Iridium-Catalyzed Direct Synthesis of Tryptamine Derivatives from Indoles: Exploiting *N*-Protected β-Amino Alcohols as Alkylating Agents

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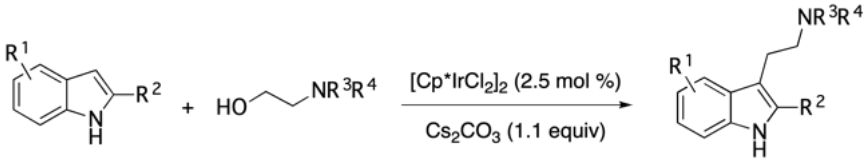
TOC



Abstract

The selective C3-alkylation of indoles with *N*-protected ethanolamines involving the "borrowing hydrogen" strategy is described. This method provides convenient and sustainable access to several tryptamine derivatives.

Introduction

The tryptamine moiety is found in a number of drugs and is a common motif in countless naturally occurring compounds that use L-tryptophan as a biosynthetic precursor.[1] The direct and selective construction of tryptamine derivatives from simple and sustainable starting materials using a catalytic system provides convenient access to a range of structurally diverse natural products, pharmaceutical compounds, potential building blocks for indole alkaloid chemistry, and other polynitrogenated compounds.[2] Although methods accessing these bioactive molecules have been reported, there are few one-step transformations that provide access to tryptamines. Classical methods involve the C-3 Friedel–Crafts alkylation of indoles[3] with either nitroalkenes[4] or aziridines[5] as the electrophilic partner, promoted by Lewis acids and/or organocatalysts. However, due to the toxicity and instability of these strong electrophilic reactants[6] as well as selectivity issues during the required extra reduction step of the nitro group and/or aziridine ring opening, a more sustainable and efficient method is highly desired.[7] In the search for new suitable two-carbon nitrogen-containing electrophiles, we recently described the efficient use of *N*-protected aminoethyl acetals for the reductive alkylation of indoles,[8] giving access to tryptamine derivatives in a single step. During the course of this study, we found that acyl protection of the amine side chain was necessary to achieve acceptable levels of reactivity. Although this approach employs safe and inexpensive reagents, proceeds under mild conditions, and tolerates several functional groups, the shortcomings associated with completely unsubstituted indoles as well as a large excess of the reducing agent and TFA prompted us to investigate a novel catalytic and less wasteful method encompassing a wider range of indoles without the need for an external reductant.

The so-called “borrowing hydrogen” methodology (also named as “hydrogen autotransfer”), in which dehydrogenation of poorly reactive alcohols is followed by *in situ* consumption of the generated hydrogen equivalents, has gained acceptance as an efficient synthetic strategy in organic synthesis. Seminal work by Grigg and Watanabe[9] as well as extensive studies by many other

groups[10] have shown that in the presence of transition metal catalysts (usually ruthenium or iridium complexes), poorly reactive alcohols are useful electrophilic partners for *N*-alkylation and C–C bond formation in which amines and methylene carbon acids are typically used as nucleophiles.[11] The use of a neutral electron-rich aromatic system with alcohols in the direct transition metal-catalyzed alkylation has also been reported. However, to the best of our knowledge, there are no examples using the "borrowing hydrogen" strategy for the synthesis of tryptamine derivatives, despite the synthetic advantages of such an approach.[12] Herein, we report the development of an effective protocol for the direct Ir-catalyzed alkylation of indoles with *N*-protected ethanolamines to afford tryptamine derivatives. This strategy could open attractive possibilities for the total synthesis of tryptamine-based alkaloids.

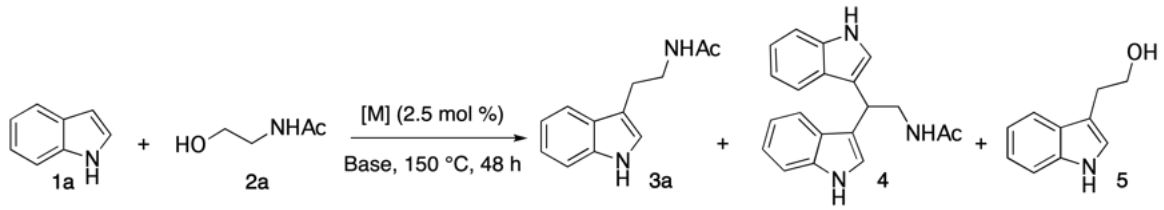
Results and Discussion

Preliminary studies were carried out at 150 °C in a sealed tube, using commercially available *N*-acetylethanolamine (**2a**) and unsubstituted indole (**1a**) in the presence of substoichiometric amounts of KOH (20%). A variety of transition-metal catalysts, well known to be highly active in hydrogen autotransfer reactions, including Pd/C, $RuCl_2(PPh_3)_3$, $[Ir(cod)Cl]_2$, $[Ir(coe)_2Cl]_2$, $[Ir(OMe)(cod)]_2$, and $RuHCl(CO)(PPh_3)_3$, were screened. We found that the iridium dimer $[Cp^*IrCl_2]_2$[13] was the most efficient catalyst. After 48 h, we observed complete consumption of the indole and selective formation of the desired *N*-acetyltryptamine (35% yield, Table 1, entry 9), without traces of the N_1-alkylated product. The discrepancy between conversion and yield (Table 1) is mainly explained by the formation of two side products: the bis(3-indolyl)methane species **4** and tryptophol (**5**). The bisindole **4**, arising from addition of indole to the transient azafulvene,[14] did not undergo conversion to **3a** upon to the reaction conditions, but some degradation of **4** did take place, suggesting that **4** is not plausibile intermediate of the reaction. On the contrary, the formation of the byproduct **5** could be explained by the formation of the intermediate amido aldehyde, which is in equilibrium/tautomerization with the reactive *N*-acetyliminium species that undergoes

amidoalkylation with the incoming indole, prior to return of hydrogen. This sequence accounts for the different regioselectivities in the alkylation process, without a less direct C–N oxidation step.[15] Although to obtain pure **3a** purification by flash chromatography on silica gel was necessary, the removal of side products is simple due to their small amount and high lipophilicity compared to tryptamines.

Next, we investigated the influence of the base on the model reaction. Increasing the quantity of base to a stoichiometric amount slightly improved the yield of the reaction (Table 1, entry 10). Most importantly, we discovered that when powdered Cs_2CO_3 was used as the base, the desired *N*-acetyltryptamine was obtained in a synthetically useful yield (Table 1, entry 16). Lower conversions were generally observed when stronger bases such as *t*-BuOK and *t*-BuONa were employed (Table 1, entries 11 and 12), presumably due to partial hydrolysis of the ethanolamide used as the electrophile. A very low amount of the desired *N*-acetyltryptamine was also obtained by using solid $NaHCO_3$ or K_3PO_4 as the base (Table 1, entries 13 and 15), highlighting the importance of Cs_2CO_3 in this reaction. As expected, the reaction without the use of catalyst failed to provide the desired product, and the starting material was recovered (Table 1, entry 21). Comparing the amounts of electrophile used, the best results were obtained by applying three equivalents of *N*-acetylethanolamine (Table 1, entries 16, 18, and 19). Interestingly, no overalkylation products were ever observed.

Table 1. Optimization of Reaction Conditions.[a]



entry	catalyst/ ligand	base	conv. (%)[b]	yield (%)[c]		
				3a	**4**	**5**
1	Pd/C	KOH[f]	0	-	-	-
2	$RuCl_2(PPh_3)_3$	KOH[f]	0	-	-	-
3	$[Cp^*RhCl_2]_2$	KOH[f]	41	11	12	6
4	$[Ir(coe)_2Cl]_2$	KOH[f]	55	30	10	5

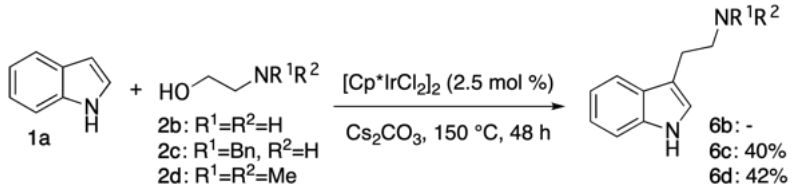
5	$[Ir(OMe)(cod)]_2$	KOH[f]	47	18	12	5
6	[Cp*Ir(bpy)Cl]	KOH[f]	52	27	9	7
7	[Cp*Ir(Pro)Cl]	KOH[f]	54	33	8	5
8	$[IrCl(cod)]_2$	KOH[f]	42	12	12	6
9	$[Cp^*IrCl_2]_2$	KOH[f]	66	35	12	7
10	$[Cp^*IrCl_2]_2$	KOH	68	39	10	9
11	$[Cp^*IrCl_2]_2$	tBuOK	62	30	12	8
12	$[Cp^*IrCl_2]_2$	tBuONa	66	30	14	8
13	$[Cp^*IrCl_2]_2$	$NaHCO_3$	63	14	20	9
14	$[Cp^*IrCl_2]_2$	KOAc	64	12	21	10
15	$[Cp^*IrCl_2]_2$	K_3PO_4	62	16	19	8
16	$[Cp^*IrCl_2]_2$	Cs_2CO_3	>95	60	9	6
17	$[Cp^*IrCl_2]_2$	Cs_2CO_3[f]	52	10	17	8
18[d]	$[Cp^*IrCl_2]_2$	Cs_2CO_3	35	14	8	5
19[e]	$[Cp^*IrCl_2]_2$	Cs_2CO_3	>95	56	10	9
20	$[Cp^*IrCl_2]_2$	-	23	5	9	-
21	-	Cs_2CO_3	0	-	-	-

[a]Conditions: Indole (1 equiv), *N*-acetylethanolamine (3 equiv), catalyst (2.5 mol %), and base (1.1 equiv) at 150 °C for 48 h. [b]Determined by ^{1}H-NMR analysis of the crude reaction mixture. [c]Isolated yield. [d]1 equiv of *N*-Acetylethanolamine was used. [e]10 equiv of *N*-Acetylethanolamine was used. [f]Base (0.2 equiv).

With the optimal reaction conditions established, we sought to probe the scope of the amine protecting groups that are amenable to this procedure. We investigated the use of alternative protecting groups that would not only allow efficient alkylation but also would be removed easily under relatively mild conditions. We tried to replace *N*-Ac with a traditional easily removable amino protecting group such *N*-$COCF_3$, *N*-Cbz, or *N*-Ts. Unfortunately, *N*-$COCF_3$ and *N*-Cbz were very unstable and decomposed quickly under the basic reaction conditions. Interestingly, using *N*-Cbz-ethanolamine, we obtained only 3-benzylindole, which probably formed by the borrowing hydrogen reaction of indole with benzyl alcohol generated by an intramolecular cyclization to the corresponding oxazolidinone. Accordingly, *N*-benzylethanolamine (**2c**) selectively furnished the desired *N*-benzyltryptamine, though in a lower yield than *N*-acetylethanolamine (**2a**) (Scheme 1). In sharp contrast, the reaction of *N*-Ts-ethanolamine failed to provide the expected product, and the

starting material was recovered almost quantitatively. We believe that a stable sulfonamido-iridium complex is formed, blocking the metal from participating productively in the catalytic cycle. Finally, when the phthalimido group was used as a protecting group, a complex mixture of products was obtained (probably because it was partly reduced), precluding its use in our protocol. When simple unprotected 2-aminoethanol was used, no reaction occurred, whereas using *N,N*-dimethylethanolamine resulted in a gratifying 42% yield (Scheme 1).[16]

Scheme 1. Alkylation of Indole with *N*-alkylethanolamines.

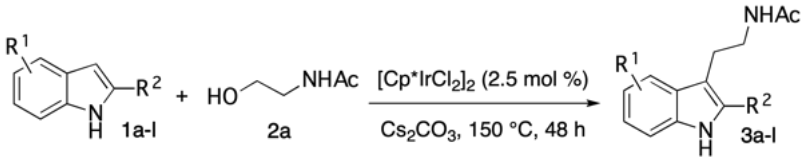


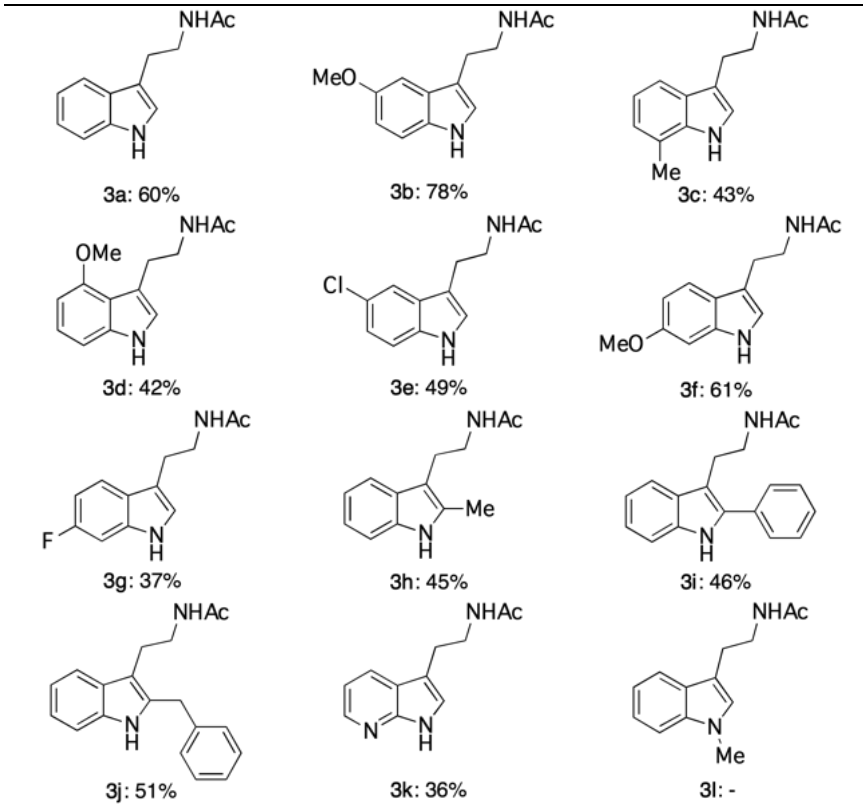
Next, we examined a spectrum of substituted indoles to explore the generality of this novel reaction. A range of differently substituted indoles (**1a-l**), with electron-donating or -withdrawing groups in all possible positions, gave moderate to good yields (36–78%) of the corresponding tryptamine derivative, although different reactivities were observed. For example, the electron-rich 5-methoxyindole was converted in a very good yield and selectivity to give melatonin (**3b**) as the desired product (Table 2), whereas lower than normal yields were recorded for the reaction with 7-methylindole (**3c**). The 4-MeO-, 5-Cl-, 6-OMe-, and 6-F-tryptamine derivatives (Table 2) were also obtained in decent yields, although the yields were lower than those of the 5-OMe analog. Pleasingly, the presence of a substituent at C-2 did not impair the reaction, despite the potential steric crowding around the reaction site. Thus, the 2-Me-, 2-Ph-, and 2-Bn-indoles reacted efficiently with *N*-acetylethanolamine to give the corresponding tryptamines in 45–51% yield (Table 2). We also examined the efficacy of unsubstituted 7-azaindole **1k** in undergoing C3-alkylation under the above reaction conditions. Treatment of **1k** with *N*-acetylethanolamine **2a** furnishing, selectively, the desired 7-azatryptamine (**3k)**, although only in poor yield. In sharp contrast, *N*-methylindole (**1l**) proved to be inert, suggesting the involvement of the indole N-H in a key interaction with the base during the rate-determining step. It is noteworthy that the present method is a step-efficient and atom-economic route to the pineal hormone melatonin (**3b**), which

has known sleep-inducing, antioxidant, and antiapoptotic properties,[17] as well as the reference MT_2 melatonin receptor ligand luzindole (**3j**), which is employed in pharmacological tests to evaluate and discriminate the roles of melatonin receptor subtypes.[18]

However, nearly complete recovery of the starting material was observed when C3-substituted indole, such as 3-methyl and 3-benzylindoles, were allowed to react with *N*-Acetylethanolamine **2a** under the reaction conditions reported above. Neither indole annulations with dearomatization of the indole nucleus to pyrroloindolines products, nor C3- to C2-alkyl migration and rearomatization to afford 2-substituted tryptamines were detected, in spite of recent reports.[19]

Table 2. Alkylation of Substituted Indoles with *N*-Acetylethanolamine using $[Cp^*IrCl_2]_2$ and Cs_2CO_3.[a]

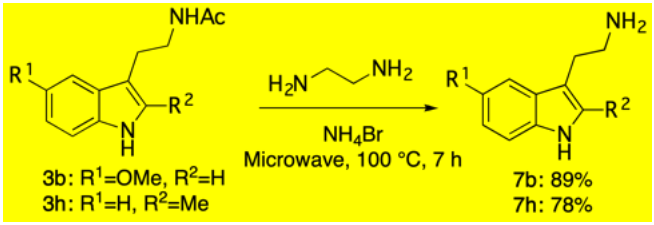




[a] Reactions were carried out in a sealed vial at 150 °C for 48 h with indole (0.25 mmol), *N*-acetylethanolamine (0.75 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol %), and Cs_2CO_3 (0.275 mmol). Isolated yield.

As mentioned previously, a major concern regarding *N*-protected ethanolamine reactions is the removal of the protecting group following successful functionalization/alkylation. To demonstrate the advantages of utilizing the *N*-acetyl protecting group, we sought to deprotect melatonin (**3b**) and N-acetyl-2-methyltryptamine (**3h**). To our delight, by treating **3b** and **3h** with a combination of ammonium bromide and ethylenediamine under microwave irradiation,[20] we were able to isolate the free 5-methoxytryptamine (**7b**) and 2-methyltryptamine (**7h**)[21] in 89% and 78% yield respectively, avoiding the use of strong acids or bases (Scheme 2).

Scheme 2. Removal of the *N*-Acetyl Protecting Group



Conclusion

In summary, the direct synthesis of diversely functionalized *N*-acetyltryptamines, including melatonin and luzindole, via the modern "borrowing hydrogen" strategy is presented. The new iridium-catalyzed C3-indole dehydration/alkylation protocol utilizes *N*-acetylethanolamine as a simple aminoethylene alkylating agent and source of hydrogen, avoiding the use of an external reducing agent. The experimental procedure for this metal-catalyzed direct alkylation of different indoles is simple and there is no problem for removal of side products. This highly atom economical and environmentally benign process requires only inexpensive reagents, tolerates a range of functionalities, and may have applications in natural product synthesis and medicinal chemistry. The identification of more efficient catalytic systems to access a wider range of nitrogen-containing alcohols beyond ethanolamine as well as milder reaction conditions is the focus of current efforts in our laboratories.

Experimental Section

General Methods. All reactions were performed in a glass vial, under nitrogen atmosphere. Column chromatography purifications were performed in flash conditions using 230-400 Mesh silica gel. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 F_{254}), that were visualized by exposure to ultraviolet light and an aqueous solution of cerium ammonium molybdate (CAM) or p-anisaldehyde. Copies of ^{1}H NMR and ^{13}C NMR spectra are provided. ^{1}H NMR and ^{13}C NMR were recorded on a 200/50 or 400/100 spectrometer, using $CDCl_3$ as solvent. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (*J* values) are given in Hertz (Hz). Molecular ions (M + 1) are given for ESI-MS analysis. Optical absorbances are reported cm^{-1} for the IR analysis. Melting points were determined on a capillary melting point apparatus and are uncorrected. Microwave assisted reactions were carried out in a CEM Discover SP microwave reactor. Elemental analyses are within ± 0.4 of the theoretical values (C,H,N). 2-benzyl-1*H*-indole,[22] 2,2,2-trifluoro-N-(2-hydroxyethyl)acetamide,[23] benzyl 2-hydroxyethylcarbamate,[24] 2-(2-hydroxyethyl)isoindoline-1,3-dione,[25] N-(2-hydroxyethyl)-4-methylbenzenesulfonamide[26] were synthesized according to the literature procedure. Other chemicals were purchased from commercial suppliers, and were used without further purification.

General procedure for the synthesis of *N*-protected Tryptamines. A mixture of the suitable indole **1a-h** (0.25 mmol), Cs_2CO_3 (90 mg, 0.275 mmol), $[Cp^*IrCl_2]_2$ (5 mg, 0.00625 mmol) and the appropriate *N*-protected ethanolamine **2a-c** (0.75 mmol) was stirred under N_2 atmosphere at 150 °C for 48h in a sealed vial. After cooling to room temperature the reaction mixture was dissolved in 1 ml of EtOAc/MeOH 9:1 and filtered through a silica gel pad. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel.

N-(2-(1*H*-indol-3-yl)ethyl)acetamide (3a). Prepared according to general procedure from 1*H*-indole and N-(2-hydroxyethyl)acetamide. Flash chromatography (EtOAc) gave **3a** as a grey solid

(30 mg, 0.15 mmol). Yield: 60%. M.p.: 74-76 °C (CH_2Cl_2/ptroleum ether); MS (ESI): 203 $[M+H]^+$; ^1H NMR (200 MHz, $CDCl_3$): δ 1.92 (s, 3H), 2.98 (t, 2H, *J*=6.6 Hz), 3.60 (dt, 2H, $J_1 \approx J_2$=6.6 Hz), 5.71 (brs, 1H), 7.05-7.27 (m, 3H), 7.39 (d, 1H, *J*=8 Hz), 7.61 (d, 1H, *J*= 7.6 Hz), 8.51 (brs, 1H). The chemical-physical data are according to the literature.[27]

N-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)acetamide (3b). Prepared according to general procedure from 5-methoxy-1*H*-indole and N-(2-hydroxyethyl)acetamide. Flash chromatography (EtOAc) gave **3b** as a white solid (45 mg, 0.19 mmol). Yield: 78%. M.p.: 114-116 °C (EtOAc); MS (ESI): 233 $[M+H]^+$. ^1H NMR (200 MHz, $CDCl_3$): δ 1.94 (s, 3H), 2.94 (t, 2H, *J*=6.6 Hz), 3.59 (dt, 2H, $J_1 \approx J_2$=6.6 Hz), 3.86 (s, 3H), 5.74 (brs, 1H), 6.87 (dd, 1H, *J*=2.4 and *J*=8.8 Hz), 7.00-7.05 (m, 2H), 7.27 (d, 1H, *J*=8.8 Hz), 8.33 (brs, 1H). The chemical-physical data are according to the literature.[28]

N-(2-(7-methyl-1*H*-indol-3-yl)ethyl)acetamide (3c). Prepared according to general procedure from 7-methyl-1*H*-indole and N-(2-hydroxyethyl)acetamide. Flash chromatography (EtOAc) gave **3c** as a brown oil (23 mg, 0.11 mmol). Yield: 43%. R.f.=0.28 (EtOAc); MS (ESI): 217 $[M+H]^+$; ^1H NMR (200 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.51 (s, 3H), 2.98 (t, 2H, *J*=6.5 Hz), 3.61 (dt, 2H, $J_1 \approx J_2$=6.5 Hz), 5.64 (brs, 1H), 7.01-7.12 (m, 3H), 7.45-7.48 (m, 1H), 8.28 (brs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.7, 23.4, 25.4, 39.9, 113.4, 116.4, 119.7, 120.6, 121.9, 122.7, 126.9, 136.0, 170.2; FTIR (film, cm^{-1}): 3399, 3285, 1646; Anal. Calcd. For $C_{13}H_{16}N_2O$ (216.13): C, 72.19; H, 7.46; N, 12.95; Found: C, 72.28; H, 7.39; N, 12.90.

N-(2-(4-methoxy-1*H*-indol-3-yl)ethyl)acetamide (3d). Prepared according to general procedure from 4-methoxy-1*H*-indole and N-(2-hydroxyethyl)acetamide. Flash chromatography (cyclohexane:EtOAc=1:1 to EtOAc) gave **3d** as a brown oil (25 mg, 0.11 mmol). Yield: 42%. MS (ESI): 233 $[M+H]^+$. ^1H NMR (200 MHz, $CDCl_3$): δ 1.89 (s, 3H), 3.08 (t, 2H, *J*=6.2 Hz), 3.58 (dt, 2H, $J_1 \approx J_2$=6.2 Hz), 3.96 (s. 3H), 6.05 (brs, 1H), 6.52 (d, 1H, *J*=7.6 Hz), 6.88-7.27 (m, 3H), 8.35 (brs, 1H). The chemical-physical data are according to the literature.[29]

N-(2-(5-chloro-1*H*-indol-3-yl)ethyl)acetamide (3e). Prepared according to general procedure from 5-chloro-1*H*-indole and N-(2-hydroxyethyl)acetamide. Flash chromatography (EtOAc:cyclohexane=9:1) gave **3e** as a grey solid (29 mg, 0.12 mmol). Yield: 49%. M.p.: 149-151

°C (EtOAc/petroleum ether); MS (ESI): 237 $[M+H]^+$. ^1H NMR (200 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.91 (t, 2H, *J*=6.8 Hz), 3.55 (dt, 2H, $J_1 \approx J_2$=6.8 Hz), 5.78 (brs, 1H), 7.03-7.04 (m, 1H), 7.11-7.31 (m, 2H), 7.53-7.54 (m, 1H), 8.72 (brs, 1H). The chemical-physical data are according to the literature.[30]

N-(2-(6-methoxy-1*H*-indol-3-yl)ethyl)acetamide (3f). Prepared according to general procedure from 6-methoxy-1*H*-indole and N-(2-hydroxyethyl)acetamide. Flash chromatography (EtOAc) gave **3f** (35 mg, 0.15 mmol). Yield: 61%. M.p.: 136-137 °C; MS (ESI): 233 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.94 (t, 2H, *J*=6.6 Hz), 3.59 (dt, 2H, $J_1 \approx J_2$=6.6 Hz), 3.86 (s, 3H), 5.57 (brs, 1H), 6.81 (dd, 1H, *J*=2.2 e *J*=8.6 Hz), 6.88 (d, 1H, *J*=2.2), 6.93 (d, 1H, *J*=2.0), 7.47 (d, 1H *J*=8.6 Hz), 8.04 (brs, 1H). The chemical-physical data are according to the literature.[30]

N-(2-(6-fluoro-1*H*-indol-3-yl)ethyl)acetamide (3g). Prepared according to general procedure from 6-fluoro-1*H*-indole and N-(2-hydroxyethyl)acetamide. Flash chromatography (EtOAc) gave **3g** as a brown oil (20 mg, 0.09 mmol). Yield: 37%. MS (ESI): 221 $[M+H]^+$. ^1H NMR (200 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.95 (t, 2H, *J*=6.7 Hz), 3.59 (dt, 2H, $J_1 \approx J_2$=6.7 Hz), 5.67 (brs, 1H), 6.84-6.94 (m, 1H), 7.01-7.09 (m, 2H), 7.46-7.53 (m, 1H), 8.43 (brs, 1H). The chemical-physical data are according to the literature.[31]

N-(2-(2-methyl-1*H*-indol-3-yl)ethyl)acetamide (3h). Prepared according to general procedure from 2-methyl-1*H*-indole and N-(2-hydroxyethyl)acetamide. Flash chromatography (EtOAc) gave **3h** as a yellow solid (24 mg, 0.11 mmol). Yield: 45%. M.p.: 83-85 °C (CH_2Cl_2/petroleum ether); MS (ESI): 217 $[M+H]^+$. ^1H NMR (200 MHz, $CDCl_3$): δ 1.90 (s, 3H), 2.39 (s, 3H), 2.92 (t, 2H, *J*=6.5 Hz), 3.50 (dt, 2H, $J_1 \approx J_2$=6.5 Hz), 5.59 (brs, 1H), 7.08-7.15 (m, 2H) 7.27-7.32 (m, 1H), 7.48-7.52 (m, 1H), 8.08 (brs, 1H). The chemical-physical data are according to the literature.[8a]

N-(2-(2-phenyl-1*H*-indol-3-yl)ethyl)acetamide (3i). Prepared according to general procedure from 2-phenyl-1*H*-indole and N-(2-hydroxyethyl)acetamide. Flash chromatography (EtOAc:cyclohexane=6:4 to EtOAc:cyclohexane=9:1) gave **3i** as a yellow solid (32 mg, 0.12 mmol). Yield: 46%. M.p.: 114-116 °C (CH_2Cl_2/petroleum ether); MS (ESI): 279 $[M+H]^+$; ^1H NMR (200 MHz, $CDCl_3$): δ 1.77 (s, 3H), 3.14 (t, 2H, *J*= 6.6 Hz), 3.56 (dt, 2H, $J_1 \approx J_2$=6.6 Hz), 5.51 (brs,

1H), 7.13-7.29 (m, 2H), 7.35-7.68 (m, 7H), 8.31 (brs, 1H). The chemical-physical data are according to the literature.[8a]

N-(2-(2-benzyl-1*H*-indol-3-yl)ethyl)acetamide (3j). Prepared according to general procedure from 2-benzyl-1*H*-indole and N-(2-hydroxyethyl)acetamide. Flash chromatography (EtOAc:cyclohexane=1:1 to EtOAc) gave **3j** as a light oil (37mg, 0.13 mmol). Yield: 51%. MS (ESI): 293 $[M+H]^+$. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.76 (s, 3H), 2.98 (t, 2H, *J*= 6.5 Hz), 3.51 (dt, 2H, $J_1 \approx J_2$= 6.5 Hz), 4.10 (s, 2H), 5.51 (brs, 1H), 7.09-7.31 (m, 8H), 7.51-7.60 (m, 1H) 7.99 (brs, 1H). The chemical-physical data are according to the literature.[8a]

N-(2-(1*H*-pyrrolo[2,3-b]pyridin-3-yl)ethyl)acetamide (3k). Prepared according to general procedure from 1*H*-pyrrolo[2,3-b]pyridine and N-(2-hydroxyethyl)acetamide. Flash chromatography (EtOAc:MeOH=95:5 to EtOAc:MeOH=9:1) gave **3k** as a white solid (18 mg, 0.09 mmol). Yield: 36%. M.p.: 175-177 °C (EtOAc); R.f.= 0.23 (EtOAc:MeOH=95:5); MS (ESI): 204 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.98 (t, 2H, *J*= 6.7 Hz), 3.60 (dt, 2H, $J_1 \approx J_2$= 6.7 Hz), 5.58 (brs, 1H), 7.11 (dd, 1H, *J*=4.7 Hz and *J*=7.8 Hz), 7.19 (s, 1H), 7.96 (d, 1H, *J*=7.8 Hz), 8.33 (d, 1H, *J*=3.6 Hz), 10.03 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.3, 25.5, 39.8, 111.6, 115.6, 120.0, 122.5, 127.3, 142.9, 148.7, 170.1; FTIR (film, cm^{-1}): 3285, 1630. Anal. Calcd. For $C_{11}H_{13}N_3O$ (203.11): C, 65.01; H, 6.45; N, 20.68; Found: C, 65.09; H, 6.39; N, 20.71.

N-(2,2-di(1*H*-indol-3-yl)ethyl)acetamide (4). Obtained and isolated as reaction byproduct in the conditions reported by the general procedure employing 1*H*-indole and N-(2-hydroxyethyl)acetamide. Yield: 9% (7 mg, 0.02 mmol). MS (ESI): 318 $[M+H]^+$. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.90 (s, 3H), 4.07 (m, 2H), 4.75 (t, 1H, *J*=7.1 Hz), 5.60 (brs, 1H), 7.04-7.11 (m, 4H), 7.16-7.24 (m, 2H), 7.37-7.41 (m, 2H), 7.60-7.64 (m, 2H), 8.07 (brs, 2H). The chemical-physical data are according to the literature.[32]

2-(1*H*-indol-3-yl)ethanol (5). Obtained and isolated as reaction byproduct in the conditions reported by the general procedure employing 1*H*-indole and N-(2-hydroxyethyl)acetamide. Yield: 6% (2 mg, 0.015 mmol). MS (ESI): 162 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.03 (dt, 2H, J=0.5 Hz and J=6.3 Hz), 3.91 (t, 2H, J=6.3 Hz), 7.07-7.26 (m, 3H), 7.38 (d, 1H, J=8.0 Hz), 7.62 (d,

1H, J=8.0 Hz), 8.07 (brs, 1H). The chemical-physical data are according to the literature.[33]

N-benzyl-2-(1*H*-indol-3-yl)ethanamine (6c). Prepared according to general procedure from 1*H*-indole and 2-(benzylamino)ethanol. Flash column chromatography (EtOAc to EtOAc:MeOH=9:1) gave compound as a brown oil (25 mg, 0.1 mmol). Yield: 40%. MS (ESI): 251 $[M+H]^+$. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.00 (app. s, 4H), 3.81 (s, 2H), 6.99-7.35 (m, 10H), 7.60 (d, 1H *J*=7.5 Hz), 8.15 (brs, 1H). The chemical-physical data are according to the literature.[34]

2-(1*H*-indol-3-yl)-N,N-dimethylethanamine (6d). Prepared according to general procedure from 1*H*-indole and 2-(dimethylamino)ethanol. Flash chromatography (CH_2Cl_2:MeOH:TEA=93:6:1) gave **6d** as a brown oil (20 mg, 0.11 mmol). Yield: 42%. MS (ESI): 189 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 6H), 2.64-2.68 (m, 2H), 2.94-2.98 (m, 2H), 7.03 (s, 1H), 7.11-7.15 (m, 1H), 7.18-7.22 (m. 1H), 7.36 (d, *J*=8.0 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 1H), 8.11 (brs, 1H). The chemical-physical data are according to the literature.[35]

General procedure for the N-deacetylation. Ammonium bromide (49 mg, 0.5 mmol), ethylenediamine (0.135 ml, 2 mmol) and N-Acetyltryptamine derivative (0.5 mmol) are mixed in a suitable vial fitted with magnetic stirring. The mixture is then heated to 100 °C in a microwave apparatus (250 W) for 7 hours. After cooling to room temperature the crude reaction mixture is diluted with CH_2Cl_2 and the desired tryptamine is extracted with an aqueous solution of 1M HCl. The aqueous layer is then made basic by addition of aqueous NaOH (1M) and then extracted with CH_2Cl_2. The combined organic phases are washed with brine, dried over Na_2SO_4 and concentrated by distillation at reduced pressure, obtaining a crude residue which was purified by filtration on a Flash column cromatography of silica gel (CH_2Cl_2:MeOH:TEA = 90:9:1).

2-(5-methoxy-1*H*-indol-3-yl)ethanamine (7b). Colorless oil (85 mg, 0.45 mmol). Yield: 89%. MS (ESI): 191 $[M+H]^+$. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.98 (brs, 2H), 2.85-2.91 (m, 2H), 2.99-3.06 (m, 2H), 3.87 (s, 3H), 6.83-6.89 (m, 1H), 7.0 (s, 1H), 7.04-7.05 (m, 1H), 7.22-7.27 (m, 1H), 8.46 (brs, 1H). The chemical-physical data are according to the literature.[36]

2-(2-methyl-1*H*-indol-3-yl)ethanamine (7h). Pale Yellow amorphous solid (68 mg, 0.39 mmol). Yield 78%. MS (ESI): 175 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76 (brs, 2H), 2.38 (s, 3H),

2.83-2.87 (m, 2H), 2.95-2.99 (m, 2H), 7.05-7.13 (m, 2H), 7.26 (d, *J*=7.5 Hz, 1H), 7.50 (d, *J*=7.5 Hz, 1H), 8.00 (brs, 1H). The chemical physical data are according to the literature.[8a]

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Supporting Information Available Copies of ^{1}H NMR, ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Mizoguchi, H.; Oikawa, H.; Oguri, H. *Nat. Chem.* **2014**, *6*, 57. (b) Runguphan, W.; O'Connor, S. E. *Org. Lett.* **2013**, *15*, 2850. (c) Dewick, P. M.; *Medicinal Natural Products: A Biosynthetic Approach,* 3rd ed.; John Wiley & Sons, Ltd., 2009.

(2) (a) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29. (b) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res*. **2011**, *44*, 447. (c) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489. (d) Cao, R.; Peng, W.; Wang, Z.; Xu, A. *Curr. Med. Chem.* **2007**, *14*, 479. (e) Czarnocki, Z.; Siwicka, A.; Szawkało, J. *Curr. Org. Synth.* **2005**, *2*, 301. (f) Barceloux, D. G.; *Tryptamine Designer Drugs, in Medical Toxicology of Drug Abuse*, John Wiley & Sons, Inc., 2012, 193.

(3) (a) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449. (b) Zeng, M.; You, S.-L. *Synlett* **2010**, *9*, 1289. (c) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (d) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, *8*, 1199.

(4) (a) Harrington, P. E.; Kerr, M. A. *Synlett* **1996**, *11*, 1047. (b) Bandini, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2002**, *8*, 1110. (c) Bandini, M.; Garelli, A.; Rovinetti, M.; Tommasi, S.; Umani-Ronchi, A. *Chirality* **2005**, *17*, 522. (d) Yokohama, N.; Arai, T. *Chem. Commun.* **2009**, *22*, 3285. (e) Ara, T.; Wasai, M.; Yokohama, N. *J. Org. Chem.* **2011**, *76*, 2909. (f)

Jia, Y.; Yang, W.; Du, D. M. *Org. Biomol. Chem.* **2012**, *10*, 4739 (g) Zhang, W.; Hazell, R. G.; Jorgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 2566. (h) Dessole, G.; Herrera, R. P.; Ricci, A. *Synlett* **2004**, *13*, 2374. (i) Wu, P.; Wan, Y.; Cai, J. *Synlett* **2008**, *8*, 1193.

(5) For selected examples, see: (a) Wang, S.; Chai, Z.; Zhou, S.; Wang, S.; Zhu, X.; Wei, Y. *Org. Lett.* **2013**, *15*, 2628. (b) Ghorai, M. K.; Tiwari, D. P.; Jain, N. *J. Org. Chem.* **2013**, *78*, 7121. (c) Kaiser, H. M.; Lo, W.; Riahi, A. M.; Spannenberg, A.; Beller, M.; Tse, M. K. *Org. Lett.* **2006**, *8*, 5761. (d) Ezquerra, J.; Pedregal, C.; Lamas, C. *Tetrahedron Lett.* **1996**, *37*, 683. For selected examples of ring-opening reaction of enantioenriched aziridines with indoles, see: (e) Hudlicky, T.; Rinner, U.; Finn, K. J.; Ghiviriga, I. *J. Org. Chem.* **2005**, *70*, 3490. (f) Rinner, U.; Hudlicky, T.; Gordon, H.; Pettit, G. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 5342; *Angew. Chem.* **2004**, *116*, 5456. (g) Tirotta, I.; Fifer, N. L.; Eakins, J.; Hutton, C. A. *Tetrahedron Lett.* **2013**, *54*, 618. (h) Li, Y.; Haymanb, E.; Plesescua, M.; Prakash, S. R. *Tetrahedron Lett.* **2008**, *49*, 1480. (i) Menguy, L.; Lo, C.; Marrot, J.; Couty, F. *Tetrahedron* **2014**, *70*, 4512. For an elegant highly regioselective and enantiospecific ring-opening reaction of enantioenriched aziridines with indoles, see: (j) Cockrell, J.; Wilhelmsen, C.; Rubin, H.; Martin, A.; Morgan, J. B. *Angew. Chem., Int. Ed.* **2012**, *51*, 9842; *Angew. Chem.* **2012**, *124*, 9980.

(6) (a) Woo, Y.; Lai, D. Y.; Argus, M. F.; Arcos, J. C. *Toxicol. Lett.* **1995**, *79*, 219. (b) Talalay, P.; De Long, M. J.; Prochaska, H. J. *Proc. Natl. Acad. Sci.* **1988**, *85*, 8261.

(7) Lancianesi, S.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2014**, *114*, 7108.

(8) (a) Righi, M.; Topi, F.; Bartolucci, S.; Bedini, A.; Piersanti, G.; Spadoni, G. *J. Org. Chem.* **2012**, *77*, 6351. For other use of α-amidoacetals, see: (b) Righi, M.; Bedini, A.; Piersanti, G.; Romagnoli, F.; Spadoni, G. *J. Org. Chem.* **2011**, *76*, 704.

(9) (a) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *Tetrahedron Lett.* **1981**, *22*, 4107. (b) Tsuji, T.; Huh, K.-T.; Ohsugi, Y.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 1365.

(10) For selected reviews, see: (a) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 249. (b) Bähn, S.; Imm, S.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. *ChemCatChem* **2011**, *3*, 1853. (c)

Watson, A. J. A.; Williams, J. M. J. *Science* **2010**, *329*, 635. (d) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681. (e) Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611.

(11) For recent reviews with regard to C–C couplings, see: (a) Obora, Y. *ACS Catal.* **2014**, *4*, 3972. (b) Pan, S.; Shibata, T. *ACS Catal.* **2013**, *3*, 704.

(12) For an example of a tandem oxidative cyclization/alkylation of 2-aminophenyl ethyl alcohol and *N,N*-dimethylethanolamine, for the synthesis of *N,N*-dimethyltryptamine, see: (a) Whitney, S.; Grigg, R.; Derrick, A.; Keep, A. *Org. Lett.* **2007**, *9*, 3299. For other coupling reactions of indoles with simple benzylic alcohols or aliphatic alcohols, see: (b) Bahn, S.; Imm, S.; Mevius, K.; Neubert, L.; Tillack, A.; Williams, J. M. J.; Beller, M. *Chem. Eur. J.* **2010**, *16*, 3590. (c) Putra, A. E.; Takigawa, K.; Tanaka, H.; Ito, Y.; Oe, Y.; Ohta, T. *Eur. J. Org. Chem.* **2013**, *28*, 6344. (d) Hakim Siddiki, S. M. A.; Kon, K.; Shimizu, K. *Chem. Eur. J.* **2013**, *43*, 14416. (e) Cano, R.; Yus, M.; Ramón, D. J. *Tetrahedron Lett.* **2013**, *54*, 3394.

(13) For other uses of the catalyst $[Cp^*IrCl_2]_2$ for C–C couplings with hydrogen borrowing methodologies, see: (a) Löfberg, C.; Grigg, R.; Whittaker, M. A.; Keep, A.; Derrick, A. *J. Org. Chem.* **2006**, *71*, 8023. (b) Anxionnat, B.; Pardo, D. G.; Ricci, G.; Cossy, J. *Org. Lett.* **2011**, *13*, 4084. (c) Anxionnat, B.; Domingo, G. P.; Ricci, G.; Cossy, J. *Eur. J. Org. Chem.* **2012**, *24*, 4453. (d) Anxionnat, B.; Pardo, D. G.; Ricci, G.; Rossen, K.; Cossy, J. *Org. Lett.* **2013**, *15*, 3876.

(14) (a) Mari, M.; Tassoni, A.; Lucarini, S.; Fanelli, M.; Piersanti, G.; Spadoni, G. *Eur. J. Org. Chem.* **2014**, *18*, 3822. (b) For a nice review, see: Palmieri, A., Petrini, M., Shaikh, R.R. *Org. Biomol. Chem.* **2010**, *8*, 1259.

(15) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J *J. Am. Chem. Soc.* **2009**, *131*, 1766.

(16) For alkylations of indole using amines, see: (a) Imm, S.; Bhan, S.; Tillack, A.; Mevius, K.; Neubert, L.; Beller, M. *Chem. Eur. J.* **2010**, *16*, 2705. (b) Lerch, S.; Unkel, L.-N.; Brasholz, M. Angew. Chem. Int. Ed. **2014**, *53*, 6558.

(17) (a) Tan, D.-X.; Manchester, L. C.; Terron, M. P.; Flores, L. J.; Reiter, R. J. *J. Pineal Res.* **2007**, *42*, 28. (b) Spadoni, G.; Bedini, A.; Rivara, S.; Mor, M. *CNS Neurosci. Ther*. **2011**, *17*, 733.

(18) Dubocovich, M. L.; Yun, K.; Al-Ghoul, W. M.; Benloucif, S.; Masana, M. I. *FASEB J*. **1998**, *12*, 1211.

(19) (a) Mari, M.; Lucarini, S.; Bartoccini, F.; Piersanti, G.; Spadoni, G. *Beilstein J. Org. Chem.* **2014**, *10*, 1991. (b) Wang, H.; Reisman, S. E. *Angew. Chem., Int. Ed.* **2014**, *53*, 6206. (c) Wang, L.; Yang, D.; Han, F.; D. Li, D.; D. Zhao, D.; R.Wang, R. *Org. Lett.,* **2015**, *17*, 176. (d) Kandukuri, S. R.; Bahamonde, A.; Chatterjee, I.; Jurberg, I. D.; Escudero-Adàn, E. C.; Melchiorre P. *Angew. Chem. Int. Ed.* **2015**, *54*, 1485.

(20) Shimizu, Y.; Morimoto, H.; Zhang, M.; Ohshima, T., *Angew. Chem., Int. Ed.* **2012**, *51*, 8564.

(21) For the importance of 2-methyltryptamine in medicinal chemistry, see: (a) Slade, J.; Parker, D.; Girgis, M.; Wu, R.; Joseph, S.; Repič, O. *Org. Process Res. Dev.* **2007**, *11*, 721. (b) René, O.; Fauber, B. P. *Tetrahedron Lett.* **2014**, *55*, 830.

(22) Wiedenau, P.; Blechert, S. *Synth. Commun*. **1997**, *27*, 2033.

(23) Khuizen, E. C.; Kiessling, L. L., *Org.Let*. **2009**, *11*, 193.

(24) De Cola, C.; Manicardi, A.; Corradini, R.; Izzo, I.; De Riccardis, F. *Tetrahedron* **2012**, *68*, 499.

(25) Kolomiets, E.; Buhler, E.; Candau, S. J.; Lehn, J.-M. *Macromolecules* **2006**, *39*, 1173.

(26) Balaji, P. V.; Chandrasekaran, S. *ChemCommn* **2014**, *50*, 70-72.

(27) Schuck, D. C.; Jordao, A. K.; Nakabashi, M.; Cunha, A. C.; Ferreira, V. F.; Garcia, C. R. S. *Eur. J. Med. Chem.* **2014**, *78*, 375.

(28) Hwang, K. J.; Lee, T. S. *Synth. Commun.* **1999**, *29*, 2099.

(29) Yamada, F.; Saida, Y.; Somei, M. *Heterocycles* **1986**, *24*, 2619.

(30) Mor, M.; Rivara, S.; Silva, C.; Bordi, F.; Palazzi, P. V.; Spadoni, G.; Diamantini, G.; Tarzia, G.; Fraschini, F.; Lucini, V.; Nonno, R.; Stankov, B. M. *J. Med. Chem.* **1998**, *41*, 3831.

(31) Yang, S.-W.; Cordell, G. A. *J. Nat. Prod.* **1997**, *60*, 44.

(32) Chakrabarty, M.; Ghosh, N.; Basak, R.; Harigaya, Y. *Synth. Commun.* **2004**, *34*, 421–434;

(33) Du, Y.; Huang, H.-Y.; Liu, H.; Ruan, Y.-P.; Huang, P.-Q. *Synlett* **2011**, *4*, 565.

(34) Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Org. Chem.* **2001**, *66*, 9020.

(35) Shi-Jin, Q.; Wang, G.-F.; Duan, W.-H.; Yao, S.-Y.; Zuo, J.-P.; Tan, C.-H.; Zhu, D.-Y. *Bioorg. Med. Chem.* **2011**, *19*, 3120.

(36) Revial, G.; Jabin, I.; Lim, S.; Pfau, M. *J. Org. Chem.* **2002**, *67*, 2252.