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Supporting Information

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Supporting Information for "Radical Cyclization Cascades of *N*-Acylcyanamides: Total Synthesis of Luotonin A"

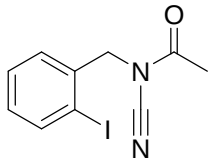
Aurore Servais, Mériam Azzouz, David Lopes, Christine Courillon and Max Malacria

Laboratoire de Chimie Organique, UMR CNRS 7611
Institut de Chimie Moléculaire, FR 2769
Université Pierre et Marie Curie, Paris 6, case 229,
4, place Jussieu, F-75252 Paris
Fax: (+33) 1 44 27 73 60
E-mail: christine.courillon@upmc.fr, max.malacria@upmc.fr

The symbols IV, III, II, I will be used to refer to quaternary, tertiary, secondary and primary carbons respectively.
δ is expressed in ppm.

General procedure for synthesis of compound 6

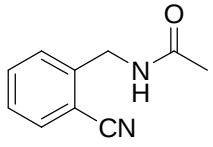
To a cold (0°C) stirred solution of cyanamide (5 mmol) in THF (15 ml) was added sodium hydride (10 mmol). When gas evolution had ceased, acyl chloride was introduced at 0°C and the mixture was stirred at room temperature for 48 hours. Then the solution was treated with 2-iodobenzyl-methanesulfonate (5 mmol) and refluxed overnight before a solution of saturated sodium carbonate was added. Extraction with diethyl ether and drying over $MgSO_4$ gave crude expected compound which could be purified by chromatography on silica gel.



6

75% ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.86 (dd, *J* = 7.6, 1.0 Hz, 1H, H_{arom}), 7.36 (td, *J* = 7.6, 1.0 Hz, 1H, H_{arom}), 7.30 (dd, *J* = 7.6, 1.7 Hz, 1H, H_{arom}), 7.04 (td, *J* = 7.6, 1.7 Hz, 1H, H_{arom}), 4.74 (s, 2H, ArCH_2), 2.44 (s, 3H, COCH_3) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ 169.1 (IV), 140.0 (III), 135.7 (IV), 130.6 (III), 130.2 (III), 128.8 (III), 110.1 (IV), 99.2 (IV), 53.7 (II), 22.1 (I) ; IR (neat): 3035, 2232, 1725, 1224, 1013, 740 cm^{-1} .

Procedure for the formation of compound 8 :



8

To a degassed solution of *N*-acylcyanamide (0.5 mmol) and AIBN (0.18 mmol) in benzene (19 mL) under reflux was added tributyltin hydride (0.6 mmol) and AIBN (0.57 mmol) in benzene (5 mL) over 1 hour. The reflux was maintained until the monitoring of the reaction by TLC showed total consumption of the starting material. The mixture was then

concentrated and the crude product was purified by silica gel flash chromotography (eluting with dichloromethane / ethanol 95:5) to afford the compound **4** in 53% yield.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.63 (m, 1H, H_{arom}), 7.50 (m, 2H, H_{arom}), 7.34 (m, 1H, H_{arom}), 6.56 (s, 1H, N*H*), 4.57 (d, *J = 6.1 Hz*, 2H, ArCH_2), 2.02 (s, 3H, COCH_3) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ 170.4 (IV), 142.3 (IV), 133.2 (III), 132.9 (III), 128.6 (III), 128.0 (III), 117.7 (IV), 111.5 (IV), 42.0 (II), 23.1 (I) ; IR (neat): 3285, 3072, 2928, 2224, 1652, 1543 1292 cm^{-1}.

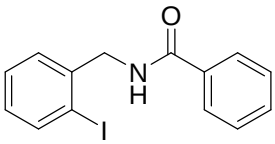
General procedure for the synthesis of amides 2

General procedure for the formation of acyl chloride :

To a solution of acid (5 mmol) in benzene (15 ml) were added DMF (2 drops) and oxalyl chloride (1 mL, 1.5 equiv). When gas evolution had ceased, the reaction mixture was concentrated under vacuum to afford the crude acyl chloride which was used without further purification.

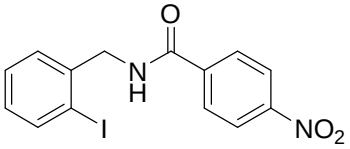
General procedure for amide formation :

To a solution of 2-iodobenzylamine (5 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (15 mmol). To this mixture was added acyl chloride (5 mmol) in CH_2Cl_2 (20 mL). After 30 minutes, a solution of saturated ammonium chloride was added. Extraction with CH_2Cl_2 and drying over $MgSO_4$ gave crude amides which could be purified by chromatography on silica gel or used without further purification.



2a

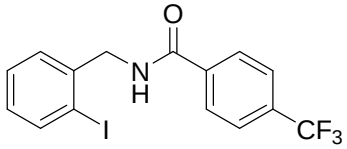
86% ; white solid ; T_f : 150-152°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.85 (dd, *J* = 7.8, 1.0 Hz, 1H, H_{arom}), 7.80 (m, 2H, H_{arom}), 7.51-7.42 (m, 4H, H_{arom}), 7.34 (td, *J* = 7.6, 1.3 Hz, 1H, H_{arom}), 7.0 (td, *J* = 7.6, 1.5 Hz, 1H, H_{arom}), 6.62 (broad s, 1H, N*H*), 4.68 (d, *J* = 6.0 Hz, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 167.4 (IV), 140.4 (IV), 139.6 (III), 134.2 (IV), 131.8 (III), 130.2 (III), 129.6 (III), 128.8 (III, 3C), 127.1 (III, 2C), 99.2 (IV), 48.7 (II); IR (neat): 3273, 3058, 1785, 1647, 1437 cm^{-1} ; MS : MH^+ 338; Anal calcd for $C_{14}H_{12}INO$: C, 49.87; H, 3.59; N, 4.15; found : C, 49.74; H, 3.51; N, 4.11.



2b

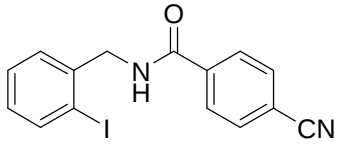
44% ; yellow solid ; T_f : 144-149°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.26 (d, *J* = 8.8 Hz, 2H, H_{arom}), 7.94 (d, *J* = 8.8 Hz, 2H, H_{arom}), 7.84 (dd, *J* = 7.8, 1.0 Hz, 1H, H_{arom}), 7.43 (dd, *J* = 7.6, 1.5 Hz, 1H, H_{arom}), 7.34 (td, *J* = 7.3, 1.0 Hz, 1H, H_{arom}), 7.01 (td, *J* = 7.8, 1.8 Hz, 1H, H_{arom}), 6.85 (broad s, 1H, NH), 4.66 (d, *J* = 6.0 Hz, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ

165.4 (IV), 149.7 (IV), 139.8 (IV), 139.7 (III, IV), 130.4 (III), 129.9 (III), 128.9 (III), 128.4 (III, 2C), 123.9 (III, 2C), 99.3 (IV), 48.9 (II); IR (neat): 3294, 3067, 1647, 1600, 1523, 1345 cm^{-1} .



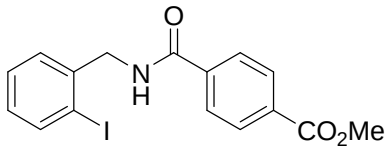
2c

60% ; white solid ; T_f : 170-171°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.90 (d, *J* = 8.1 Hz, 2H, H_{arom}), 7.85 (dd, *J* = 8.1, 1.0 Hz, 1H, H_{arom}), 7.69 (d, *J* = 8.1 Hz, 2H, H_{arom}), 7.44 (dd, *J* = 7.6, 1.5 Hz, 1H, H_{arom}), 7.34 (td, *J* = 7.3, 1.0 Hz, 1H, H_{arom}), 7.01 (td, *J* = 7.6, 1.5 Hz, 1H, H_{arom}), 6.76 (broad s, 1H, N*H*), 4.67 (d, *J* = 5.8 Hz, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.1 (IV), 140.0 (IV), 139.7 (III), 137.6 (IV), 130.4 (III), 129.8 (III + IV), 128.9 (III), 127.6 (III, 2C), 125.8 (III), 125.7 (III), 125.1 (IV), 99.3 (IV), 48.9 (II); IR (neat): 3268, 1642,1543, 1325 cm^{-1} ; Anal calcd for $C_{15}H_{11}F_3INO$: C, 44.47; H, 2.74; N, 3.46; found : C, 44.51; H, 2.61; N, 3.34.



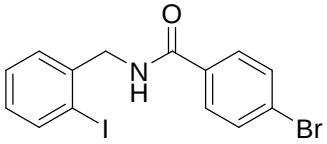
2d

73% ; white solid ; T_f : 135-137°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.86 (d, *J* = 8.6 Hz, 2H, H_{arom}), 7.82 (dd, *J* = 7.8, 1.0 Hz, 1H, H_{arom}), 7.67 (d, *J* = 6.6 Hz, 2H, H_{arom}), 7.36 (dd, *J* = 7.6, 1.8 Hz, 1H, H_{arom}), 7.30 (td, *J* = 7.3, 1.0 Hz, 1H, H_{arom}), 7.02 (m, 1H, NH), 6.99 (td, *J* = 7.6, 1.8 Hz, 1H, H_{arom}), 4.60 (d, *J* = 6.0 Hz, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.7 (IV), 139.7 (IV), 139.6 (III), 138.1 (IV), 132.5 (III, 2C), 129.9 (III), 129.7 (III), 128.8 (III), 127.9 (III, 2C), 118.1 (IV), 115.2 (IV), 99.2 (IV), 48.9 (II); IR (neat): 3300, 3062, 2924, 2231, 1645, 1537, 1303 cm^{-1} ; Anal calcd for $C_{15}H_{11}F_3INO$: C, 49.75; H, 3.06; N, 7.73; found : C, 49.73; H, 3.22; N, 7.39.



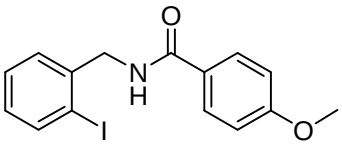
2e

90% ; white solid ; T_f : 135-136°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.10 (m, 2H, H_{arom}), 7.86 (m, 3H, H_{arom}), 7.47 (dd, *J* = 7.8, 1.8 Hz, 1H, H_{arom}), 7.35 (td, *J* = 7.6, 1.0 Hz, 1H, H_{arom}), 7.01 (td, *J* = 7.8, 1.8 Hz, 1H, H_{arom}), 6.67 (broad s, 1H, NH), 4.68 (d, *J* = 6.0 Hz, 2H, ArCH_2), 3.94 (s, 3H, CH_3) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.8 (IV, 2C), 139.5 (IV), 139.0 (III), 137.5 (IV), 132.3 (IV), 129.7 (III), 129.3 (III, 2C), 129.0 (III), 128.2 (III), 126.5 (III, 2C), 98.7 (IV), 51.9 (I), 48.2 (II); IR (neat): 3306, 1721, 1644 cm^{-1} ; Anal calcd for $C_{16}H_{14}INO_3$: C, 48.63; H, 3.57; N, 3.54; found : C, 48.56; H, 3.41; N, 3.69.



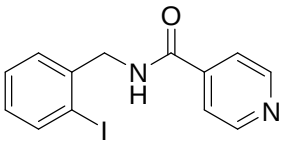
2f

78% ; white solid ; T_f : 160-163°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.85 (dd, *J* = 8.0, 1.3 Hz, 1H, H_{arom}), 7.67 (t, *J* = 2.0 Hz, 1H, H_{arom}), 7.65 (t, *J* = 2.0 Hz, 1H, H_{arom}), 7.58 (t, *J* = 2.0 Hz, 1H, H_{arom}), 7.55 (t, *J* = 2.0 Hz, 1H, H_{arom}), 7.44 (dd, *J* = 7.6, 1.5 Hz, 1H, H_{arom}), 7.34 (td, *J* = 7.6, 1.2 Hz, 1H, H_{arom}), 7.0 (td, *J* = 7.6, 1.5 Hz, 1H, H_{arom}), 6.78 (broad s, 1H, N*H*), 4.61 (d, *J* = 6.0 Hz, 2H, ArC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.4 (IV), 140.2 (IV), 139.7 (III), 133.1 (IV), 131.9 (III, 2C), 130.2 (III), 129.6 (III), 129.5 (III, 3C), 126.5 (IV),99.2 (IV), 48.8 (II); IR (neat): 3274, 3062, 2922, 1637, 1589, 1537 cm^{-1} ; Anal calcd for $C_{14}H_{11}BrINO$: C, 40.42; H, 2.66; N, 3.37 ; found : C, 40.43; H, 2.61; N, 3.21.



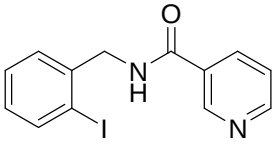
2g

57% ; off-white solid ; T_f : 157-160°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.84 (d, *J* = 8.1 Hz, 1H, H_{arom}), 7.76 (dd, *J* = 6.8, 2.3 Hz, 2H, H_{arom}), 7.44 (dd, *J* = 7.6, 1.5 Hz, 1H, H_{arom}), 7.34 (td, *J* = 7.6, 1.3 Hz, 1H, H_{arom}), 6.99 (td, *J* = 1.8, 7.6 Hz, 1H, H_{arom}), 6.92 (dd, *J* = 1.2, 7.3 Hz, 2H, H_{arom}), 6.59 (broad s, 1H, N*H*), 4.65 (d, *J* = 6.0 Hz, 2H, ArC*H*$_2$), 3.84 (s, 3H, OC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.5 (IV), 162.4 (IV), 140.7 (IV), 139.6 (III), 130.3 (III), 129.5 (III), 128.9 (III, 2C), 128.8 (III), 126.6 (IV), 113.9 (III, 2C), 99.3 (IV), 55.6 (I), 48.7 (II); IR (neat): 3320, 3060, 1638, 1607, 1503, 1254 cm^{-1} ; HRMS (ES+): calcd for $C_{15}H_{14}NO_2NaI$ 389.9967, found 389.953 ; Anal calcd for $C_{15}H_{14}NO_2I$: C, 49.07; H, 3.84; N, 3.81; found : C, 48.84; H, 3.61; N, 3.72.



2h

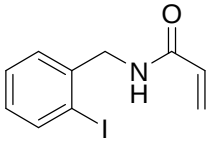
73% ; orange solid ; T_f : 131-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.64 (m, 2H, H_{arom}), 7.81 (d, *J* = 7.8 Hz, 1H, H_{arom}), 7.60 (m, 2H, H_{arom}), 7.37 (dd, *J* = 7.8, 1.8 Hz, 1H, H_{arom}), 7.29 (t, *J* = 7.6 Hz, 1H, H_{arom}), 7.22 (broad s, 1H, N*H*), 6.98 (td, *J* = 7.6, 1.5 Hz, 1H, H_{arom}), 4.62 (d, *J* = 5.8 Hz, 2H, ArC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.5 (IV), 150.6 (III, 2C), 141.4 (IV), 139.8 (IV), 139.7 (III), 130.1 (III), 129.7 (III), 128.8 (III), 121.9 (III, 2C), 99.2 (IV), 48.8 (II); IR (neat): 3282, 3051, 1649, 1536, 1304 cm^{-1} ; Anal calcd for $C_{13}H_{11}IN_2O$: C, 46.18; H, 3.28; N, 8.28; found : C, 46.72; H, 3.36; N, 7.74.



2i

56% ; orange solid ; T_f 98-104°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.0 (dd, *J* = 1.5, 0.8 Hz, 1H, H_{arom}), 8.73 (dd, *J* = 4.8, 1.5 Hz, 1H, H_{arom}), 8.12 (dt, *J* = 8.0, 1.8 Hz, 1H, H_{arom}), 7.86 (dd, *J* = 7.6, 1.3 Hz, 1H, H_{arom}), 7.47 (dd, *J* = 7.6, 1.8 Hz, 1H, H_{arom}), 7.41-7.35 (m, 2H,

H_{arom}), 7.02 (td, *J* = 7.6, 1.8 Hz, 1H, H_{arom}), 6.68 (broad s, 1H, N*H*), 4.69 (d, *J* = 6.0 Hz, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.6 (IV), 152.3 (III), 148.1 (III), 139.9 (IV), 139.6 (III), 135.3 (III), 132.1 (IV), 130.0 (III), 129.6 (III), 128.7 (III), 123.6 (III), 99.2 (IV), 48.8 (II); IR (neat): 3273, 3056, 1642, 1591, 1536, 1304 cm^{-1} .



2j

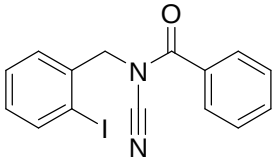
60% ; off-white solid ; T_f : 99-101°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.83 (dd, *J* = 8.1, 1.0 Hz, 1H, H_{arom}), 7.40 (dd, *J* = 7.8, 1.8 Hz, 1H, H_{arom}), 7.32 (td, *J* = 7.6, 1.0 Hz, 1H, H_{arom}), 6.99 (td, *J* = 7.6, 1.8 Hz, 1H, H_{arom}), 6.33 (dd, *J* = 16.9, 1.3 Hz, 1H, HCH_{trans}=CHC=O), 6.13 (dd, *J* = 16.9, 10.4 Hz, 1H, CH_2=C*H*C=O), 6.05 (broad s, 1H, N*H*), 5.68 (dd, *J* = 10.4, 1.3 Hz, 1H, HCH_{cis}=CHC=O), 4.55 (d, *J* = 6.0 Hz, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.4 (IV), 140.3 (IV), 139.6 (III), 130.6 (III), 130.2 (III), 129.6 (III), 128.8 (III), 127.2 (II), 99.3 (IV), 48.3 (II); IR (neat): 3275, 3062, 1656, 1625, 1544 cm^{-1} ; MS : M+H 288.

General Procedure for the preparation of *N*-acylcyanamides

As cyanogen bromide is very toxic and corrosive, one should work cautiously and use gloves, work in a ventilated area, use a bleach and potassium hydroxide solution to wash glassware and to quench any excess of cyanogen bromide.

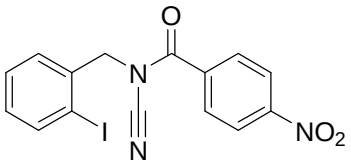
Method A

To a solution of the amide (1 mmol) in distilled THF (8 mL) was added sodium hydride (1.1 equiv.). After gas elution cyanogen bromide (3 equiv.) was added and the mixture was stirred at room temperature. After 20 hours the reaction mixture was filtered through a short pad of silica gel and the filtrate was concentrated. The solid obtained was purified on silica gel to give the acylcyanamide. The remaining starting material was recovered as well.



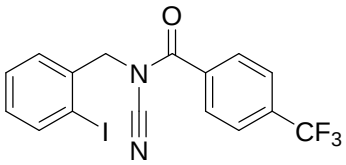
3a

73%; white solid; T_f 78-82°C; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.96 (m, 1H, H_{arom}); 7.87 (m, 2H, H_{arom}); 7.64 (m, 1H, H_{arom}); 7.52 (m, 2H, H_{arom}); 7.46 (m, 2H, H_{arom}); 7.10 (m, 1H, H_{arom}); 4.95 (s, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 168.4 (IV); 140.3 (III); 135.9 (IV); 133.6 (III, 2C); 131.1 (III, 2C); 131.0 (II); 130.8 (IV); 129.0 (III, 2C); 128.8 (III, 2C); 99.5 (IV); 55.5 (II); IR (neat): 2233, 1706, 1277 cm^{-1} ; MS : MH^+ 363, MNH_4^+ 380; HRMS (ES+): calcd for $C_{15}H_{11}N_2ONaI$ 384.9814, found 384.9832 ; Anal calcd for $C_{15}H_{11}N_2OI$: C, 49.75; H, 3.06; N, 7.73; found : C, 50.16; H, 3.13; N, 7.52.



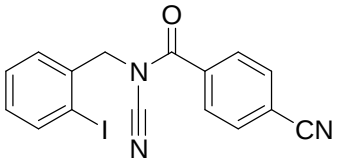
3b

68%; yellow solid; T_f 117-123°C; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.36 (m, 2H, H_{arom}); 8.04 (m, 2H, H_{arom}); 7.97 (m, 1H, H_{arom}); 7.46 (m, 2H, H_{arom}); 7.15 (m, 1H, H_{arom}); 4.97 (s, 2H, ArC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.5 (IV); 150.3 (IV); 140.3 (III); 136.1 (IV); 135.1 (IV); 131.5 (III); 131.2 (III); 129.5 (III, 2C); 129.0 (III); 124.0 (III, 2C); 109.5 (IV); 99.5 (IV); 55.5 (II); IR (neat): 2236, 1710, 1525, 1282 cm^{-1} ; MS : MNH_4^+ 425; Anal calcd for $C_{15}H_{10}N_3O_3I$: C, 44.25; H, 2.48; N, 10.32; found : C, 44.52; H, 2.51; N, 9.84.



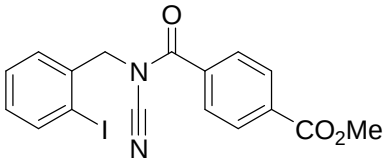
3c

58% ; white solid ; T_f : 92-93°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.97 (t, *J* = 8.1 Hz, 3H, H_{arom}), 7.76 (d, *J* = 8.1 Hz, 2H, H_{arom}), 7.45-7.41 (m, 2H, H_{arom}), 7.12 (m, 1H, H_{arom}), 4.97 (s, 2H, ArC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 167.2 (IV), 140.4 (III, IV), 135.5 (IV), 134.0 (IV), 131.4 (III), 131.2 (III), 129.4 (III, 2C), 129.0 (III), 125.9 (III, 2C+ IV), 109.0 (IV), 99.6 (IV), 55.5 (II); IR (neat): 2235, 1707, 1323 cm^{-1} ; Anal calcd for $C_{16}H_{10}IF_3N_2O$: C, 44.67; H, 2.34; N, 6.51; found : C, 44.66; H, 2.26; N,6.58.



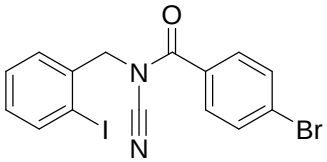
3d

33% ; pale yellow solid ; T_f : 151-153°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.95 (d, *J* = 8.6 Hz, 3H, H_{arom}), 7.80 (d, *J* = 8.6 Hz, 2H, H_{arom}), 7.43 (m, 2H, H_{arom}), 7.15-7.11 (m, 1H, H_{arom}), 4.96 (s, 2H, ArC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.8 (IV), 140.4 (III), 135.3 (IV), 134.6 (IV), 132.6 (III, 2C), 131.6 (III), 131.3 (III), 129.5 (III, 2C), 129.1 (III), 117.5 (IV), 116.9 (IV), 109.7 (IV), 99.6 (IV), 55.6 (II); IR (neat): 3063, 2927, 2234, 1709 cm^{-1} ; Anal calcd for $C_{16}H_{10}IN_3O$: C, 49.63; H, 2.60; N, 10.85; found : C, 49.61; H, 2.33; N, 10.69.



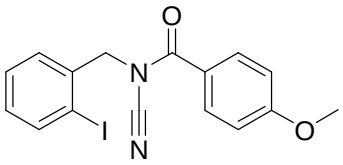
3e

33% ; white solid ; T_f : 105-106°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.10 (d, *J* = 8.84 Hz, 2H, H_{arom}), 7.90 (m, 3H, H_{arom}), 7.43 (m, 2H, H_{arom}), 7.09 (m, 1H, H_{arom}), 4.95 (s, 2H, ArC*H*$_2$), 3.94 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 167.6 (IV), 165.8 (IV), 140.3 (III), 135.5 (IV), 134.5 (IV), 134.3 (IV), 131.3 (III), 131.0 (III), 129.9 (III, 2C), 128.9 (III), 128.8 (III, 2C), 110.0 (IV), 99.5 (IV), 55.4 (II), 52.7 (I); IR (neat): 2234, 1708, 1568, 1271 cm^{-1} ; Anal calcd for $C_{21}H_{13}INO_3$: C, 48.59; H, 3.12; N, 6.67; found : C, 48.56; H, 3.03; N, 6.64.



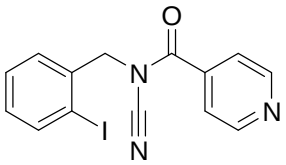
3f

47% ; white solid ; T_f : 111-113°C; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.94 (d, *J* = 7.8 Hz, 1H, H_{arom}), 7.74 (d, *J* = 8.3 Hz, 2H, H_{arom}), 7.64 (d, *J* = 8.3 Hz, 2H, H_{arom}), 7.42 (m, 2H, H_{arom}), 7.10 (m, 1H, H_{arom}), 4.93 (s, 2H, ArC*H*$_2$).; ^{13}C NMR (100 MHz, $CDCl_3$) : δ 167.4 (IV), 140.3 (III), 135.6 (IV), 132.2 (III,2C), 131.3 (III), 131.0 (III), 130.4 (III, 2C), 129.4 (IV), 128.9 (III), 128.6 (IV), 110.3 (IV), 99.5 (IV), 55.5 (II); IR (neat): 2233, 1702, 1274 cm^{-1} ; HRMS (ES+): calcd for $C_{15}H_{10}N_2ONa^{79}BrI$ 462.8919, found 462.8938; Anal calcd for $C_{15}H_{10}BrIN_2O$: C, 40.85; H, 2.29; N, 6.35; found : C, 40.63; H, 2.23; N,6.02.



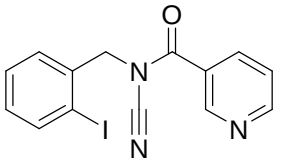
3g

28% ; off-white solid ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.94-7.88 (m, 3H, H_{arom}), 7.42 (m, 2H, H_{arom}), 7.10 (t, *J* = 6.8 Hz, 1H, H_{arom}), 6.97 (m, 2H, H_{arom}), 4.92 (s, 2H, ArC*H*$_2$), 3.86 (s, 3H, OC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 167.6 (IV), 163.8 (IV), 140.2 (III), 136.2 (IV), 131.4 (III, 2C), 130.9 (III), 130.8 (III), 128.9 (III), 122.7 (IV), 114.1 (III, 2C), 111.1 (IV), 99.4 (IV), 55.6 (II), 55.5 (I); IR (neat): 2954, 2231, 1700, 1605, 1258 cm^{-1} .



3h

61% ; orange paste ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.82 (dd, *J* = 4.5, 1.8 Hz, 2H, H_{arom}), 7.94 (d, *J* = 7.8 Hz, 1H, H_{arom}), 7.67 (dd, *J* = 4.5, 1.8 Hz, 2H, H_{arom}), 7.42 (m, 2H, H_{arom}), 7.11 (m, 1H, H_{arom}), 4.95 (s, 2H, ArC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.6 (IV), 150.8 (III, 2C), 140.4 (III), 137.9 (IV), 135.2 (IV), 131.4 (III), 131.2 (III), 129.0 (III), 121.9 (III, 2C), 109.5 (IV), 99.6 (IV), 55.5 (II); IR (neat): 2236, 1711, 1284 cm^{-1} ; HRMS (ES+): calcd for $C_{14}H_{11}N_3OI$, 363.9947, found 363.9955 .



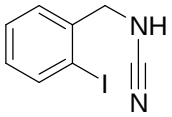
3i

49% ; orange paste ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.09 (dd, *J* = 2.3, 0.8 Hz, 1H, H_{arom}), 8.83 (dd, *J* = 5.0, 1.8 Hz, 1H, H_{arom}), 8.18 (dt, *J* = 8.0, 2.3 Hz, 1H, H_{arom}), 7.94 (dd, *J* = 8.0, 0.8 Hz, 1H, H_{arom}), 7.45 (m, 3H, H_{arom}), 7.13 (m, 1H, H_{arom}), 4.97 (s, 2H, ArC*H*$_2$).; ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.5 (IV), 153.9 (III), 149.9 (III), 140.4 (III), 136.2 (III), 135.4 (IV), 131.5 (III), 131.2 (III), 129.0 (III), 127.1 (IV), 123.3 (III), 110.0 (IV), 99.6 (IV), 55.5 (II); IR (neat): 2235, 1709, 1284 cm^{-1} .

Method B

2-iodobenzylic amine was obtained as previously described by reduction of the corresponding azide. The crude reaction mixture was concentrated, dissolved in dichloromethane and acidified with 10% aqueous HCl. The aqueous phase was then neutralized with a saturated

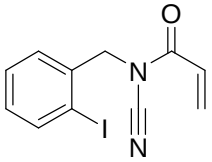
solution of sodium carbonate, extracted with dichloromethane. The organic phase was dried on magnesium sulfate, filtered and concentrated to give the pure amine quantitatively.
In a solution of cyanogen bromide (10 mmol, 1 equiv) in diethylether (2.5 mL) at –15 to –20°C was added sodium carbonate (2 equiv) and the amine (1 equiv) in ether (2.5 mL). The reaction mixture was stirred for 2 hours and then allowed to reach 0°C. The mixture was filtered through celite and concentrated. It was then purified on silica gel (petroleum ether/ ethyl acetate 8/2) to afford the cyanamide as a white solid (64%).



5

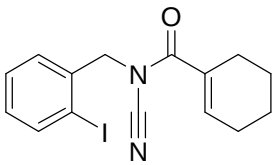
64%; white solid ; T_f : 91°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.87 (d, *J* = 7.8 Hz, 1H, H_{arom}), 7.39 (m, 2H, H_{arom}), 7.06 (m, 1H, H_{arom}), 4.27 (d, *J* = 6.3 Hz, 2H, ArC*H*$_2$), 4.05 (broad s, 1H, N*H*CN); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 139.8 (III), 138.5 (IV), 130.3 (III), 129.6 (III), 128.9 (III), 115.8 (IV), 98.9 (IV), 54.5 (II); IR (neat): 3196, 2923, 2218 cm^{-1} ; HRMS (ES-): calcd for $C_8H_6N_2I$ 256.9576, found 256.9565; Anal calcd for $C_8H_7IN_2$: C, 37.23; H, 2.73; N, 10.86; found : C, 37.38; H, 2.71; N, 10.88.

Cyanamide **5** (258 mg, 1 mmol, 1 equiv) was dissolved in a mixture of water and THF (1/1, 3 mL) and KOH (56 mg, 1 equiv) was added. The mixture was stirred for 30 minutes and concentrated under reduced pressure. Water was removed by azeotropic evaporation with toluene.
The previously prepared potassium salt of the cyanamide was taken up in benzene (1 mL) and the acyl chloride (2 equiv) was added dropwise at 0°C. After 2 hours the mixture was extracted with dichloromethane, washed with water. The organic phase was dried with magnesium sulfate, filtered and concentrated under reduced pressure. It was purified on silica gel to afford the acyl cyanamide.



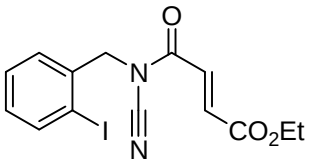
3j

70% ; white solid ; T_f 117-123°C; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.93 (m, 1H, H_{arom}); 7.42-7.35 (m, 2H, H_{arom}); 7.10 (m, 1H, H_{arom}); 6.91 (dd, *J* = 16.7, 10.4 Hz, 1H, CH_2=C*H*C=O); 6.70 (dd, *J* = 16.7, 1.3 Hz, 1H, HC*H*$_{trans}$=CHC=O); 6.10 (dd, *J* = 10.4, 1.3 Hz, 1H, CH*H*$_{cis}$=CHC=O); 4.87 (s, 2H, ArC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 140.3 (III); 135.7 (IV); 134.9 (II); 130.8 (III, IV); 130.4 (III); 129.0 (III); 124.9 (III); 110.0 (IV); 99.4 (IV); 54.3 (II); IR (neat): 2350, 1675 cm^{-1} ; MS : MNH_4^+ 330; HRMS (ES+): calcd for $C_{11}H_9N_2ONaI$ 334.9657, found 334.9666 ; Anal calcd for $C_{11}H_9IN_2O$: C, 42.33; H, 2.91; N, 8.98; found : C, 42.89; H, 3.11; N, 8.82.



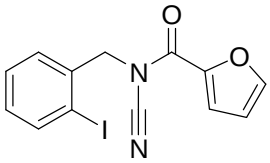
3k

67%; pale yellow solid ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.90 (d, *J* = 7.8 Hz, 1H, H_{arom}), 7.40-7.33 (m, 2H, H_{arom}), 7.07 (td, *J* = 7.8, 2.0 Hz, 1H, H_{arom}), 6.80 (m, 1H, C=C*H*), 4.80 (s, 2H, ArCH_2), 2.34 (m, 2H, CH_2), 2.26 (m, 2H, CH_2), 1.73-1.64 (m, 4H, 2 CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 168.9 (IV), 139.9 (III), 139.1 (III), 136.0 (IV), 130.8 (IV), 130.5 (III), 130.4 (III), 128.6 (III), 110.7 (IV), 99.1 (IV), 54.7 (II), 25.2 (II), 24.8 (II), 21.6 (II), 21.0 (II); IR (neat): 2936, 2861, 2232, 1700 cm^{-1}; HRMS (ES+): calcd for $C_{15}H_{15}N_2ONaI$ 389.0127, found 389.0121.



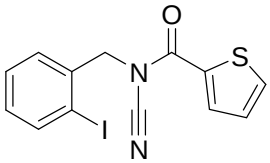
3l

54% ; white solid ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.92 (d, *J* = 7.8 Hz, 1H, H_{arom}), 7.52 (d, *J* = 15.1 Hz, 1H, C=OC*H*=CHCO_2Et), 7.40 (t, *J* = 7.6 Hz, 1H, H_{arom}), 7.34 (dd, *J* = 7.6, 1.5 Hz, 1H, H_{arom}), 7.09 (td, *J* = 7.6, 1.8 Hz, 1H, H_{arom}), 7.07 (d, *J* = 15.1 Hz, 1H, C=OCH=C*H*CO_2Et), 4.88 (s, 2H, ArCH_2), 4.28 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 1.33 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 164.2 (IV), 163.2 (IV), 140.3 (III), 137.4 (III), 135.2 (IV), 131.1 (III), 130.7 (III), 129.1 (III), 129.0 (III), 108.9 (IV), 99.5 (IV), 61.9 (II), 54.7 (II), 14.2 (I); IR (neat): 2238, 1711 cm^{-1} .



3m

73% ; white solid ; T_f : 88-89°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.88 (d, *J* = 7.8 Hz, 1H, H_{arom}), 7.67 (d, *J* = 1.3 Hz, 1H, H_{furane}), 7.58 (d, *J* = 3.8 Hz, 1H, H_{furane}), 7.37 (m, 2H, H_{arom}), 7.08-7.04 (m, 1H, H_{arom}), 6.58 (m, 1H, H_{furane}), 4.95 (s, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 156.1 (IV), 147.5 (III), 143.6 (IV), 140.1 (III), 135.6 (IV), 130.7 (III), 130.4 (III), 128.8 (III), 120.9 (III), 112.5 (III), 109.9 (IV),99.3 (IV), 55.3 (II); IR (neat): 2234, 1694, 1438 cm^{-1} ; Anal calcd for $C_{13}H_9IN_2O_2$: C, 44.34; H, 2.58; N, 7.96; found : C, 44.77; H, 2.36; N, 7.55.

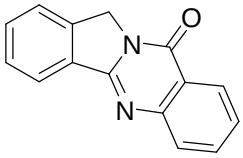


3n

74% ; brown solid ; T_f: 62-64°C. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.15 (dd, *J* = 4.04, 1.0 Hz, 1H, $H_{thiophene}$), 7.91 (dd, *J* = 7.6, 0.8 Hz, 1H, H_{arom}), 7.71 (dd, *J* = 5.0, 1.0 Hz, 1H, $H_{thiophene}$), 7.40 (m, 2H, H_{arom}), 7.14 (td, *J* = 4.0, 1.0 Hz, 1H, $H_{thiophene}$), 7.08 (m, 1H, H_{arom}), 4.96 (s, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 160.3 (IV), 140.1 (III), 135.7 (IV), 134.8 (III), 133.9 (III), 133.5 (IV), 130.8 (III), 130.7 (III), 128.9 (III), 128.3 (III), 110.7 (IV), 99.4 (IV), 55.8 (II); IR (neat): 2232, 1774, 1674 cm^{-1} .

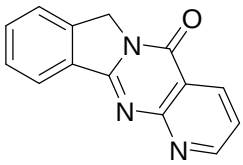
Typical cyclization procedure

To a degassed solution of *N*-acylcyanamide (0.25 mmol) in benzene (11 mL) under reflux was added tributyltin hydride (0.5 mmol, 2 equiv) and AIBN (0.25 mmol, 1 equiv) in benzene (4 mL) over 2 hours. The reflux was maintained until the monitoring of the reaction by TLC showed total consumption of the starting material. Once the mixture was back to room temperature, aq NaOH (1M, 15 mL) was added and stirred for 30 minutes. The organic phase was extracted with ethyl acetate (2 x 20 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification of the residue by silica gel flash chromotography afforded the cyclization products.

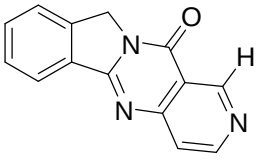


9a

71% ; white solid ; T_f : 209-214°C; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.36 (dd, *J* = 8.0, 1.0 Hz, 1H, H_{arom}), 8.16 (d, *J* = 7.6 Hz, 1H, H_{arom}), 7.80 (m, 2H, H_{arom}), 7.63 (m, 2H, H_{arom}), 7.58 (m, 1H, H_{arom}), 7.49 (m, 1H, H_{arom}), 5.16 (s, 2H, ArC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 160.8 (IV), 155.0 (IV), 149.6 (IV), 139.7 (IV), 134.4 (III), 132.8 (IV), 132.4 (III), 129.0 (III), 127.5 (III), 126.6 (III), 126.5 (III), 123.6 (III, 2C), 120.7 (IV), 49.9 (II); IR (neat): 1666, 1618, 1463 cm^{-1} ; MS : MH$^+$ 235; HRMS (ES+): calcd for $C_{15}H_{10}N_2ONa$ 257.0691, found 257.0680.

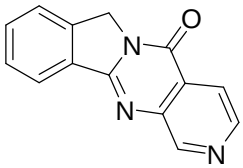


9i



10

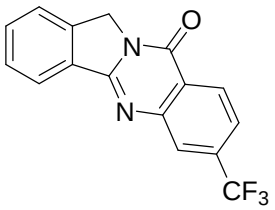
79%, 2 dias (2.2/1) ; orange solid ; Major regioisomer :^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.02 (dd, *J* = 7.8, 2.0 Hz, 1H, H_{arom}), 8.71 (dd, *J* = 7.8, 2.0 Hz, 1H, H_{arom}), 8.33 (d, *J* = 7.6 Hz, 1H, H_{arom}), 7.73-7.62 (m, 3H, H_{arom}), 7.46 (dd, *J* = 7.8, 4.5 Hz, 1H, H_{arom}), 5.20 (s, 2H, ArC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 160.6 (IV), 159.6 (IV), 158.0 (IV), 155.9 (III), 139.81 (IV), 136.1 (III), 133.1 (III), 132.2 (IV), 129.2 (III), 124.4 (III), 123.4 (III), 121.7 (III), 115.8 (IV), 49.9 (II); Minor regioisomer : ^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.6 (s, 1H, H_{arom}), 8.87 (d, *J* = 5.6 Hz, 1H, H_{arom}), 8.21 (d, *J* = 7.8 Hz, 1H, H_{arom}), 7.73-7.62 (m, 4H, H_{arom}), 5.19 (s, 2H, ArC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 159.6 (IV), 158.9 (IV), 154.7 (IV), 153.4 (III), 150.4 (III), 140.3 (IV), 133.4 (III), 131.9 (IV), 129.2 (III), 124.1 (III), 123.6 (III), 120.6 (III), 116.1 (IV), 50.1 (II); IR (neat): 3370, 3058, 2993, 1683, 1623, 1593 cm^{-1} ; HRMS (ES+): calcd for $C_{14}H_9N_3O$ 258.0643, found 258.0649.



9h

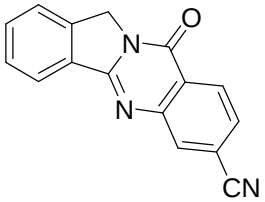
56% ; orange solid ; T_f : 233°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.24 (s, 1H, H_{arom}), 8.68 (d, *J* = 5.3 Hz, 1H, H_{arom}), 8.18 (d, *J* = 7.6 Hz, 1H, H_{arom}), 8.11 (d, *J* = 5.3 Hz, 1H, H_{arom}), 7.68-7.59 (m, 3H, H_{arom}), 5.17 (s, 2H, ArC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 159.6 (IV), 156.7 (IV), 151.3 (III), 146.0 (III), 144.2 (IV), 139.6 (IV), 133.1 (III), 132.3 (IV), 129.3 (III), 125.5

(IV), 123.9 (III), 123.7 (III), 118.6 (III), 50.1 (II); IR (neat): 1682, 1618, 903 cm^{-1} ; Anal calcd for $C_{14}H_9N_3O$: C, 71.48 ; H, 3.86 ; N, 17.86 ; found : C, 70.99 ; H, 4.11 ; N, 17.34.



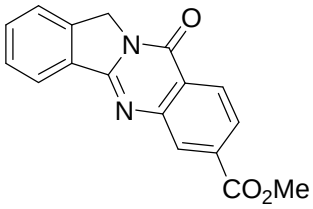
9c

72% ; white crystals ; T_f : 238°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.48 (d, *J* = 8.1 Hz, 1H, H_{arom}), 8.18 (d, *J* = 7.8 Hz, 1H, H_{arom}), 8.11 (s, 1H, H_{arom}), 7.70-7.59 (m, 4H, H_{arom}), 5.18 (s, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 159.9 (IV), 156.3 (IV), 149.7 (IV), 139.9 (IV), 136.1 (IV), 135.8 (IV), 133.0 (III), 132.4 (IV), 129.3 (III), 127.8 (III), 125.1 (III), 123.9 (III), 123.7 (III), 122.9 (IV), 122.4 (III), 50.1 (II); IR (neat): 1683, 1616, 1315, 1061 cm^{-1} ; Anal calcd for $C_{16}H_9N_2OF_3$: C, 63.58 ; H, 3.00 ; N, 9.27 ; found : C, 63.58 ; H, 3.04 ; N, 9.38.



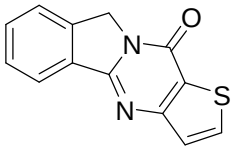
9d

100% ; white solid ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.48 (d, *J* = 7.6 Hz, 1H, H_{arom}), 8.20 (d, *J* = 7.6 Hz, 1H, H_{arom}), 8.15 (d, *J* = 1.0 Hz, 1H, H_{arom}), 7.71-7.64 (m, 4H, H_{arom}), 5.20 (s, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 149.7 (IV), 139.9 (IV), 133.3 (III), 132.3 (III), 132.2 (IV), 129.4 (III), 128.3 (III), 127.9 (III), 124.1 (III), 123.8 (III), 123.7 (IV), 118.0 (IV), 117.8 (IV), 50.2 (II), 2 IV not visible; IR (neat): 2925, 2854, 1677, 1632 cm^{-1} .



9e

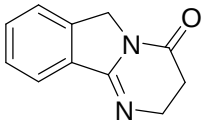
86% ; white solid ; T_f : 238-239°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.56 (s, 1H, H_{arom}), 8.47 (d, *J* = 8.1 Hz, 1H, H_{arom}), 8.24 (d, *J* = 7.6 Hz, 1H, H_{arom}), 8.14 (d, *J* = 8.1 Hz, 1H, H_{arom}), 7.71 (m, 3H, H_{arom}), 5.22 (s, 2H, ArCH_2), 4.03 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 162.3 (IV), 160.2 (IV), 155.7 (IV), 149.5 (IV), 139.8 (IV, 2C), 135.4 (IV), 132.8 (III), 132.5 (IV), 129.4 (III), 129.1 (III), 126.9 (III), 126.5 (III), 123.8 (III), 123.6 (III), 52.7 (I), 49.9 (II); IR (neat): 1726, 1672 cm^{-1} .



9n

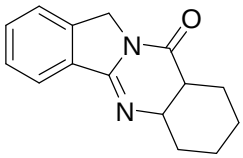
57% ; brown solid ; T_f : 224-226°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.13 (d, *J* = 7.6 Hz, 1H, H_{arom}), 7.83 (d, *J* = 5.3 Hz, 1H, H_{arom}), 7.64 (d, *J* = 3.8 Hz, 2H, H_{arom}), 7.58 (m, *J* = 5.3 Hz,

1H, H_{arom}), 7.43 (d, *J* = 5.3 Hz, 1H, H_{arom}), 5.17 (s, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 158.6 (IV), 157.1 (IV), 157.0 (IV), 139.6 (IV), 134.3 (III), 132.5 (IV), 132.3 (III), 129.1 (III), 125.3 (III), 123.9 (IV), 123.7 (III), 123.4 (III), 49.8 (II); IR (neat): 2923, 2853, 1659 cm^{-1}.



9j

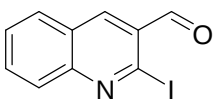
66% ; white solid ; T_f : 146-147°C . ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.86 (d, *J* = 7.8 Hz, 1H, H_{arom}), 7.54 (td, *J* = 7.3, 0.8 Hz, 1H, H_{arom}), 7.46 (t, *J* = 7.6 Hz, 2H, H_{arom}), 4.85 (s, 2H, ArCH_2), 3.92 (t, *J* = 7.7 Hz, 2H, C=OCH$_2$CH_2N), 2.59 (t, *J* = 7.7 Hz, 2H, C=OCH_2CH$_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 168.7 (IV), 155.7 (IV), 139.8 (IV), 132.3 (III), 132.2 (IV), 128.7 (III), 123.6 (III), 123.3 (III), 48.6 (II), 45.3 (II), 29.8 (II); IR (neat): 2959, 2925, 1678 cm^{-1} ; HRMS (ES+): calcd for $C_{11}H_{11}N_2O$ 187.0871, found 187.0888;



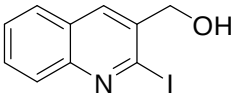
9k

71%, 2 separated dias (1.6/1) ; white crystals ; minor dias; T_f : 197-198°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.89 (d, *J* = 8.1 Hz, 1H, H_{arom}), 7.52 (t, *J* = 6.8 Hz, 1H, H_{arom}), 7.44-7.41 (m, 2H, H_{arom}), 4.84, 4.74 (AB, d, *J* = 16.7 Hz, 1H each, ArCH_2), 3.31 (td, *J* = 12.9, 3.8 Hz, 1H, $H_{cyclohexyl}$), 2.47-2.38 (m, 2H, $H_{cyclohexyl}$), 2.01 (m, 1H, $H_{cyclohexyl}$), 1.88 (m, 2H, $H_{cyclohexyl}$), 1.54 (qd, *J* = 12.4, 3.6 Hz, 1H, $H_{cyclohexyl}$), 1.39-1.23 (m, 3H, $H_{cyclohexyl}$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 171.47 (IV), 154.8 (IV), 140.1 (IV), 132.2 (IV), 132.1 (III), 128.5 (III), 123.5 (III), 123.3 (III), 59.6 (III), 48.6 (II), 43.6 (III), 34.7 (II), 25.5 (II), 25.4 (II), 25.3 (II); major dias ; T_f : 122-123°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.89 (d, *J* = 7.4 Hz, 1H, H_{arom}), 7.52 (t, *J* = 6.6 Hz, 1H, H_{arom}), 7.44-7.41 (t, *J* = 7.0 Hz, 2H, H_{arom}), 4.80 (s, 2H, ArCH_2), 3.92 (m, 1H, C=OC*H*), 2.68 (m, 1H, C=OCHC*H*), 2.05 (m, 1H, $H_{cyclohexyl}$), 1.81 (m, 1H, $H_{cyclohexyl}$), 1.71 (m, 2H, $H_{cyclohexyl}$), 1.58 (m, 1H, $H_{cyclohexyl}$), 1.48 (m, 3H, $H_{cyclohexyl}$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 171.4 (IV), 154.4 (IV), 140.0 (IV), 132.0 (III), 128.6 (III), 123.5 (III), 123.3 (III), 56.5 (III), 48.4 (II), 41.0 (III), 29.6 (II), 23.8 (II), 23.6 (II), 23.4 (II); IR (neat): 2930, 1696, 1673, 1362 cm^{-1} ; Anal calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66; found : C, 74.64; H, 6.72; N, 11.74. The crystal structure of compound **9k** has been deposited at the Cambridge Crystallographic Data Centre and was allocated the deposition number CCDC 624763.

Total synthesis of Luotonin A

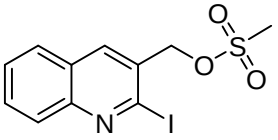


2-iodo-quinoline-3-carbaldehyde was prepared from 2-chloro-quinoline-3-carbaldehyde following Meth-Cohn's procedure in 70% yield.[1] NMR, IR, and mass spectra consistent with literature.



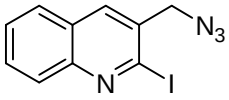
[1] O. Meth-Cohn, B. Narine, B. Tarnowski, R. Hayes, A. Keyzad, S. Rhouati, A. Robinson, *J. Chem Soc. Perkin Transactions 1* **1981**, *9,* 2509-2517**.**

(2-iodoquinolin-3-yl)methanol was prepared by reduction of 2-iodo-quinoline-3-carbaldehyde in 84% yield.[2] NMR, IR, and mass spectra consistent with literature.



To a solution of (2-iodoquinolin-3-yl)methanol (3.66 g, 12.88 mmol) in dichloromethane (100 mL) at 0°C was added triethylamine (3.6 mL, 25.76 mmol) and after five minutes of stirring the mesyl chloride (1.5 mL, 19.32 mmol) was added dropwise and the temperature was raised to room temperature. After 10 minutes the mixture was quenched with saturated solution of ammonium chloride and extracted twice with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give the product quantitatively.

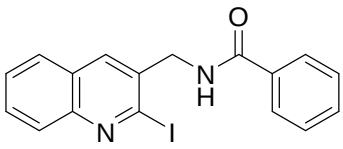
^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.14 (s, 1H, H_{arom}), 8.08 (d, *J* = 8.6 Hz, 1H, H_{arom}), 7.86 (d, *J* = 7.8 Hz, 1H, H_{arom}), 7.77 (t, *J* = 8.6 Hz, 1H, H_{arom}), 7.63 (t, *J* = 8.1 Hz, 1H, H_{arom}), 5.39 (s, 2H, C*H*$_2$Ar), 3.14 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 149.3 (IV), 136.9 (III), 131.3 (III), 130.1 (IV), 128.7 (III), 128.1 (III), 128.0 (III), 126.9 (IV), 121.6 (IV), 72.9 (II), 38.3 (I); IR (neat): $\tilde{\nu}_{max}$ = 1171, 1351 cm^{-1}; MS: MH^+ 364; T_f: 110-112°C.



11

To (2-iodoquinolin-3-yl)methyl methanesulfonate (4.68 g, 12.88 mmol) dissolved in dimethylformamide (28 mL) was added sodium azide (1.34 g, 20.6 mmol). After one hour the reaction was quenched with water (70 mL), extracted with ethyl acetate and the organic layer was dried on magnesium sulfate, concentrated, then filtered on a silica bed with petroleum ether/ethyl acetate (90/10). The organic layer was concentrated under reduced pressure to give the pure azide as a yellow solid (3.79 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.06 (d, *J* = 8.1 Hz, 1H, H_{arom}), 8.04 (s, 1H, H_{arom}), 7.90 (d, *J* = 8.1 Hz, 1H, H_{arom}), 7.73 (t, *J* = 7.1 Hz, 1H, H_{arom}), 7.60 (t, *J*=7.1 Hz, 1H, H_{arom}), 4.60 (s, 2H, C*H*$_2$Ar); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 148.8 (IV), 135.2 (III), 132.0 (IV), 130.5 (III), 128.5 (III), 127.7 (2C, III), 127.0 (IV), 122.9 (IV), 57.4 (II); IR (neat): $\tilde{\nu}_{max}$ = 2103 cm^{-1} ; MS: MH^+ 311; T_f: 58-59°C; Anal. calcd for $C_{10}H_7IN_4$: C, 40.16 ; H, 2.37 ; N, 19.13 ; found : C, 39.97 ; H, 2.39 ; N, 19.07.



12

To a solution of azide **11** (1.24 g, 4 mmol) in a mixture of tetrahydrofurane and water (40 mL and 10 mL) was added triphenylphosphine (1.59 g, 6 mmol). After 3 hours the reaction mixture was extracted with dichloromethane, dried on magnesium sulfate and concentrated

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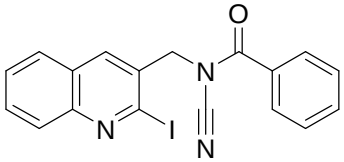
[2] D. Gallagher, P. Beak, *J. Am. Chem. Soc.*, **1991**, *113*, 7984-7987; N. S. Narasimhan, N. M. Sunder, R. Ammanamanchi, B. D. Bonde, *J. Am. Chem. Soc.* **1990**, *112*, 4431-4435.

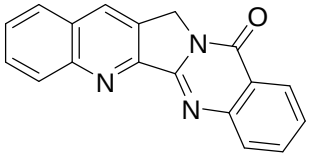
under reduced pressure to give the crude amine as a white solid. The crude amine was dissolved in dry dichloromethane. To the crude amine dissolved in dichloromethane (40 mL) was added triethylamine (1.8 mL, 12 mmol). After 5 minutes of stirring the acyl chloride (511 µL, 4.4 mmol) was added dropwise. After 19 hours, the reaction mixture was quenched with saturated solution of ammonium chloride, extracted with dichloromethane. The organic layers were dried on magnesium sulfate and concentrated under reduced pressure. Purification on silica gel (petroleum ether/ethyl acetate 90/10 to 70/30) afforded the amide as a white solid (729 mg, 47%).

47% ; white solid ; T_f : 119-123°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.29 (s, 1H, H_{arom}), 8.0 (d, *J* = 8.6 Hz, 1H, H_{arom}), 7.82 (m, 3H, H_{arom}), 7.71 (td, *J* = 7.6, 1.5 Hz, 1H, H_{arom}), 7.58-7.51 (m, 2H, H_{arom}), 7.45 (t, *J* = 7.6 Hz, 2H, H_{arom}), 6.85 (broad s, 1H, N*H*), 4.84 (d, *J* = 6.3 Hz, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 167.7 (IV), 150.2 (IV), 147.2 (IV), 138.8 (III), 133.9 (IV), 132.0 (III), 130.7 (III), 129.6 (IV), 128.9 (III, 2C), 128.3 (III), 127.8 (III), 127.5 (III), 127.4 (IV), 127.1 (III, 2C), 41.9 (II); IR (neat): 3324, 3061, 1635, 1536, 1270 cm^{-1} ; MS: MNa^+ 411, MK^+ 427.



Method A was used to afford this *N*-acylcyanamide **13**.

41% ; white solid ; T_f : 143-145°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.1 (m, 1H, H_{arom}), 7.92-7.84 (m, 4H, H_{arom}), 7.77 (m, 1H, H_{arom}), 7.65-7.61 (m, 2H, H_{arom}), 7.50 (m, 2H, H_{arom}), 5.1 (s, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 168.2 (IV), 149.9 (IV), 147.8 (IV), 140.5 (III), 133.8 (III), 131.6 (III), 130.5 (IV), 129.0 (III, 2C), 128.9 (III, 2C), 128.6 (III), 127.9 (III, 2C), 126.9 (IV), 125.2 (IV), 110.7 (IV), 49.3 (II); IR (neat): 2234, 1708, 1273 cm^{-1} ; HRMS (ES+): calcd for $C_{18}H_{12}N_3ONaI$ 435.9923, found 435.9936.



A degassed solution of *N*-acylcyanamide **13** (206 mg, 0.5 mmol) and hexabutylditin (380 µL, 0.75 mmol) in toluene (29 mL) was refluxed and irradiated with a sun lamp (300W) until the monitoring of the reaction by TLC showed total consumption of the starting material. The reaction mixture was concentrated and purified on silica gel (petroleum ether/ethyl acetate 5/5) to give luotonin A (61 mg, 43%).

43% ; pale yellow solid ; T_f : 283-284°C ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.47-8.41 (m, 3H, H_{arom}), 8.11 (d, *J* = 8.1 Hz, 1H, H_{arom}), 7.93 (d, *J* = 8.1 Hz, 1H, H_{arom}), 7.84 (m, 2H, H_{arom}), 7.67 (t, *J* = 7.3 Hz, 1H, H_{arom}), 7.58 (t, *J* = 7.3 Hz, 1H, H_{arom}), 5.33 (s, 2H, ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 160.8 (IV), 152.7 (IV), 151.3 (IV), 149.6 (IV), 149.5 (IV), 134.8 (III), 131.7 (III), 130.9 (III, 2C), 129.6 (IV), 128.9 (III, IV), 128.7 (III), 128.1 (III), 127.6 (III), 126.6 (III), 121.4 (IV), 47.5 (II); IR (neat): 2923, 2853, 1726, 1666 cm^{-1} ; MS: MNa^+ 308, MK^+ 324; all data consistent with literature.[3]

[3] S. B. Mhaske, N. P. Argade, *J. Org. Chem.*, **2004**, *69*, 4563-4566.