Novel, Versatile Three-Step Synthesis of 1,2,3,4,10,10a-Hexahydropyrazino[1,2-*a*]indoles by Intramolecular Carbene-Mediated C–H Insertion

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Abstract: A new convenient three-step synthesis of the privileged CNS scaffold 1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indoles has been developed. The method makes use of an intramolecular carbene-mediated C–H insertion in phenylpiperazine-derived tosylhydrazones made from 2-fluorobenzaldehydes. Notably, the piperazine can be replaced with other cyclic nitrogen bases and the methodology is successfully extended to pyrrolidine, piperidine, azepane, morpholine, and homopiperazine.

Key words: 1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indoles, C–H insertion, phenylpiperazine, carbene, cyclization

The classical archetype pharmacophoric motif of a compound acting in the central nervous system (CNS) is the combination of a phenyl group and an aliphatic amine, since 80% of currently marketed CNS drugs contain a phenyl group and 60% contain an amine.[1] The term 'privileged structure' was introduced in medicinal chemistry in the late 1980s by Evans and co-workers to define scaffolds, which were capable of providing useful ligands for diverse receptors, and clever modification of such structures could be a viable alternative for design of new receptor ligands.[2] In this context, the 1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indole (**1**) (Figure 1) makes up a rigid template, which is ideally placed within the CNS drugability space.[1b,c]

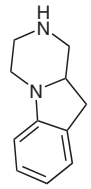

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Figure 1 The structure of 1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indole (**1**)

The hexahydropyrazinoindole can also be considered a privileged scaffold derived from two other privileged scaffolds, namely the arylpiperazine and the indole by formal ring-closure and hydrogenation.[3] Thus, in this context, the hexahydropyrazinoindoles could be considered as tricyclic indoline-based phenylpiperazine derivatives. Indeed, hexahydropyrazinoindole fulfills the definition of a privileged scaffold since its derivatives have been proven to provide ligands for several diverse targets like, for example, 5-HT_{2C} receptor agonists,[4] nicotinic receptor ligands,[5] antiviral agents,[6] serotonin ligands,[7] fibrinogen receptor antagonists,[8] and Gly-T-1 inhibitors for treating neurological and neuropsychiatric disorders.[9]

The currently published methods for the syntheses of 1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indole are relatively long and tedious using between 6–10 chemical steps starting from indoles or indole-2-carboxylic esters.[4a,b] During our exploration of the thermal carbene-mediated C–H insertion,[10] it became evident that tricyclic phenylpiperazine derivatives could be synthesized in three steps from readily available starting materials. Due to the larger number of commercially available substrates, this protocol represents a more general approach than what has previously been described. In this paper, we wish to describe a short and convenient three-step synthesis of hexahydropyrazinoindoles **5** (Scheme 1).

The Boc-protected 2-piperazinobenzaldehydes with substituents in the phenyl ring of **3a**–**j** were readily synthesized from the corresponding commercially available 2-fluorobenzaldehydes **2a**–**j** (Scheme 1). In our hands, DMSO became the solvent of choice for the preparation of the piperazinobenzaldehydes **3a**–**i**. Even though short reaction times for the S_NAr have been reported in the literature, it was not possible to reproduce the literature conditions.[11–13] Mostly, the use of DMF has been reported as the preferred solvent for the nucleophilic substitution, but DMSO was reported as an alternative[12,14] and became our preferred solvent, since 2-*N*,*N*-dimethylaminobenzaldehyde was formed as a side product, when DMF was used as solvent. One limitation to the S_NAr reaction was found with the 3-substituted 2-fluorobenzaldehydes, which were poor substrates for the S_NAr possibly due to steric hindrance, and only the 3-chloro analogue was successfully synthesized, albeit in low yields.[12] As expected, another limitation to this S_NAr was the presence of electron-donating groups (EDGs) *para* to the fluorine leaving group. Weak electron donors, such as a methyl group, had a significant effect on the yields, and stronger electron-donating groups such as a methoxy group significantly inhibited the S_NAr reaction in agreement with literature

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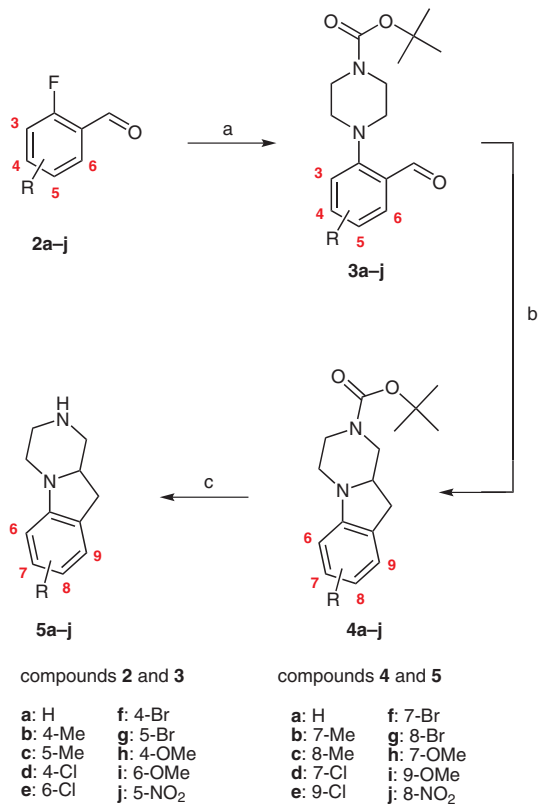
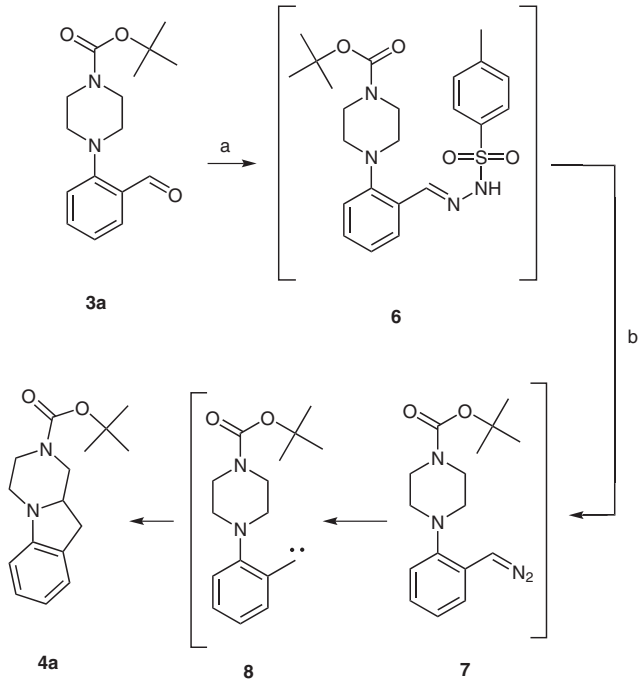


Scheme 1 Synthesis of hexahydropyrazinoindoles **5**. *Reagents and conditions*: (a) Boc-piperazine, K_2CO_3, DMSO, 95 °C, 4 d; (b) 1. *p*-$TsNHNH_2$, toluene, microwave irradiation, 135 °C, 12 min, 2. NaH (60%), toluene, microwave irradiation, 135 °C, 12 min; (c) Et_2O, MeOH, 2 M HCl in Et_2O, r.t., 18 h.

reports.[12] The piperazinobenzaldehydes **3a–j** were used as substrates for the key step, the carbene-mediated intramolecular C–H insertion forming the Boc-protected tricyclic phenylpiperazines **4a–j** (Table 1). The details of the reaction are described in Scheme 2.



Scheme 2 The intermediates of the carbene-mediated C–H insertion. *Reagents and conditions*: (a) *p*-$TsNHNH_2$, toluene, microwave irradiation, 135 °C, 12 min; (b) NaH (60%), toluene, microwave irradiation, 135 °C, 12 min.

Table 1 Compounds **3–5** Prepared

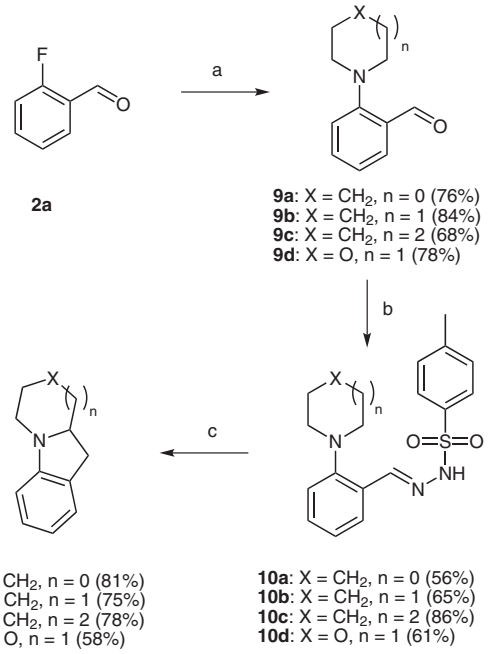
Entry	R	Yield (%) of **3**	R	Yield (%) of **4**	Yield (%) of **5**
a	H	48	H	58	90
b	4-Me	40	7-Me	58	93
c	5-Me	39	8-Me	62	77
d	4-Cl	76	7-Cl	67	97
e	6-Cl	67	9-Cl	35	91
f	4-Br	56	7-Br	45	80
g	5-Br	35	8-Br	65	84
h	4-OMe	76	7-OMe	61	91
i	6-OMe	87	9-OMe	52	89
j	5-NO_2	80	8-NO_2	52	94

The insertion of a carbene into a carbon–hydrogen bond has attracted considerable interest because of its potential in forming carbon–carbon bonds.[15,16] Carbenes being neutral electrophilic species with only six valence electrons, exist either as a free carbene or bound to a transition state metal as a metallocarbenoid. The highly reactive carbenes are generated in situ from a precursor, most often a diazo compound.[17] The synthetic protocols for preparation of diazo compounds are numerous, but a common procedure involves conversion of a ketone or an aldehyde into the corresponding tosylhydrazone, followed by deprotonation and thermal elimination of the sulfinate to yield the diazo compound.[17,18] The hydrazone **6** was easily formed in high yield. On small scale, the hydrazones were conveniently synthesized under microwave conditions. When conversion of larger portions of substrate is required, sonication is an effective and mild synthetic alternative. This latter approach does not have the volume restrictions of the standard laboratory microwave reactors and is compatible with more heat sensitive functional groups. The downside of the sonication method is the longer reaction times.

Thorough drying was conducted to avoid side reactions after in situ generation of the diazo compound and carbene. Removal of water could be conducted either by treatment of the reaction mixture with $MgSO_4$ (in the cases with homogeneous reaction mixtures) or simply by azeotropic evaporation in a rotavapor. The crude hydrazone could normally be used without further purification.

The reaction sequence in Scheme 2 is conveniently performed in one-pot with thermal in situ generation of the characteristic red-orange solution of the diazo compound **7** at 135 °C and sustained heating promoted the thermal generation of the carbene **8**, which immediately perform the intramolecular C–H insertion. Conversion of the hydrazone to form the intermediate diazo compounds **7** could be accomplished using various bases, for example, potassium *tert*-butoxide or sodium hydroxide under phase-transfer conditions. Whereas no significant differences in yield were detected, the use of sodium hydride appeared to produce fewer by-products and was for this reason selected as the preferred base for the deprotonation. After the addition of sodium hydride to a solution of the hydrazone, the reaction mixture was purged with argon until the hydrogen formation had ceased, and the reaction mixture was subjected to heating using microwave irradiation for the C–H insertion to reach completion. A limitation to this carbene-mediated C–H insertion was observed, when a strong electron-withdrawing group was situated *para* to the benzylic carbene center. Thus, with a nitro group placed in this position, the carbene was not able to react in a C–H insertion reaction, and only unidentified side products were formed. The Boc-protection group could be removed in high yield by standard procedures such as treatment with anhydrous hydrochloric acid in a mixture of methanol–diethyl ether, and the hexahydropyrazinoindoles were isolated as the hydrochloride salts.

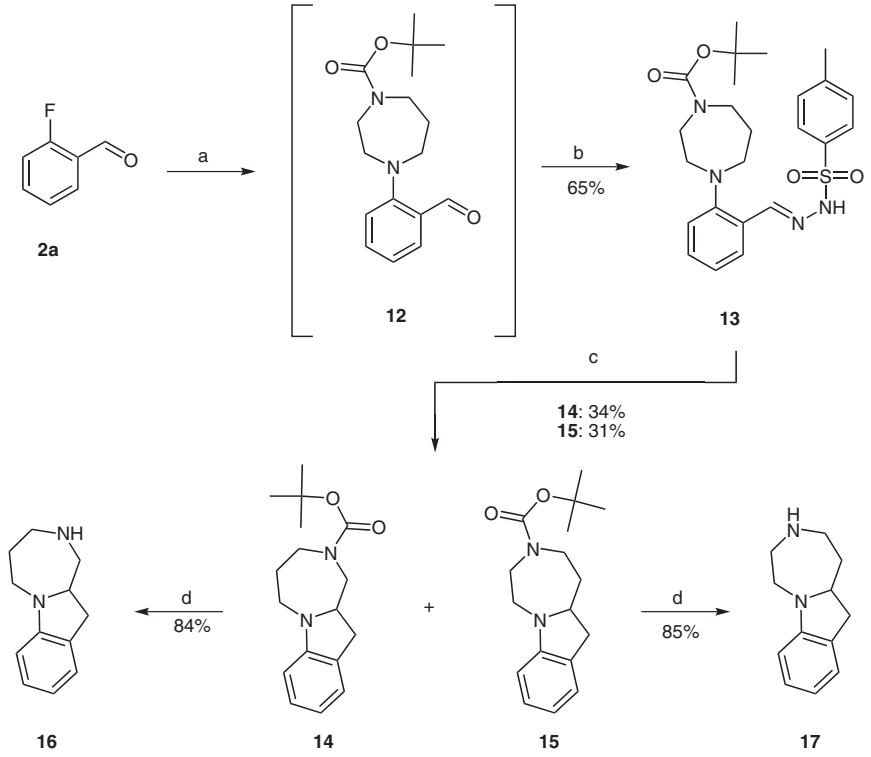
Notably, the piperazine moiety can be replaced with other cyclic nitrogen bases and the scope of the methodology was successfully extended to pyrrolidine, piperidine, azepane, morpholine, and homopiperazine. All steps in the reaction sequence, that is, the S_NAr reactions, hydrazone formations, diazo generations, and cyclization reactions gave comparable high yields leading to the products shown in Scheme 3, namely 2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (**11a**),[19] 6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indole (**11b**),[20] 7,8,9,10,10a,11-hexahydro-6*H*-azepino[1,2-*a*]indole (**11c**), 3,4,10,10a-tetrahydro-1*H*-[1,4]oxazino[4,3-*a*]indole (**11d**).



Scheme 3 Formation of products **11a–d**. *Reagents and conditions*: (a) cyclic amine, K_2CO_3, DMSO, 95 °C, 4 d; (b) *p*-TsNHNH$_2$, toluene, microwave irradiation, 135 °C, 10 min; (c) NaH (60%), toluene, microwave irradiation, 135 °C, 12 min.

The carbene-mediated C–H insertion into homopiperazine **13** (Scheme 4) proceeded without complications and in good yield. The methodology was completely analogous to the previously identified protocols described in Schemes 1 and 3. The main issues in this case were whether regioselectivity could be achieved and the two isomers could be separated. NMR studies showed no significant regioselectivity, which was probably the result of both insertion kinetics and the temperature at which the reaction was performed. However, the separation of the two Boc-protected compounds was remarkably straightforward and could be achieved by reverse phase column chromatography. A surprisingly large difference in the R_f value of the two regioisomers **14** and **15** may be due to different molecular conformations and consequently a differentiated interaction with solid phase during chromatography under the given conditions.

Simple thermally generated carbenes without significant stabilization such as methylene, dichlorocarbene, and the

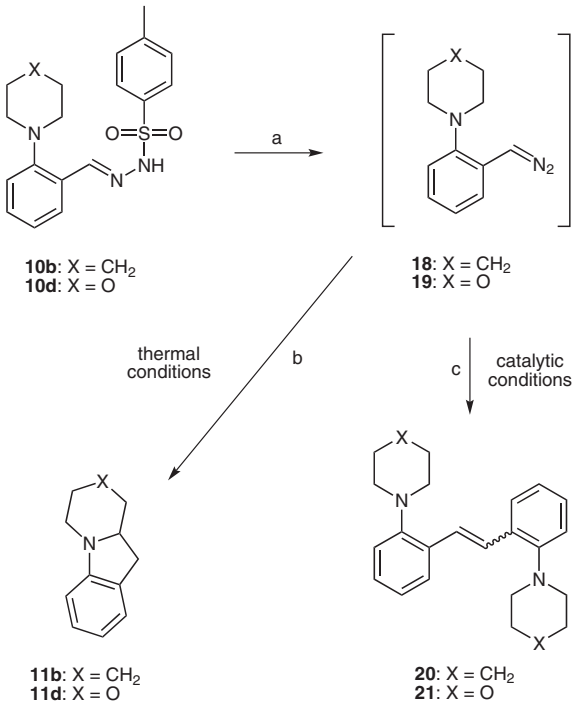


Scheme 4 Carbene-mediated C–H insertion into homopiperazine **13**. *Reagents and conditions*: (a) Boc-piperazine, K_2CO_3, DMSO, 95 °C, 4 d; (b) *p*-$TsNHNH_2$, toluene, microwave irradiation, 135 °C, 10 min; (c) NaH (60%), toluene, microwave irradiation, 135 °C, 12 min; (d) 2 M HCl in Et_2O, Et_2O, MeOH, r.t., 18 h.

benzylcarbenes are normally not considered regioselective towards insertion.[15–17] However, in this paper, we have confirmed that C–H insertion reactions using thermally generated carbenes have potential for synthetically meaningful transformations, when applied to intramolecular cyclization reactions forming five-membered rings.

When the carbene is stabilized as a metallocarbenoid, the selectivity of C–H insertions has been reported to increase.[15,16] During the last thirty years, the reactivity of carbenes has been successfully modified while still maintaining their reactivity toward C–H insertion by application of transition metal carbenes, such as rhodium.[15,16] Dirhodium catalysts were found to be especially effective and the first such reaction involving dirhodium tetraacetate was reported in 1981 by Teyssié.[21]

We were therefore interested in investigating whether our cyclization methodology could be modified to use a metal carbene, especially with the aim of being able to obtain some stereoselectivity in the cyclization reaction. As a model substrate for investigation and optimization of the catalytic C–H insertion, the piperidine derivative **18** and morpholine derivative **19** (Scheme 5) were chosen. The reason for choosing these two derivatives was to investigate whether a second hetero atom had any influence on the C–H insertion potential due to its inductively destabilizing effect of the C–H insertion transition state, which is observed when intermolecular C–H insertion into morpholine is attempted.



Scheme 5 Formation of dimeric products in the attempted catalytic C–H insertion reaction. *Reagents and conditions*: (a) $BnNEt_3Cl$, NaOH (14%), toluene–CH_2Cl_2, 70 °C, 3 h; (b) microwave irradiation, 135 °C, 10 min; (c) $Rh_2(OAc)_4$, toluene, –78 °C.

In situ generation and in situ purification of the diazo intermediates **18** and **19** were achieved under highly basic phase-transfer conditions[22]followed by phase separation and drying/dehydration of the organic phase using sodium sulfate. The standard method for generating the transient metal carbenes is by metal-induced extrusion of nitrogen from diazo compounds.[15]To our surprise, all catalytic conditions tested resulted in the formation of the dimers **20** and **21** as the main products (*E*/*Z* ratio 4:1) and, notably, no C–H insertion was observed. Dimer formation is a very common side reaction (Scheme 5) when applying carbene chemistry,[23] but the dimer being the main, or in most cases the sole, product was unexpected.

In conclusion, the synthesis of a series of novel, tricyclic indoline based phenyl piperazines was successfully accomplished. The synthesis utilized a versatile carbene mediated intramolecular C–H insertion α to nitrogen and turned out to be a fast and robust reaction. The methodology offers a simple and more general approach to the synthesis of tricyclic derivatives of compound **1** due to the commercial availability of substrates. However, the limitations of the S_NAr reaction and carbene–mediated C–H insertion in addition to absence of stereoselectivity make this novel method complementary to the existing methods.

Microwave-assisted reactions were performed using the following instruments: Emrys Optimizer (300 W), Emrys Synthesizer (300 W), Biotage Initiater (400 W), and Biotage Advancer (300 W). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AV-500 operating at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. The solvents applied were $CDCl_3$ or DMSO-d_6. TMS was used as internal reference in $CDCl_3$ or DMSO-d_6. Multiplicities of ^{1}H NMR signals are given as follows: s, singlet; br s, broad singlet; s(m), multiplet that appears as a singlet; d, doublet; br d, broad doublet; t, triplet; q, quartet; quint, quintet; v br = very broad. High-resolution mass spectrometry (HRMS) analyses were performed on an Agilent/Bruker Daltonics LC-SPE-MS spectrometer. Elemental analyses were performed on a Flash EA1112 from Thermo Fischer Scientific. Chromatography was either performed manually on silica gel columns (Kieselgel 40, 0.040–0.063 mm) or by using the following instruments: FlashMasterII from JonesChromatography with prepacked IST columns, ISCO Companion 4X or ISCO CompanionXL. Preparative LC-MS was performed on a Sciex API150ex from Applied Biosystems. Analytical LC-MS were performed on either a Sciex API150ex or a API300 from Applied Biosystems. Reactions and product mixtures were analyzed by TLC on silica gel precoated Merck 60 F_{254} 0.25 mm silica gel plates and visualized under UV light.

Substituted 2-Piperazinobenzaldehydes 3a–j, 9a–d, and 12; General Procedure

Aldehyde **2a–i** (2 g, 1 equiv), *tert*-butyl piperazine-1-carboxylate (1.2 equiv), and K_2CO_3 (1.3 equiv) were suspended in DMSO (12 mL). The mixture was heated to 95 °C in a sealed vessel for 4 d. The mixture was poured into a separatory funnel containing EtOAc (100 mL) and Et_2O (100 mL) and the organic phase was washed with phosphate buffer pH 7 (2 × 100 mL), brine–H_2O (1:1, 2 × 100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (heptane–EtOAc) (Tables 1 and 2).

Boc-Protected 1,2,3,4,10,10a-Hexahydropyrazino[1,2-*a*]indoles 4a–j; General Procedure

To a solution of 2-piperazinebenzaldehyde **3a–i** (1 g, 1 equiv) in toluene (10 mL) was added tosylhydrazide (1.05 equiv). The mixture was sonicated at r.t. for 3 h. In the cases where the mixtures were homogeneous, they were dried ($MgSO_4$) and filtered after 10 min into a 20 mL microwave vial. In the cases where the mixtures were heterogeneous, the H_2O was removed by azeotropic evaporation with toluene. In both cases toluene was added until a total volume of 20 mL, followed by the addition of NaH (1.08 equiv) (vigorous bubbling) and the mixture was purged with argon for 20 min (until bubbling ceased). The vial was sealed and heated using microwave irradiation at 135 °C for 10 min. EtOAc (100 mL) was added to the mixture and washed with sat. aq $NaHCO_3$ (75 mL), brine (75 mL), dried ($MgSO_4$), and concentrated in vacuo. the residue was purified by flash chromatography (heptane–EtOAc) (Tables 1 and 3).

1,2,3,4,10,10a-Hexahydropyrazino[1,2-*a*]indoles 5a–j; General Procedure

To the protected tricycle **4a–j** (500 mg, 1 equiv) in MeOH (2.5 mL) were added Et_2O (5 mL) and 2 M HCl in Et_2O (5 mL) [if the reagent formed a thick gum, an additional amount of MeOH (2.5 mL) was added]. The mixture was stirred at r.t. for 2 d and then concentrated in vacuo.

Isolation of the HCl Salt: The solid was suspended/dissolved in a very small amount of MeOH and then triturated with Et_2O. The suspension was filtered, the solid washed with a small amount of Et_2O, and dried in a vacuum oven.

Isolation of the Free Base: The solid was dissolved in aq 1 M HCl (75 mL) and washed with Et_2O (2 × 75 mL). The aqueous phase was basified with concd NaOH and extracted with CH_2Cl_2 (2 × 75 mL). The combined organic phases were washed with brine (75 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo (Tables 1 and 4).

Hydrazones 10a–d and 13; General Procedure

To a solution of the 2-amino-substituted benzaldehyde **9a–d** or **12** (1 g, 1 equiv) in toluene (10 mL) was added tosyl hydrazide (1.05 equiv). The mixture was sonicated at r.t. for 3 h or heated using microwave irradiation at 135 °C for 10 min. In the case of a clear solution, the mixture was filtered and concentrated in vacuo, however, if the mixture had turned into a mash it was transferred into a separatory funnel containing EtOAc (100 mL) and sat. aq $NaHCO_3$ (75 mL). The organic phase was washed with brine (75 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The solid obtained was crystallized by dissolving in EtOAc–MeOH and diluting with heptane (Table 5).

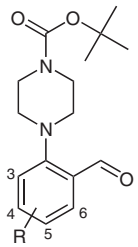
C–H Insertion with Hydrazones 10a–d and 13 as Substrates; Formation of 11a–d, 14, and 15; General Procedure

The hydrazone **10a–d** or **13** (500 mg, 1 equiv) was dissolved in toluene (20 mL) and NaH (1.08 equiv) was added carefully to the solution (vigorous bubbling). The mixture was purged with argon for 20 min until H_2 formation had ceased. The vial was sealed and heated using microwave irradiation at 135 °C for 10 min. To the mixture was added EtOAc (75 mL) and the organic layer was washed with sat. aq $NaHCO_3$ (75 mL), brine (75 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (heptane–EtOAc) (Table 5).

Carbene-Mediated Dimerization of the Hydrazones 10b,d; General Procedure

To a solution of hydrazone **10b**,**d** (500 mg, 1 equiv) in toluene (20 mL) and CH_2Cl_2 (5 mL) were added $BnNEt_3Cl$ (5 mol%) and aq NaOH (14%, 20 mL). The mixture was heated to 70 °C for 3 h. The organic phase was separated, dried (Na_2SO_4), and filtered. The organic phase was slowly added (3 h) to a suspension of $Rh_2(OAc)_4$

Table 2 Spectral Data of Compounds **3**

Entry	Product (R)	^{1}H NMR (500 MHz, $CDCl_3$): δ, *J* (Hz)	^{13}C NMR (125 MHz, $CDCl_3$): δ, *J* (Hz)	HRMS: *m*/*z* (M + H$^+$)	LC-MS	TLC
						
3a	H	1.49 (9 H, s), 3.04 (4 H, br s), 3.63 (4 H, m), 7.11 (1 H, d, *J* = 8), 7.16 (1 H, t, *J* = 8), 7.54 (1 H, dt, *J* = 8, 1.5), 7.83 (1 H, dd, *J* = 8, 1.5), 10.35 (1 H, s)	–	–	UV = 98.6% (t_R = 1.55 min), ELS = 100% (t_R = 1.60 min), *m*/*z* = 291.2	R_f = 0.27 heptane–EtOAc (3:2)
3b	4-Me	1.49 (9 H, s), 2.39 (3 H, s), 3.02 (4 H, m), 3.63 (4 H, m), 6.89 (1 H, s), 6.96 (1 H, d, *J* = 8), 7.72 (1 H, d, *J* = 8), 10.27 (1 H, s)	22.1, 28.4, 43.2 (br), 44.2 (br), 53.6, 79.9, 119.6, 123.9, 126.3, 130.5, 146.2, 154.6, 155.3, 190.5	$C_{17}H_{25}N_2O_3$ calcd: 305.1860; found: 305.1866	UV = 99.3% (t_R = 1.55 min), ELS = 100% (t_R = 1.60 min), *m*/*z* = 305.2	R_f = 0.21 heptane–EtOAc (4:1)
3c	5-Me	1.50 (9 H, s), 2.35 (3 H, s), 3.00 (4 H, m), 3.63 (4 H, m), 7.03 (1 H, d, *J* = 8), 7.36 (1 H, dd, *J* = 9, 1.5), 7.64 (1 H, d, *J* = 1.5), 10.37 (1 H, s)	20.5, 28.4, 43.3 (br), 44.2 (br), 53.9, 79.9, 119.3, 128.7, 130.0, 132.8, 135.8, 153.3, 154.7, 191.3	$C_{17}H_{25}N_2O_3$ calcd: 305.1860; found: 305.1869	UV = 100% (t_R = 1.57 min), ELS = 100% (t_R = 1.62 min), *m*/*z* = 305.3	R_f = 0.23 heptane–EtOAc (4:1)
3d	4-Cl	1.49 (9 H, s), 3.04 (4 H, m), 3.63 (4 H, m), 7.07 (1 H, d, *J* = 1.5), 7.12 (1 H, dd, *J* = 8, 1.5), 7.75 (1 H, d, *J* = 9), 10.24 (1 H, s)	28.3, 43.0 (br), 44.0 (br), 53.5, 80.0, 119.5, 123.1, 126.9, 131.7, 141.1, 154.5, 155.8, 189.5	$C_{16}H_{22}ClN_2O_3$ calcd: 325.1313; found: 325.1319	UV = 99.8% (t_R = 1.65 min), ELS = 100% (t_R = 1.70 min), *m*/*z* = 325.5	R_f = 0.24 heptane–EtOAc (4:1)
3e	6-Cl	1.49 (9 H, s), 3.02 (4 H, m), 3.63 (4 H, m), 7.00 (1 H, d, *J* = 9), 7.12 (1 H, d, *J* = 8), 7.40 (1 H, t, *J* = 8), 10.38 (1 H, s)	28.2, 43.0 (br), 44.1 (br), 53.1 (br), 79.7, 117.7, 124.5, 125.7, 134.1, 137.0, 154.5, 155.4, 189.0	$C_{16}H_{22}ClN_2O_3$ calcd: 325.1313; found: 325.1321	UV = 99.1% (t_R = 1.58 min), ELS = 100% (t_R = 1.64 min), *m*/*z* = 325.4	R_f = 0.19 heptane–EtOAc (4:1)
3f	4-Br	1.49 (9 H, s), 3.01 (4 H, m), 3.63 (4 H, m), 7.00 (1 H, d, *J* = 9), 7.62 (1 H, dd, *J* = 9, 2.5), 7.92 (1 H, d, *J* = 2.5), 10.26 (1 H, s)	28.8, 43.4 (br), 44.5 (br), 54.1 (br), 80.4, 116.5, 121.6, 130.4, 132.8, 137.9, 154.5, 154.9, 189.7	$C_{16}H_{22}BrN_2O_3$ calcd: 369.0808; found: 369.0822	UV = 100% (t_R = 1.72 min), ELS = 100% (t_R = 1.77 min), *m*/*z* = 369.2	R_f = 0.33 heptane–EtOAc (5:2)
3g	5-Br	1.49 (9 H, s), 3.04 (4 H, m), 3.63 (4 H, m), 7.23 (1 H, d, *J* = 2), 7.29 (1 H, dd, *J* = 9, 2), 7.67 (1 H, d, *J* = 9), 10.24 (1 H, s)	28.8, 43.5 (br), 44.4 (br), 54.0, 80.5, 123.0, 126.6, 127.7, 130.4, 132.2, 155.0, 156.2, 190.2	$C_{16}H_{22}BrN_2O_3$ calcd: 369.0815; found: 369.0821	UV = 100% (t_R = 1.70 min), ELS = 100% (t_R = 1.75 min), *m*/*z* = 371.1	R_f = 0.36 heptane–EtOAc (5:2)
3h	4-OMe	1.47 (9 H, s), 3.01 (4 H, m), 3.61 (4 H, m), 3.84 (3 H, s), 6.51 (1 H, d, *J* = 2), 6.64 (1 H, dd, *J* = 9, 2), 7.78 (1 H, d, *J* = 9), 10.13 (1 H, s)	28.5, 43.3 (br), 44.3 (br), 53.6, 55.6, 80.1, 105.0, 108.1, 122.5, 133.4, 154.8, 157.3, 165.3, 189.5	$C_{17}H_{25}N_2O_4$ calcd: 321.1809; found: 321.1804	UV = 100% (t_R = 1.44 min), ELS = 100% (t_R = 1.49 min), *m*/*z* = 321.2	R_f = 0.42 heptane–EtOAc (1:1)
3i	6-OMe	1.46 (9 H, s), 3.00 (4 H, m), 3.61 (4 H, m), 3.88 (3 H, s), 6.62 (2 H, d, *J* = 8), 7.42 (1 H, t, *J* = 8), 10.36 (1 H, s)	28.5, 43.4 (br), 44.4 (br), 53.2 (br), 56.1, 79.9, 105.1, 111.1, 117.5, 135.6, 154.9, 155.4, 162.9, 189.1	$C_{17}H_{25}N_2O_4$ calcd: 321.1809; found: 321.1809	UV = 97.7% (t_R = 1.33 min), ELS = 100% (t_R = 1.38 min), *m*/*z* = 321.2	R_f = 0.37 heptane–EtOAc (1:1)
3j	5-NO_2	1.47 (9 H, s), 3.25 (4 H, m), 3.66 (4 H, m), 7.08 (1 H, d, *J* = 9), 8.29 (1 H, dd, *J* = 9, 2), 8.60 (1 H, d, *J* = 2), 10.09 (1 H, s)	28.5, 43.0 (br), 43.9 (br), 52.9, 80.6, 118.6, 126.4, 128.9, 129.5, 141.4, 154.6, 157.9, 188.3	$C_{16}H_{22}N_3O_5$ calcd: 336.1554; found: 336.1545	UV = 98.3% (t_R = 1.41 min), ELS = 100% (t_R = 1.47 min), *m*/*z* = 335.2	R_f = 0.40 heptane–EtOAc (1:1)

(2 mol%) in toluene (10 mL) at –78 °C under N_2 using a syringe pump. After stirring for 30 min at –78 °C, the mixture was allowed to warm up to r.t. and filtered through a small plug of Celite and concentrated in vacuo. The residue was purified by flash chromatography (heptane–EtOAc) (Table 5).

Table 3 Spectral Data of Compounds **4**

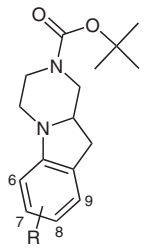
Entry	Product (R)	^{1}H NMR (500 MHz, $CDCl_3$): δ, *J* (Hz)	^{13}C NMR (125 MHz, $CDCl_3$): δ	HRMS: *m*/*z* (M + H^+)	LC-MS	TLC
						
4a	H	1.48 (9 H, s), 2.58 (1 H, dd, *J* = 15, 9), 2.74–3.05 (4 H, m), 3.38 (1 H, m), 3.52 (1 H, br d, *J* = 11), 3.95–4.33 (2 H, m), 6.46 (1 H, d, *J* = 8), 6.68 (1 H, t, *J* = 7), 7.05–7.12 (2 H, m)	28.5, 32.4, 42.1 (br), 43.2 (br), 44.1, 47.2 (br), 48.2 (br), 62.6, 80.0, 106.3, 118.3, 124.9, 127.5, 128.8, 150.5, 154.8	$C_{16}H_{23}N_2O_2$ calcd: 275.1754; found: 275.1763	UV = 100% (t_R = 1.53 min), ELS = 100% (t_R = 1.58 min), *m*/*z* = 274.5	R_f = 0.32 heptane–EtOAc (3:1)
4b	7-Me	1.48 (9 H, s), 2.28 (3 H, s), 2.53 (1 H, dd, *J* = 15, 9), 2.70–3.09 (3 H, v br m), 2.93 (1 H, dd, *J* = 15, 8), 3.36 (1 H, m), 3.50 (1 H, m), 3.95–4.35 (2 H, v br m), 6.29 (1 H, s), 6.50 (1 H, d, *J* = 7), 6.97 (1 H, d, *J* = 7)	21.8, 28.5, 32.1, 42.1 (br), 43.2 (br), 44.2, 47.2 (br), 48.2 (br), 62.8, 80.0, 107.4, 118.9, 124.6, 126.0, 137.4, 150.7, 154.9	$C_{17}H_{25}N_2O_2$ calcd: 289.1911; found: 289.1905	UV = 95.2% (t_R = 1.70 min), ELS = 100% (t_R = 1.76 min), *m*/*z* = 289.3	R_f = 0.36 heptane–EtOAc (3:1)
4c	8-Me	1.48 (9 H, s), 2.24 (3 H, s), 2.55 (1 H, dd, *J* = 15, 9), 2.70–3.09 (3 H, m), 2.93 (1 H, dd, *J* = 15, 8), 3.32 (1 H, m), 3.49 (1 H, m), 3.95–4.30 (2 H, m), 6.38 (1 H, d, *J* = 8), 6.88 (1 H, d, *J* = 8), 6.93 (1 H, s)	20.9, 28.5, 32.5, 42.0 (br), 43.1 (br), 44.5, 47.0 (br), 48.1 (br), 63.0, 80.0, 106.3, 125.9, 127.6, 129.2, 148.4, 154.9	$C_{17}H_{25}N_2O_2$ calcd: 289.1911; found: 289.1900	UV = 97.7% (t_R = 1.64 min), ELS = 100% (t_R = 1.70 min), *m*/*z* = 289.2	R_f = 0.36 heptane–EtOAc (3:1)
4d	7-Cl	1.48 (9 H, s), 2.53 (1 H, dd, *J* = 15, 9), 2.66–3.06 (3 H, v br m), 2.95 (1 H, dd, *J* = 15, 8), 3.46 (2 H, m), 3.95–4.35 (2 H, v br m), 6.40 [1 H, s(m)], 6.62 (1 H, dd, *J* = 8, 1), 6.96 (1 H, d, *J* = 8)	28.5, 31.9, 42.0 (br), 43.1 (br), 43.9, 47.1 (br), 48.1 (br), 62.7, 80.2, 106.7, 117.7, 125.5, 127.3, 133.3, 151.7, 154.8	$C_{16}H_{22}ClN_2O_2$ calcd: 309.1364; found: 309.1351	UV = 99.4% (t_R = 1.78 min), ELS = 100% (t_R = 1.84 min), *m*/*z* = 308.3	R_f = 0.34 heptane–EtOAc (3:1)
4e	9-Cl	1.48 (9 H, s), 2.60 (1 H, dd, *J* = 16, 9), 2.68–3.03 (3 H, v br m), 3.07 (1 H, dd, *J* = 16, 8), 3.48 (2 H, m), 3.95–4.35 (2 H, m), 6.31 (1 H, d, *J* = 8), 6.64 (1 H, d, *J* = 8), 7.00 (1 H, t, *J* = 8)	28.4, 31.6, 41.9 (br), 43.1 (br), 44.0, 47.1 (br), 48.1 (br), 61.7, 80.1, 104.3, 118.1, 126.8, 129.0, 130.9, 151.7, 154.7	$C_{16}H_{22}ClN_2O_2$ calcd: 309.1364; found: 309.1353	UV = 97.8% (t_R = 1.80 min), ELS = 100% (t_R = 1.86 min), *m*/*z* = 308.5	R_f = 0.34 heptane–EtOAc (3:1)
4f	7-Br	1.48 (9 H, s), 2.57 (1 H, dd, *J* = 11, 4), 2,65–3.04 (3 H, v br m), 2.97 (1 H, dd, *J* = 11, 3), 3.36–3.52 (2 H, m), 3.95–4.35 (2 H, v br m), 6.31 (1 H, d, *J* = 9), 7.16 (2 H, m)	28.8, 32.6, 42.2 (br), 43.4 (br), 44.5, 47.3 (br), 48.3 (br), 62.9, 80.5, 107.9, 110.1, 128.3, 130.5, 131.6, 150.0, 155.1	$C_{16}H_{22}BrN_2O_2$ calcd: 353.0859; found: 359.0863	UV = 99.7% (t_R = 1.82 min), ELS = 100% (t_R = 1.88 min), *m*/*z* = 354.3	R_f = 0.30 heptane–EtOAc (4:1)
4g	8-Br	1.48 (9 H, s), 2.51 (1 H, dd, *J* = 15, 9), 2.66–3.03 (3 H, m), 2.94 (1 H, dd, *J* = 15, 8), 3.45 (2 H, m), 3.92–4.32 (2 H, m), 6.55 [1 H, br s(m)], 6.77 (1 H, dd, *J* = 7.5, 1.5), 6.91 (1 H, dm, *J* = 7.5)	28.5, 32.0, 42.0 (br), 43.1 (br), 43.9, 47.1 (br), 48.2 (br), 62.6, 80.2, 109.5, 120.7, 121.3, 126.0, 127.9, 151.9, 154.8	$C_{16}H_{22}BrN_2O_2$ calcd: 353.0859; found: 353.0861	UV = 99.7% (t_R = 1.83 min), ELS = 100% (t_R = 1.89 min), *m*/*z* = 352.6	R_f = 0.33 heptane–EtOAc (4:1)

Table 3 Spectral Data of Compounds **4** (continued)

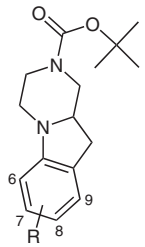
Entry	Product (R)	^{1}H NMR (500 MHz, $CDCl_3$): δ, *J* (Hz)	^{13}C NMR (125 MHz, $CDCl_3$): δ	HRMS: *m*/*z* (M + H^+)	LC-MS	TLC
						
4h	7-OMe	1.48 (9 H, s), 2.51 (1 H, dd, *J* = 15, 9), 2.71–3.03 (3 H, m), 2.92 (1 H, dd, *J* = 15, 8), 3.41 (1 H, m), 3.47 (1 H, m), 6.06 (1 H, d, *J* = 2.5), 6.20 (1 H, dd, *J* = 8, 2.5), 6.97 (1 H, d, *J* = 8)	28.8, 32.0, 42.5 (br), 43.5 (br), 44.5, 47.5 (br), 48.6 (br), 55.8, 63.4, 80.4, 94.6, 102.3, 121.5, 125.3, 152.2, 155.2, 160.6	$C_{17}H_{25}N_2O_3$ calcd: 305.1860; found: 305.1866	UV = 99.0% (t_R = 1.60 min), ELS = 100% (t_R = 1.65 min), *m*/*z* = 305.3	R_f = 0.33 heptane–EtOAc (5:2)
4i	9-OMe	1.48 (9 H, s), 2.50 (1 H, dd, *J* = 15, 9), 2.71–3.02 (3 H, v br m), 2.99 (1 H, dd, *J* = 15, 8), 3.43 (1 H, m), 3.51 (1 H, m), 6.16 (1 H, d, *J* = 8), 6.30 (1 H, d, *J* = 8), 7.06 (1 H, t, *J* = 8)	27.6, 28.5, 41.2 (br), 42.4 (br), 43.4, 46.2 (br), 47.3 (br), 54.4, 61.6, 79.1, 99.4, 100.9, 133.8, 128.1, 151.2, 154.0, 155.6	$C_{17}H_{25}N_2O_3$ calcd: 305.1860; found: 305.1868	UV = 99.6% (t_R = 1.60 min), ELS = 100% (t_R = 1.66 min), *m*/*z* = 305.3	R_f = 0.38 heptane–EtOAc (5:2)
4j	8-NO_2	1.41 (9 H, s), 2.56 (1H, dd, *J* = 16, 8), 2.70 [1 H, br s(m)], 2.83 [1 H, br s(m)], 3.02 (2 H, m), 3.53 (1 H, dm, *J* = 7), 3.67 (1 H, m), 3.95–4.30 (2 H, m), 6.22 (1 H, d, *J* = 9), 7.76 [1 H, s(m)], 7.91 (1 H, dd, *J* = 9, 1.5)	28.2, 31.0, 42.0 (br), 43.1*, 47.6 (br), 48.6 (br), 61.2, 80.3, 103.4, 120.8, 126.4, 128.5, 138.2, 154.3, 155.2 * merged with the second broad piperazine peak	Anal. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.17; H, 6.63; N, 13.16. Found: C, 60.26; H, 6.70; N, 13.08	UV = 99.2% (t_R = 1.49 min), ELS = 100% (t_R = 1.55 min), *m*/*z* = 264.1	R_f = 0.44 heptane–EtOAc (1:1)

Table 4 Spectral Data of Compounds **5**

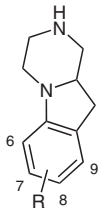
Entry	Product (R)	^{1}H NMR (500 MHz, $CDCl_3$): δ, *J* (Hz)	^{13}C NMR (125 MHz, $CDCl_3$): δ	HRMS: *m*/*z* (M + H^+)	LC-MS	TLC
						
5a	H	1.69 [1 H, br s], 2.55 (1 H, dd, *J* = 15, 10), 2.77 (1 H, t, *J* = 11), 2.87 (2 H, m), 2.91–3.01 (2 H, m), 3.07 (1 H, dd, *J* = 12, 3), 3.40 (1 H, m), 3.53 (1 H, m), 6.43 (1 H, d, *J* = 8), 6.64 (1 H, t, *J* = 7.5), 7.07 (2 H, m)	33.3, 45.0, 46.0, 50.6, 64.5, 106.2, 118.1, 125.1, 127.8, 129.3, 151.5	$C_{11}H_{15}N_2$ calcd: 175.1230; found: 175.1236	UV = 100% (t_R = 0.59 min) ELSD = 100% (t_R = 0.65 min), *m*/*z* = 175.3	R_f = 0.34 EtOAc–MeOH–Et_3N (3:2:1)
5b	7-Me	2.29 (3 H, s), 2.56 (1 H, dd, *J* = 15, 8), 2.94 (1 H, t, *J* = 12), 3.04 (2 H, m), 3.39 (3 H, m), 3.68 (1 H, dd, *J* = 13, 3), 3.88 (1 H, m), 6.31 (1 H, s), 6.55 (1 H, d, *J* = 7.5), 6.99 (1 H, d, *J* = 7.5), 8.1–8.6 (1 H, br s)	21.7, 32.4, 41.8, 42.2, 46.5, 60.0, 107.9, 119.8, 124.9, 125.0, 137.8, 149.5	$C_{12}H_{17}N_2$ calcd: 189.1386; found: 189.1383	UV = 98.3% (t_R = 0.82 min) ELSD = 100% (t_R = 0.88 min), *m*/*z* = 189.4	R_f = 0.32 EtOAc–MeOH–Et_3N (3:2:1)

Table 4 Spectral Data of Compounds **5** (continued)

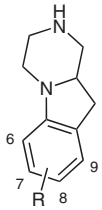
Entry	Product (R)	^{1}H NMR (500 MHz, $CDCl_3$): δ, *J* (Hz)	^{13}C NMR (125 MHz, $CDCl_3$): δ	HRMS: *m/z* (M + H^+)	LC-MS	TLC
						
5c	8-Me	2.26 (3 H, s), 2.68 (1 H, dd, *J* = 15.5, 6), 3.01 (1 H, t, *J* = 12), 3.12 (2 H, m), 3.30 (1 H, dt, *J* = 13.5, 3), 3.41 (2 H, m), 3.81 (1 H, m), 3.89 (1 H, dd, 14.5, 2.5), 6.70 (1 H, d, *J* = 8), 7.07 (1 H, d, *J* = 8), 7.14 (1 H, s)	20.3, 32.3, 41.6, 41.7, 45.2, 59.6, 108.8, 126.8, 128.4, 129.8, 130.6, 146.6	$C_{12}H_{17}N_2$ calcd: 189.1386; found: 189.1385	UV = 100% (t_R = 0.83 min) ELSD = 100% (t_R = 0.89 min), *m/z* = 189.3	R_f = 0.33 EtOAc–MeOH–Et_3N (3:2:1)
5d	7-Cl	1.79 [1 H, br s], 2.48 (1 H, dd, *J* = 15, 9), 2.72 (1 H, t, *J* = 11), 2.77–2.98 (4 H, m), 3.03 (1 H, dd, *J* = 12, 3), 3.45 (2 H, m), 6.35 (1 H, d, *J* = 1.5), 6.57 (1 H, dd, *J* = 7.5, 1.5), 6.93 (1 H, d, *J* = 7.5)	32.3, 44.5, 45.3, 50.2, 64.0, 106.1, 117.1, 125.2, 127.4, 133.2, 152.3	$C_{11}H_{14}ClN_2$ calcd: 209.0840; found: 209.0832	UV = 100% (t_R = 0.92 min) ELSD = 100% (t_R = 0.98 min), *m/z* = 208.8	R_f = 0.33 EtOAc–MeOH–Et_3N (3:2:1)
5e	9-Cl	1.84 [1 H, br s], 2.56 (1 H, dd, *J* = 15.5, 9 Hz), 2.74 (1 H, t, *J* = 11), 2.82 (1 H, m), 2.88–3.00 (2 H, m), 3.00–3.09 (2 H, m), 3.49 (2 H, m), 6.27 (1 H, d, *J* = 8), 6.59 (1 H, d, *J* = 8), 6.98 (1 H, t, *J* = 8)	32.1, 44.6, 45.5, 50.3, 63.1, 103.9, 117.6, 126.9, 129.0, 130.9, 152.3	$C_{11}H_{14}ClN_2$ calcd: 209.0840; found: 209.0831	UV = 99.1% (t_R = 0.91 min) ELSD = 100% (t_R = 0.97 min), *m/z* = 208.8	R_f = 0.35 EtOAc–MeOH–Et_3N (3:2:1)
5f	7-Br	1.79 [1 H, br s], 2.52 (1 H, dd, *J* = 15, 9), 2.73 (1 H, t, *J* = 11), 2.79–3.00 (4 H, m), 3.04 (1 H, dd, *J* = 12, 2.5), 3.44 (2 H, m), 6.27 (1 H, d, *J* = 8), 7.13 (1 H, d, *J* = 8), 7.14 (1 H, s)	32.7, 44.5, 45.5, 50.1, 63.9, 107.0, 109.0, 127.7, 130.0, 131.3, 150.2	$C_{11}H_{14}BrN_2$ calcd: 253.0335; found: 253.0325	UV = 100% (t_R = 0.97 min) ELSD = 100% (t_R = 1.03 min), *m/z* = 255.3	R_f = 0.32 EtOAc–MeOH–Et_3N (3:2:1)
5g	8-Br	1.85 [1 H, br s], 2.46 (1 H, dd, *J* = 15, 9), 2.71 (1 H, t, *J* = 11), 2.81 (1 H, dt, *J* = 12, 3), 2.88 (2 H, m), 2.95 (1 H, dm, *J* = 12), 3.03 (1 H, dd, *J* = 12, 3), 3.44 (2 H, m), 6.49 [1 H, s(m)], 6.71 (1 H, dd, *J* = 8, 1.5), 6.88 (1 H, d, *J* = 8)	32.3, 44.5, 45.3, 50.2, 63.9, 108.9, 120.0, 121.1, 125.7, 128.0, 152.5	$C_{11}H_{14}BrN_2$ calcd: 253.0335; found: 253.0325	UV = 100% (t_R = 0.97 min) ELS = 100% (t_R = 1.03 min), *m/z* = 255.4	R_f = 0.34 EtOAc–MeOH–Et_3N (3:2:1)
5h	7-OMe	2.26 [1 H, br s], 2.49 (1 H, ddd, *J* = 15, 9, 0.5), 2.77 (1 H, dd, *J* = 12, 11), 2.83–2.94 (3 H, m), 3.00 (1 H, m), 3.07 (1 H, dd, *J* = 12, 3), 3.41–3.57 (2 H, m), 3.76 (3 H, s), 6.03 (1 H, d, *J* = 2), 6.17 (1 H, dd, *J* = 8, 2), 6.95 (1 H, d, *J* = 8)	32.5, 44.8, 45.7, 50.4, 55.8, 64.7, 94.1, 101.8, 121.6, 125.1, 152.7, 160.6	$C_{12}H_{17}N_2O$ calcd: 205.1335; found: 205.1334	UV = 96.4% (t_R = 0.76 min) ELS = 100% (t_R = 0.82 min), *m/z* = 205.2	R_f = 0.35 EtOAc–MeOH–Et_3N (3:2:1)
5i	9-OMe	2.12 [1H, br s], 2.46 (1 H, dd, *J* = 15, 9), 2.77 (1 H, dd, *J* = 12, 11), 2.81–3.00 (4 H, m), 3.05 (1 H, dd, *J* = 12, 3), 3.45 (1 H, m), 3.52 (1 H, m), 6.13 (1 H, d, *J* = 8), 6.27 (1 H, d, *J* = 8), 7.04 (1 H, t, *J* = 8)	30.2, 45.0, 46.1, 50.5, 55.7, 64.3, 100.3, 101.7, 115.0, 129.2, 153.1, 156.8	$C_{12}H_{17}N_2O$ calcd: 205.1335; found: 205.1330	UV = 98.7% (t_R = 0.76 min) ELS = 100% (t_R = 0.82 min), *m/z* = 205.3	R_f = 0.38 EtOAc–MeOH–Et_3N (3:2:1)
5j	8-NO_2	2.58 (1 H, dd, *J* = 16, 8), 2.64 (1 H, t, *J* = 12), 2.75 (1 H, dt, *J* = 12, 3.5), 3.01 (1 H, dm, *J* = 13), 3.04–3.14 (3 H, m), 3.70 (1 H, dd, *J* = 13, 2.5), 3.77 (1 H, m), 6.35 (1 H, d, *J* = 9), 7.78 [1 H, s(m)], 7.94 (1 H, dd, *J* = 9, 4)	32.8, 45.3, 45.6, 51.5, 63.6, 104.8, 122.1, 128.0, 130.7, 139.4, 157	$C_{11}H_{14}N_3O_2$ calcd: 220.1081; found: 220.1071	UV = 97.7% (t_R = 0.57 min) ELS = 100% (t_R = 0.63 min), *m/z* = 220.2	R_f = 0.29 EtOAc–MeOH–Et_3N (3:2:1)

Table 5 Spectral Data of Compounds **9**–**17**, **20**, and **21**

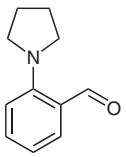
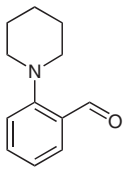
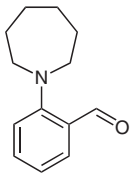
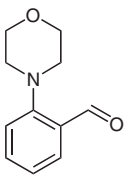
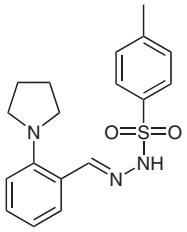
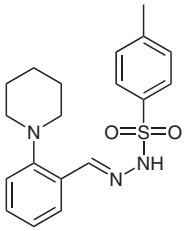
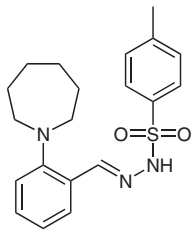
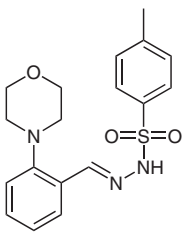
Entry	Product	^{1}H NMR (500 MHz, $CDCl_3$): δ, *J* (Hz)	^{13}C NMR (125 MHz, $CDCl_3$): δ	HRMS: *m*/*z* (M + H^+)	LC-MS	TLC
9a		1.93–2.00 (4 H, m), 3.31–3.37 (4 H, m), 6.79 (1 H, t, *J* = 8), 6.82 (1 H, d, *J* = 9), 7.36 (1 H, m), 7.69 (1 H, dd, *J* = 8, 2), 10.08 (1 H, s)	26.0, 52.7, 114.6, 116.4, 123.0, 133.1, 134.2, 150.0, 190.1	known compound	UV = 100% (t_R = 0.72 min), ELS = no signal, *m*/*z* = 176.5	–
9b		1.61 (2 H, m), 1.76 (4 H, m), 3.05 (4 H, m), 7.06 (1 H, t, *J* = 8), 7.09 (1 H, d, *J* = 8), 7.49 (1 H, dt, *J* = 8, 2), 7.80 (1 H, dd, *J* = 8, 2), 10.31 (1 H, s)	24.4, 26.6, 56.0, 119.4, 122.3, 129.0, 129.6, 135.2, 157.4, 192.0	$C_{12}H_{16}NO$ calcd: 190.1226; found: 190.1226	UV = 100% (t_R = 0.51 min), ELS = no signal, *m*/*z* = 190.2	R_f = 0.63 heptane–EtOAc (3:1)
9c		1.66 [4 H, br s(m)], 1.79 [4 H, br s(m)], 3.38 (4 H, m), 6.91 (1 H, t, *J* = 7), 7.06 (1 H, d, *J* = 9), 7.40 (1 H, t, *J* = 8), 7.72 (1 H, d, *J* = 8), 10.19 (1 H, s)	27.8, 28.7, 56.0, 118.6, 119.6, 126.7, 130.6, 134.3, 156.2, 191.3	$C_{13}H_{18}NO$ calcd: 204.1383; found: 204.1383	UV = 99.4% (t_R = 0.63 min), ELS = no signal, *m*/*z* = 204.5	R_f = 0.52 heptane–EtOAc (2:1)
9d		3.08 (4 H, m), 3.89 (4 H, m), 7.11 (1 H, d, *J* = 8), 7.14 (1 H, t, *J* = 8), 7.54 (1 H, tm, *J* = 8), 7.81 (1 H, dd, *J* = 8, 1), 10.33 (1 H, s)	54.0, 66.8, 118.7, 122.8, 128.5, 130.1, 135.0, 155.2, 190.9	$C_{11}H_{14}NO_2$ calcd: 192.1019; found: 192.1007	UV = 99.6% (t_R = 0.81 min), ELS = no signal, *m*/*z* = 192.2	R_f = 0.35 heptane–EtOAc (3:1)
10a		1.84 (4 H, m), 2.39 (3 H, s), 3.09 (4 H, m), 6.80 (2 H, m), 7.21 (1 H, tm, *J* = 8), 7.29 (2 H, d, *J* = 8), 7.58 (1 H, dt, *J* = 8), 7.88 (2 H, d, *J* = 8), 8.16 (1 H, s), 8.39 (1 H, v br s)	21.7, 25.3, 52.8, 115.6, 119.6, 122.5, 128.0, 128.7, 129.7, 130.8, 135.5, 144.1, 149.8	$C_{18}H_{22}N_3O_2S$ calcd: 344.1427; found: 344.1428	could not be obtained due to precipitation	R_f = 0.39 heptane–EtOAc (1:1)
10b		1.52 (2 H, m), 1.63 (4 H, m), 2.38 (3 H, s), 2.79 (4 H, m), 7.00 (2 H, m), 7.27 (3 H, m), 7.72 (1 H, d, *J* = 8), 7.88 (2 H, d, *J* = 8), 8.15 (1 H, br s), 8.2–8.7 (1 H, v br s)	21.7, 24.1, 26.3, 54.8, 119.3, 123.1, 127.0, 127.4, 128.0, 129.7, 131.1, 135.6, 144.1, 147.3, 153.6	$C_{19}H_{24}N_3O_2S$ calcd: 358.1584; found: 358.1581	could not be obtained due to precipitation	R_f = 0.35 heptane–EtOAc (2:1)
10c		1.64 [8 H, s(m)], 2.39 (3 H, s), 3.04 (4 H, m), 6.95 (1 H, t, *J* = 8), 7.04 (1 H, d, *J* = 8), 7.26 (1 H, tm, *J* = 8), 7.29 (2 H, d, *J* = 8), 7.68 (1 H, d, *J* = 8), 7.89 (2 H, d, *J* = 8), 8.19 (1 H, s), 8.36 (1 H, v br s)	21.7, 27.2, 29.1, 56.8, 120.8, 122.4, 127.0, 127.5, 128.0, 129.7, 131.0, 135.6, 144.1, 148.1, 155.3	$C_{20}H_{26}N_3O_2S$ calcd: 372.1740; found: 372.1739	could not be obtained due to precipitation	R_f = 0.38 heptane–EtOAc (2:1)
10d		2.40 (3 H, s), 2.84 (4 H, m), 3.78 (4 H, m), 7.03 (1 H, d, *J* = 8), 7.06 (1 H, t, *J* = 8), 7.30 (2 H, d, *J* = 8), 7.34 (1 H, tm, *J* = 8), 7.75 (1 H, d, *J* = 8), 7.89 (2 H, d, *J* = 8), 8.22 (1 H, s), 8.53 (1 H, br s)	21.7, 53.5, 67.1, 119.2, 123.9, 127.3, 127.6, 128.0, 129.8, 131.3, 135.5, 144.3, 146.7, 152.2	$C_{18}H_{21}N_3O_3S$ calcd: 360.1376; found: 360.1372	could not be obtained due to precipitation	R_f = 0.25 heptane–EtOAc (1:1)

Table 5 Spectral Data of Compounds **9**–**17**, **20**, and **21** (continued)

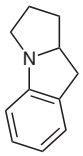
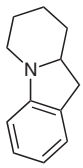
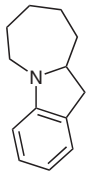
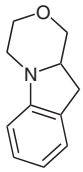
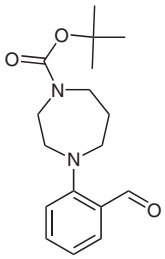
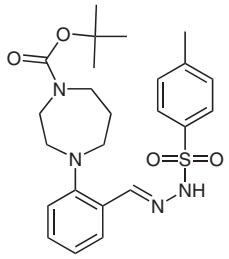
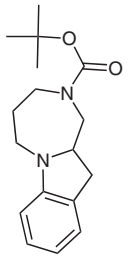
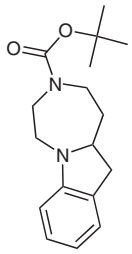
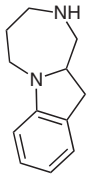
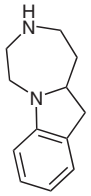
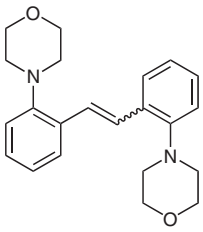
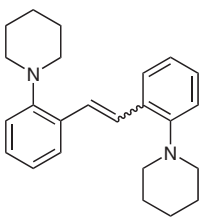
Entry	Product	^{1}H NMR (500 MHz, $CDCl_3$): δ, *J* (Hz)	^{13}C NMR (125 MHz, $CDCl_3$): δ	HRMS: *m*/*z* (M + H$^+$)	LC-MS	TLC
11a		1.29–1.41 (1 H, m), 1.80–1.95 (3 H, m), 2.98 (1 H, dd, *J* = 11, 2), 3.17–3.26 (2 H, m), 3.42–3.49 (1 H, m), 3.92–3.99 (1 H, m), 6.62 (1 H, d, *J* = 8), 6.78 (1 H, dm, *J* = 8), 7.10 (1 H, d, *J* = 8), 7.12 (1 H, t, *J* = 8)	25.9, 31.4, 34.0, 52.4, 65.4, 111.1, 119.3, 124.9, 127.6, 130.0, 154.8	$C_{11}H_{14}N$ calcd: 160.1121; found: 160.1120	UV = 100% (t_R = 0.29 min), ELS = no signal, *m*/*z* = 160.0	not determined (highly lipophilic)
11b		1.37–1.47 (1 H, m), 1.50–1.67 (2 H, m), 1.69–1.75 (1 H, m), 1.83–1.92 (2 H, m), 2.58 (1 H, dd, *J* = 15, 11), 2.64 (1 H, dt, *J* = 7, 3), 2.97 (1 H, dd, *J* = 15, 8), 3.17–3.26 (1 H, m), 3.61–3.67 (1 H, m), 6.45 (1 H, d, *J* = 8), 6.65 (1 H, t, *J* = 8), 7.04–7.10 (2 H, m)	24.6, 24.8, 30.8, 35.7, 45.3, 65.4, 105.9, 117.6, 124.6, 127.3, 129.5, 1151.9	$C_{12}H_{16}N$ calcd: 174.1277; found: 174.1275	UV = 97.8% (t_R = 0.57 min), ELS = no signal, *m*/*z* = 174.2	not determined (highly lipophilic)
11c		1.49 (1 H, m), 1.60 (1 H, m), 1.72 (2 H, m), 1.83 (2 H, m), 1.94 (2 H, m), 2.69 (1 H, dd, *J* = 16, 8), 3.07 (1 H, ddd, *J* = 13, 7, 4), 3.26 (1 H, dd, *J* = 16, 10), 3.47 (1 H, ddd, *J* = 12, 9, 5), 3.85 (1 H, dq, *J* = 9, 3), 6.35 (1 H, d, *J* = 8), 6.60 (1 H, t, *J* = 7), 7.02 (1 H, d, *J* = 7), 7.08 (1 H, t, *J* = 8)	27.27, 27.30, 28.4, 37.3, 37.8, 48.4, 64.3, 105.8, 116.5, 123.9, 127.5, 128.7, 152	$C_{13}H_{18}N$ calcd: 188.1434; found: 188.1435	UV = 100% (t_R = 0.58 min), ELS = no signal, *m*/*z* = 188.1	not determined (highly lipophilic)
11d		2.55 (1 H, dd, *J* = 15, 8), 3.00 (1 H, dd, *J* = 15, 8), 3.19 (1 H, dt, *J* = 13, 4), 3.47–3.56 (2 H, m), 3.61–3.72 (2 H, m), 3.90 (2 H, dt, *J* = 10, 4), 6.50 (1 H, d, *J* = 8), 6.72 (1 H, t, *J* = 8), 7.10–7.16 (2 H, m)	31.5, 45.2, 62.3, 65.9, 70.6, 106,6, 118.4, 125.4, 128.0, 129.2, 150.9	$C_{11}H_{13}NO$ calcd: 176.1070; found: 176.1067	UV = 99.3% (t_R = 1.21 min), ELS = no signal, *m*/*z* = 176.1	R_f = 0.56 heptane–EtOAc (3:1)
12		–	–	$C_{17}H_{25}N_2O_3$ calcd: 305.1860; found: 305.1867	UV = 99.2% (t_R = 1.29 min), ELS = 100% (t_R = 1.35 min) *m*/*z* = 305.3	–
13		DMSO-d_6, 80 °C: 1.43 (9 H, s), 1.81 (2 H, m), 2.37 (3 H, s), 2.98 (2 H, m), 3.03 (2 H, m), 3.46 (2 H, m), 3.51 (2 H, m), 7.01 (1 H, t, *J* = 8), 7.12 (1 H, d, *J* = 8), 7.29 (1 H, tm, *J* = 8), 7.38 (2 H, d, *J* = 8), 7.54 (1 H, d, *J* = 8), 7.76 (2 H, d, *J* = 8), 8.27 (1 H, s), 11.07 (1 H, v br s)	20.4, 27.6, 27.8, 44.9, 47.1, 55.0, 55.7, 78.3, 120.8, 122.5, 126.0, 126.7, 127.2, 129.0, 130.2, 136.3, 142.8, 145.8, 153.2, 154.2	$C_{24}H_{32}N_4O_4S$ calcd: 473.2217; found: 473.2207	could not be obtained due to precipitation	R_f = 0.35 heptane–EtOAc (1:1)

Table 5 Spectral Data of Compounds **9**–**17**, **20**, and **21** (continued)

Entry	Product	^{1}H NMR (500 MHz, $CDCl_3$): δ, *J* (Hz)	^{13}C NMR (125 MHz, $CDCl_3$): δ	HRMS: *m/z* (M + H^+)	LC-MS	TLC
14		1.49 (9 H, s), 1.95 (2 H, m), 2.61 (1 H, dd, *J* = 16, 8), 2.91 (1.5 H, m), 3.00 (0.5 H, dd, *J* = 13, 10), 3.17 (2 H, m), 3.71 (2 H, m), 3.78–3.95 (1.5 H, m), 4.16 (0.5 H, dm, *J* = 14), 6.43 (1 H, d, *J* = 8), 6.64 (1 H, t, *J* = 7), 7.06 (2 H, m)	26.3, 26.9, 28.5, 33.1, 33.2, 45.7, 46.1, 46.3, 46.4, 53.7, 54.0, 65.9, 66.1, 79.6, 106.3, 106.5, 117.4, 124.56, 124.63, 127.5, 127.6, 128.1, 128.3, 151.5, 151.7, 155.3, 155.5	$C_{17}H_{24}N_2O_2$ calcd: 289.1991; found: 289.1906	UV = 100% (t_R = 1.52 min), ELS = only slightly detectable and therefore analytically unsuitable, *m/z* = 289.2	R_f = 0.45 heptane–EtOAc (2:1)
15		1.47 (9 H, s), 1.94 (1 H, m), 2.07 (1 H, m), 2.71 (1 H, dd, *J* = 16, 10), 2.89 (1 H, m), 3.20 (1 H, m), 3.38–3.77 (6 H, m), 6.43 (1 H, d, *J* = 8), 6.67 (1 H, m), 7.01–7.12 (2 H, m)	28.6, 35.6, 36.1, 36.8, 36.9, 44.9, 45.8, 46.1, 46.6, 48.4, 64.9, 65.1, 79.7, 106.9, 107.1, 117.8, 118.0, 124.1, 124.2, 127.5, 127.6, 128.6, 128.8, 152.7, 155.4	$C_{17}H_{24}N_2O_2$ calcd: 289.1911; found: 289.1903	UV = 100% (t_R = 1.49 min), ELS = only slightly detectable and therefore analytically unsuitable, *m/z* = 289.3	R_f = 0.41 heptane–EtOAc (2:1)
16		1.85 (1 H, m), 2.04 (2 H, m), 2.64 (1 H, dd, *J* = 16, 9), 2.79 (2 H, m), 3.16 (4 H, m), 3.52 (1 H, ddd, *J* = 13, 8, 5), 3.88 (1 H, dq, *J* = 9, 2), 6.37 (1 H, d, *J* = 8), 6.61 (1 H, t, *J* = 7), 7.01 (1 H, d, *J* = 7), 7.07 (1 H, t, *J* = 8)	30.0, 34.2, 47.1, 48.8, 57.0, 67.1, 106.0, 116.9, 124.0, 127.5, 128.3, 152.5	$C_{12}H_{16}N_2$ calcd: 189.1386; found: 189.1385	UV = 100% (t_R = 0.48 min) ELSD = 100% (t_R = 0.54 min), *m/z* = 189.3	R_f = 0.24 EtOAc–MeOH–Et_3N (8:4:1)
17		1.85 (1 H, m), 1.97 (1 H, m), 2.20 (1 H, br s), 2.69 (1 H, dd, *J* = 16, 9), 2.82 (1 H, ddd, *J* = 14, 11, 4), 3.00 (2 H, m), 3.09–3.28 (3 H, m), 3.55 (1 H, m), 3.90 (1 H, dq, *J* = 9, 4), 6.36 (1 H, d, *J* = 8), 6.62 (1 H, t, *J* = 7), 7.01 (1 H, d, *J* = 7), 7.06 (1 H, t, *J* = 8)	37.1, 39.4, 48.0, 48.2, 50.8, 64.2, 106.2, 117.1, 123.9, 127.5, 128.7, 152.7	$C_{12}H_{16}N_2$ calcd: 189.1386; found: 189.1391	UV = 100% (t_R = 0.47 min), ELSD = 100% (t_R = 0.53 min), *m/z* = 189.3	R_f = 0.24 EtOAc–MeOH–Et_3N (8:4:1)
20		3.04 [2 H (*cis*), m], 3.14 [8 H (*trans*), m], 3.87–3.98 [10 H (*cis*/*trans*), m], 6.76 [2 H (*trans*), s], 6.84 [2 H (*trans*), t, *J* = 7], 7.03 [2 H (*trans*), d, *J* = 8], 7.10 [0.5 H (*cis*), d, *J* = 8], 7.16 [0.5 H (*cis*), t, *J* = 7], 7.18–7.28 [4 H (*trans*), m], 7.32 [0.5 H (*cis*), t, *J* = 8], 7.49 [0.5 H (*cis*), s], 7.67 [0.5 H (*cis*), d, *J* = 8]	52.6 (t), 53.2 (*cis*), 67.8 (*cis*/*trans*), 118.1 (*trans*), 119.1 (*cis*), 122.6 (*trans*), 123.9 (*cis*), 125.9 (*cis*), 126.8 (*trans*), 127.0 (*cis*), 128.5 (*trans*), 128.7 (*cis*), 130.2 (*trans*), 131.1 (*trans*), 132.6 (*cis*), 151.1 (*cis*), 151.5 (*trans*)	$C_{22}H_{27}N_2O_2$ calcd: 351.2067; found: 351.2067	UV = 99.2% (*trans* = 64.9%, *cis* = 22.8%), (*trans*: t_R = 2.05 min, *cis*: t_R = 2.10 min) ELS = 100% (*trans*/*cis* = 100%) (*trans*: t_R = 2.11 min, *cis*: t_R = 2.16 min); *trans*/*cis*: *m/z* = 351.3	R_f = 0.33 heptane–EtOAc (3:1)
21		1.63–1.72 [5 H (*cis*/*trans*), m], 1.78–1.90 [10 H (*cis*/*trans*), m], 3.03 [2 H (*cis*), m], 3.12 [8 H (*trans*), m], 6.78 [2 H (*trans*), s], 6.83 [2 H (*trans*), t, *J* = 8], 7.07 [2 H (*trans*), d, *J* = 8], 7.12 [0.5 H (*cis*), d, *J* = 8], 7.14 [0.5 H (*cis*), t, *J* = 8], 7.23 [2 H (*trans*), dt, *J* = 15, 2], 7.31 [0.5 H (*cis*), dt, *J* = 15, 2], 7.37 [2 H (*trans*), dd, *J* = 8, 1], 7.53 [0.5 H (*cis*), s], 7.76 [0.5 H (*cis*), dm, *J* = 8]	24.9 (c/t), 27.1 (*cis*/*trans*), 53.8 (*trans*), 54.4 (*cis*), 118.3 (*trans*), 119.1 (*cis*), 121.7 (*trans*), 123.0 (*cis*), 125.7 (*cis*), 126.5 (*trans*), 126.8 (*cis*), 128.1 (*trans*), 128.3 (*cis*), 130.0 (*trans*), 131.5 (*trans*), 132.9 (*cis*), 152.7 (*cis*), 153.1 (*trans*)	$C_{24}H_{31}N_2$ calcd: 347.2482; found: 347.2476	UV = 99.6% (*trans* = 72.1%, *cis* = 23.2%), (*trans*: t_R = 2.27 min, *cis*: t_R = 2.46 min) ELS = 100% (*trans*: 89.0%, *cis*: 11.0%) (*trans*: t_R = 2.33 min, *cis*: t_R = 2.52 min) *trans*: *m/z* = 346.9, *cis*: *m/z* = 346.9	R_f = 0.60 heptane–EtOAc (10:1)

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