
2	**9e**	4-BrC_6H_4	Piperidin-1-yl	94
3	**9f**	2,4-$Cl_2C_6H_4$	Piperidin-1-yl	92
4	**9n**	1-Naphthyl	Morpholin-1-yl	88
5	**9o**	2-Naphthyl	Piperidin-1-yl	90

(CHNS) was performed using an Elemental varioMICRO select analyzer (serial no. 15162036).

General Procedure for the Synthesis of N-tert-*Butyloxycarbonyl-Protected Tetrahydroisoquinoline Derivative 7*

A mixture containing 3-cyano-4-methylsulfanyl-2*H*-pyran-2-ones **5** (1.0 mmol, 1.0 equiv.), *tert*-butyl-4-oxopiperidine-1-carboxylate (**6**) (199 mg, 1.0 mmol, 1.0 equiv.) and crushed KOH (67 mg, 1.2 mmol, 1.2 equiv.) was stirred in DMF (5 mL) at room temperature. The progress of the reaction was checked by TLC. The reaction was completed in 12 h, after which cold water was added to the reaction mixture and neutralized with 2 M HCl, followed by extraction with EtOAc (3 × 10 mL). The aqueous layer was discarded and the collected organic layer was further dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue obtained was purified through neutral alumina column chromatography using EtOAc/hexane (1 : 49) as an eluent and the isolated product was characterized as *tert*-butyl-5-cyano-6-(methylthio)-8-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**7**): White solid (0.171 g, 45 % yield). Mp 143–145°C. δ_H (400 MHz, $CDCl_3$) 1.35 (br s, 9H, 3 × Me), 2.46 (s, 3H, SMe), 3.01 (t, *J* 5.6, 2H, CH_2), 3.60 (t, *J* 6.0, 2H, NCH_2), 4.28 (s, 2H, NCH_2), 6.94 (s, 1H, ArH), 7.16–7.21 (m, 2H, ArH), 7.34–7.40 (m, 3H, ArH). δ_C (100 MHz, $CDCl_3$) 154.5, 141.8, 138.6, 129.7, 128.7, 128.4, 125.3, 115.7, 110.6, 80.2, 28.4, 15.9. ν_{max} (ATR)/cm^{-1} 2210 (C≡N), 1690 (C=O). *m*/*z* (GC-MS) 381 $[M + 1]^+$. Anal. Calc. for $C_{22}H_{24}N_2O_2S$: C 69.44, H 6.36, N 7.36, S 8.43. Found: C 69.40, H 6.33, N 7.39, S 8.41 %.

General Procedure for the Synthesis of N-tert-*Butyloxycarbonyl-Protected Tetrahydroisoquinolines 9*

To a mixture of 6-aryl-2*H*-pyran-2-ones **8** (1.0 mmol, 1.0 equiv.), *tert*-butyl-4-oxopiperidine-1-carboxylate (**6**) (199 mg, 1.0 mmol, 1.0 equiv.) and DMF (5 mL), crushed KOH (67 mg, 1.2 mmol, 1.2 equiv.) was added. The reaction mixture was allowed to stir at room temperature for 10–16 h. The progress of the reaction was checked by TLC. On completion cold water was added to the reaction mixture and neutralized with 2 M HCl, followed by extraction with EtOAc (3 × 10 mL). The aqueous layer was discarded and the collected organic layer was further dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue obtained was purified by neutral alumina column chromatography using EtOAc/hexane (1 : 49) as an eluent and isolated products were characterized as *N-tert*-butyloxycarbonyl protected tetrahydroisoquinolines **9** by their spectroscopic analysis.

tert-*Butyl-5-cyano-8-phenyl-6-(piperidin-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9a**)*

The title compound was obtained as a white solid (0.396 g, 95 % yield). Mp 150–152°C. δ_H (400 MHz, $CDCl_3$) 1.33 (br s, 9H, 3 × Me), 1.45–1.55 (m, 2H, CH_2), 1.63–1.74 (m, 4H, 2 × CH_2), 2.98 (t, *J* 6.0, 2H, CH_2), 3.05 (t, *J* 5.2, 4H, 2 × NCH_2), 3.57 (t, *J* 6.0, 2H, NCH_2), 4.24 (s, 2H, NCH_2), 6.66 (s, 1H, ArH), 7.17 (d, *J* 7.6, 2H, ArH), 7.29–7.37 (m, 3H, ArH). δ_C (100 MHz, $CDCl_3$) 155.8, 154.5, 139.4, 128.6, 128.4, 128.0, 125.5, 118.4, 117.2, 105.3, 79.9, 53.4, 43.9, 28.4, 26.2, 24.1. ν_{max} (ATR)/cm^{-1} 2212 (C≡N), 1682 (C=O). *m*/*z* (GC-MS) 418 $[M + 1]^+$. Anal. Calc. for $C_{26}H_{31}N_3O_2$: C 74.79, H 7.48, N 10.06. Found: C 74.20, H 7.30, N 10.01 %.

tert-*Butyl-5-cyano-8-phenyl-6-(4-phenylpiperazin-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9b**)*

The title compound was obtained as a white solid (0.439 g, 89 % yield). Mp 162–164°C. δ_H (400 MHz, $CDCl_3$) 1.33 (br s, 9H, 3 × Me), 2.99 (t, *J* 5.6, 2H, CH_2), 3.23–3.32 (m, 8H, 4 × NCH_2), 3.58 (t, *J* 6.0, 2H, NCH_2), 4.26 (s, 2H, NCH_2), 6.71 (s, 1H, ArH), 6.78 (t, *J* 7.2, 1H, ArH), 6.87 (d, *J* 8.0, 2H, ArH), 7.13–7.21 (m, 4H, ArH), 7.30–7.36 (m, 3H, ArH). δ_c (100 MHz, $CDCl_3$) 153.4, 153.3, 150.1, 138.1, 128.1, 127.6, 127.3, 127.1, 125.4, 119.1, 117.3, 115.9, 115.3, 78.9, 50.7, 48.4, 42.9, 27.3. ν_{max} (ATR)/cm^{-1} 2216 (C≡N), 1691 (C=O). *m*/*z* (GC-MS) 495 $[M + 1]^+$. Anal. Calc. for $C_{31}H_{34}N_4O_2$: C 75.28, H 6.93, N 11.33. Found: C 75.22, H 6.76, N 11.20 %.

tert-*Butyl-5-cyano-6-(diethylamino)-8-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9c**)*

The title compound was obtained as a white solid (0.340 g, 84 % yield). Mp 128–130°C. δ_H (400 MHz, $CDCl_3$) 1.17 (t, *J* 5.6, 6H, 2 × Me), 1.44 (br s, 9H, 3 × Me), 3.07 (t, *J* 5.6, 2H, CH_2), 3.36 (q, *J* 6.8, 4H, 2 × NCH_2), 3.68 (t, *J* 6.0, 2H, NCH_2), 4.33 (s, 2H, NCH_2), 6.74 (s, 1H, ArH), 7.25–7.31 (m, 2H, ArH), 7.38–7.46 (m, 3H, ArH). δ_c (100 MHz, $CDCl_3$) 154.5, 152.7, 139.5, 128.6, 128.4, 127.9, 124.4, 119.1, 117.8, 103.9, 79.9, 46.7, 43.9, 28.4, 12.8. ν_{max} (ATR)/cm^{-1} 2213 (C≡N), 1682 (C=O). *m*/*z* (GC-MS) 406 $[M + 1]^+$. Anal. Calc. for $C_{25}H_{31}N_3O_2$: C 74.04, H 7.70, N 10.36. Found: C 73.78, H 7.39, N 10.39 %.

tert-*Butyl-8-(4-chlorophenyl)-5-cyano-6-(piperidin-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9d**)*

The title compound was obtained as a white solid (0.333 g, 74 % yield). Mp 158–160°C. δ_H (400 MHz, $CDCl_3$) 1.35 (br s, 9H, 3 × Me), 1.46–1.57 (m, 2H, CH_2), 1.65–1.74 (m, 4H, 2 × CH_2), 2.98 (t, *J* 6.0, 2H, CH_2), 3.06 (t, *J* 5.2, 4H, 2 × NCH_2), 3.57 (t, *J* 6.0, 2H, NCH_2), 4.21 (s, 2H, NCH_2), 6.62 (s, 1H, ArH), 7.12 (d, *J* 8.4, 2H, ArH), 7.32 (d, *J* 8.0, 2H, ArH). δ_c (100 MHz, $CDCl_3$) 155.9, 154.5, 137.8, 134.2, 129.8, 128.8, 125.3, 118.2, 117.0,

105.6, 80.1, 53.3, 43.8, 28.4, 26.1, 24.0. ν_{max} (ATR)/cm^{-1} 2218 (C≡N), 1691 (C=O). *m/z* (GC-MS) 452 [M + 1]$^+$, 453 [M + 2]$^+$. Anal. Calc. for $C_{26}H_{30}ClN_3O_2$: C 69.09, H 6.69, N 9.30. Found: C 68.89, H 7.07, N 8.85 %.

tert-*Butyl-8-(4-bromophenyl)-5-cyano-6-(piperidin-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9e**)*

The title compound was obtained as a white solid (0.386 g, 78 % yield). Mp 156–158°C. δ_H (400 MHz, $CDCl_3$) 1.34 (br s, 9H, 3 × Me), 1.45–1.55 (m, 2H, CH_2), 1.64–1.72 (m, 4H, 2 × CH_2), 2.97 (t, *J* 6.0, 2H, CH_2), 3.05 (t, *J* 5.2, 4H, 2 × NCH_2), 3.57 (t, *J* 6.0, 2H, NCH_2), 4.21 (s, 2H, NCH_2), 6.62 (s, 1H, ArH), 7.06 (d, *J* 8.4, 2H, ArH), 7.47 (d, *J* 7.6, 2H, ArH). δ_c (100 MHz, $CDCl_3$) 155.9, 154.5, 140.4, 138.3, 131.8, 130.1, 125.2, 122.3, 118.1, 117.0, 105.6, 80.1, 53.3, 43.8, 28.4, 26.1, 24.0. ν_{max} (ATR)/cm^{-1} 2217 (C≡N), 1688 (C=O). *m/z* (GC-MS) 497 [M + 1]$^+$, 498 [M + 2]$^+$. Anal. Calc. for $C_{26}H_{30}BrN_3O_2$: C 62.90, H 6.09, N 8.46. Found: C 62.70, H 5.95, N 8.46 %.

tert-*Butyl-5-cyano-8-(2,4-dichlorophenyl)-6-(piperidin-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9f**)*

The title compound was obtained as a white solid (0.320 g, 66 % yield). Mp 162–164°C. δ_H (400 MHz, $CDCl_3$) 1.35 (br s, 9H, 3 × Me), 1.45–1.56 (m, 2H, CH_2), 1.65–1.74 (m, 4H, 2 × CH_2), 2.95–2.99 (m, 2H, CH_2), 3.03–3.10 (m, 4H, 2 × NCH_2), 3.42–3.75 (m, 2H, NCH_2), 3.99–4.20 (m, 2H, NCH_2), 6.57 (s, 1H, ArH), 7.06 (d, *J* 8.0, 1H, ArH), 7.25 (d, *J* 7.6, 1H, ArH), 7.42 (s, 1H, ArH). δ_c (100 MHz, $CDCl_3$) 155.8, 154.5, 136.5, 134.9, 133.5, 131.0, 129.7, 127.5, 125.7, 118.0, 116.9, 106.1, 80.1, 53.3, 43.2, 28.4, 26.1, 24.0. ν_{max} (ATR)/cm^{-1} 2223 (C≡N), 1688 (C=O). *m/z* (GC-MS) 487 [M + 1]$^+$, 488 [M + 2]$^+$. Anal. Calc. for $C_{26}H_{29}Cl_2N_3O_2$: C 64.20, H 6.01, N 8.64. Found: C 63.60, H 5.92, N 8.45 %.

tert-*Butyl-5-cyano-8-(2,4-dichlorophenyl)-6-(pyrrolidin-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9g**)*

The title compound was obtained as a white solid (0.330 g, 70 % yield). Mp 127–129°C. δ_H (400 MHz, $CDCl_3$) 1.35 (br s, 9H, 3 × Me), 1.91 (t, *J* 6.4, 4H, 2 × CH_2), 2.36 (t, *J* 6.4, 1H, CH), 2.93 (t, *J* 5.2, 2H, CH_2), 3.52 (t, *J* 6.4, 4H, 2 × NCH_2), 3.64 (t, *J* 6.4, 1H, CH), 3.83–4.15 (m, 2H, NCH_2), 6.25 (s, 1H, ArH), 7.06 (d, *J* 8.0, 1H, ArH), 7.23 (d, *J* 7.6, 1H, ArH), 7.40 (s, 1H, ArH). δ_c (100 MHz, $CDCl_3$) 154.5, 149.5, 136.9, 134.7, 133.5, 131.1, 129.5, 127.4, 120.5, 119.3, 113.5, 79.9, 50.2, 43.1, 28.4, 25.8. ν_{max} (ATR)/cm^{-1} 2205 (C≡N), 1690 (C=O). *m/z* (GC-MS) 473 [M + 1]$^+$, 474 [M + 2]$^+$. Anal. Calc. for $C_{25}H_{27}Cl_2N_3O_2$: C 63.56, H 5.76, N 8.89. Found: C 62.86, H 5.79, N 8.75 %.

tert-*Butyl-5-cyano-8-(3,4-dimethoxyphenyl)-6-(piperidin-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9h**)*

The title compound was obtained as a white solid (0.429 g, 90 % yield). Mp 160–162°C. δ_H (400 MHz, $CDCl_3$) 1.35 (br s, 9H, 3 × Me), 1.45–1.57 (m, 2H, CH_2), 1.65–1.74 (m, 4H, 2 × CH_2), 2.98 (t, *J* 6.0, 2H, CH_2), 3.06 (t, *J* 5.2, 4H, 2 × NCH_2), 3.57 (t, *J* 6.0, 2H, NCH_2), 3.81 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.27 (s, 2H, NCH_2), 6.66–6.71 (m, 2H, ArH), 6.73 (dd, J_1 8.0, J_2 1.6, 1H, ArH), 6.84 (d, *J* 8.0, 1H, ArH). δ_c (100 MHz, $CDCl_3$) 155.8, 154.6, 148.9, 148.8, 140.3, 132.0, 125.7, 120.8, 118.4, 117.2, 111.7, 111.2, 105.1, 79.9, 56.1, 56.0, 53.4, 43.9, 28.4, 26.2, 24.1. ν_{max} (ATR)/cm^{-1} 2214 (C≡N), 1692 (C=O). *m/z* (GC-MS) 478 [M + 1]$^+$. Anal. Calc. for $C_{28}H_{35}N_3O_4$: C 70.42, H 7.39, N 8.80. Found: C 70.39, H 7.37, N 8.78 %.

tert-*Butyl-5-cyano-8-(4-methoxyphenyl)-6-(piperidin-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9i**)*

The title compound was obtained as a white solid (0.420 g, 94 % yield). Mp 168–170°C. δ_H (400 MHz, $CDCl_3$) 1.34 (br s, 9H, 3 × Me), 1.45–1.55 (m, 2H, CH_2), 1.63–1.75 (m, 4H, 2 × CH_2), 2.97 (t, *J* 6.0, 2H, CH_2), 3.05 (t, *J* 5.6, 4H, 2 × NCH_2), 3.57 (t, *J* 6.0, 2H, NCH_2), 3.76 (s, 3H, OMe), 4.26 (s, 2H, NCH_2), 6.65 (s, 1H, ArH), 6.87 (d, *J* 8.4, 2H, ArH), 7.11 (d, *J* 8.4, 2H, ArH). δ_c (100 MHz, $CDCl_3$) 159.4, 155.8, 154.6, 131.7, 129.6, 125.7, 118.5, 117.3, 114.0, 105.0, 79.9, 55.4, 53.4, 43.9, 28.4, 26.2, 24.1. ν_{max} (ATR)/cm^{-1} 2208 (C≡N), 1690 (C=O). *m/z* (GC-MS) 448 [M + 1]$^+$. Anal. Calc. for $C_{27}H_{33}N_3O_3$: C 72.46, H 7.43, N 9.39. Found: C 71.88, H 7.24, N 9.34 %.

tert-*Butyl-5-cyano-8-(4-methoxyphenyl)-6-(4-phenylpiperazin-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9j**)*

The title compound was obtained as a white solid (0.461 g, 88 % yield). Mp 148–150°C. δ_H (400 MHz, $CDCl_3$) 1.35 (br s, 9H, 3 × Me), 2.32 (s, 3H, OMe), 3.00 (t, *J* 5.6, 2H, CH_2), 3.24–3.33 (m, 8H, 4 × NCH_2), 3.58 (t, *J* 6.0, 2H, NCH_2), 4.27 (s, 2H, NCH_2), 6.71 (s, 1H, ArH), 6.80 (t, *J* 7.2, 1H, ArH), 6.89 (d, *J* 8.0, 2H, ArH), 7.08 (d, *J* 8.0, 2H, ArH), 7.14–7.24 (m, 4H, ArH). δ_c (100 MHz, $CDCl_3$) 154.6, 154.4, 151.2, 138.1, 136.2, 129.3, 129.2, 128.3, 126.6, 120.1, 118.4, 117.0, 116.4, 105.3, 80.0, 51.8, 49.5, 44.0, 28.4, 21.2. ν_{max} (ATR)/cm^{-1} 2211 (C≡N), 1689 (C=O). *m/z* (GC-MS) 525 [M + 1]$^+$. Anal. Calc. for $C_{32}H_{36}N_4O_3$: C 73.26, H 6.92, N 10.68. Found: C 73.21, H 6.90, N 10.80 %.

tert-*Butyl-5-cyano-6-(piperidin-1-yl)-8-(*p*-tolyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9k**)*

The title compound was obtained as a white solid (0.413 g, 96 % yield). Mp 148–150°C. δ_H (400 MHz, $CDCl_3$) 1.34 (br s, 9H, 3 × Me), 1.44–1.55 (m, 2H, CH_2), 1.64–1.75 (m, 4H, 2 × CH_2), 2.32 (s, 3H, Me), 2.98 (t, *J* 6.0, 2H, CH_2), 3.05 (t, *J* 5.6, 4H, 2 × NCH_2), 3.57 (t, *J* 6.0, 2H, NCH_2), 4.25 (s, 2H, NCH_2), 6.66 (s, 1H, ArH), 7.07 (d, *J* 8.0, 2H, ArH), 7.15 (d, *J* 7.6, 2H, ArH). δ_c (100 MHz, $CDCl_3$) 155.8, 154.6, 137.8, 136.5, 129.2, 128.3, 125.6, 118.4, 117.2, 105.1, 79.9, 53.4, 43.9, 28.4, 26.2, 24.1, 21.2. ν_{max} (ATR)/cm^{-1} 2216 (C≡N), 1686 (C=O). *m/z* (GC-MS) 432 [M + 1]$^+$. Anal. Calc. for $C_{27}H_{33}N_3O_2$: C 75.14, H 7.71, N 9.74. Found: C 75.10, H 7.69, N 9.62 %.

tert-*Butyl-5-cyano-6-(4-phenylpiperazin-1-yl)-8-(*p*-tolyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9l**)*

The title compound was obtained as a white solid (0.457 g, 0.90 mmol, 90 % yield). Mp 145–147°C. δ_H (400 MHz, $CDCl_3$) 1.34 (br s, 9H, 3 × Me), 2.32 (s, 3H, Me), 3.00 (t, *J* 6.0, 2H, CH_2), 3.25–3.31 (m, 8H, 4 × NCH_2), 3.58 (t, *J* 6.0, 2H, NCH_2), 4.27 (s, 2H, NCH_2), 6.71 (s, 1H, ArH), 6.80 (t, *J* 7.2, 1H, ArH), 6.89 (d, *J* 8.0, 2H, ArH), 7.08 (d, *J* 8.0, 2H, ArH), 7.14–7.24 (m, 4H, ArH). δ_c (100 MHz, $CDCl_3$) 154.6, 154.4, 151.2, 138.1, 136.2, 129.3, 129.2, 128.3, 126.6, 120.1, 118.4, 117.0, 116.4, 105.4, 80.0, 51.8, 49.5, 44.0, 28.4, 21.2. ν_{max} (ATR)/cm^{-1} 2220 (C≡N), 1691 (C=O). *m/z* (GC-MS) 509 [M + 1]$^+$. Anal. Calc. for $C_{32}H_{36}N_4O_2$: C 75.56, H 7.13, N 11.01. Found: C 75.13, H 6.82, N 10.88 %.

tert-*Butyl-5-cyano-8-(naphthalen-1-yl)-6-(piperidin-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9m**)*

The title compound was obtained as a white solid (0.396 g, 85 % yield). Mp 174–176°C. δ_H (400 MHz, $CDCl_3$)1.10–1.38 (m, 9H, 3 × Me), 1.45–1.54 (m, 2H, CH_2), 1.63–1.72 (m, 4H, 2 × CH_2),

2.36 (t, *J* 6.0, 1H, CH), 3.00–3.15 (m, 6H, 3 × NCH_2), 3.42–3.58 (m, 1H, CH), 3.64 (t, *J* 6.0, 1H, CH), 3.80–3.87 (m, 1H, CH), 6.73 (s, 1H, ArH), 7.21 (d, *J* 7.2, 1H, ArH), 7.27–7.37 (m, 2H, ArH), 7.36–7.49 (m, 2H, ArH), 7.82 (t, *J* 6.8, 2H, ArH). δ_c (100 MHz, $CDCl_3$) 155.8, 154.5, 154.4, 136.9, 133.6, 131.1, 128.5, 126.6, 126.5, 126.2, 126.1, 125.4, 125.2, 118.9, 117.2, 105.6, 79.9, 53.4, 43.7, 28.4, 28.3, 26.2, 24.0. ν_{max} (ATR)/cm^{-1} 2200 (C≡N), 1692 (C=O). *m/z* (GC-MS) 468 $[M + 1]^+$. Anal. Calc. for $C_{30}H_{33}N_3O_2$: C 77.06, H 7.11, N 8.99. Found: C 76.95, H 6.98, N 8.86 %.

tert-*Butyl-5-cyano-6-morpholino-8-(naphthalen-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9n**)*

The title compound was obtained as a white solid (0.375 g, 80 % yield). Mp 192–194°C. δ_H (400 MHz, $CDCl_3$) 1.10–1.60 (m, 9H, 3 × Me), 2.99–3.05 (m, 2H, CH_2), 3.06–3.20 (m, 4H, 2 × CH_2), 3.41–3.66 (m, 2H, NCH_2), 3.82 (t, *J* 4.8, 4H, 2 × NCH_2), 3.95–4.25 (m, 2H, NCH_2), 6.75 (s, 1H, ArH), 7.22 (d, *J* 6.8, 1H, ArH), 7.28 (d, *J* 8.4, 1H, ArH), 7.34 (t, *J* 8.0, 1H, ArH), 7.39–7.49 (m, 2H, ArH), 7.84 (d, *J* 7.2, 2H, ArH). δ_c (100 MHz, $CDCl_3$) 154.4, 133.6, 131.0, 128.7, 128.6, 127.8, 126.2, 126.1, 125.4, 125.0, 116.9, 79.9, 66.9, 52.1, 43.6, 28.3. ν_{max} (ATR)/cm^{-1} 2219 (C≡N), 1690 (C=O). *m/z* (GC-MS) 470 $[M + 1]^+$. Anal. Calc. for $C_{29}H_{31}N_3O_3$: C 74.18, H 6.65, N 8.95. Found: C 73.69, H 6.54, N 9.10 %.

tert-*Butyl-5-cyano-8-(naphthalen-2-yl)-6-(piperidin-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9o**)*

The title compound was obtained as a white solid (0.420 g, 90 % yield). Mp 132–134°C. δ_H (400 MHz, $CDCl_3$) 1.31 (br s, 9H, 3 × Me), 1.45–1.55 (m, 2H, CH_2), 1.64–1.75 (m, 4H, 2 × CH_2), 3.00 (t, *J* 6.0, 2H, CH_2), 3.07 (t, *J* 5.2, 4H, 2 × NCH_2), 3.58 (t, *J* 6.0, 2H, NCH_2), 4.28 (s, 2H, NCH_2), 6.75 (s, 1H, ArH), 7.29 (dd, J_1 8.4, J_2 1.6, 1H, ArH), 7.40–7.46 (m, 2H, ArH), 7.63 (s, 1H, ArH), 7.72–7.83 (m, 3H, ArH). δ_c (100 MHz, $CDCl_3$) 155.9, 154.5, 136.9, 133.2, 132.8, 128.3, 128.1, 127.8, 127.5, 126.6, 126.5, 126.3, 125.6, 118.6, 117.2, 105.4, 79.9, 53.4, 44.1, 28.4, 26.2, 24.1. ν_{max} (ATR)/cm^{-1} 2214 (C≡N), 1694 (C=O). *m/z* (GC-MS) 468 $[M + 1]^+$. Anal. Calc. for $C_{30}H_{33}N_3O_2$: C 77.06, H 7.11, N 8.99. Found: C 76.99, H 7.10, N 8.72 %.

tert-*Butyl-5-cyano-7-methyl-8-phenyl-6-(piperidin-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9p**)*

The title compound was obtained as a white solid (0.327 g, 76 % yield). Mp 142–144°C. δ_H 400 MHz, $CDCl_3$) 1.34 (m, 9H, 3Me), 1.62 (br s, 6H, 3 × CH_2), 1.85 (s, 3H, Me), 2.90–2.95 (m, 2H, CH_2), 3.01–3.25 (m, 4H, 2 × NCH_2), 3.55 (t, *J* 6.0, 2H, NCH_2), 3.97 (s, 2H, NCH_2), 6.99 (d, *J* 7.2, 2H, ArH), 7.26–7.32 (m, 1H, ArH), 7.36 (t, *J* 7.2, 2H, ArH). δ_c (100 MHz, $CDCl_3$) 153.4, 152.5, 137.6, 132.5, 128.0, 127.8, 127.0, 126.6, 116.7, 107.9, 78.8, 50.9, 43.8, 27.3, 25.8, 23.1, 14.8. ν_{max} (ATR)/cm^{-1} 2211 (C≡N), 1697 (C=O). *m/z* (GC-MS) 432 $[M + 1]^+$. Anal. Calc. for $C_{27}H_{33}N_3O_2$: C 75.14, H 7.71, N 9.74. Found: C 75.12, H 7.47, N 9.59 %.

tert-*Butyl-5-cyano-7-methyl-8-phenyl-6-(4-phenylpiperazin-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9q**)*

The title compound was obtained as a white solid (0.406 g, 80 % yield). Mp 156–158°C. δ_H (400 MHz, $CDCl_3$) 1.35 (br s, 9H, 3 × Me), 1.90 (s, 3H, Me), 2.92–2.96 (m, 2H, CH_2), 3.05–3.48 (m, 8H, 4 × NCH_2), 3.56 (t, *J* 6.0, 2H, NCH_2), 4.00 (s, 2H, NCH_2), 6.80 (t, *J* 7.2, 1H, ArH), 6.91 (d, *J* 8.0, 2H, ArH), 7.00 (d, *J* 6.8, 2H, ArH), 7.16–7.24 (m, 2H, ArH), 7.29–7.42 (m, 3H, ArH). δ_c (100 MHz, $CDCl_3$) 154.5, 151.9, 151.7, 129.8, 129.1, 128.0, 127.8, 120.0, 116.6, 109.8, 79.9, 50.6, 50.5, 28.4, 16.2. ν_{max} (ATR)/cm^{-1} 2217 (C≡N), 1694 cm^{-1} (C=O). *m/z* (GC-MS) 509 $[M + 1]^+$. Anal. Calc. for $C_{32}H_{36}N_4O_2$: C 75.56, H 7.13, N 11.01. Found: C 75.51, H 7.10, N 10.99 %.

tert-*Butyl-5-cyano-8-(4-methoxyphenyl)-7-methyl-6-(4-phenylpiperazin-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9r**)*

The title compound was obtained as a white solid (0.457 g, 85 % yield). Mp 158–160°C. δ_H (400 MHz, $CDCl_3$) 1.34 (br s, 9H, 3 × Me), 1.91 (s, 3H, Me), 2.91–2.95 (m, 2H, CH_2), 3.00–3.38 (m, 8H, 4 × NCH_2), 3.56 (t, *J* 6.0, 2H, NCH_2), 3.77 (s, 3H, OMe), 4.01 (s, 2H, NCH_2), 6.79 (t, *J* 7.6, 1H, ArH), 6.87–6.93 (m, 6H, ArH), 7.19 (t, *J* 7.6, 2H, ArH). δ_c (100 MHz, $CDCl_3$) 159.1, 154.5, 151.7, 134.1, 130.3, 129.2, 129.1, 120.0, 117.5, 116.6, 114.6, 109.7, 79.9, 55.3, 50.6, 50.5, 44.9, 28.4, 16.2. ν_{max} (ATR)/cm^{-1} 2211 (C≡N), 1690 (C=O). *m/z* (GC-MS) 539 $[M + 1]^+$. Anal. Calc. for $C_{33}H_{38}N_4O_3$: C 73.58, H 7.11, N 10.40. Found: C 72.49, H 6.83, N 10.25 %.

tert-*Butyl-5-cyano-6-(piperidin-1-yl)-8-(thiophen-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**9s**)*

The title compound was obtained as a white solid (0.372 g, 88 % yield). Mp 128–130°C. δ_H (400 MHz, $CDCl_3$) 1.37 (br s, 9H, 3 × Me), 1.47–1.56 (m, 2H, CH_2), 1.65–1.76 (m, 4H, 2 × CH_2), 2.98 (t, *J* 6.0, 2H, CH_2), 3.06 (t, *J* 5.2, 4H, 2 × NCH_2), 3.59 (t, *J* 6.0, 2H, NCH_2), 4.47 (s, 2H, NCH_2), 6.83 (s, 1H, ArH), 6.99–7.04 (m, 2H, ArH), 7.30–7.35 (m, 1H, ArH). δ_c (100 MHz, $CDCl_3$) 155.7, 154.6, 139.9, 127.5, 127.4, 126.6, 125.9, 119.2, 117.0, 105.8, 80.1, 53.3, 44.2, 28.4, 26.1, 24.0. ν_{max} (ATR)/cm^{-1} 2214 (C≡N), 1691 (C=O). *m/z* (GC-MS) 424 $[M + 1]^+$. Anal. Calc. for $C_{24}H_{29}N_3O_2S$: C 68.05, H 6.90, N 9.92, S 7.57. Found: C 68.02, H 6.64, N 9.80, S 7.55 %.

*General Procedure for the Synthesis of Tetrahydroisoquinolines **13a**,**e**,**f**,**n**,**o***[31]

A solution containing *N-tert*-butyloxycarbonyl-protected tetrahydroisoquinoline derivatives **9a**,**e**,**f**,**n**,**o** (0.32 mmol, 0.32 equiv.) in DCM (3 mL) was treated with TFA (0.2 mL) at room temperature for 1 h. The progress of the reaction was checked by TLC. Once the reaction was complete, the reaction mixture was extracted with DCM (3 × 10 mL) and further washed with a saturated brine solution (2 × 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude residue was purified by silica column chromatography with the use of EtOAc/hexane (5 : 45) as an eluent. Finally, the products isolated were characterized as tetrahydroisoquinolines **13a**,**e**,**f**,**n**,**o** by their spectroscopic analysis.

*8-Phenyl-6-(piperidin-1-yl)-1,2,3,4-tetrahydroisoquinoline-5-carbonitrile (**13a**)*

The title compound was obtained as a white solid (0.273 g, 86 % yield). Mp 219–221°C. δ_H (400 MHz, $CDCl_3$) 1.48–1.57 (m, 2H, CH_2), 1.66–1.74 (m, 4H, 2 × CH_2), 3.11 (t, *J* 5.2, 4H, 2 × NCH_2), 3.17 (t, *J* 5.6, 2H, CH_2), 3.27 (t, *J* 5.6, 2H, NCH_2), 3.88 (s, 2H, NCH_2), 6.70 (s, 1H, ArH), 7.11 (d, *J* 7.2, 2H, ArH), 7.33–7.38 (m, 3H, ArH), 9.87 (br s, 1H, NH). δ_c (100 MHz, $CDCl_3$) 156.8, 146.1, 138.3, 136.8, 128.9, 128.6, 128.2, 119.2, 118.5, 117.7, 116.6, 104.5, 53.0, 42.9, 40.4, 26.0, 24.9, 23.9. ν_{max}

(ATR)/cm^{-1} 2217 (C≡N), 3340 (NH). *m/z* (GC-MS) 318 $[M + 1]^+$. Anal. Calc. for $C_{21}H_{23}N_3$: C 79.46, H 7.30, N 13.24. Found: C 79.39, H 7.30, N 13.22 %.

*8-(4-Bromophenyl)-6-(piperidin-1-yl)-1,2,3,4-tetrahydroisoquinoline-5-carbonitrile (**13e**)*

The title compound was obtained as a white solid (0.372 g, 94 % yield). Mp 168–170°C. δ_H (400 MHz, $CDCl_3$) 1.45–1.55 (m, 2H, CH_2), 1.64–1.74 (m, 4H, $2CH_2$), 1.79 (br s, 1H, NH), 2.93 (t, *J* 6.0, 2H, CH_2), 3.01–3.11 (m, 6H, $3NCH_2$), 3.64 (s, 2H, NCH_2), 6.58 (s, 1H, ArH), 7.04 (d, *J* 8.4, 2H, ArH), 7.47 (d, *J* 8.4, 2H, ArH). δ_c (100 MHz, $CDCl_3$) 155.7, 144.1, 140.5, 138.8, 131.6, 130.2, 127.2, 122.1, 117.7, 117.1, 106.2, 53.4, 47.0, 43.2, 28.9, 26.2, 24.1. ν_{max} (ATR)/cm^{-1} 2222 (C≡N), 3338 (NH). *m/z* (GC-MS) 397 $[M + 1]^+$, 398 $[M + 2]^+$. Anal. Calc. for $C_{21}H_{22}BrN_3$: C 63.64, H 5.60, N 10.60. Found: C 63.20, H 5.42, N 10.46 %.

*8-(2,4-Dichlorophenyl)-6-(piperidin-1-yl)-1,2,3,4-tetrahydroisoquinoline-5-carbonitrile (**13f**)*

The title compound was obtained as a white solid (0.355 g, 92 % yield). Mp 170–172°C. δ_H (400 MHz, $CDCl_3$) 1.47–1.57 (m, 2H, CH_2), 1.64–1.75 (m, 4H, 2 × CH_2), 1.76–1.80 (m, 2H, CH_2), 3.04–3.12 (m, 6H, 3 × NCH_2), 3.64 (q, *J* 16.0, 2H, NCH_2), 6.57 (s, 1H, ArH), 7.04 (d, *J* 8.0, 1H, ArH), 7.26 (dd, J_1 8.4, J_2 2.0, 1H, ArH), 7.42 (ds, *J* 2.0, 1H, ArH), 8.55 (br s, 1H, NH). δ_c (100 MHz, $CDCl_3$) 156.3, 141.7, 138.3, 135.9, 135.2, 133.4, 131.1, 129.8, 127.7, 122.3, 118.4, 116.5, 105.8, 53.1, 43.2, 40.9, 26.2, 26.0, 24.0. ν_{max} (ATR)/cm^{-1} 2219 (C≡N), 3332 (NH). *m/z* (GC-MS) 387 $[M + 1]^+$, 388 $[M + 2]^+$. Anal. Calc. for $C_{21}H_{21}Cl_2N_3$: C 65.29, H 5.48, N 10.88. Found: C 65.16, H 5.00, N 10.84 %.

*6-Morpholino-8-(naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-5-carbonitrile (**13n**)*

The title compound was obtained as a white solid (0.324 g, 88 % yield). Mp 160–162°C. δ_H (400 MHz, $CDCl_3$) 3.03–3.20 (m, 8H, 4 × CH_2), 3.39 (d, *J* 16.4, 1H, CH), 3.55 (d, *J* 16.4, 1H, CH), 3.82 (t, *J* 4.8, 4H, 2 × NCH_2), 4.62 (br s, 1H, NH), 6.73 (s, 1H, ArH), 7.16–7.20 (m, 1H, ArH), 7.27 (d, *J* 8.4, 1H, ArH), 7.34 (t, *J* 8.0, 1H, ArH), 7.39–7.49 (m, 2H, ArH), 7.84 (dd, J_1 8.0, J_2 3.2, 2H, ArH). δ_c (100 MHz, $CDCl_3$) 154.6, 144.4, 139.4, 136.4, 133.6, 130.9, 128.7, 128.6, 126.9, 126.7, 126.3, 126.1, 125.4, 125.0, 118.7, 116.7, 105.9, 66.9, 51.9, 44.6, 41.8, 27.5. ν_{max} (ATR)/cm^{-1} 2220 (C≡N), 3336 (NH). *m/z* (GC-MS) 370 $[M + 1]^+$. Anal. Calc. for $C_{24}H_{23}N_3O$: C 78.02, H 6.27, N 11.37. Found: C 77.98, H 6.24, N 11.34 %.

*8-(Naphthalen-2-yl)-6-(piperidin-1-yl)-1,2,3,4-tetrahydroisoquinoline-5-carbonitrile (**13o**)*

The title compound was obtained as a white solid (0.330 g, 90 % yield). Mp 135–137°C. δ_H (400 MHz, $CDCl_3$) 1.47–1.56 (m, 2H, CH_2), 1.65–1.75 (m, 4H, 2 × CH_2), 3.01 (t, *J* 6.0, 2H, CH_2), 3.06–3.16 (m, 6H, 3 × NCH_2), 3.77 (s, 2H, NCH_2), 5.63 (br s, 1H, NH), 6.74 (s, 1H, ArH), 7.25 (dd, J_1 8.4, J_2 1.2, 1H, ArH), 7.42–7.50 (m, 2H, ArH), 7.61 (s, 1H, ArH), 7.74–7.85 (m, 3H, ArH). δ_c (100 MHz, $CDCl_3$) 156.1, 145.7, 138.9, 136.7, 133.1, 132.7, 128.3, 128.0, 127.8, 127.4, 126.8, 126.7, 126.2, 118.6, 117.0, 105.4, 53.3, 45.0, 41.7, 27.2, 26.1, 24.1. ν_{max} (ATR)/cm^{-1} 2218 (C≡N), 3337 (NH). *m/z* (GC-MS) 368 $[M + 1]^+$. Anal. Calc. for $C_{25}H_{25}N_3$: C 81.71, H 6.86, N 11.43. Found: C 81.72, H 6.43, N 10.99 %.

Supplementary Material

^{1}H and ^{13}C NMR spectroscopic data of all the synthesized products are available on the Journal's website.

Conflicts of Interest

The authors declare no conflicts of interest.

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