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AN EFFICIENT SYNTHESIS OF *N*-AlKYL-4-SUBSTITUTED *3H*-PYRIDINE-2,6-DIONE. SYNTHESIS OF ISOGUVACINE AND MDL-11,939

Meng-Yang Chang,[a] Shui-Tein Chen,*[a] and Nein-Chen Chang[b]

[a]*Institute of Biological Chemistry, Academia Sinica, Nankang, Taipei 115, Taiwan*

[b]*Department of Chemistry, National Sun Yat-Sen University, Kaohsiung 804, Taiwan*

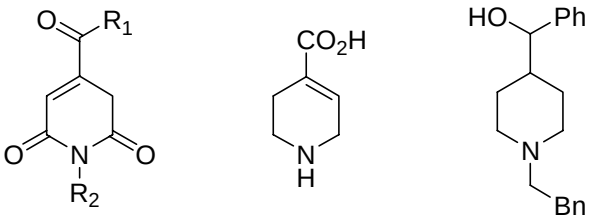
Abstract—An efficient route towards the synthesis of *N*-alkyl-4-substituted *3H*-pyridine-2,6-dione using various *N*-alkyl-α-sulfonylacetamides and two α,β-unsaturated esters as starting materials is described. Isoguvacine and MDL-11,939 with have potential biological activities were synthesized *via* this strategy.

1. INTRODUCTION

Glutarimides possess various biological activities,[1-3] therefore, the synthesis of these cyclic imides has attracted considerable attention.[4-15] Glutarimides are in most cases obtained by heating δ-dinitriles *via* cyclization in an acidic solution[10] or by cyclization of monoamides with acid in presence of thionyl chloride[8] or BOP.[9] Owing to the harsh classical conditions, some milder methods has been proposed,[5,6,11] such as the condensation of a diacidic compound with amine. Recently, we developed an efficient synthesis of an unsymmetrical glutarimide with the sulfonyl group at α-position, and proposed a mechanism of reaction.[12-15] We examined this reaction strategy using different α-sulfonylacetamides with

various α,β-unsaturated esters to yield diverse substituents on the skeleton.

Here, we report an efficient route towards the synthesis of *N*-alkyl-4-substituted *3H*-pyridine-2,6-dione (**1**) and it's application of the synthesis of isoguvacine and MDL-11,939 which have potential biological activities (Figure 1).



1 isoguvacine MDL-11,939

Figure 1. Structure of **1**, isoguvacine and MDL-11,939

Among a variety of γ-Abu (γ-aminobutyric acid, $GABA_A$) analogs, isoguvacine[16-20] is a potent and selective γ-Abu agonist that interacts specifically with the γ-Abu receptor and shows considerable pharmacological potential. In the synthesis of isoguvacine analogs, Krogsgaard-Larsen has developed some potential prodrugs for preventating passage through the blood-brain barrier.[16] Isoguvacine is more active than γ-Abu on cells *in vivo*[19] and *in vitro*,[20] these findings prompt us to develop a new synthetic strategy for this compound.

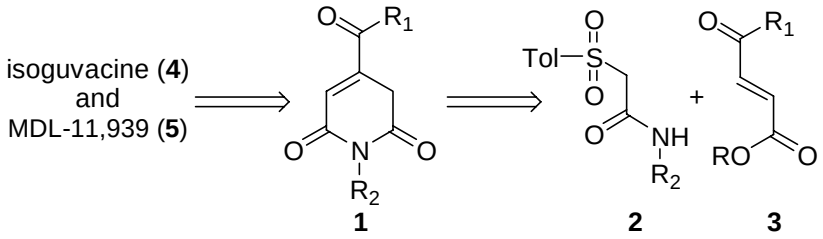
MDL-11,939 (glemanserin)[21-30] is a potent class III antiarrhythmic agent with electrophysiological effects *in vitro* and *in vivo*,[25-26] it is a selective antagonist (K_i= 12.2 nM)[28] to the 5-HT_{2A} receptor based on *in vitro* and *in vivo* studies of central and peripheral serotonergic activities.[24]

2. RESULTS AND DISCUSSION

2.1. Retrosynthetic analysis of isoguvacine (4) and MDL-11,939 (5)

The retrosynthetic analysis for isoguvacine (**4**) and MDL-11,939 (**5**) is shown in Scheme 1. Isoguvacine (**4**) and MDL-11,939 (**5**) were synthesized from piperidine-2,6-diones (**1**), which in turn were derived from the reaction of α-sulfonylacetamides (**2**) with α,β-unsaturated esters (**3**). The enzymatic resolution of racemic acetylated MDL-11,939 has been carried out on a multi-gram scale utilizing a lipase catalyzed

hydrolysis from *Aspergillus niger* in high entantiomeric purity (>97% ee).[21]

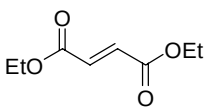
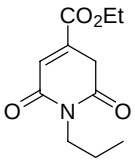
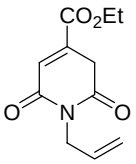
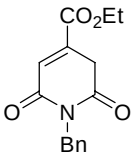
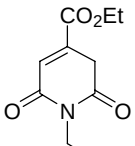
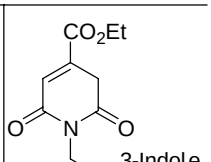
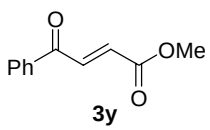
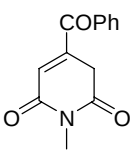
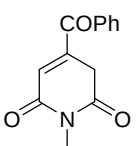
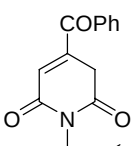
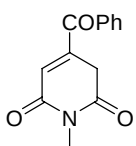
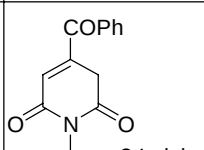


Scheme 1. Retrosynthetic analysis of isoguvacine (**4**) and MDL-11,939 (**5**)

2.2. Reaction and proposed mechanism of α-sulfonylacetamides (2) with esters (3)

α-Sulfonylacetamides (**2**) were produced in 85-90% yield.[12-15] Acetamides (**2**) reacted with α,β-unsaturated esters (**3**) to give 4-substituted piperidine-2,6-diones (**1**) using the concise reaction. The ^{1}H-NMR spectra of cyclized products (**1**) showed the chemical shifts of the olefinic proton (for **x**: *ca.* δ 6.8; for **y**: *ca.* δ 7.9, t, 1H) and the allylic proton (for x and y: *ca.* δ 3.7, d, 2H) to prove the formation of desired products. Using this protocol, various *N*-alkyl-4-substituted *3H*-pyridine-2,6-diones (**1**) were produced in moderate yields (Table 1).

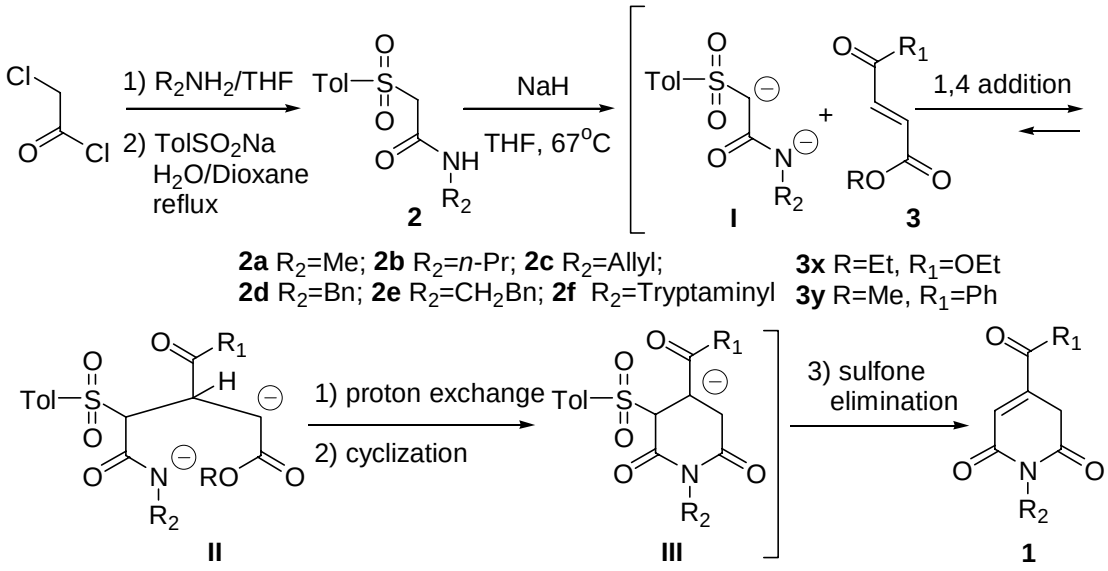
Table 1. Reaction of dianions of acetamides (**2**) with two Michael acceptors (**3x**) and (**3y**)

Michael acceptors	Products: *N*-alkyl-4-substituted *3H*-pyridine-2,6-dione (**1**)				
 **3x**	 **1xb** (53%)	 **1xc** (47%)	 **1xd** (41%)	 **1xe** (58%)	 **1xf** (49%)
 **3y**	 **1ya** (53%)	 **1yb** (61%)	 **1yc** (50%)	 **1ye** (55%)	 **1yf** (51%)

The reaction mechanism of α-sulfonylacetamides (**2**) with α,β-unsaturated esters (**3**) is shown in Scheme

2. Sequential treatment of chloroacetyl chloride with various amines and *p*-toluenesulfinic acid sodium salt furnished α-sulfonylacetamides (**2**). After reaction of acetamides (**2**) with sodium hydride, the resulting dianion reacted with two kinds of α,β-unsaturated esters (**3**) at reflux temperature to yield the corresponding compounds (**1**).

First, the formed dianion (**I**) attacks the β-position of the esters (**3**) to produce dianion (**II**) by Michael addition reaction. From this state, dianion (**II**) has two possible pathways: the reverse reaction of retro-Michael reaction and the forward reaction of proton exchange. In the reverse reaction, the less stable dianion (**II**) goes back to the more stable dianion (**I**) *via* a retro-Michael reaction. In the forward reaction, the less stable dianion (**II**) exchanges the neighboring proton and then follows the intramolecular cyclization to form anion (**III**). Anion (**III**) eliminates the sulfonyl group to produce compounds (**1**).

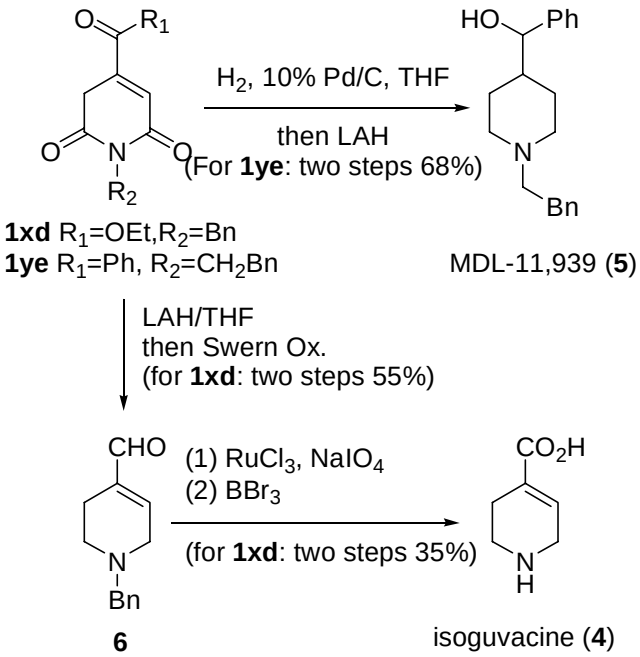


Scheme 2. An efficient synthesis of *N*-alkyl-4-substituted *3H*-pyridine-2,6-dione (**1**)

2.3. Synthesis of isoguvacine (4) and MDL-11,939 (5)

The synthesis of isoguvacine (**4**) and MDL-11939 (**5**) was begun from **1xd** (R_1=OEt, R_2=Bn) and **1ye** (R_1=Ph, R_2=CH_2Bn), which were the cycloadducts of reactions as shown in Scheme 3. Reduction of the symmetric piperidine-2,6-dione (**1xd**) by lithium aluminum hydride produced the allylic alcohol, and Swern oxidation of the corresponding alcohol produced an aldehyde (**6**) in 55% yield (two steps). Further

mild oxidation of aldehyde (**6**) with ruthenium(III) chloride and sodium periodate yielded the carboxylic acid and subsequent debenzylation with boron tribromide produced isoguvacine (**4**) in 35% yield (two steps). In the synthesis of MDL-11,939 (**5**), reaction of **1ye** using catalytic hydrogenation (10% palladium on activated carbon as catalyst) and subsequent reduction with lithium aluminum hydride produced target (**5**) in 68% yield (two steps). We successfully transformed **1xd** into isoguvacine (**4**) in four steps and **1ye** into MDL-11939 (**5**) in two steps.



Scheme 3. Synthesis of isoguvacine (**4**) and MDL-11,939 (**5**)

3. CONCLUSION

We have developed an efficient strategy that is useful for constructing *N*-alkyl-4-substituted *3H*-pyridine-2,6-diones (**1**). The strategy was applied to the synthesis of isoguvacine (**4**) and MDL-11939 (**5**).

4. EXPERIMENTAL

4.1. General. Methylene chloride and tetrahydrofuran were distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic

solvents were dried with anhydrous magnesium sulfate before concentration *in vacuo*. All reported melting temperatures were uncorrected.

4.2. Synthesis of *N*-alkyl-2-substituted sulfonylacetamide (**2**)

A solution of chloroacetyl chloride (600 mg, 5.3 mmol) in tetrahydrofuran (20 mL) was added to a stirred solution of *N*-alkylamines (5.0 mmol) and triethylamine (560 mg, 5.5 mmol) in tetrahydrofuran (30 mL) in an ice bath for 1 h. The reaction mixture was stirred at rt for 4 h and concentrated under reduced pressure. The residue was diluted with water (30 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (2 x 50 mL), dried, filtered and evaporated. Without further purification, the crude product was refluxed with 4-methylphenylsulfinic acid sodium salt (7.5 mmol) in dioxane (50 mL) and water (50 mL) for 10 h. Then the mixture was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (2 x 10 mL), dried, filtered and evaporated. Recrystallization from hexane (30 mL) and ethyl acetate (15 mL) produced 85%~90% of compounds (**2**) as the starting materials.

4.3. Procedure of stepwise [3+3] reaction[12-15]

A solution of acetamide (**2**) (2.0 mmol) in tetrahydrofuran (15 mL) was added to a rapidly stirred suspension of sodium hydride (176 mg, 4.4 mmol, 60%) in tetrahydrofuran (10 mL). After the reaction mixture was stirred at rt for 15 min, a solution of α,β-unsaturated esters (**3**) (2.0 mmol) in tetrahydrofuran (5 mL) was added. The resulting mixture was refluxed for 30 min, quenched with saturated ammonium chloride solution (1 mL) in an ice bath, and concentrated under reduced pressure. The residue was diluted with water (5 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 4/1~2/1) produced products.

1-*n*-Propyl-2,6-dioxo-1,2,3,6-tetrahydropyridine-4-carboxylic acid ethyl ester (**1xb**)

oil; IR ($CHCl_3$) cm^{-1} 3044, 2349, 1714, 1666; EI-MS: $C_{11}H_{15}NO_4$ m/z (%) = 67 (42), 138 (83), 179 (100), 225 (M^+, 41); HRMS (EI, M^+) calcd for $C_{11}H_{15}NO_4$ 225.1001, found 225.0999; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (t, *J* = 2.5 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.64 (d, *J* = 2.5 Hz, 2H), 3.55 (t, *J* = 7.5 Hz, 2H), 1.65-1.57 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.55, 168.99, 164.88, 140.13, 122.20, 61.35, 40.68, 34.32, 21.07, 14.13, 11.26; Anal. Calcd for $C_{11}H_{15}NO_4$ C, 58.66; H, 6.71. Found C, 58.78; H, 6.89.

1-Allyl-2,6-dioxo-1,2,3,6-tetrahydropyridine-4-carboxylic acid ethyl ester (**1xc**)

oil; IR ($CHCl_3$) cm^{-1} 3045, 2350, 1714, 1669; EI-MS: $C_{11}H_{13}NO_4$ m/z (%) = 67 (26), 84 (24), 112 (32), 149 (72), 177 (100), 223 (M^+, 21); HRMS (EI, M^+) calcd for $C_{11}H_{13}NO_4$ 223.0845, found 223.0842; ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (t, *J* = 2.6 Hz, 1H), 5.82-5.74 (m, 1H), 5.25-5.17 (m, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.20-4.18 (m, 2H), 3.67 (d, *J* = 2.6 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.99, 168.46, 164.80, 139.96, 130.22, 122.50, 118.90, 61.40, 41.16, 34.38, 14.13; Anal. Calcd for $C_{11}H_{13}NO_4$ C, 59.19; H, 5.87. Found C, 59.36; H, 6.11.

1-Benzyl-2,6-dioxo-1,2,3,6-tetrahydropyridine-4-carboxylic acid ethyl ester (**1xd**)

oil; IR ($CHCl_3$) cm^{-1} 3048, 2351, 1719, 1659; EI-MS: $C_{15}H_{15}NO_4$ m/z (%) = 91 (37), 199 (91), 227 (47), 273 (M^+, 100); HRMS (EI, M^+) calcd for $C_{15}H_{15}NO_4$ 273.1001, found 273.0998; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.37 (m, 2H), 7.32-7.26 (m, 3H), 6.78 (t, *J* = 2.6 Hz, 1H), 4.74 (s, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.66 (d, *J* = 2.6 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.14, 168.63, 164.78, 140.02, 135.32, 128.96, 128.74 (2x), 128.17 (2x), 122.55, 61.39, 42.70, 34.43, 14.13; Anal. Calcd for $C_{15}H_{15}NO_4$ C, 65.92; H, 5.53. Found C, 66.22; H, 5.72.

1-Phenylethyl-2,6-dioxo-1,2,3,6-tetrahydropyridine-4-carboxylic acid ethyl ester (**1xe**)

mp 86-88 ^oC (hexane/ethyl acetate); IR ($CHCl_3$) cm^{-1} 3043, 2345, 1722, 1667; EI-MS: $C_{16}H_{17}NO_4$ m/z (%) = 91 (22), 104 (100), 204 (11), 287 (M^+, 17); HRMS (EI, M^+) calcd for $C_{16}H_{17}NO_4$ 287.1158, found

287.1151; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.18 (m, 5H), 6.77 (t, *J* = 2.6 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.84 (m, 2H), 3.61 (d, *J* = 2.6 Hz, 2H), 2.91 (t, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.25, 168.72, 164.85, 139.94, 137.48, 128.78 (2x), 128.61 (2x), 126.81, 122.32, 61.39, 42.24, 34.26, 33.54, 14.14; Anal. Calcd for $C_{16}H_{17}NO_4$ C, 66.89; H, 5.96. Found C, 67.31; H, 5.86.

1-[2-(3-Indolyl)ethyl]-2,6-dioxo-1,2,3,6-tetrahydropyridine-4-carboxylic acid ethyl ester (**1xf**)

mp 166-168 ^{o}C (hexane/ethyl acetate); IR ($CHCl_3$) cm^{-1} 3045, 2349, 1724, 1671; EI-MS: $C_{18}H_{18}N_2O_4$ m/z (%) = 130 (100), 143 (85), 281 (9), 326 (M^+, 63); HRMS (EI, M^+) calcd for $C_{18}H_{18}N_2O_4$ 326.1267, found 326.1263; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.17-7.10 (m, 2H), 7.04 (d, *J* = 2.2 Hz, 1H), 6.76 (t, *J* = 2.6 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.92 (t, *J* = 7.5 Hz, 2H), 3.58 (d, *J* = 2.6 Hz, 2H), 3.08 (t, *J* = 7.5 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.47, 168.95, 164.88, 140.15, 136.22, 129.96, 127.37, 122.20, 122.15, 119.60, 118.62, 111.97, 111.20, 61.38, 39.72, 34.35, 23.45, 14.15; Anal. Calcd for $C_{18}H_{18}N_2O_4$ C, 66.25; H, 5.56. Found C, 66.53; H, 5.46.

1-Methyl-4-benzoyl-*3H*-pyridine-2,6-dione (**1ya**)

mp 88-90 ^{o}C (hexane/ethyl acetate); IR ($CHCl_3$) cm^{-1} 3045, 2930, 1765, 1726, 1680; ESI-MS: $C_{13}H_{11}NO_3$ m/z (%) = 77 (49), 105 (100), 229 (M^+, 75); HRMS (EI, M^+) calcd for $C_{13}H_{11}NO_3$ 229.0739, found 229.0733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-8.00 (m, 2H), 7.90 (t, *J* = 2.6 Hz, 1H), 7.64-7.60 (m, 1H), 7.53-7.49 (m, 2H), 3.72 (d, *J* = 2.6 Hz, 2H), 3.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.66, 174.13, 169.87, 139.66, 137.30, 134.04, 129.02 (3x), 128.60, 123.12, 34.76, 29.66; Anal. Calcd for $C_{13}H_{11}NO_3$ C, 68.11; H, 4.84. Found C, 68.34; H, 5.01.

1-*n*-Propyl-4-benzoyl-*3H*-pyridine-2,6-dione (**1yb**)

mp 82-84 ^{o}C (hexane/ethyl acetate); IR ($CHCl_3$) cm^{-1} 3048, 2952, 1770, 1718, 1669; EI-MS: $C_{15}H_{15}NO_3$ m/z (%) = 77 (26), 105 (100), 199 (21), 257 (M^+, 37); HRMS (EI, M^+) calcd for $C_{15}H_{15}NO_3$ 257.1052,

found 257.1055; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.97 (m, 2H), 7.84 (t, *J* = 2.6 Hz, 1H), 7.60-7.56 (m, 1H), 7.49-7.45 (m, 2H), 3.72 (d, *J* = 2.6 Hz, 2H), 3.58 (t, *J* = 7.4 Hz, 2H), 1.67-1.57 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.65, 174.11, 169.79, 139.82, 137.31, 133.95, 128.98 (3x), 128.55, 122.96, 44.66, 34.69, 21.12, 11.30; Anal. Calcd for $C_{15}H_{15}NO_3$ C, 70.02; H, 5.88. Found C, 70.29; H, 5.98.

1-Allyl-4-benzoyl-*3H*-pyridine-2,6-dione (**1yc**)

mp 55-58 ^{o}C (hexane/ethyl acetate); IR ($CHCl_3$) cm^{-1} 3044, 2999, 1770, 1720, 1675, 1366, 1167; EI-MS: $C_{15}H_{13}NO_3$ m/z (%) = 77 (32), 105 (100), 178 (12), 229 (13), 255 (M^+, 18); HRMS (EI, M^+) calcd for $C_{15}H_{13}NO_3$ 255.0895, found 255.0894; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.99 (m, 2H), 7.89 (t, *J* = 2.6 Hz, 1H), 7.63-7.59 (m, 1H), 7.52-7.48 (m, 2H), 5.86-5.76 (m, 1H), 5.27-5.19 (m, 2H), 4.23 (d, *J* = 5.9 Hz, 2H), 3.78 (d, *J* = 2.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.64, 173.55, 169.29, 139.59, 137.28, 134.03, 130.31, 129.02 (2x), 128.57 (2x), 123.31, 118.86, 41.16, 34.77; Anal. Calcd for $C_{15}H_{13}NO_3$ C, 70.58; H, 5.13. Found C, 70.68; H, 4.89.

1-Phenylethyl-4-benzoyl-*3H*-pyridine-2,6-dione (**1ye**)

mp 139-141 ^{o}C (hexane/ethyl acetate); IR ($CHCl_3$) cm^{-1} 3058, 2977, 1764, 1716, 1678; EI-MS: $C_{20}H_{17}NO_3$ m/z (%) = 77 (18), 104 (100), 204 (28), 319 (M^+, 29); HRMS (EI, M^+) calcd for $C_{20}H_{17}NO_3$ 319.1208, found 319.1214; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-8.00 (m, 2H), 7.86 (t, *J* = 2.6 Hz, 1H), 7.64-7.60 (m, 1H), 7.53-7.50 (m, 2H), 7.30-7.21 (m, 5H), 3.90-3.87 (m, 2H), 3.72 (d, *J* = 2.6 Hz, 2H), 2.96-2.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.67, 173.82, 169.54, 139.54, 139.58, 137.55, 134.03, 129.02 (4x), 128.82 (2x), 128.63, 128.58, 126.82, 123.13, 40.25, 34.66, 33.62; Anal. Calcd for $C_{20}H_{17}NO_3$ C, 75.22; H, 5.37. Found C, 75.34; H, 5.12.

1-[2-(3-Indolyl)ethyl]-4-benzoyl-*3H*-pyridine-2,6-dione (**1yf**)

mp 179-181 ^{o}C (hexane/ethyl acetate); IR ($CHCl_3$) cm^{-1} 3218, 2978, 1769, 1715, 1681; EI-MS:

$C_{22}H_{18}N_2O_3$ m/z (%) = 105 (17), 130 (100), 143 (83), 326 (9), 358 (M^+, 13); HRMS (EI, M^+) calcd for $C_{22}H_{18}N_2O_3$ 358.1317, found 358.1313; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 8.00 (d, *J* = 7.4 Hz, 2H), 7.85 (t, *J* = 2.4 Hz, 1H), 7.68-7.60 (m, 2H), 7.53-7.49 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.19-7.09 (m, 2H), 7.07 (br s, 1H), 3.96 (t, *J* = 7.5 Hz, 2H), 3.70 (d, *J* = 2.4 Hz, 2H), 3.11 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.73, 174.03, 169.76, 139.76, 137.33, 136.22, 134.01, 129.01, 128.91, 128.57 (2x), 127.40, 123.04, 122.24, 122.12, 119.63, 118.66, 112.08, 111.20, 39.74, 34.73, 23.50; Anal. Calcd for $C_{22}H_{18}N_2O_3$ C, 73.73; H, 5.06. Found C, 73.84; H, 4.75.

4.4. Synthesis of isoguvacine (**4**)

1-Benzyl-1,2,3,6-tetrahydropyridine-4-carbaldehyde (**6**)

A solution of compound (**1xd**) (273 mg, 1.0 mmol) in tetrahydrofuran (10 mL) was added to a solution of lithium aluminum hydride (285 mg, 7.5 mmol) and aluminum chloride (1.0 g, 7.5 mmol) in tetrahydrofuran (20 mL) *via* syringe at 0 ^{o}C for 30 min. The mixture was refluxed for 2 h, quenched with saturated aqueous ammonium chloride solution (2 mL) under cooling, and concentrated. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with brine and water, dried, filtered and concentrated to produce crude alcohol (162 mg, 80%). Without further purification, a solution of oxalyl chloride (0.14 mL, 1.56 mmol) in dichloromethane (10 mL) at –78 ^{o}C, and dimethyl sulfoxide (0.19 mL, 2.67 mmol) were added carefully. The solution was warmed to –40 ^{o}C for 5 min and recooled to –78 ^{o}C, and then a solution of alcohol in dichloromethane (5 mL) was added dropwise for 20 min followed by excess triethylamine (4 mL) for 30 min. The reaction mixture was warmed to rt and poured into saturated aqueous ammonium chloride solution (2 mL), and concentrated. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with brine and water, dried, filtered and concentrated to produce crude compound (**6**). Purification on silica gel (hexane/ethyl acetate = 2/1) produced compound (**6**) (110 mg, 69%) as an oil.

IR ($CHCl_3$) cm^{-1} 3008, 2840, 1758, 1178; EI-MS: $C_{13}H_{15}NO$ m/z (%) = 91 (100), 110 (56), 201 (M^++1, 44); HRMS (ESI, M^+) calcd for $C_{13}H_{15}NO$ 201.1154, found 201.1160; ^{1}H NMR (500 MHz, $CDCl_3$) δ

9.48 (s, 1H), 7.35-7.27 (m, 5H), 6.72 (t, *J* = 1.5 Hz, 1H), 3.67 (br s, 2H), 3.28 (br s, 2H), 2.64 (br s, 2H), 2.37 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.82, 139.54, 130.10, 129.10 (2x), 128.42 (3x), 127.42, 62.25, 52.87, 48.69, 22.34.

1,2,3,6-Tetrahydropyridine-4-carboxylic acid hydrogen chloride (isoguvacine-HCl **4**)[18]

The aldehyde (**6**) (100 mg, 0.5 mmol) was dissolved in carbon tetrachloride (2 mL), acetonitrile (2 mL) and water (3 mL) with vigorous stirring. Then a mixture of sodium periodate (210 mg, 1.0 mmol) and ruthenium(III) chloride hydrate (5 mg) was added. The reaction was stopped after 6 h, diluting with methylene chloride (10 mL) and the organic layer was separated. The aqueous layer was then extracted with methylene chloride (2 x 10 mL) and the organic layers were filtered on a Celite pad, collected and concentrated to give crude acid (76 mg, 70%). Without further purification, a solution of acid (76 mg, 0.35 mmol) in dichloromethane (10 mL) was cooled at –78 ^{o}C, and a solution of boron tribromide (0.5 mL, 0.5 mmol, 1.0 M in dichloromethane) was added at –78 ^{o}C. The solution was warmed to –40 ^{o}C for 20 min and recooled to –78 ^{o}C for 20 min, and then methanol (0.5 mL) was added to the reaction mixture. The reaction mixture was warmed to rt and concentrated. Water (5 mL) was added to the residue, and extracted with ethyl acetate (3 x 5 mL). 37% Hydrogen chloride was added to the aqueous layer, and the reaction mixture was refluxed for 1 h and concentrated to produce isoguvacine-HCl (**4**) (28 mg, 50%).

mp 274-277 ^{o}C (isopropanol/H_2O) (decomp); EI-MS: $C_6H_{10}NO_2Cl$ m/z (%) = 53 (18), 83 (100), 128 (M^+-HCl, 17); ^{1}H NMR (400 MHz, D_2O) δ 7.01 (br s, 1H), 3.98 (br s, 2H), 3.47 (t, *J* = 6.1 Hz, 2H), 2.68 (br s, 2H); ^{13}C NMR (100 MHz, D_2O) δ 169.37, 132.04, 129.09, 42.43, 41.03, 21.14; Anal. Calcd for $C_6H_{10}NO_2Cl$ C, 44.05; H, 6.16. Found C, 44.12; H, 5.95.

4.5. Synthesis of MDL-11939 (**5**)

α-Phenyl-1-(2-phenylethyl)-4-piperidinemethanol (MDL-11939, **5**)[22]

10% Palladium on activated carbon (30 mg) was added to the solution of compound (**1ye**) (320 mg, 1.0 mmol) in tetrahydrofuran (20 mL). Then hydrogen was bubbled into the mixture for 10 min, and the

reaction mixture was continued to stir for 3 h at rt. The catalyst was filtered through a short plug of Celite and washing with tetrahydrofuran (2 x 10 mL), and the filtrate was cooled in an ice bath and lithium aluminum hydride (285 mg, 7.5 mmol) and aluminum chloride (1.0 g, 7.5 mmol) were added to the filtrate in an ice bath. The mixture was warmed to rt and then refluxed for 2 h, quenched with saturated aqueous ammonium chloride solution (2 mL) under cooling, and concentrated. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with brine and water, dried, filtered and concentrated to produce crude alcohol (**5**). Recrystallization from hexane and ethyl acetate (*ca.* = 3/1) yielded pure **5** (200 mg, 68%) as a solid.

mp 78-80 ^{o}C; EI-MS: $C_{20}H_{25}NO$ m/z (%) = 77 (33), 105 (43), 159 (55), 204 (100), 295 (M^{+}, 4); HRMS (EI, M^{+}) calcd for $C_{20}H_{25}NO$ 295.1936, found 295.1944; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 6H), 7.24-7.15 (m, 4H), 4.34 (d, *J* = 7.1 Hz, 1H), 3.07-3.05 (m, 1H), 2.93-2.90 (m, 1H), 2.79-2.75 (m, 2H), 2.56-2.41 (m, 2H), 2.05-1.87 (m, 4H), 1.63-1.59 (m, 1H), 1.47-1.42 (m, 1H), 1.30-1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.67, 140.46, 128.69 (2x), 128.38, 128.30 (2x), 127.56, 126.73 (2x), 126.00 (2x), 78.69, 60.81, 53.67, 53.63, 43.27, 33.55, 28.72, 28.41.

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