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Synthesis of pyrimido[6,1-*a*]isoquinolines via a one-pot, four-component reaction

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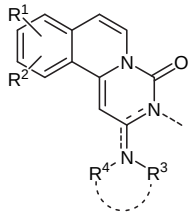
ABSTRACT

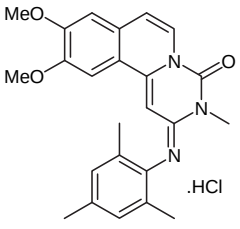
An efficient one-pot synthesis of pyrimido[6,1-*a*]isoquinoline-1-carboxylate derivatives is described. This involves the four-component reaction between primary amines, alkyl acetoacetates, isoquinoline and trichloromethylchloroformate (diphosgene) under mild conditions at ambient temperature.

1. Introduction

Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and unnatural products, many of which exhibit useful biological activity and are used in pharmaceutical preparations.[1-4] A broad range of biological activities has been reported for compounds containing the pyrimido-[6,1-*a*]isoquinoline ring system and a number of these compounds (pyrimidoisoquinoline derivatives **1**) are patented as potential therapeutic agents (Scheme 1).[5,6] Amongst the reported ones are antihypertensive, bronchodilator, blood pressure lowering, anti inflammatory and anti-allergic activities. The antihypertensive agent Trequinsin **2** (Scheme 1), for instance,[7] is one of the most potent in vitro inhibitors of platelet phosphodiesterase and platelet aggregation known to date.[2] This makes the pyrimido[6,1-*a*]isoquinoline skeleton an important synthetic target and a lot of research has been directed towards it.



Pyrimidoisoquinoline derivatives **1**



Trequinsin **2**

Scheme 1.

Compounds of this type are usually synthesized by ring closure of suitable tetrahydroisoquinolines,[5,7–14] Bischler–Napieralsky cyclization of 1-(3,4-dimethoxyphenylethyl) barbituric acid[5] or other appropriate *N*-phenethyl amides.[15,16] An interesting and versatile pyrimido-[6,1-*a*]isoquinoline synthesis involves enaminones.[17] Enaminones and related compounds possessing this structural unit are versatile synthetic intermediates in organic chemistry that combine the ambient nucleophilicity of an enamine and the electrophilicity of enones.[18] They are frequently applied in the preparation of heterocycles.[19]

As part of our continuing effort into the design of new routes for the preparation of biologically active heterocyclic compounds using the synthesis and reactions of enamines and enaminones,[20–23] herein we describe a simple, one-pot, four-component synthesis of pyrimido-[6,1-*a*]isoquinoline-4-one derivatives.

2. Results and discussion

Our new synthetic method leading to the formation of the title compounds is given in Scheme 2. Reaction between an enaminone, derived from the addition of various primary amines **3** to alkyl acetoacetates **4**, with trichloromethylchloroformate in the presence of isoquinoline in dry CH_2Cl_2 at ambient temperature to produce the methyl or ethyl 3-alkyl-2-methyl-4-oxo-3,11b-dihydro-4*H*-

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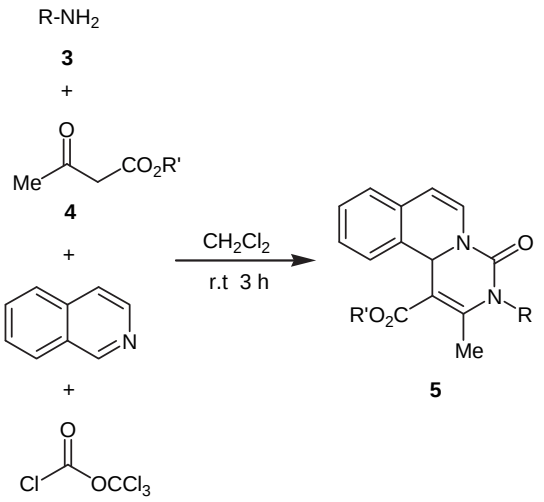
pyrimido[6,1-*a*]isoquinoline-1-carboxylate derivatives in 80–90% yields (Scheme 2).



Scheme 2. The reaction of primary amine **3**, alkyl acetoacetates **4**, isoquinoline and trichloromethylchloroformate (diphosgene).

The diversity of the MCR with respect to the amine component was investigated and indicated in Table 1.

The structures of compounds **5a**–**f** were deduced from their elemental analysis, IR and high-field ^{1}H and ^{13}C NMR spectra. The mass spectrum of **5a** displayed the molecular ion peak at *m*/*z* 360, which is in agreement with the proposed structure. The IR spectrum of this compound showed absorption bands due to the two carbonyl groups at 1710, 1673 and a NC=C group at 1633 cm^{-1}. The ^{1}H NMR spectrum of **5a** showed three sharp singlets for CH_3, OCH_3 and CH groups (δ=2.50, 3.66 and 5.47 ppm), a multiplet for CH_2Ph (δ=4.99–5.02 ppm), two doublets for the N–CH=CH (δ=6.45 ppm, J=9.0 Hz) and N–CH=CH (δ=6.95 ppm, J=9.0 Hz), and the aromatic moieties gave rise to multiplets in the aromatic region of the spectrum (δ=7.12–7.34 ppm). The ^{1}H decoupled ^{13}C NMR spectrum of **5a** showed 20 distinct resonances in agreement with the suggested structure. Finally, the structure of **5**, for example, **5d** was further confirmed by a single crystal X-ray diffraction analysis (Fig. 1).

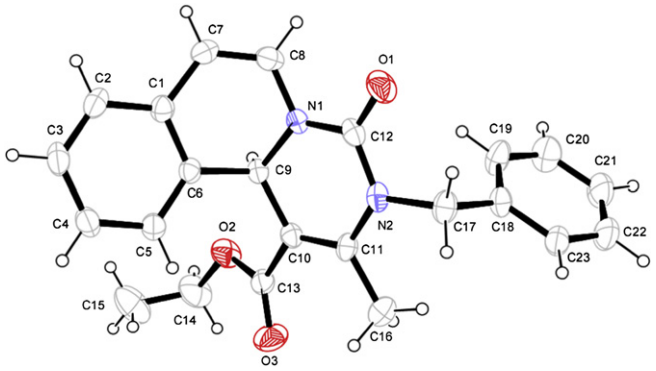
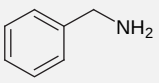
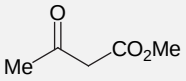
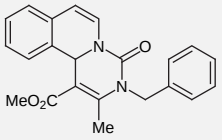
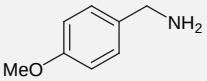
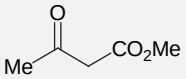
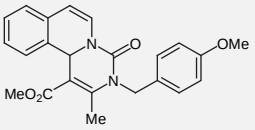
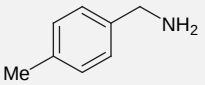
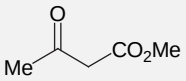
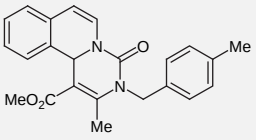
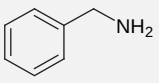
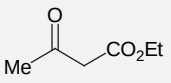
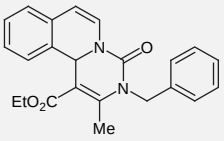
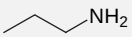
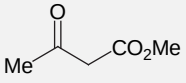
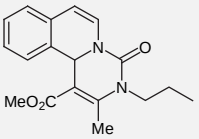
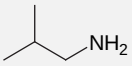
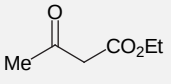
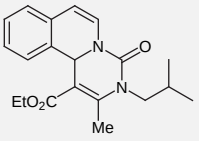
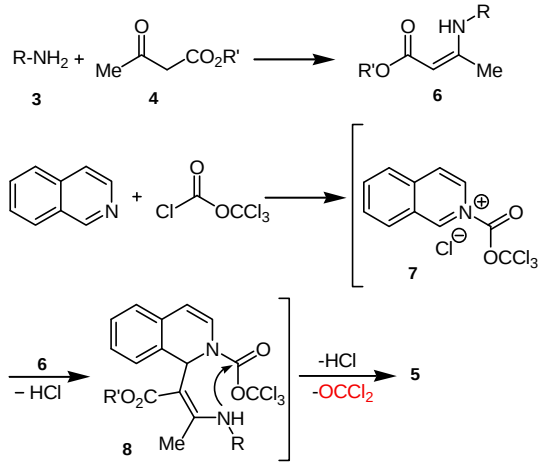


Figure 1. The molecular structure of compound **5d**.

Table 1
Methyl or ethyl 3-alkyl-2-methyl-4-oxo-3,11b-dihydro-4*H*-pyrimido[6,1-*a*]isoquinoline-1-carboxylate derivatives prepared by the mentioned reaction

Entry	Primary amine **3**	Alkyl acetoacetates **4**	Product **5**	Yield %
a				85
b				87
c				85
d				90
e				80
f				85

Although we have not established the mechanism of reaction experimentally, a possible explanation is proposed in Scheme 3. On the basis of the well-established chemistry of enaminone nucleophiles,[24–26] it is reasonable to assume that enaminone **6**, produced by the addition of primary amine **3** to alkyl acetoacetates **4**, can add to the electrophilic C=N bond of *N*-acyliminium compound **7** (which is derived from the addition of isoquinoline to trichloromethylchloroformate) resulting in the formation of **8**. Finally, cyclization of the intermediate **8** and subsequent elimination of $OCCl_2$ and HCl leads to pyrimido[6,1-*a*]isoquinoline-1-carboxylate derivatives **5**.



Scheme 3. Possible mechanism for the formation of pyrimido[6,1-*a*]isoquinoline-1-carboxylate derivatives.

3. Conclusion

In summary, we have demonstrated that the one-pot four-component reaction between primary amines, alkyl acetoacetates, isoquinoline and trichloromethylchloroformate (diphosgene) provides a simple method for the preparation of pyrimido-isoquinolines of potential synthetic and pharmacological interest. Fairly high yields of the products without any activation, the ready availability of the starting materials, the reaction's simplicity and its mild conditions are the main advantages of this method.

4. Experimental

4.1. General

Primary amines, alkyl acetoacetates, and trichloromethylchloroformate were obtained from Merck (Germany) and Fluka (Switzerland). Elemental analyses for C, H and N were performed using a Heraeus CHN–O–Rapid analyzer. ^1H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 AVANCE spectrometer at 500.13 and 125.75 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 230–240 mesh. Mass spectra were obtained using a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV.

4.2. General synthesis procedure: (for example, 5a)

To a magnetically stirred solution of benzylamine (0.11 g, 1 mmol) and methyl acetoacetate (0.12 g, 1 mmol) in anhydrous CH_2Cl_2 (5 mL) after 1 h was added isoquinoline (0.13 g, 1 mmol), and finally a solution of trichloromethylchloroformate (0.20 g, 1 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise at rt over 15 min. The reaction mixture was stirred for 3 h, then the solvent was removed under reduced pressure and the residue was purified by column chromatography (*n*-hexane–EtOAc, 8:1).

*4.2.1. Methyl 3-benzyl-2-methyl-4-oxo-3,11b-dihydro-4H-pyrimido[6,1-a]isoquinoline-1-carboxylate (**5a**).* Yellow oil, 0.30 g, yield 85%. IR (KBr) (ν_{max}, cm^{-1}): 1710 (CO_2Me), 1673 (NCON), 1633 (NC=C), 1267 and 1215 (C-O of ester). Anal. Calcd for $C_{22}H_{20}N_2O_3$ (360.41): C, 73.32; H, 5.59; N, 7.77%. Found: C, 73.14; H, 5.43; N, 7.82%. MS (EI, 70 eV): *m*/*z* (%)=360 (M^+, 7), 345 (4), 328 (6), 289 (15), 223 (14), 158 (30), 128 (95), 106 (41), 91 (100). ^1H NMR (500.13 MHz, $CDCl_3$): δ_H=2.50 (3H, s, CH_3), 3.66 (3H, s, OCH_3), 5.00 (2H, AB quartet, $^3J_{HH}$=15.3 Hz, CH_2), 5.47 (1H, s, CH), 6.45 (1H, d, $^3J_{HH}$=7.2 Hz, NCH=*CH*), 6.95 (1H, d, $^3J_{HH}$=7.6, N*CH*=CH), 7.12–7.34 (9H, m, 9×CH of isoquinoline and Ph). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=16.80 (CH_3), 46.79 (CH_2), 51.55 (OCH_3), 55.20 (CH), 99.79 (NCH=*C*H), 116.10 (*C*=C–CH_3), 122.67 (CH of isoquinoline), 124.24 (CH of isoquinoline), 125.86 (2×CH of Ph), 127.13 (CH of isoquinoline), 127.20 (NCH=CH), 127.55 (CH of isoquinoline), 128.57 (CH_{para} of Ph), 128.83 (2×CH of Ph), 131.86 (C^{11a}), 131.94 (C^{7a}), 137.76 (C_{ipso} of Ph), 149.23 (CH_3C=C), 149.54 (NCON), 167.22 (CO_2Me).

*4.2.2. Methyl 3-(4-methoxybenzyl)-2-methyl-4-oxo-3,11b-dihydro-4H-pyrimido[6,1-a]isoquinoline-1-carboxylate (**5b**).* Yellow oil, 0.33 g, yield 87%. IR (KBr) (ν_{max}, cm^{-1}): 1709 (CO_2Me), 1671 (NCON), 1631 (NC=C), 1247 and 1219 (C–O of ester). Anal. Calcd for $C_{23}H_{22}N_2O_4$ (390.43): C, 70.75; H, 5.68; N, 7.17%. Found: C, 70.78; H, 5.59; N, 7.11%. MS (EI, 70 eV): *m*/*z* (%)=390 (M^+, 21), 374 (15), 359 (14), 269 (16), 255 (12), 237 (16), 167 (30), 149 (60), 121 (100). ^1H NMR (500.13 MHz, $CDCl_3$): δ_H=2.52 (3H, s, CH_3), 3.65 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.90 (2H, AB quartet, $^3J_{HH}$=15.0 Hz, CH_2), 5.45 (1H, s, CH), 6.44 (1H, d, $^3J_{HH}$=7.2 Hz, NCH=CH), 6.94 (1H, d, $^3J_{HH}$=7.1 Hz, N*CH*=CH), 6.80–7.26 (8H, m, 8×CH of isoquinoline and Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=16.78 (CH_3), 46.31 (CH_2), 51.52 (OCH_3), 55.19 (OCH_3), 55.30 (CH), 99.73 (NCH=*C*H), 114.27 (2×CH of Ar), 116.02 (*C*=C–CH_3), 122.67 (CH of isoquinoline), 124.21 (CH of isoquinoline), 127.10 (CH of isoquinoline), 127.29 (2×CH of Ar), 127.52 (CH of isoquinoline), 128.60 (NCH=CH), 129.81 (C_{ipso}–CH_2), 131.87 (C^{11a}), 131.95 (C^{7a}), 149.30 (CH_3C=C), 149.57 (NCON), 158.83 (C_{ipso}–OCH_3), 167.24 (CO_2Me).

*4.2.3. Methyl 2-methyl-3-(4-methylbenzyl)-4-oxo-3,11b-dihydro-4H-pyrimido[6,1-a]isoquinoline-1-carboxylate (**5c**).* Yellow oil, 0.31 g, yield 85%. IR (KBr) (ν_{max}, cm^{-1}): 1722 (CO_2Me), 1675 (NCON), 1622 (NC=C), 1267 and 1214 (C–O of ester). Anal. Calcd for $C_{23}H_{22}N_2O_3$ (374.43): C, 73.78; H, 5.92; N, 7.48%. Found: C, 73.90; H, 6.00; N, 7.12%. MS (EI, 70 eV): *m*/*z* (%)=374 (M^+, 38), 359 (27), 314 (9), 269 (22), 255 (22), 167 (47), 149 (85), 105 (100), 71 (54), 57 (85), 43 (84). ^1H NMR (500.13 MHz, $CDCl_3$): δ_H=2.30 (3H, s, CH_3), 2.50 (3H, s, CH_3), 3.65 (3H, s, OCH_3), 4.97 (2H, AB quartet, $^3J_{HH}$=15.2 Hz, CH_2), 5.45 (1H, s, CH), 6.44 (1H, d, $^3J_{HH}$=7.25 Hz, NCH=CH), 6.94 (1H, d, $^3J_{HH}$=7.10 Hz, N*CH*=CH), 7.14–7.28 (8H, m, 8×CH of isoquinoline and Ar). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=16.80 (CH_3), 21.02 (CH_3), 46.60 (CH_2), 51.51 (OCH_3), 55.19 (CH), 99.70 (NCH=*C*H), 116.02 (*C*=C–CH_3), 122.67 (CH of isoquinoline), 124.21 (CH of isoquinoline), 125.88 (2×CH of Ar), 127.10 (CH of isoquinoline), 127.52 (CH of isoquinoline), 128.62 (NCH=CH), 129.47 (2×CH of Ar), 131.88 (C^{11a}), 131.96 (C^{7a}), 134.73 (C_{ipso}–CH_2), 136.83 (C_{ipso}–CH_3), 149.34 (CH_3C=C), 149.55 (NCON), 167.24 (CO_2Me).

*4.2.4. Ethyl 3-benzyl-2-methyl-4-oxo-3,11b-dihydro-4H-pyrimido[6,1-a]isoquinoline-1-carboxylate (**5d**).* Yellow oil, 0.33 g, yield 90%. IR (KBr) (ν_{max}, cm^{-1}): 1702 (CO_2Me), 1669 (NCON), 1629 (NC=C),

1264 and 1216 (C–O of ester). Anal. Calcd for $C_{23}H_{22}N_2O_3$ (374.44): C, 73.78; H, 5.92; N, 7.48%. Found: C, 73.69; H, 5.87; N, 7.56%. MS (EI, 70 eV): *m*/*z* (%)=374 (M^+, 45), 359 (14), 345 (84), 300 (16), 237 (16), 195 (5), 167 (18), 129 (12), 91 (100). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=1.13 (3H, t, $^3J_{HH}$=7.1 Hz, OCH_2CH_3), 2.51 (3H, s, CH_3), 4.12–4.22 (2H, m, OCH_2CH_3), 4.96 (2H, AB quartet, $^3J_{HH}$=15.0 Hz, CH_2), 5.49 (1H, s, CH), 6.45 (1H, d, $^3J_{HH}$=7.3 Hz, NCH=C*H*), 6.99 (1H, d, $^3J_{HH}$=6.9 Hz, NC*H*=CH), 7.13–7.30 (9H, m, 9×CH of isoquinoline and Ph). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=14.08 (OCH_2CH_3), 16.75 (CH_3), 46.76 (CH_2), 55.21 (CH), 60.43 (OCH_2CH_3), 100.12 (NCH=*C*H), 116.04 (*C*=C–CH_3), 122.86 (CH of isoquinoline), 124.15 (CH of isoquinoline), 125.86 (2×CH of Ph), 126.96 (CH of isoquinoline), 127.17 (NCH=CH), 127.51 (CH of isoquinoline), 128.52 (CH_{para} of Ph), 128.80 (2×CH of Ph), 131.76 (C^{11a}), 131.89 (C^{7a}), 137.81 (C_{ipso} of Ph), 148.83 (CH_3C=C), 149.56 (NCON), 166.72 (CO_2Me). Crystal data for **5d** $C_{23}H_{22}N_2O_3$ (CCDC 771562): M_W=374.4, monoclinic, space group Cc, a=21.0287(7) Å, b=9.6284(4) Å, c=19.1859(8) Å, α=90 β=92.730(3), γ=90°, V=3880.21(6) Å^3, Z=8, D_c=1.282 mg/m^3, F (000)=1584, crystal dimension 0.46×0.20×0.16 mm, radiation, Mo Kα (λ=0.71073 Å), 3.6≤2θ≤25.2, intensity data were collected at 295(2) K with a Bruker APEX area-detector diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of −25≤*h*≤21, −11≤*k*≤11, −19≤*l*≤22; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 2372 observed reflections with R (into)= 0.0643 by a full-matrix least-squares technique converged to R=0.042 and Raw=0.105 [I>2sigma(I)].

*4.2.5. Methyl 2-methyl-4-oxo-3-propyl-3,11b-dihydro-4H-pyrimido [6,1-a]isoquinoline-1-carboxylate (**5e**).* Yellow oil, 0.25 g, yield 80%. IR (KBr) (ν_{max}, cm^{-1}): 1704 (CO_2Me), 1671 (NCON), 1627 (NC=C), 1264 and 1224 (C–O of ester). Anal. Calcd for $C_{18}H_{20}N_2O_3$ (312.37): C, 69.21; H, 6.45; N, 8.97%. Found: C, 69.25; H, 6.32; N, 8.84%. MS (EI, 70 eV): *m*/*z* (%)=312 (M^+, 89), 297 (100), 269 (28), 255 (49), 237 (18), 211 (20), 167 (31), 129 (27), 43 (39). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=0.94 (3H, t, $^3J_{HH}$=7.30 Hz, CH_3), 1.61–1.66 (2H, m, CH_2), 2.60 (3H, s, CH_3), 3.67 (3H, s, OCH_3), 3.61–3.68 (2H, m, NCH_2), 5.38 (1H, s, CH), 6.40 (1H, d, $^3J_{HH}$=7.30 Hz, NCH=C*H*), 6.90 (1H, d, $^3J_{HH}$=7.10 Hz, NC*H*=CH) 7.10–7.26 (4H, m, 4×CH of isoquinoline). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=10.94 (CH_3), 16.45 (CH_3), 22.94 (CH_2), 45.22 (NCH_2), 51.44 (OCH_3), 55.06 (CH), 99.09 (NCH=*C*H), 115.61 (*C*=C–CH_3), 122.59 (CH of isoquinoline), 124.06 (CH of isoquinoline), 126.95 (CH of isoquinoline), 127.39 (CH of isoquinoline), 128.47 (NCH=CH), 131.84 (C^{11a}), 131.90 (C^{7a}), 148.90 (CH_3C=C), 148.97 (NCON), 167.41 (CO_2Me).

*4.2.6. Ethyl 3-isobutyl-2-methyl-4-oxo-3,11b-dihydro-4H-pyrimido [6,1-a]isoquinoline-1-carboxylate (**5f**).* Yellow oil, 0.29 g, yield 85%. IR (KBr) (ν_{max}, cm^{-1}): 1704 (CO_2Me), 1672 (NCON), 1630 (NC=C), 1273 and 1228 (C–O of ester). Anal. Calcd for $C_{20}H_{24}N_2O_3$ (340.42): C, 70.57; H, 7.11; N, 8.23%. Found: C, 70.66; H, 7.03; N, 7.33%. MS (EI, 70 eV): *m*/*z* (%)=340 (M^+, 93), 325 (17), 311 (100), 283 (16), 266 (20), 255 (90), 211 (21), 167 (21), 129 (15), 57 (18), 41 (36). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=0.75 (3H, d, $^3J_{HH}$=6.75 Hz, CH_3), 0.85 (3H, d, $^3J_{HH}$=6.75 Hz, CH_3), 1.12 (3H, t, $^3J_{HH}$=7.10 Hz, OCH_2CH_3), 1.82–1.90 (1H, m, CH), 2.58 (3H, s, CH_3), 3.37 (1H, dd, $^2J_{HH}$=13.7 Hz, $^3J_{HH}$=7.0 Hz, CH_2N), 3.82 (1H, dd, $^2J_{HH}$=13.8 Hz, $^3J_{HH}$=7.1 Hz, CH_2N), 4.16–4.20 (2H, m, OCH_2CH_3), 5.39 (1H, s, CH), 6.40 (1H, d, $^3J_{HH}$=7.25 Hz, NCH=C*H*), 6.95 (1H, d, $^3J_{HH}$=7.25 Hz, NC*H*=CH), 7.09–7.22 (4H, m, 4×CH of isoquinoline). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=14.07 (OCH_2CH_3), 16.88 (CH_3), 19.67 (CH_3), 19.82 (CH_3), 28.77 (CH), 49.73(CH_2N), 55.07 (CH), 60.35 (OCH_2CH_3), 100.27 (NCH=*C*H), 115.82 (*C*=C–CH_3), 122.69 (CH of isoquinoline), 124.07 (CH of isoquinoline), 126.87 (CH of isoquinoline), 127.37 (NCH=CH), 128.68 (CH of isoquinoline), 131.82 (C^{11a}), 131.86 (C^{7a}), 148.86 (CH_3C=C), 149.60 (NCON), 166.89 (CO_2Me).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.06.033. These data include MOL files and InChIKeys of the most important compounds described in this article.

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