Author(s): Miklós, Ferenc; Bozó, Kristóf; Galla, Zsolt; Haukka, Matti; Fülöp, Ferenc

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Traceless chirality transfer from a norbornene β-amino acid to pyrimido[2,1-*a*]isoindole enantiomers

Ferenc Miklós [a], Kristóf Bozó [a], Zsolt Galla [a], Matti Haukka [c], Ferenc Fülöp [a,b,*]

[a] *Institute of Pharmaceutical Chemistry, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary*
[b] *Stereochemistry Research Group of the Hungarian Academy of Sciences, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary*
[c] *Department of Chemistry, University of Jyväskylä, FIN-40014 Jyväskylä, Finland*

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Dedicated to the Memory of Professor Howard Flack

ABSTRACT

The synthesis of two enantiomeric pairs of pyrimidoisoindoles **9a**, **9b** and **10a**, **10b** is reported. During a domino ring-closure reaction, followed by cycloreversion, the chirality of *diendo*-(−)-(1*R*,2*S*,3*R*,4*S*)-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxamide [(−)-**1**] was successfully transfered to heterocycles (+)-**9a**, (+)-**10a**, (−)-**9b**, (−)-**10b** and (−)-**10c**.

1. Introduction

Several pyrimido[2,1-*a*]isoindoles are well known for their potential biological and pharmacological properties such as prolactin-inhibition,[1] antidepressant and diuretic,[2] anxiolytic,[3] vasorelaxant,[4] antiplasmodial[5] and antifungal[6] activity. In contrast to these findings, derivatives of these heterocyles are still insufficiently studied, even less their enantiomers. To our best knowledge so far, as single enantiomers, 1*N*-Me,[7] -OMe,[8] and -OBn[8] substituted pyrimidoisoindole derivatives have been synthetized. Compounds were prepared by the application of retro Diels–Alder (rDA) reaction.[9]

2. Results and discussion

In an earlier paper,[7] we described an enantioselective synthesis of pyrimido[2,1-*a*]isoindoles by microwave-induced retro Diels–Alder[10] reaction. *diexo*-(−)-3-Amino-norbornene-2-carboxylic acid readily available through an enzymatic resolution was used as a starting chiral source.[11]

The goal of the present work was to explore further extensions of the above methodology that includes (i) the introduction of *diendo*-(−)-ethyl-3-aminonorbornene-2-carboxylate as a chiral source, (ii) the use of 2-formyl-, 2-acetyl- and 2-(4-methylbenzoyl)-benzoic acid for the preparation of isoindoloquinazolinone intermediates, (iii) the investigation of the steric effect of the 2-formyl and 2-acyl groups on the diastereoselectivity of the ring-closure reaction, (iv) separation of diastereomers, and (v) removal of cyclopentadiene in a retro Diels–Alder reaction to obtain pyrimido[2,1-*a*]isoindole racemates and enantiomers.

Both racemic and enantiomeric *diendo*-3-aminonorbornene-2-carboxamide for the synthesis of isoindolo-quinazolines were prepared by a known literature protocol.[12] A preparative-scale resolution of racemic ethyl *diendo*-3-aminocicyclo[2.2.1]hept-5-ene-2-carboxylates was achieved by adopting the diastereomeric salt formation with (*R*)-(−)-mandelic acid.[13] The reaction afforded ethyl (−)-(1*R*,2*S*,3*R*,4*S*)-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylate applied in the synthesis of (−)-(1*R*,2*S*,3*R*,4*S*)-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxamide (−)-**1**.

In preliminary studies on the three-step domino reaction,[14] racemic *diendo*-3-aminonorbornene-2-carboxamide (±)-**1** was reacted with 2-formylbenzoic acid (R = H), 2-acetylbenzoic acid (R = Me) or 2-(4-methylbenzoyl)benzoic acid (R = 4-MeC_6H_4) in toluene under reflux in the presence of *p*-toluenesulfonic acid (*p*-TSA) as catalyst. The reaction mixture of (±)-**1** (monitored by TLC) was transferred to a neutral Al_2O_3 column and the cyclization products (±)-**2a**–**4b** were eluted with EtOAc. The solvent was then removed and diastereomeric ratios of (±)-**2a**–**4a** and (±)-**2b**–**4b** were determined by the integration of ^{1}H NMR spectra. The diastereomerically pure isoindoloquinazolinones were readily separated by silica gel chromatography [*n*–hexane–EtOAc (2:1)]. The structures of (±)-**2a**, (±)-**2b**, (±)-**3a**; and (±)-**3b**, (±)-**4a** and (±)-**4b** were elucidated on the basis of spectroscopic data, in particular, information acquired by 2D-NMR (Scheme 1). The relative configurations of diastereomeric pairs (±)-**2a** and (±)-**2b** as well as (±)-**3a** and (±)-**3b** were determined by employing X-ray crystallographic analysis (Fig. 1). In accordance with the literature data, mutual NOEs were observed for ArH-2,6 and 12a-H (NC*H*), and also for ArH-2,6 and 4a-H [C*H*(C=O)] in (±)-**4b**,[15] while the structure of

* Corresponding author.
E-mail address: fulop@pharm.u-szeged.hu (F. Fülöp).

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(±)-**4a** was supported by a strong NOE measured between ArH-2,6 and 3-H (olefinic) atoms.[16]

With the isoindoloquinazolinones in hand, considerable efforts were made to accomplish their thermal decomposition under microwave irradiation. On the basis of the optimized reaction conditions shown in Scheme 1, pyrimidoisoindoles (±)-**5a**–**5c** were obtained almost quantitatively and in high purity from both **2a**–**4a** and **2b**–**4b**. Interestingly, in our earlier study,[17] (±)-**5a** formed directly on cyclization and thermolysis through the reaction of *diexo*-3-amino-7-oxanorbornene-2-carboxamide with 2-formylbenzoic acid, when the non-isolated oxygen-bridged intermediate decomposed *via* the loss of furan in a retro Diels–Alder reaction.

To establish the generality and synthetic potential of the cyclization of (±)-**1** with 2-formylbenzoic acid or 4-oxo acids followed by the easy separation of the diastereomers and the successful retro Diels–Alder reaction, the preparation of enantiomerically pure pyrimido[2,1-*a*]isoindoles was attempted. By the ammonolysis of ethyl (−)-(1*R*,2*S*,3*R*,4*S*)-3-aminobicyclo[2.2.1] hept-5-ene-2-carboxylate, the amorphous free base (−)-**1** was obtained with an *ee* value about 98%. To determine the physical and optical properties of poorly crystallized (−)-**1** its HCl salt was prepared. In a stereocontrolled cyclization, (−)-**1** was treated with 2-formylbenzoic acid, 2-acetylbenzoic acid and 2-(4-toluoyl) benzoic acid under reaction conditions similar to those presented in Scheme 1. The reactions gave epimeric pentacycle pairs (−)-**6a** and (+)-**6b**, (+)-**7a** and (−)-**7b** and **8a** and (+)-**8b** (Scheme 2). The presence of diastereomer **8a** was observed only in the proton spectrum of the crude diastereomeric mixture, and a sufficient amount of **8a** was not available for further investigations. The purified isomers were subjected to microwave-assisted retro Diels–Alder reaction, resulting in the enantiomeric (+)-**9a** and (+)-**10a** from (−)-**6a** and (+)-**7b**, respectively. Furthermore, the counterpart (−)-**9b** and (−)-**10b** from (+)-**6b** and (−)-**7b** could also be obtained. The single enantiomer (−)-**10c** was prepared by the thermolysis of (+)-**8b**. The ready loss of cyclopentadiene afforded the expected enantiomers in yields of 89–97% and with *ee* values of ≥99%.

It should be noted that all spectroscopic data of the enantiopure compounds were identical with those of the racemic samples.

3. Conclusions

In conclusion, an efficient synthesis of pyrimidoisiondole enatiomers has been accomplished. The chirality of parent β-amino carboxamide (−)-**1** was completely preserved during the stereocontrolled three-step domino reaction to give epimeric pairs. The effective separation of diastereomers followed by their racemization-free retro Diels–Alder reaction allowed the formation of enantiomerically pure pyrimidoisoindoles (+)-**9a** and (+)-**10a**, (−)-**9b**, and (−)-**10b** and (−)-**10c**.

4. Experimental

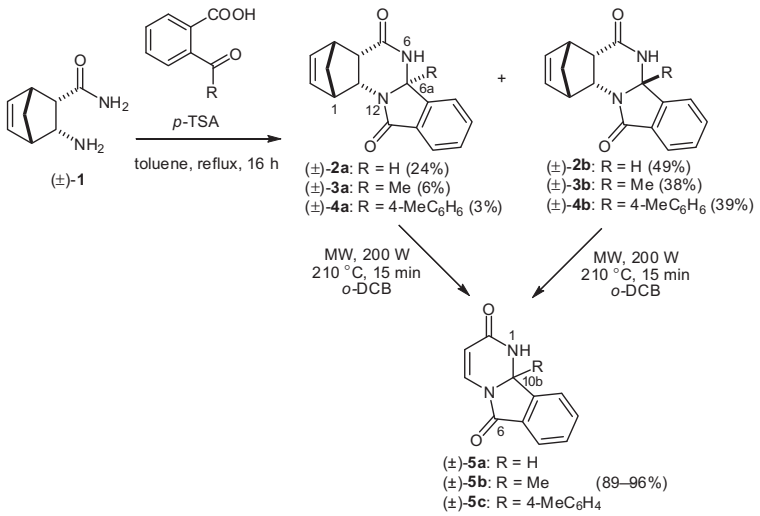
4.1. General

Melting points were determined on a Kofler apparatus and are uncorrected. ^{1}H NMR (400 Hz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance DRX 400 spectrometer, with TMS as internal reference and DMSO-d_6 or $CDCl_3$ as solvent. FTIR spectra were recorded on a Perkin-Elmer 100 FT-IR spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400 elemental analyser. Microwave-promoted reactions were performed in sealed reaction vials (10 mL) by means of a CEM, Discover microwave reactor. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. Mass spectra were recorded on a Finnigan MAT 95S spectrometer.

The *ee* values of (+)-**10a** and (−)-**10b** were determined on a Chiralpak IA column (4.6 × 250 mm); detection at 332 nm; eluent: *n*-hexane/Et_2NH/*i*-PA (75/0.1/25); flow rate: 0.5 mL/min; retention times (min) for (+)-**10a**: 23.96 (antipode, (−)-**10b**: 25.66). Conditions for (+)-**11a** and (−)-**11b**: Chiralpak IA column (4.6 × 250 mm); detection at 236 nm; eluent: *n*–hexane/Et_2NH/*i*-PA (90/0.1/10); flow rate: 0.5 mL/min; retention times (min) for (+)-**11a**: 41.26 (antipode, (−)-**11b**: 46.02). Data for (+)-**9a** and (−)-**9b**: Chiralpak IA column (4.6 × 250 mm); detection at 220 nm; eluent: *n*–hexane/Et_2NH/*i*-PA (90/0.1/10); flow rate: 0.5 mL/min; retention times (min) for (+)-**9a**: 49.19 (antipode, (−)-**9b**: 51.57). The *ee* value of (−)-**1** was determined on a GC equipped with a Chrompack Chirasil-Dex CB column after a simple derivatization with Ac_2O in the presence of 4-dimethylaminopyridine and pyridine [120 °C for 4 min → 170 °C (temperature rise 10 °C min^{-1}; 140 kPa; retention times (min), (−)-**1**: 22.25 (antipode: 23.25)].

4.1.1. X-ray structure determination

The crystals of **2a**, **2b**, **3a**, and **3b** were immersed in cryo-oil, mounted in a MiTeGen loop, and measured at 120–170 K on a Rigaku Oxford Diffraction Supernova or on a Bruker Kappa Apex



Scheme 1. Preparation of pyrimidoisoindoles (±)-**5a**–**5c** by domino ring closure, followed by thermal cycloreversion.

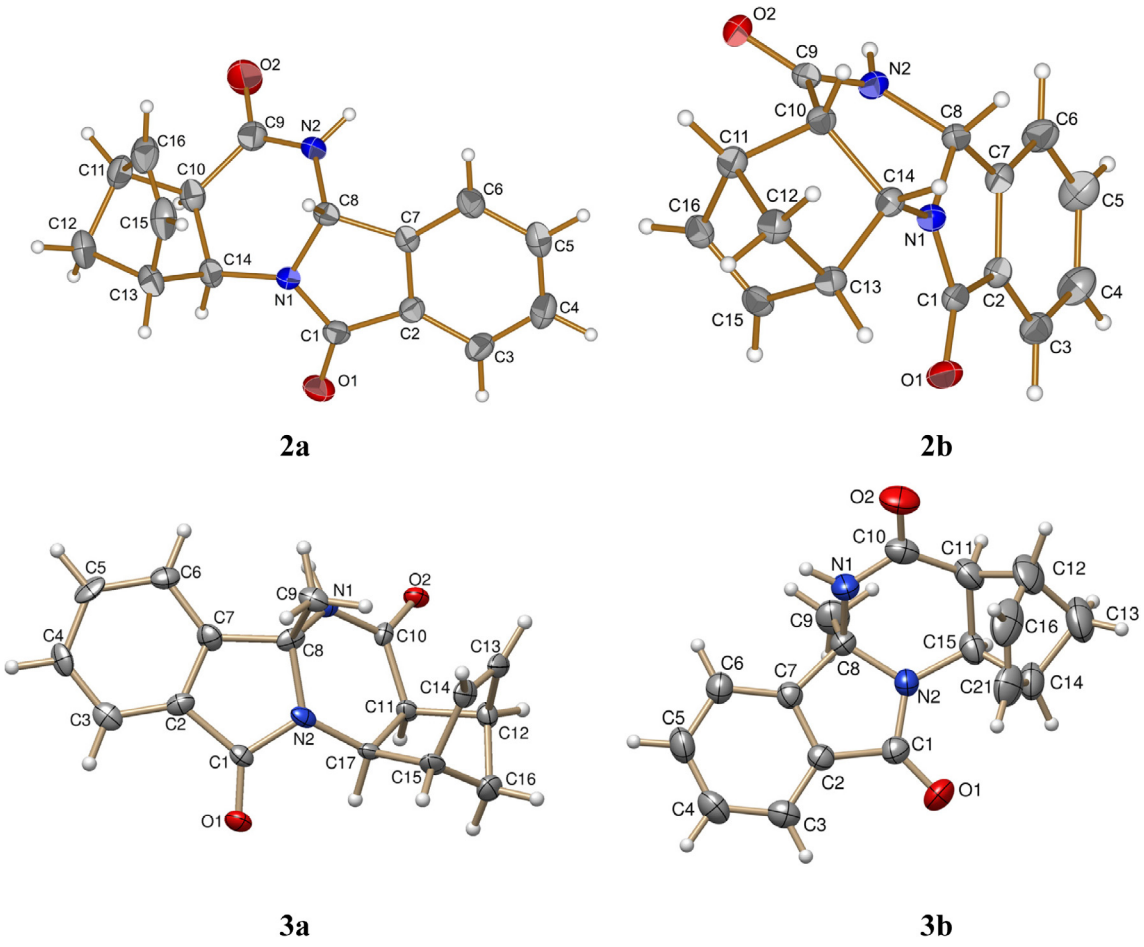
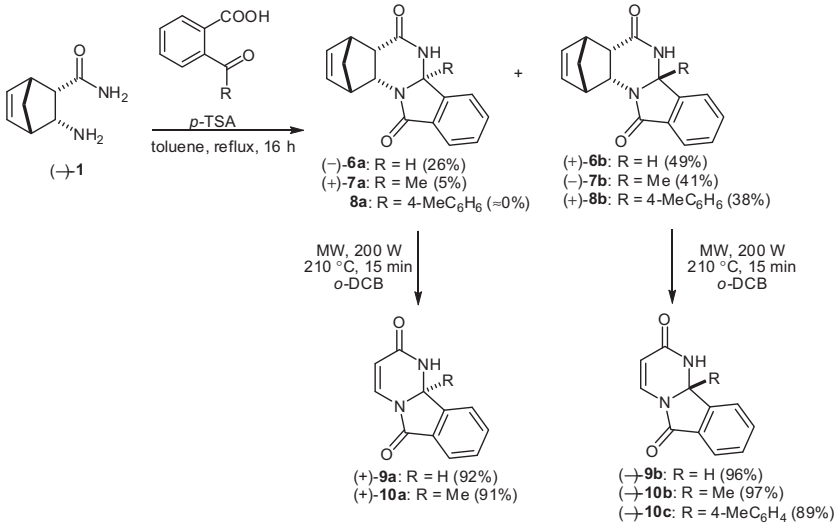


Figure 1. ORTEP views of diastereomeric pairs **2a**–**2b** and **3a**–**3b**.



Scheme 2. Synthesis of antipode pairs [(+)-**9a**–(−)-**9b** and [(+)-**10a**–(−)-**10b**] and single enantiomeric pyrimidoisoindoles.

II diffractometer using Cu Kα ($\lambda = 1.54184$ Å) or Mo Kα ($\lambda = 0.71073$) radiation. The *CrysAlisPro*[18] or *Denzo-Scalepack*[19] program packages were used for cell refinements and data reductions. Multi-scan absorption corrections (*CrysAlisPro*[18] or *SADABS*[20]) were applied to the intensities before structure solution. The structures were solved by charge flipping method using the *SUPERFLIP*[21] software. Structural refinements were carried out using *SHELXL-2014*.[22] The high R-values and residual densities in **3a** are due to the low data quality and possible twinning. However, not satisfactory twin model could be found and therefore no twin model was used in the final refinement. In **2b** and **3b** the NH hydrogen atoms were located from the difference Fourier map and refined isotropically. Other hydrogen atoms were positioned geometrically and constrained to ride on their parent

atoms, with C–H = 0.95–1.00 Å, N–H = 0.88 Å and U_{iso} = 1.2–1.5·U_{eq}(parent atom). The crystallographic details are summarized in Table XS1.

4.2. Synthesis of isoindolo[2,1-*a*]quinazolines (±)-2a, (±)-2b, (±)-3a, (±)-3b, (±)-4a and (±)-4b

A mixture of *diendo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxamide (±)-**1**, (0.76 g, 5.0 mmol) 2-formylbenzoic acid, 2-acetylbenzoic acid or 2-(4-methylbenzoyl)benzoic acid (5.2 mmol) and *p*-TSA (0.05 g) in toluene (40 mL) was refluxed for 16 h. The solvent was then evaporated off, the residue was dissolved in EtOAc (15 mL) and the solution was transferred to a neutral Al_2O_3 column and eluted with EtOAc. After evaporation, a small amount (10 mg) of the residue was separated to determine the diastereomeric ratio by ^{1}H NMR analysis. The major fraction was transferred to a silica gel column and eluted with a mixture of *n*-hexane–EtOAc (2:1).

4.2.1. (1*S**,4*R**,4a*S**,6a*R**,12a*R**)-1,4,4a,6,6a,12a-Hexahydro-1,4-methanoisoindolo[2,1-*a*]quinazoline-5,11-dione (±)-2a

Yield: 24%, colourless crystals, mp 302–304 °C (EtOH). IR (KBr): 3218, 3112, 3062, 2969, 1683, 1665, 1654, 1470, 1398, 737 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.45 (1H, d, J = 8.8 Hz, H-13), 1.62 (1H, d, J = 8.7 Hz, H-13), 2.90 (1H, dd, J = 9.1 Hz, J = 4.1 Hz, H-4a), 3.17 (1H, s, H-4), 3.26 (1H, s, H-1), 5.03 (1H, dd, J = 9.1 Hz, J = 3.5 Hz, H-12a), 5.64 (1H, s, H-6a), 6.38 (1H, dd, J = 5.8 Hz, J = 2.8 Hz, H-2), 6.42 (1H, dd, J = 5.7 Hz, J = 2.8 Hz, H-3), 7.53–7.79 (4H, m, H-Ar), 8.81 (1H, s, CONH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 42.1, 47.2, 48.8, 49.3, 51.1, 66.1, 123.8, 124.5, 130.4, 131.5, 133.0, 136.6, 137.6, 143.3, 167.2, 171.5. Anal. calcd. for $C_{16}H_{14}N_2O_2$ (%): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.03; H, 5.51; N, 10.65. MS: (ESI) m/z = 267.32 $[M+H]^+$.

4.2.2. (1*S**,4*R**,4a*S**,6a*S**,12a*R**)-1,4,4a,6,6a,12a-Hexahydro-1,4-methanoisoindolo[2,1-*a*]quinazoline-5,11-dione (±)-2b

Yield: 49%, colourless crystals, mp 263–265 °C (EtOAc). IR (KBr): 3244, 3045, 2968, 2870, 1673, 1661, 1466, 1348, 731 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.46 (2H, m, H-13), 3.03 (1H, dd, J = 8.8 Hz, J = 4.1 Hz, H-4a), 3.26 (1H, s, H-4), 4.02 (1H, s, H-1), 4.36 (1H, dd, J = 8.8 Hz, J = 3.6 Hz, H-12a), 5.80 (1H, s, H-6a), 5.95 (1H, dd, J = 6.0 Hz, J = 2.9 Hz, H-2), 6.06 (1H, dd, J = 5.6 Hz, J = 2.7 Hz, H-3), 7.51–7.74 (4H, m, H-Ar), 8.92 (1H, s, CONH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 44.7, 46.0, 46.1, 46.2, 54.9, 66.7, 123.5, 124.5, 130.3, 132.5, 133.5, 135.3, 137.7, 141.5, 165.4, 172.1. Anal. calcd. for $C_{16}H_{14}N_2O_2$ (%): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.15; H, 5.45; N, 10.45. MS: (ESI) m/z = 201.26 $[M^+_{rDA}H]^+$ and 267.23 $[M+H]^+$.

4.2.3. (1*S**,4*R**,4a*S**,6a*R**,12a*R**)-6a-Methyl-1,4,4a,6,6a,12a-hexahydro-1,4-methanoisoindolo[2,1-*a*]quinazoline-5,11-dione (±)-3a

Yield: 6%, colourless crystals, mp 297–299 °C (EtOAc). IR (KBr): 3170, 3047, 3023, 2985, 2978, 2902, 1701, 1655, 1466, 1347, 736 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.49 (1H, m, H-13), 1.57–1.63 (4H, m, H-13 and CH_3), 2.94 (1H, dd, J = 9.6 Hz, J = 4.0 Hz, H-4a), 3.14 (1H, s, H-4), 3.28 (1H, s, H-1), 5.01 (1H, dd, J = 9.7 Hz, J = 3.5 Hz, H-12a), 6.36 (2H, m, H-2 and H-3), 7.49–7.85 (4H, m, H-Ar), 8.88 (1H, s, CONH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 34.1, 41.1, 47.1, 48.4, 49.5, 54.0, 74.4, 122.7, 123.8, 128.9, 130.1, 133.8, 137.3, 138.3, 150.8, 170.1, 170.5. Anal. calcd. for $C_{17}H_{16}N_2O_2$ (%): C, 72.84; H, 5.75; N, 9.99. Found: C, 72.65; H, 5.95; N, 10.05 MS: (ESI) m/z = 281.45 $[M+H]^+$.

4.2.4. (1*S**,4*R**,4a*S**,6a*S**,12a*R**)-6a-Methyl-1,4,4a,6,6a,12a-hexahydro-1,4-methanoisoindolo[2,1-a]quinazoline-5,11-dione (±)-3b

Yield: 38%, colourless crystals, mp 264–266 °C (EtOAc). IR (KBr): 3246, 3165, 3064, 3014, 2970, 2930, 2890, 1707, 1683, 1666, 1655, 1468, 1383, 737 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.46 (2H, m, H-13), 1.67 (3H, s, CH_3), 3.17 (1H, dd, J = 8.6 Hz, J = 4.1 Hz, H-4a), 3.25 (1H, s, H-4), 4.07 (1H, s, H-1), 4.35 (1H, dd, J = 8.6 Hz, J = 3.6 Hz, H-12a), 5.92 (1H, dd, J = 5.6 Hz, J = 2.8 Hz, H-2), 6.15 (1H, dd, J = 5.6 Hz, J = 2.8 Hz, H-3), 7.48–7.79 (4H, m, H-Ar), 8.94 (1H, s, CONH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 29.3, 44.1, 45.9, 46.0, 46.3, 53.1, 73.9, 123.1, 123.6, 130.2, 131.6, 132.8, 135.4, 137.6, 146.6, 164.7, 171.3. Anal. calcd. for $C_{17}H_{16}N_2O_2$ (%): C, 72.84; H, 5.75; N, 9.99. Found: C, 72.69; H, 5.65; N, 9.75. MS: (ESI) m/z = 215.48 $[M_{rDA}+H]^+$, 281.70 $[M+H]^+$.

Table XS1
Crystal data

	2a	2b	3a	3b
Empirical formula	$C_{16}H_{14}N_2O_2$	$C_{16}H_{14}N_2O_2$	$C_{17}H_{16}N_2O_2$	$C_{17}H_{16}N_2O_2$
fw	266.29	266.29	280.32	280.32
Temp (K)	170(2)	120(2)	120(2)	170(2)
λ (Å)	0.71073	1.54184	1.54184	0.71073
Cryst syst	Monoclinic	Monoclinic	Orthorhombic	Triclinic
Space group	$P2_1/n$	$P2_1/c$	$Pca2_1$	$P\bar{1}$
a (Å)	6.6492(6)	21.07531(12)	12.78094(14)	9.3061(2)
b (Å)	10.4134(11)	13.71333(7)	11.91104(12)	11.8133(3)
c (Å)	18.0859(14)	8.74579(5)	18.28733(19)	13.0880(3)
α (°)	90	90	90	98.2230(10)
β (°)	92.658(8)	94.4336(5)	90	98.7360(10)
γ (°)	90	90	90	90.9940(10)
V (Å^3)	1250.94(19)	2520.08(2)	2783.96(5)	1406.40(6)
Z	4	8	8	4
ρ_{calc} (Mg/m^3)	1.414	1.404	1.338	1.324
μ(Kα) (mm^{-1})	0.095	0.762	0.716	0.088
No. reflns.	4527	63286	33800	27156
Unique reflns.	2572	5306	4893	7258
GOOF (F^2)	1.053	1.028	1.415	1.110
R_{int}	0.0352	0.0291	0.2771	0.0581
R1[a] ($I \geq 2\sigma$)	0.0535	0.0355	0.1254	0.0702
wR2[b] ($I \geq 2\sigma$)	0.1089	0.0906	0.2771	0.1112

[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$.
[b] $wR2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

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4.2.5. (1*S**,4*R**,4a*S**,6a*R**,12a*R**)-6a-(*p*-Tolyl)-1,4,4a,6,6a,12a-hexahydro-1,4-methanoisoindolo[2,1-a]quinazoline-5,11-dione (±)-4a

Yield: 3%, colourless crystals, mp 230–232 °C (EtOAc). IR (KBr): 3291, 3075, 3018, 2986, 2944, 2904, 1756, 1676, 1652, 1611, 1487, 1355, 1322, 738 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.38 (2H, m, H-13), 2.26 (3H, s, CH_3), 2.34 (1H, dd, J = 8.8 Hz, J = 3.9 Hz, H-4a), 2.94 (1H, d, J = 10.3 Hz, CONH), 3.04 (1H, s, H-4), 3.20 (1H, s, H-1), 3.79 (1H, m, H-12a), 6.16 (1H, dd, J = 5.6 Hz, J = 2.9 Hz, H-2), 6.23 (1H, dd, J = 5.6 Hz, J = 2.8 Hz, H-3), 7.17–7.77 (8H, m, H-Ar). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 21.4, 46.3, 46.5, 46.7, 47.6, 57.8, 83.9, 124.2, 125.2, 126.2 (2 × C), 128.7, 130.5, 130.9 (2 × C), 135.4, 135.5, 138.5, 138.9, 139.4, 149.3, 165.9, 170.7. Anal. calcd. for $C_{23}H_{20}N_2O_2$ (%): C, 77.51; H, 5.66; N, 7.86. Found: C, 77.68; H, 5.75; N, 7.75. MS: (ESI) m/z = 291.39 $[M_{rDA}+H]^+$ and 357.26 $[M+H]^+$.

4.2.6. (1*S**,4*R**,4a*S**,6a*S**,12a*R**)-6a-(*p*-Tolyl)-1,4,4a,6,6a,12a-hexahydro-1,4-methanoisoindolo[2,1-a]quinazoline-5,11-dione (±)-4b

Yield: 39%, colourless crystals, mp 265–267 °C (EtOAc) (lit. mp 270–271 °C)[15] The NMR spectrum was identical with that of an authentic sample.

4.3. Synthesis of pyrimido[2,1-*a*]isoindole (±)-5a, (±)-5b and (±)-5c by microwave-induced retro Diels–Alder reaction

All microwave-mediated reactions were carried out in reaction vials sealed with a Teflon cap. Heterocycles (±)-**2a**, (±)-**2b**, (±)-**3a**, (±)-**3b**, (±)-**4a** or (±)-**4b** (25–100 mg) were placed in a microwave test tube (10 mL) containing a magnetic stirrer and 1,2-DCB (2 mL). The test-tube was placed in the cavity of the CEM Discover microwave reactor. The solutions were irradiated during a period of 15 min at 210 °C (power 250 W). The cooled solution diluted with $CHCl_3$ (6 mL) was then transferred to a SiO_2 column and eluted with *n*-hexane–EtOAc (1:1).

4.3.1. 1,10b-Dihydropyrimido[2,1-*a*]isoindole-2,6-dione (±)- 5a

Yield: 89–95%, colourless crystals, mp 270–272 °C (EtOH) (lit. mp 242–244 °C)[17] Spectroscopic data were identical with that of an authentic sample.

4.3.2. 10b-Methyl-1,10b-dihydropyrimido[2,1-*a*]isoindole-2,6-dione (±)-5b

Yield: 91–94%, colourless crystals, mp 200–202 °C (EtOAc–iPr$_2$O). IR (KBr): 3425, 3178, 3043, 2974, 2899, 1724, 1657, 1617, 1472, 1310, 808 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm)) 1.72 (3H, s, CH_3-10b), 5.64 (1H, dd, J = 7.6 Hz, J = 2.0 Hz, H-3), 7.60–7.93 (5H, m, H-4 and H-Ar), 8.84 (1H, s, CONH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 27.7, 74.9, 107.4, 123.7, 125.3, 129.5, 130.9, 133.0, 135.0, 148.3, 164.8, 165.5. Anal. calcd. for $C_{12}H_{10}N_2O_2$ (%): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.12; H, 5.95; N, 12.91. MS: (ESI) m/z = 215.35 $[M+H]^+$.

4.3.3. 10b-(*p*-Tolyl)-1,10b-dihydropyrimido[2,1-*a*]isoindole-2,6-dione (±)-5c

Yield: 90–96%, colourless crystals, mp 268–270 °C (EtOAc–iPr$_2$O). IR (KBr): 3430, 3184, 3062, 2922, 1722, 1665, 1651, 1465, 1316, 822, 810 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm)) 1.99 (3H, s, p-CH_3-Ar-10 b), 5.36 (1H, dd, J = 7.7 Hz, J = 2.1 Hz, H-3), 7.10–7.94 (9H, m, H-4 and H-Ar), 9.71 (1H, d, J = 1.8 Hz, CONH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 21.4, 78.0, 108.7, 124.4, 125.4, 125.8 (2 × C), 129.2, 130.2 (2 × C), 130.9, 133.2, 135.3, 138.8, 140.0, 148.2, 165.6, 166.1. Anal. calcd. for $C_{18}H_{14}N_2O_2$ (%): C, 74.47; H, 4.86; N, 9.65. Found: C, 74.62; H, 5.00; N, 9.81; MS: (ESI) m/z = 291.30 $[M+H]^+$.

4.4. Synthesis of (−)-(1*R*,2*S*,3*R*,4*S*)-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxamide (−)-1

(−)-(1*R*,2*S*,3*R*,4*S*)-Ethyl-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylate[13] (3.5 g, 19.3 mmol,) was left to stand at rt for 5 weeks in a 26% ammonia–methanol solution (200 mL). The solution was then evaporated to dryness, the residue was dissolved in EtOAc (20 mL), and the solution was transferred to a silica gel column and eluted, first with EtOAc and then with EtOAc/MeOH (3:1). The residue of the eluates afforded (−)-**1** (1.41 g, 48%) as pale-yellow semi-crystalline solid. 100 mg of (−)-**1** was treated with ethanolic hydrogen chloride to obtain crytalline (−)-**1** × HCl. Mp 239–241 °C (EtOH–Et_2O); $[\alpha]_D^{25}$=−14.8 (c 0.485, H_2O), ee > 99% (GC).

4.5. Synthesis of isoindolo[2,1-*a*]quinazolines (−)-6a, (+)-6b, (+)-7a, (−)-7b and (+)-8b enantiomers

A mixture of (−)-(1*R*,2*S*,3*R*,4*S*)-3-norbornene-2-carboxamide (−)-**1**, (350 mg, 2.3 mmol), 2-formylbenzoic acid, 2-acetylbenzoic acid or 2-(4-methylbenzoyl)benzoic acid (2.5 mmol), and *p*-TSA (0.03 g) in toluene (25 mL) was refluxed for 16 h. The solvent was then evaporated off, the residue was dissolved in EtOAc (10 mL), and the solution was transferred to a neutral Al_2O_3 column and eluted with EtOAc. The residue of the eluates was transferred to a silica gel column and eluted with a mixture of *n*-hexane–EtOAc (2:1). The ^1H NMR spectra for optically active compounds were in accordance with those reported for the racemates.

4.5.1. (1*S*,4*R*,4a*S*,6a*R*,12a*R*)-(−)-1,4,4a,6,6a,12a-Hexahydro-1,4-methanoisoindolo[2,1-*a*]quinazoline-5,11-dione (−)-6a

Yield: 26%, colourless crystals, mp 262–264 °C (EtOH). $[\alpha]_D^{25}$ = −100.5 (c 0.49, EtOH).

4.5.2. (1*S*,4*R*,4a*S*,6a*S*,12a*R*)-(+)-1,4,4a,6,6a,12a-Hexahydro-1,4-methanoisoindolo[2,1-*a*]quinazoline-5,11-dione (+)-6b

Yield: 38%, colourless crystals, mp 254–256 °C (EtOAc). $[\alpha]_D^{25}$ = +38.0 (c 0.50, EtOH).

4.5.3. (1*S*,4*R*,4a*S*,6a*R*,12a*R*)-(+)-6a-Methyl-1,4,4a,6,6a,12a-hexahydro-1,4-methanoisoindolo[2,1-*a*]quinazoline-5,11-dione (+)-7a

Yield: 5%, colourless crystals, mp 258–259 °C (iPr$_2$O–EtOAc). $[\alpha]_D^{25}$ = +10.0 (c 0.19, EtOH).

4.5.4. (1*S*,4*R*,4a*S*,6a*S*,12a*R*)-(−)-6a-Methyl-1,4,4a,6,6a,12a-hexahydro-1,4-methanoisoindolo[2,1-a]quinazoline-5,11-dione (−)-7b

Yield: 41%, colourless crystals, mp 141–142 °C (EtOAc). $[\alpha]_D^{25}$ = −27.0 (c 0.16, EtOH).

4.5.5. (1*S*,4*R*,4a*S*,6a*S*,12a*R*)-(+)-6a-(*p*-Tolyl)-1,4,4a,6,6a,12a-hexahydro-1,4-methanoisoindolo[2,1-a]quinazoline-5,11-dione (+)-8b

Yield: 34%, colourless crystals, mp 265–267 °C (iPr$_2$O–EtOAc). $[\alpha]_D^{25}$ = +106.8 (c 0.37, EtOH).

4.6. Synthesis of enantiomeric pyrimido[2,1-*a*]isoindole (+)-9a, (−)-9b, (+)-10a, (−)-10b and (−)-11b by microwave-induced retro Diels–Alder reaction

The reactions were performed as described for the racemates, on 25–100 mg scale. All ^1H NMR spectra recorded for the enantiomeric substances were the same as those for the racemic counterparts.

4.6.1. (*R*)-(+)-1,10b-Dihydropyrimido[2,1-*a*]isoindole-2,6-dione (+)-9a

Yield: 92%, colourless crystals, mp 265–267 °C (EtOAc–*n*-hexane). $[\alpha]_D^{25}$ = +441 (*c* 0.11, EtOH), *ee* 99%.

4.6.2. (*S*)-(−)-1,10b-Dihydropyrimido[2,1-*a*]isoindole-2,6-dione (−)-9b

Yield: 96%, colourless crystals, mp 267–269 °C (EtOAc–*n*–hexane). $[\alpha]_D^{25}$ = −428 (*c* 0.12, EtOH), *ee* 99%.

4.6.3. (*R*)-(+)-10b-Methyl-1,10b-dihydropyrimido[2,1-*a*] isoindole-2,6-dione (+)-10a

Yield: 91%, colourless crystals, mp 201–202 °C (EtOAc–*i*-Pr_2O). $[\alpha]_D^{25}$ = +429 (*c* 0.11, EtOH), *ee* 99%.

4.6.4. (*S*)-(−)-10b-Methyl-1,10b-dihydropyrimido[2,1-*a*] isoindole-2,6-dione (−)-10b

Yield: 97%, colourless crystals, mp 199–201 °C (EtOAc–*i*-Pr_2O). $[\alpha]_D^{25}$ = −450 (*c* 0.17, EtOH), *ee* > 99%.

4.6.5. (*S*)-(−)-10b-(*p*-Tolyl)-1,10b-dihydropyrimido[2,1-*a*] isoindole-2,6-dione (−)-11b

Yield: 89%, colourless crystals, mp 245–247 °C (*i*-Pr_2O). $[\alpha]_D^{25}$ = −21.8 (*c* 0.36, EtOH), *ee* > 99%.

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A. Supplementary data

Supplementary data (Copies of the ^{1}H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.07.006.

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