Synthesis F. La Spisa et al. Paper

Synthesis of Heteroarylogous 1*H*-Indole-3-carboxamidines via a Three-Component Interrupted Ugi Reaction

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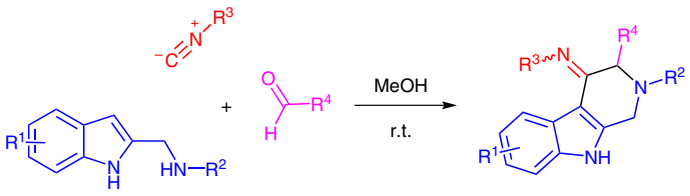

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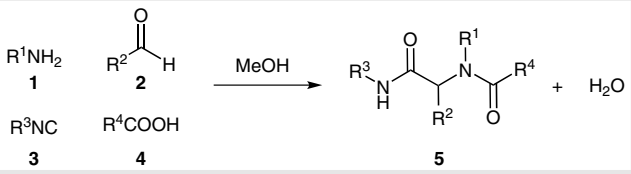
Abstract A novel one-pot multicomponent synthesis of heteroarylogous 1*H*-indole-3-carboxamidines starting from readily available *N*-alkyl-*N*-(1*H*-indol-2-ylmethyl)amines, isocyanides, and carbonyl compounds is reported. The strategy exploits the ability of the indole nucleus to interrupt the classical Ugi reaction, by intercepting the nascent nitrilium ion.

Key words isocyanides, secondary amines, Ugi reaction, multicomponent reactions, indoles

Although the Ugi reaction (Scheme 1) was discovered in the late 1950s,[1] this multicomponent transformation can still be the starting point and the inspiration in the search for novel and important multicomponent reactions (MCRs).

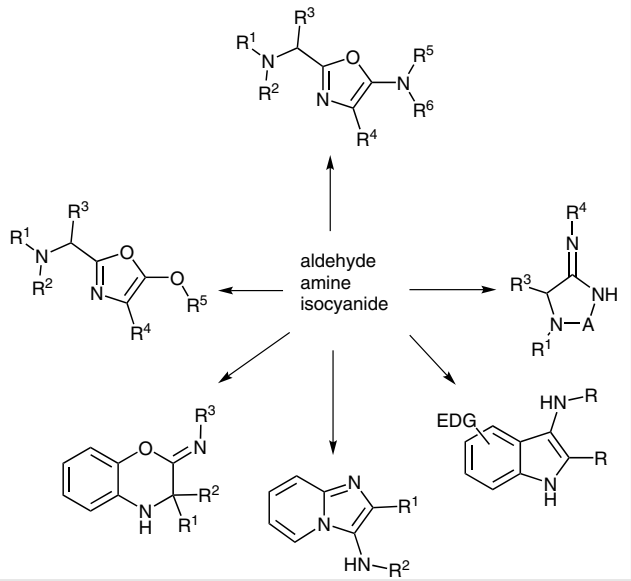


Scheme 1 The four-component Ugi reaction

Indeed, following studies on the mechanism of the Ugi reaction,[2] different strategies have been disclosed over the last decades for the identification of novel true isocyanide-mediated MCRs.[3] For example, shortly after the disclosure of the four-component Ugi reaction, Ugi-like transformations using surrogates of amines (hydroxylamine,[4] hydrazine[5]) or carboxylic acids (HN_3,[6] HNCO[7]) were reported, affording novel molecular frameworks. Apart from the use of bifunctionalized substrates in the Ugi reaction, only over the past few years have intellectually deeper approaches been systematically searched for and found.[8] Four main strategies have been considered: i) the use of a secondary amine and a nucleophile grafted in one of the four components which allows for the interception of the formed imino anhydride;[9] ii) the use of electron-deficient phenols as carboxylic acid surrogates which can trigger a Smiles rearrangement in place of the Mumm-type rearrangement;[10] iii) the identification of novel electrophiles, as substitutes for the iminium ion, able to be attacked by the isocyanides [acyl cyanides,[11] trimethylsilanol,[12] acyl isocyanates,[13] (*Z*)-chloro oximes[14]]; finally, iv) the intramolecular interception of the nascent nitrilium ion by a nucleophile, avoiding, in this case, the use of the carboxylic acid. The latter, three-component reaction is usually referred to as the interrupted Ugi reaction, and a series of transformations which have followed this strategy have been disclosed. To date, reactions with isocyanoacetamides,[15] isocyano esters,[15b,16] diamines,[17] electron-rich anilines,[18] 2-aminophenols,[19] 2-aminopyridines, and related heterocycles[20] represent the state of the art for the interrupted multicomponent Ugi reaction (Scheme 2).

As shown in Scheme 2, it appears evident that despite the fact that most of the above transformations have been carried out using methanol as solvent, signs of the successful formation of an imidate by the reaction between methanol and the nitrilium ion have never been reported. This result indicates either the reversibility of the process or the inability of methanol to attack the nitrilium ion. In the same way, the direct attack of the nitrilium ion by the amine nitrogen to afford an aziridin-2-imine has never been described.

Stimulated by these results and aware that this strategy has not been fully exploited yet, we started to consider which nucleophile would be able to trap the ephemeral nitrilium ion in a productive manner. Firstly, we focused our attention on the indole ring. Indeed, it is well known that its

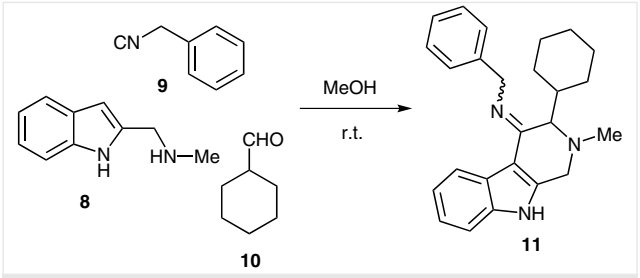


Scheme 2 Examples of interrupted multicomponent Ugi reactions; A = alkyl chain

electron-rich nature makes electrophilic aromatic substitution (S_EAr) at the C3 position extremely facile. To our surprise, a preliminary search of the literature revealed to us that this strategy had yet to be taken into consideration, despite the undeniable importance of the indole nucleus in several branches of chemistry. As proof of principle, we therefore synthesized 1-(1*H*-indol-2-yl)-*N*-methylmethanamine (**8**) which is easily obtainable starting from the commercially available 1*H*-indole-2-carboxylic acid (**6**) through an amidation and a reduction reaction (Scheme 3).

Indole **8** was then reacted with cyclohexanecarboxaldehyde (**10**) and benzyl isocyanide (**9**) in methanol at room temperature (Scheme 4). To our delight, after one hour we observed the formation of a novel product which incorporated all three starting materials. ^{1}H and ^{13}C NMR analyses revealed the structure **11**, a novel scaffold unknown in the literature. Compound **11**, which was obtained in 74% yield, can be considered as a sort of arylogous carboxamidine.[21]

In order to unequivocally confirm the molecular structure and, at the same time, to establish the spatial distribution of the functional groups, compound **11** was subjected to X-ray crystal structure analysis.[22] Its crystal structure is represented in Figure 1, as an ORTEP[23] drawing together with the relative arbitrary atom-numbering scheme.



Scheme 4 Three-component reaction

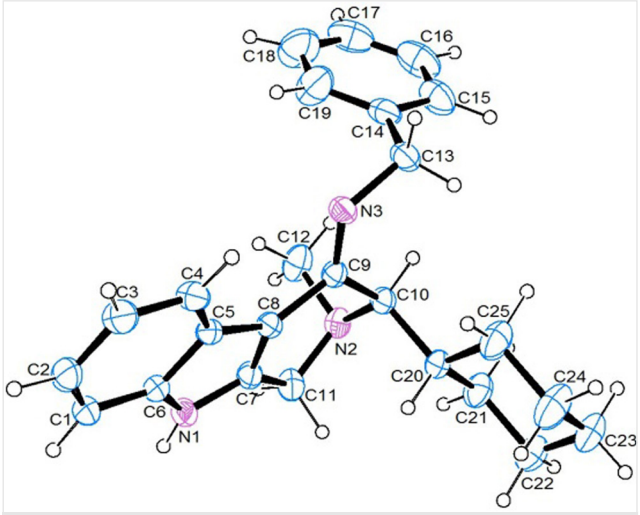
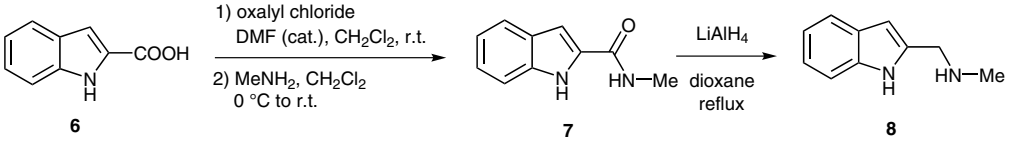


Figure 1 ORTEP[23] view of **11** and the relative atom-numbering scheme (thermal ellipsoids at 40% probability)[22]

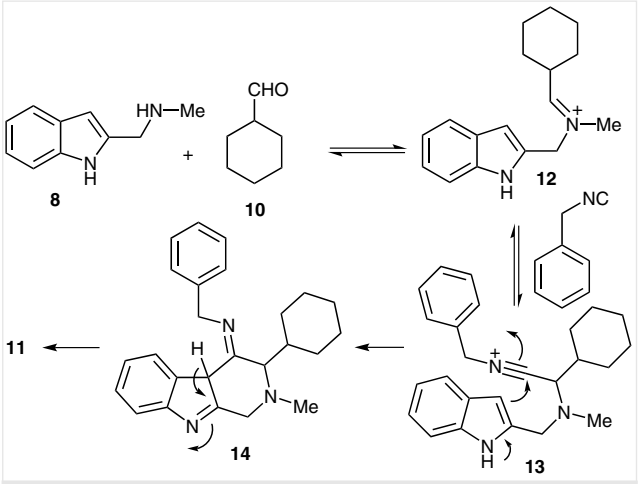
The overall molecular conformation of compound **11** is determined by the tetrahydro-β-carboline-based tricyclic framework having the side chain in the *Z* configuration and the cyclohexane axially oriented. The 1*H*-indole ring system is essentially planar and forms a dihedral angle of 77(1)° with the benzene ring attached to the tetrahydropyridine fragment. The conformation of the six-membered heterocyclic ring lies between the half-chair and envelope conformation, as shown by the asymmetry parameters Q_T = 0.593(1) Å, φ_2 = –59(2)°, and θ = 69(1)°, while the cyclohexane adopts an almost perfect chair conformation, characterized by the puckering coordinates[24] Q_T = 0.571(2) Å, φ_2 = –168(1)°, and θ = 179(2)°. The crystal packing is stabilized by intermolecular N–H···N- and Cπ–H···N-type interactions and by π–π contacts between the distal phenyl rings.



Scheme 3 Synthesis of indole derivative **8**

It is important to highlight that the decision to use a secondary amine in order to obtain the iminium ion under neutral conditions was fundamental for the success of this transformation. Indeed, when the same reaction was carried out with the nor analogue of **8** and a Lewis or Brønsted acid was used as catalyst to form the iminium ion, none of the desired product could be detected. Furthermore, when we performed the same reaction in the presence of a carboxylic acid (e.g., phenylacetic acid), we once again obtained the interrupted Ugi product in low yield (28%), along with the Passerini adduct (16%). No trace of the Ugi adduct could be detected.

Our proposed, plausible mechanism for this novel MCR is outlined in Scheme 5. The indole **8** reacts with the cyclohexanecarboxaldehyde (**10**) to generate an iminium ion **12**. The iminium ion **12** cannot participate in a Pictet–Spengler reaction with the indole nucleus as the closure would be 5-*endo*-trig, disfavored by the Baldwin ring-closure rules. Ion **12** is, however, electrophilic enough to interact with the isocyanide to form an electrophilic nitrilium ion **13**. The latter is then intramolecularly intercepted by the C3 of the indole nucleus.[25] After a prototropic rearrangement, the final product **11** is obtained. The intramolecular nitrilium trapping should presumably happen in a stereoselective way, yielding the *E*-isomer[26] which isomerizes to the more stable *Z*-isomer.



Scheme 5 Proposed mechanism for the formation of **11**

In order to verify the generality of this novel transformation, we used different indoles (**8**, **15**–**17**), isocyanides (**9**, **18**–**22**), and aldehydes (**10**, **23**–**28**) (Figure 2); the final compounds obtained are shown in Figure 3. The reaction appears to be tolerant toward almost all types of isocyanides, both primary and secondary aliphatic and aromatic, as well as less reactive isocyanides such as isocyanoacetate **21** and tosylmethyl isocyanide (TosMIC, **22**). Formaldehyde, and aliphatic and aromatic aldehydes, the latter requiring longer reaction time, are able to participate in this multicomponent transformation. Remarkably, even ketone **28** was able to react to produce a spiro compound, albeit in modest yield. Finally, both indoles bearing electron-donating or electron-withdrawing groups maintain the ability to intercept the nitrilium ion via the nucleophilic C3.

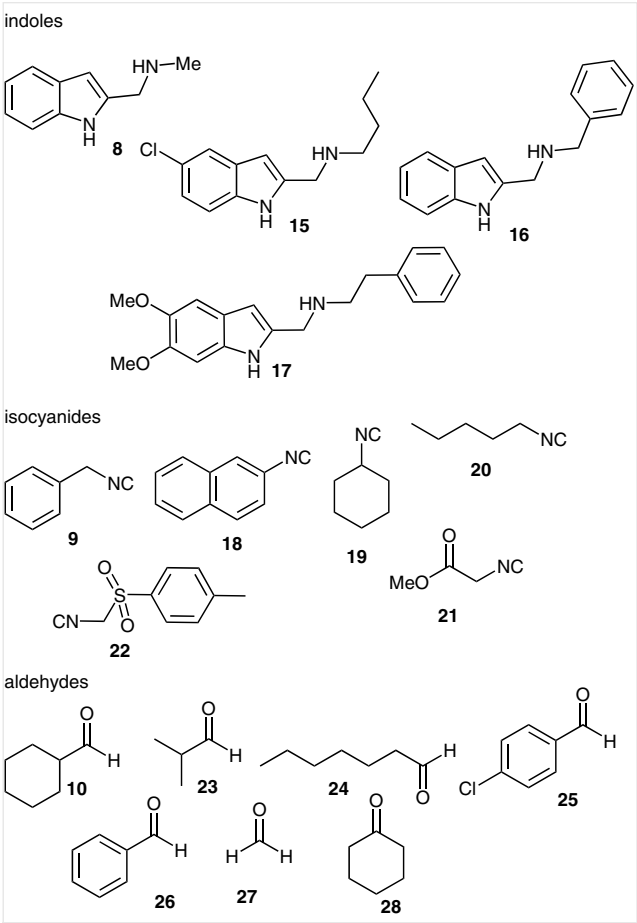


Figure 2 Building blocks used

In order to verify the amidine nature of these compounds, we tested the hydrolytic stability of the imino moiety of compound **11** under both acidic (6 M HCl, reflux) and basic (6 M NaOH, dioxane, reflux) conditions. In both cases, no sign of hydrolyzed products could be detected.

In conclusion, heteroarylogous 1*H*-indole-3-carboxamidines, a new class of indole derivatives with four points of diversity, were efficiently synthesized via a facile three-component reaction. In this novel MCR, a new carbon–nitrogen bond, two carbon–carbon bonds, a carbon–nitrogen double bond, and a six-membered ring are produced in one pot in a single operation. The reaction proceeds under mild conditions without requiring catalysts. As the indole ring can be fully considered a privileged structure in agrochemicals and drugs, these compounds may represent novel molecular scaffolds of importance. Furthermore, being completely new and never reported, there are no intellectu-

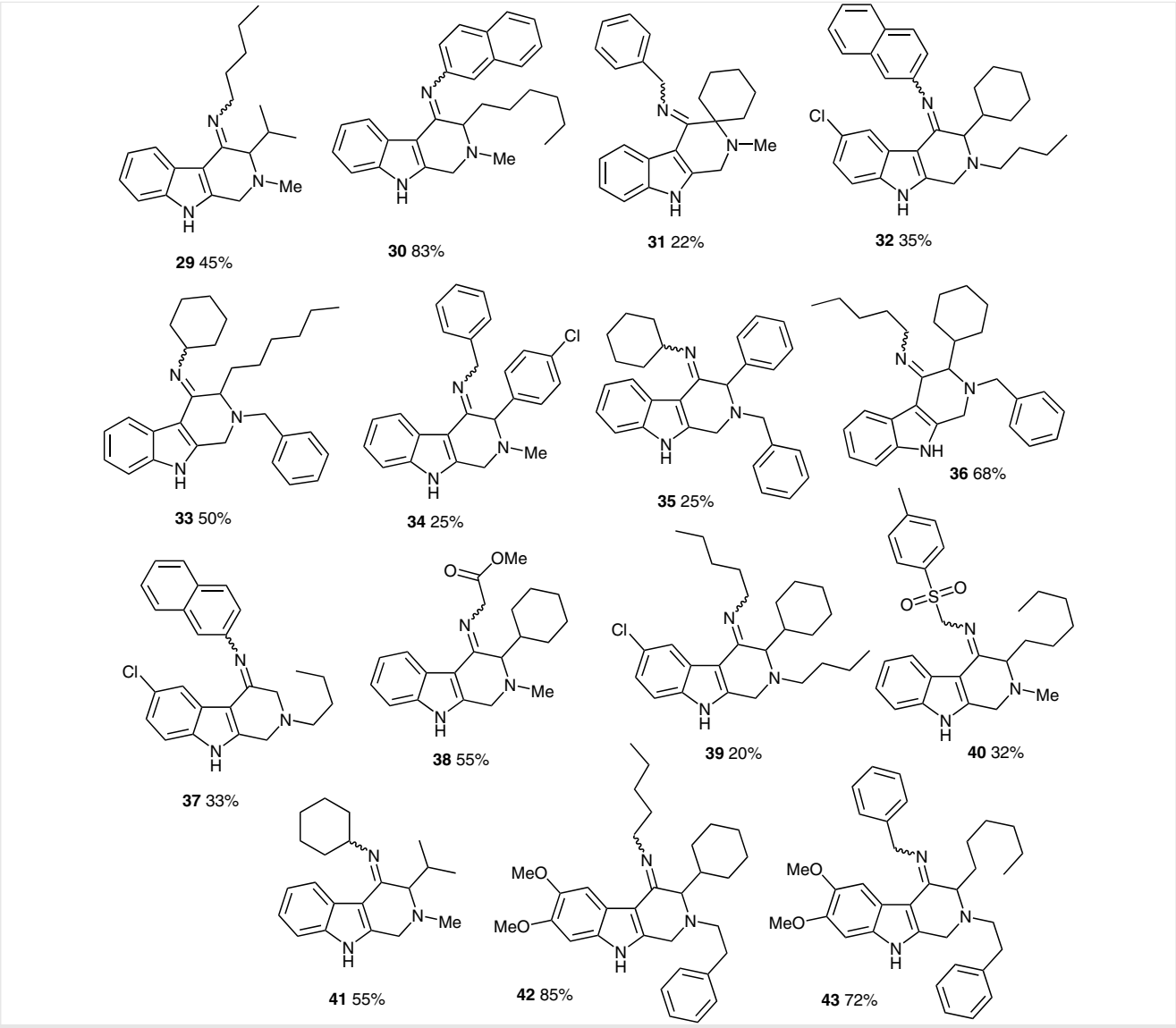


Figure 3 Arylogous 1*H*-indole-3-carboxamidines synthesized

al property rights associated with these compounds, rendering their exploitation valuable from an industrial point of view. We anticipate that other neglected heterocyclic rings (e.g., pyrroles,[27] furans, thiophenes), when properly functionalized, will be able to intercept the nitrilium ion, channeling the MCR through an interrupted Ugi transformation. Studies with these heterocyclic ring systems are in progress and the results will be reported in due course.

Commercially available reagents and solvents were purchased from Sigma-Aldrich and Alfa Aesar, and were used without further purification, unless otherwise noted. Liquid aldehydes were distilled with a Glass Oven B-585 Kugelrohr apparatus before being used. When needed, the reactions were performed in flame- or oven-dried glassware under a positive pressure of dry N_2. NMR spectra were recorded with a Jeol ECP 300 MHz spectrometer; the δ values are given in parts per million. Mass spectra were recorded using a Thermo Finnigan LCQ Deca XP Plus spectrometer equipped with an ESI source and an ion trap detector. Infrared spectra were recorded on an FT-IR Thermo Nicolet Avatar spectrometer with absorption maxima (ν_{max}) recorded in wavenumbers (cm^{-1}). Column chromatography was performed on silica gel (Merck Kieselgel, 0.063–0.200 mm, 70–230 mesh ASTM). TLC was carried out on 5 × 20 cm plates with a layer thickness of 0.25 mm (Merck silica gel 60 F254). When necessary, the plates were developed with $KMnO_4$ or the Dragendorff reagent. Elemental analysis data (C, H, N) are within ± 0.4% of the calculated values.

Amines 8, 15, 16, and 17; General Procedure

The corresponding carboxylic acid (1 equiv, 10 mmol) was dissolved (0.3 M) in CH_2Cl_2 (ACS reagent, reag. ISO), and oxalyl chloride (1.6 equiv) and catalytic DMF (0.1 equiv) were added. The resulting suspension was stirred at r.t. for 12 h, then the solvent was evaporated in vacuo. The acyl chloride was then dissolved (0.2 M) in CH_2Cl_2 (ACS reagent, reag. ISO) and the corresponding primary amine (1.2 equiv) was slowly added at 0 °C. The reaction mixture was stirred at r.t. overnight, then washed with 2 M NaOH (100 mL), 2 M HCl (100 mL), and brine (100 mL), then dried over Na_2SO_4. After evaporation of the solvent in vacuo, the crude amide was directly used for the next step without further purification. In a flame-dried flask, under N_2 atmosphere, $LiAlH_4$ (3 equiv) was dissolved in anhyd dioxane (60 mL), then the amide was added at 0 °C. The reaction mixture was refluxed overnight, then the reaction was quenched with a sat. aq solution of Na_2SO_4 (15 mL) at 0 °C; the resulting mixture was filtered. The filtrate was basified with 2 M NaOH until pH 10, then it was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine (100 mL), then dried over Na_2SO_4 and concentrated to dryness.

1-(1*H*-Indol-2-yl)-*N*-methylmethanamine (8)

Prepared from 1*H*-indole-2-carboxylic acid (**6**; 3 g, 20 mmol). **8** was obtained as a brown solid; yield: 1.04 g (35%).

The spectroscopic data were in agreement with those reported in the literature.[28]

N-[(5-Chloro-1*H*-indol-2-yl)methyl]butan-1-amine (15)

Prepared from 5-chloro-1*H*-indole-2-carboxylic acid (2 g, 10 mmol). **15** was obtained as a brown oil; yield: 774 mg (32%); R_f = 0.10 (EtOAc–MeOH, 9:1).

FT-IR (liquid film): 3735, 2240, 1598, 643 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 10.05 (br s, 1 H), 7.57 (s, 1 H), 7.23–7.01 (m, 3 H), 6.30 (s, 1 H), 3.85 (s, 2 H), 2.65 (t, *J* = 6.7 Hz, 2 H), 1.65–1.15 (m, 5 H), 0.97 (t, *J* = 7.3 Hz, 3 H).

MS (ESI): *m*/*z* = 237 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{17}ClN_2$: C, 65.95; H, 7.24; N, 11.83 Found: C, 66.30; H, 7.52; N, 12.05.

N-(1*H*-Indol-2-ylmethyl)-1-phenylmethanamine (16)

Prepared from 1*H*-indole-2-carboxylic acid (**6**; 2 g, 12 mmol). **16** was obtained as a brown oil; yield: 1.34 g (46%).

The spectroscopic data were in agreement with those reported in the literature.[29]

N-[(5,6-Dimethoxy-1*H*-indol-2-yl)methyl]-2-phenylethanamine (17)

Prepared from 5,6-dimethoxy-1*H*-indole-2-carboxylic acid (1 g, 4 mmol). **17** was obtained as a brown oil; yield: 320 mg (23%); R_f = 0.20 (EtOAc–MeOH, 9:1).

FT-IR (liquid film): 3726, 2360, 1608, 668 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.56 (br s, 1 H), 7.35–7.15 (m, 5 H), 6.99 (s, 1 H), 6.80 (s, 1 H), 6.21 (s, 1 H), 3.91 (s, 2 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 2.90 (t, *J* = 6.0 Hz, 2 H), 2.80 (t, *J* = 6.0 Hz, 2 H).

MS (ESI): *m*/*z* = 311 $[M + H]^+$.

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.43; H, 7.01; N, 9.31.

Compounds 11 and 29–43; General Procedure

The amine (1 equiv) was dissolved (0.2 M) in MeOH (ACS reagent, reag. ISO, reag. Ph. Eur.), then the aldehyde (1 equiv) and the isocyanide (1 equiv) were subsequently added. The reaction mixture was stirred at r.t. until completion (3 to 24 h). The solvent was evaporated in vacuo and the product was purified by column chromatography.

N-[(4*Z*)-3-Cyclohexyl-2-methyl-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-ylidene]-1-phenylmethanamine (11)

Prepared from **8** (100 mg, 0.62 mmol), **9** (70 mg, 0.62 mmol), and **10** (73 mg, 0.62 mmol) in 4 h. **11** was obtained as a yellow solid; yield: 170 mg (74%); mp 174–175 °C; R_f = 0.30 (EtOAc).

FT-IR (KBr): 2745, 2059, 1480, 978 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.31 (br s, 1 H), 7.55 (d, *J* = 4.0 Hz, 2 H), 7.38 (t, *J* = 4.0 Hz, 2 H), 7.31–7.21 (m, 3 H), 7.19–7.10 (m, 2 H), 4.85 (s, 2 H), 4.29 (d, *J* = 17.0 Hz, 1 H, AB), 3.62 (d, *J* = 10.0 Hz, 1 H), 3.48 (d, *J* = 17.0 Hz, 1 H, AB), 2.47 (s, 3 H), 2.28–2.15 (m, 1 H), 1.85–1.48 (m, 5 H), 1.30–0.98 (m, 5 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 164.3, 141.7, 137.1, 133.1, 128.5, 127.8, 126.5, 125.5, 122.4, 121.8, 121.2, 111.2, 109.4, 65.0, 54.5, 45.7, 43.9, 39.0, 32.0, 30.7, 26.6.

MS (ESI): *m*/*z* = 372 $[M + H]^+$.

Anal. Calcd for $C_{25}H_{29}N_3$: C, 80.82; H, 7.87; N, 11.31. Found: C, 80.65; H, 7.65; N, 11.20.

N-(3-Isopropyl-2-methyl-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-ylidene)pentan-1-amine (29)

Prepared from **8** (80 mg, 0.50 mmol), **20** (42 mg, 0.50 mmol), and **23** (36 mg, 0.50 mmol) in 3 h. **29** was obtained as a yellow solid; yield: 70 mg (45%); mp 125–126 °C; R_f = 0.15 (EtOAc–MeOH, 95:5).

FT-IR (KBr): 3520, 2780, 1486, 954 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.13 (br s, 1 H), 7.40–7.30 (m, 1 H), 7.28–7.08 (m, 3 H), 4.28 (d, *J* = 17.0 Hz, 1 H, AB), 3.65–3.35 (m, 4 H), 2.49 (s, 3 H), 1.85–1.70 (m, 3 H), 1.55–1.30 (m, 4 H), 1.15 (d, *J* = 4.6 Hz, 3 H), 1.00–0.8 (m, 6 H).

^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 163.0, 137.9, 137.2, 125.7, 121.7 (2 C), 120.3, 111.6, 109.0, 65.1, 50.8, 45.4, 43.9, 31.8, 29.9, 29.3, 22.7, 21.6, 20.3, 14.6.

MS (ESI): *m*/*z* = 312 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{29}N_3$: C, 77.12; H, 9.38; N, 13.49. Found: C, 77.41; H, 9.12; N, 13.25.

N-(3-Hexyl-2-methyl-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-ylidene)naphthalen-2-amine (30)

Prepared from **8** (100 mg, 0.62 mmol), **18** (96 mg, 0.62 mmol), and **24** (71 mg, 0.62 mmol) in 6 h. **30** was obtained as a yellow solid; yield: 212 mg (83%); mp 110–111 °C; R_f = 0.25 (PE–EtOAc, 2:8).

FT-IR (KBr): 3500, 2853, 1060, 967 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.64 (br s, 1 H), 8.37 (t, *J* = 4.2 Hz, 1 H), 7.82 (d, *J* = 8.2 Hz, 2 H), 7.74 (d, *J* = 8.2 Hz, 1 H), 7.50–7.30 (m, 2 H), 7.30–7.10 (m, 5 H), 4.25 (d, *J* = 17.0 Hz, 1 H, AB), 3.62 (q, *J* = 4.5 Hz, 1 H), 3.51 (d, *J* = 17.0 Hz, 1 H, AB), 2.53 (s, 3 H), 1.78–1.40 (m, 2 H), 1.30–0.95 (m, 8 H), 0.72 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 165.5, 149.2, 139.0, 136.5, 134.4, 130.3, 128.8, 127.8, 127.3, 126.3, 125.0, 124.2, 122.9, 121.9, 121.8, 121.7, 115.6, 111.2, 109.0, 60.8, 45.6, 43.6, 31.5, 30.6, 28.9, 26.6, 22.5, 14.0.

MS (ESI): m/z = 410 $[M + H]^+$.

Anal. Calcd for $C_{28}H_{31}N_3$: C, 82.11; H, 7.63; N, 10.26. Found: C, 82.40; H, 7.32; N, 10.54.

N-(2′-Methyl-1′,2′-dihydrospiro[cyclohexane-1,3′-pyrido[3,4-*b*]indol]-4′(9′*H*)-ylidene)-1-phenylmethanamine (31)

Prepared from **8** (100 mg, 0.62 mmol), **9** (73 mg, 0.62 mmol), and **28** (61 mg, 0.62 mmol) in 14 h. **31** was obtained as a white solid; yield: 50 mg (22%); mp 189–190 °C; R_f = 0.15 (EtOAc).

FT-IR (KBr): 3425, 2363, 1653, 1140, 962 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.44 (br s, 1 H), 7.53 (d, J = 4.0 Hz, 1 H), 7.43–7.35 (m, 4 H), 7.33–7.27 (m, 1 H), 7.15–6.99 (m, 3 H), 5.02 (s, 2 H), 4.08 (s, 2 H), 2.32 (s, 3 H), 1.80–1.10 (m, 10 H).

^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 163.5, 141.4, 138.6, 127.1, 126.5, 126.3, 125.0, 124.3, 119.9, 118.7, 110.5, 104.6, 61.4, 56.1, 47.1, 36.4, 25.2, 20.9.

MS (ESI): m/z = 358 $[M + H]^+$.

Anal. Calcd for $C_{24}H_{27}N_3$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.87; H, 7.41; N, 11.41.

N-(2-Butyl-6-chloro-3-cyclohexyl-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-ylidene)naphthalen-2-amine (32)

Prepared from **15** (100 mg, 0.42 mmol), **10** (75 mg, 0.42 mmol), and **18** (78 mg, 0.42 mmol) in 6 h. **32** was obtained as a yellow solid; yield: 80 mg (35%); mp 187–188 °C; R_f = 0.30 (PE–EtOAc, 1:9).

FT-IR (KBr): 3400, 2115, 1022, 946 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.65 (br s, 1 H), 8.11 (s, 1 H), 7.83 (t, J = 7.5 Hz, 2 H), 7.72 (d, J = 8.2 Hz, 1 H), 7.55–7.30 (m, 3 H), 7.20–7.00 (m, 3 H), 4.34 (d, J = 19.0 Hz, 1 H, AB), 3.80 (d, J = 19.0 Hz, 1 H, AB), 2.80–2.70 (m, 2 H), 1.98–1.90 (m, 1 H), 1.60–0.80 (m, 18 H).

^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 164.1, 149.4, 143.1, 135.6, 134.3, 130.1, 128.7, 128.2, 127.4, 126.8, 126.2, 125.7, 124.5, 122.8, 122.2, 120.6, 115.0, 113.6, 108.6, 63.0, 54.9, 44.8, 38.2, 31.7, 30.9, 26.4, 26.2, 20.2, 14.4.

MS (ESI): m/z = 485 $[M + H]^+$.

Anal. Calcd for $C_{31}H_{34}ClN_3$: C, 76.92; H, 7.08; N, 8.68. Found: C, 76.69; H, 6.88; N, 8.87.

N-(2-Benzyl-3-hexyl-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-ylidene)cyclohexanamine (33)

Prepared from **16** (100 mg, 0.42 mmol), **19** (46 mg, 0.42 mmol), and **24** (48 mg, 0.42 mmol) in 8 h. **33** was obtained as a brown solid; yield: 93 mg (50%); mp 96–97 °C; R_f = 0.40 (EtOAc).

FT-IR (KBr): 3509, 2926, 1140, 906 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.16 (br s, 1 H), 8.19 (t, J = 7.0 Hz, 1 H), 7.45–6.95 (m, 8 H), 4.26 (d, J = 17.0 Hz, 1 H), 3.85–3.60 (m, 4 H), 3.55–3.22 (m, 3 H), 1.90–1.10 (m, 18 H), 0.95–0.85 (m, 3 H).

^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 161.5, 139.9, 138.6, 136.8, 129.1, 128.6, 127.5, 125.8, 122.3, 121.8, 120.3, 111.6, 108.8, 59.2, 57.3, 56.6, 43.5, 35.4, 31.8, 31.2, 30.3, 28.7, 26.4, 24.8, 22.7, 14.5.

MS (ESI): m/z = 442 $[M + H]^+$.

Anal. Calcd for $C_{30}H_{39}N_3$: C, 81.59; H, 8.90; N, 9.51. Found: C, 81.75; H, 9.05; N, 9.28.

N-[3-(4-Chlorophenyl)-2-methyl-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-ylidene]-1-phenylmethanamine (34)

Prepared from **8** (100 mg, 0.62 mmol), **9** (73 mg, 0.62 mmol), and **25** (87 mg, 0.62 mmol) in 18 h. **34** was obtained as a yellow solid; yield: 62 mg (25%); mp 104–105 °C; R_f = 0.25 (PE–EtOAc, 1:9).

FT-IR (KBr): 3320, 2831, 1184, 902 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.44 (s, 1 H), 8.22 (d, J = 7.0 Hz, 1 H), 7.45–7.08 (m, 12 H), 5.16 (s, 1 H), 4.77 (d, J = 16.8 Hz, 1 H, AB), 4.28 (d, J = 16.8 Hz, 1 H, AB), 3.77 (d, J = 16.5 Hz, 1 H, AB), 3.55 (d, J = 16.5 Hz, 1 H, AB), 2.46 (s, 3 H).

^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 162.4, 142.1, 141.1, 139.9, 134.2, 132.8, 131.2, 129.0, 128.7, 127.9, 126.7, 125.2, 122.4, 122.0, 121.0, 112.0, 109.7, 63.1, 53.6, 45.7, 42.6.

MS (ESI): m/z = 400 $[M + H]^+$.

Anal. Calcd for $C_{25}H_{22}ClN_3$: C, 75.08; H, 5.54; N, 10.51. Found: C, 75.30; H, 5.67; N, 10.12.

N-(2-Benzyl-3-phenyl-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-ylidene)cyclohexanamine (35)

Prepared from **16** (100 mg, 0.42 mmol), **19** (46 mg, 0.42 mmol), and **26** (45 mg, 0.42 mmol) in 15 h. **35** was obtained as a yellow solid; yield: 46 mg (25%); mp 84–85 °C; R_f = 0.20 (PE–EtOAc, 1:1).

FT-IR (KBr): 3520, 2231, 1114, 902 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.20 (br s, 1 H), 8.32–8.26 (m, 1 H), 7.80–7.00 (m, 13 H), 5.09 (s, 1 H), 3.97 (d, J = 14.0 Hz, 1 H), 3.80–3.20 (m, 4 H), 1.80–0.90 (m, 10 H).

^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 158.5, 139.5, 137.5, 136.8, 129.2 (2 C), 128.9 (2 C), 128.8, 128.0, 127.7, 122.3, 122.1, 120.6, 112.3, 110.1, 61.3, 58.5, 57.6, 43.7, 35.2, 26.2, 24.5.

MS (ESI): m/z = 434 $[M + H]^+$.

Anal. Calcd for $C_{30}H_{31}N_3$: C, 83.10; H, 7.21; N, 9.69. Found: C, 83.25; H, 7.45; N, 9.48.

N-(2-Benzyl-3-cyclohexyl-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-ylidene)pentan-1-amine (36)

Prepared from **16** (100 mg, 0.42 mmol), **10** (47 mg, 0.42 mmol), and **20** (35 mg, 0.42 mmol) in 4 h. **36** was obtained as a yellow oil; yield: 123 mg (68%); R_f = 0.15 (PE–EtOAc, 6:4).

FT-IR (liquid film): 3517, 2145, 1090, 942 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.07 (br s, 1 H), 8.13 (d, J = 7.0 Hz, 1 H), 7.40–6.98 (m, 8 H), 4.31 (d, J = 20.0 Hz, 1 H, AB), 3.82–3.60 (m, 2 H), 3.54 (d, J = 10.0 Hz, 1 H), 3.38 (s, 2 H), 3.30–3.18 (m, 1 H), 2.35 (d, J = 10.0 Hz, 1 H), 1.80–0.90 (m, 16 H), 0.87 (t, J = 7.0 Hz, 3 H).

^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 162.5, 140.1, 138.2, 137.0, 129.0, 128.7, 127.8, 127.2, 126.0, 121.9, 120.0, 111.4, 109.1, 61.9, 59.2, 51.0, 41.5 (overlapped DMSO), 38.7, 32.0, 30.5, 30.0, 26.8, 26.5, 22.8, 14.3.

MS (ESI): m/z = 428 $[M + H]^+$.

Anal. Calcd for $C_{29}H_{37}N_3$: C, 81.45; H, 8.72; N, 9.83. Found: C, 81.20; H, 8.45; N, 10.08.

N-(2-Butyl-6-chloro-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-ylidene)naphthalen-2-amine (37)

Prepared from **15** (100 mg, 0.42 mmol), **18** (65 mg, 0.42 mmol), and **27** (13 mg, 0.42 mmol) in 6 h. **37** was obtained as a yellow solid; yield: 56 mg (33%); mp 109–110 °C; R_f = 0.30 (PE–EtOAc, 1:9).

FT-IR (KBr): 3394, 2929, 1651, 1491, 1164 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.34 (s, 1 H), 7.85–7.78 (m, 2 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.49–7.35 (m, 2 H), 7.18 (s, 1 H), 7.15–6.99 (m, 2 H), 7.07 (d, *J* = 2.0 Hz, 1 H), 3.97 (s, 2 H), 3.40 (s, 2 H), 2.41 (t, *J* = 7.0 Hz, 2 H), 1.40–1.20 (m, 4 H), 0.83 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 160.7, 148.8, 143.8, 134.7, 134.3, 130.5, 128.9, 127.9, 127.5, 127.4, 126.4, 125.8, 124.4, 123.3, 121.8, 121.5, 115.9, 112.1, 110.8, 56.8, 54.2, 49.6, 29.1, 20.5, 14.0.

MS (ESI): *m*/*z* = 402 [M + H]$^+$.

Anal. Calcd for $C_{25}H_{24}ClN_3$: C, 74.71; H, 6.02; N, 10.45. Found: C, 75.03; H, 5.77; N, 10.18.

Methyl 2-[(3-Cyclohexyl-2-methyl-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-ylidene)amino]acetate (38)

Prepared from **8** (100 mg, 0.62 mmol), **10** (70 mg, 0.62 mmol), and **21** (60 mg, 0.62 mmol) in 8 h. **38** was obtained as a yellow oil; yield: 121 mg (55%); R_f = 0.35 (EtOAc).

FT-IR (liquid film): 2927, 1740, 1612, 1449, 727 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (br s, 1 H), 7.30–7.21 (m, 1 H), 7.20–7.05 (m, 3 H), 4.41 (s, 2 H), 4.30 (d, *J* = 17.0 Hz, 1 H, AB), 3.84 (s, 3 H), 3.52 (d, *J* = 17.0 Hz, 1 H, AB), 3.35 (d, *J* = 10.0 Hz, 1 H), 2.46 (s, 3 H), 2.21–2.15 (m, 1 H), 1.85–0.90 (m, 10 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 172.1, 166.8, 137.2, 136.7, 125.3, 122.4, 121.8, 121.3, 111.0, 109.6, 65.3, 53.3, 52.1, 45.6, 43.9, 38.9, 31.8, 30.5, 26.5.

MS (ESI): *m*/*z* = 354 [M + H]$^+$.

Anal. Calcd for $C_{21}H_{27}N_3O_2$: C, 71.36; H, 7.70; N, 11.89. Found: C, 71.45; H, 7.54; N, 11.67.

N-(2-Butyl-6-chloro-3-cyclohexyl-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-ylidene)pentan-1-amine (39)

Prepared from **15** (100 mg, 0.42 mmol), **10** (47 mg, 0.42 mmol), and **20** (35 mg, 0.42 mmol) in 12 h. **39** was obtained as a yellow solid; yield: 36 mg (20%).; mp 147–148 °C; R_f = 0.15 (PE–EtOAc, 1:9).

FT-IR (KBr): 3214, 2258, 1100, 896 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.29 (br s, 1 H), 8.03 (s, 1 H), 7.33 (d, *J* = 8.2 Hz, 1 H), 7.07 (d, *J* = 8.2 Hz, 1 H), 4.23 (d, *J* = 18.0 Hz, 1 H, AB), 3.70 (d, *J* = 18.0 Hz, 1 H, AB), 3.55–3.50 (m, 1 H), 2.55–2.35 (m, 2 H), 2.17 (d, *J* = 11.0 Hz, 1 H), 1.80–0.80 (m, 28 H).

^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 162.6, 144.8, 136.3, 126.7, 125.0, 121.5, 120.7, 113.3, 109.2, 62.0, 54.6, 50.9, 44.5, 31.8, 30.8, 30.5, 30.0, 26.8, 26.6, 22.6, 20.3, 14.6, 14.4.

MS (ESI): *m*/*z* = 428 [M + H]$^+$.

Anal. Calcd for $C_{26}H_{38}ClN_3$: C, 72.95; H, 8.95; N, 9.82. Found: C, 72.67; H, 8.57; N, 10.04.

N-(3-Hexyl-2-methyl-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-ylidene)-1-tosylmethanamine (40)

Prepared from **8** (100 mg, 0.62 mmol), **22** (121 mg, 0.62 mmol), and **24** (71 mg, 0.62 mmol) in 7 h. **40** was obtained as a brown oil; yield: 90 mg (32%); R_f = 0.30 (EtOAc).

FT-IR (liquid film): 2910, 1863, 1450, 964, 762 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.91 (br s, 1 H), 7.93 (t, *J* = 5.5 Hz, 3 H), 7.33–7.25 (m, 3 H), 7.20–7.02 (m, 2 H), 5.03 (q, *J* = 14.0 Hz, 2 H, AB), 4.25 (d, *J* = 17.0 Hz, 1 H, AB), 3.65–3.50 (m, 2 H), 2.41 (s, 3 H), 2.33 (s, 3 H), 1.60–1.15 (m, 10 H), 0.87 (t, *J* = 6.5 Hz, 3 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 170.8, 144.8, 139.3, 136.5, 135.0, 129.6, 129.5, 125.0, 122.7, 122.1, 121.5, 111.2, 108.8, 73.0, 60.6, 45.1, 43.6, 31.8, 30.2, 29.3, 27.0, 22.7, 21.8, 14.2.

MS (ESI): *m*/*z* = 452 [M + H]$^+$.

Anal. Calcd for $C_{26}H_{33}N_3O_2S$: C, 69.15; H, 7.36; N, 9.30. Found: C, 69.34; H, 7.21; N, 9.56.

N-(3-Isopropyl-2-methyl-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-ylidene)cyclohexanamine (41)

Prepared from **8** (100 mg, 0.62 mmol), **19** (68 mg, 0.62 mmol), and **23** (45 mg, 0.62 mmol) in 4 h. **41** was obtained as a white solid; yield: 111 mg (55%); mp 210–211 °C; R_f = 0.30 (EtOAc–MeOH, 95:5).

FT-IR (KBr): 3477, 2146, 1147, 945 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.08 (br s, 1 H), 8.05 (d, *J* = 8.2 Hz, 1 H), 7.30 (d, *J* = 7.5 Hz, 1 H), 7.06–7.02 (m, 2 H), 4.28 (d, *J* = 17 Hz, 1 H), 3.65–3.58 (m, 2 H), 3.45–3.35 (m, 1 H), 2.40 (s, 3 H), 1.90–1.20 (m, 11 H), 1.10 (d, *J* = 6.5 Hz, 3 H), 0.83 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 160.4, 138.0, 137.0, 125.7, 121.9 (2 C), 120.3, 111.6, 108.9, 65.2, 57.6, 45.3, 43.9, 35.4, 34.9, 28.7, 26.1, 24.7, 21.5, 20.1.

MS (ESI): *m*/*z* = 324 [M + H]$^+$.

Anal. Calcd for $C_{21}H_{29}N_3$: C, 77.97; H, 9.04; N, 12.99. Found: C, 78.14; H, 8.86; N, 13.15.

N-(3-Cyclohexyl-6,7-dimethoxy-2-phenethyl-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-ylidene)pentan-1-amine (42)

Prepared from **17** (100 mg, 0.32 mmol), **10** (36 mg, 0.32 mmol), and **20** (27 mg, 0.32 mmol) in 4 h. **42** was obtained as a yellow oil; yield: 137 mg (85%); R_f = 0.40 (PE–EtOAc, 1:1).

FT-IR (liquid film): 3215, 2341, 1652, 1488, 1207, 750 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.78 (br s, 1 H), 7.62 (s, 1 H), 7.30–7.10 (m, 5 H), 6.87 (s, 1 H), 4.22 (d, *J* = 17.0 Hz, 1 H, AB), 3.75 (s, 3 H), 3.72 (s, 3 H), 3.63 (d, *J* = 17.0 Hz, 1 H, AB), 3.50–3.23 (m, 3 H), 2.80–2.60 (m, 4 H), 2.13 (d, *J* = 11.6 Hz, 1 H), 1.75–0.93 (m, 16 H), 0.86 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 162.9, 146.6, 145.3, 140.8, 137.0, 131.5, 129.2, 128.6, 126.3, 118.5, 109.6, 104.7, 96.1, 62.3, 57.3, 56.4, 56.2, 50.7, 44.5, 38.9, 35.4, 32.0, 31.9, 30.6, 30.1, 26.6, 22.8, 14.7.

MS (ESI): *m*/*z* = 502 [M + H]$^+$.

Anal. Calcd for $C_{32}H_{43}N_3O_2$: C, 76.61; H, 8.64; N, 8.38. Found: C, 76.45; H, 8.34; N, 8.56.

N-(3-Hexyl-6,7-dimethoxy-2-phenethyl-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-ylidene)-1-phenylmethanamine (43)

Prepared from **17** (100 mg, 0.32 mmol), **9** (37 mg, 0.32 mmol), and **24** (36 mg, 0.32 mmol) in 4 h. **43** was obtained as a yellow oil; yield: 121 mg (72%); R_f = 0.25 (PE–EtOAc, 1:9).

FT-IR (liquid film): 2929, 2344, 1477, 1300, 733 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (br s, 1 H), 7.55 (d, *J* = 7.3 Hz, 2 H), 7.36 (t, *J* = 7.6 Hz, 2 H), 7.30–7.10 (m, 5 H), 7.08 (d, *J* = 7.6 Hz, 1 H), 6.77 (s, 1 H), 4.80 (s, 2 H), 4.23 (d, *J* = 17.0 Hz, 1 H, AB), 3.98–3.77 (m, 8 H, 2 × OMe and 2 H overlapped), 3.63 (d, *J* = 17.0 Hz, 1 H, AB), 2.85–2.60 (m, 4 H), 1.70–1.20 (m, 9 H), 0.89 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 165.4, 147.0, 145.5, 142.8, 140.7, 137.7, 129.9, 129.0, 128.7, 127.9, 126.5, 118.4, 108.8, 104.6, 96.2, 58.0, 57.3, 56.5, 56.2, 52.9, 35.2, 32.0, 29.6, 28.9, 26.6, 14.2.

MS (ESI): *m*/*z* = 524 [M + H]$^+$.

Anal. Calcd for $C_{34}H_{41}N_3O_2$: C, 77.98; H, 7.89; N, 8.02. Found: C, 78.20; H, 7.58; N, 8.33.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378921.

References

(1) Ugi, I.; Meyr, U.; Steinbrückner, A. *Angew. Chem.* **1959**, *71*, 386.
(2) Chéron, N.; Ramozzi, R.; El Kaïm, L.; Grimaud, L.; Fleurat-Lessard, P. *J. Org. Chem.* **2012**, *77*, 1361.
(3) *Multicomponent Reactions*; Zhu, J.; Bienaymé, H., Eds.; Wiley-VCH: Weinheim, **2005**.
(4) Zinner, G.; Moderhack, D.; Kliegel, W. *Chem. Ber.* **1969**, *102*, 2536.
(5) Ugi, I.; Bodesheim, F. *Chem. Ber.* **1961**, *94*, 2797.
(6) Ugi, I.; Rosendhal, F. K.; Bodesheim, F. *Justus Liebigs Ann. Chem.* **1963**, *666*, 54.
(7) Ugi, I.; Offermann, K. *Chem. Ber.* **1964**, *97*, 2996.
(8) For interesting reviews, see: (a) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463. (b) El Kaïm, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153.
(9) Tron, G. C. *Eur. J. Org. Chem.* **2013**, 1849.
(10) El Kaïm, L.; Gizolme, M.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 4169.
(11) Oaksmith, J. M.; Peters, U.; Ganem, B. *J. Am. Chem. Soc.* **2004**, *126*, 13606.
(12) Soeta, T.; Kojima, Y.; Ukaji, Y.; Inomata, K. *Org. Lett.* **2010**, *12*, 4341.
(13) Neidlein, R. *Z. Naturforsch., B* **1964**, *19*, 1159.
(14) Pirali, T.; Mossetti, R.; Galli, S.; Tron, G. C. *Org. Lett.* **2011**, *13*, 3734.
(15) (a) Sun, X.; Janvier, P.; Zhao, G.; Bienaymé, H.; Zhu, J. *Org. Lett.* **2001**, *3*, 877. For an excellent review, see: (b) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235.
(16) Lalli, C.; Bouma, M. J.; Bonne, D.; Masson, G.; Zhu, J. *Chem. Eur. J.* **2011**, *17*, 880.
(17) (a) Kysil, V.; Khvat, A.; Tsirulnikov, S.; Tkachenko, S.; Williams, C.; Churakova, M.; Ivachtchenko, A. *Eur. J. Org. Chem.* **2010**, 1525. (b) Keung, W.; Bakir, F.; Patron, A.; Rogers, D.; Priest, C. D.; Darmohusodo, V. *Tetrahedron Lett.* **2004**, *45*, 733.
(18) (a) Deyrup, J. A.; Vestling, M. M.; Hagan, W. V.; Yun, H. Y. *Tetrahedron* **1969**, *25*, 1467. (b) Schneekloth, J. S.; Kim, J.; Sorensen, E. J. *Tetrahedron* **2009**, *65*, 3096. (c) Kim, J.; Schneekloth, J. S.; Sorensen, E. J. *Chem. Sci.* **2012**, *3*, 2849.
(19) Varadi, A.; Palmer, T. C.; Notis, P. R.; Redel-Traub, G. N.; Afonin, D.; Subrath, J. J.; Pasternak, G. W.; Hu, C.; Sharma, I.; Majumdar, S. *Org. Lett.* **2014**, *16*, 1668.
(20) (a) Bienaymé, H.; Bouzid, K. *Angew. Chem.* **1998**, *110*, 2349. (b) Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661. (c) Blackburn, B.; Guan, P.; Fleming, K.; Shiosaki, S.; Tsai, S. *Tetrahedron Lett.* **1998**, *39*, 3635.
(21) Vinylogous amidines have been described; see: (a) LaBarbera, D. V.; Skibo, E. B. *J. Org. Chem.* **2013**, *78*, 11887. (b) Gartshore, G. J.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 4113.
(22) CCDC 1003584 contains the supplementary crystallographic data for compound **11** reported in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(23) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354.
(24) Farrugia, L. J. *J. Appl. Crystallogr.* **2012**, *45*, 849.
(25) For an example of interception of the nitrilium ion by the C3 of indole, see: (a) Wang, X.; Wang, S. Y.; Ji, S. J. *Org. Lett.* **2013**, *15*, 1954. (b) Kobayashi, K.; Izumi, Y.; Hayashi, K.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 2171.
(26) Hegarthy, A. F. *Acc. Chem. Res.* **1980**, *13*, 448.
(27) To the best of our knowledge, only some work where the pyrrole ring was able to trap the nitrilium ion has been described, by the Kobayashi group; see: (a) Kobayashi, K.; Matsumoto, T.; Irisawa, S.; Yoneda, K.; Morikawa, O.; Konishi, H. *Heterocycles* **2001**, *55*, 973. (b) Kobayashi, K.; Takanohashi, A.; Hashimoto, K.; Morikawa, O.; Konishi, H. *Tetrahedron* **2006**, *62*, 10379. (c) Kobayashi, K.; Himei, Y.; Izumi, Y.; Fukamachi, S.; Morikawa, O.; Konishi, H. *Heterocycles* **2007**, *71*, 691.
(28) Miller, W. H.; Newlander, K. A.; Seefeld, M. A.; Uzinskas, I. N.; DeWolf, W. E.; Jakas, D. R. PCT Int. Appl WO 2001027103, **2001**.
(29) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* **2004**, *6*, 3199.