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A one-pot three-component reaction for the preparation of highly functionalized tryptamines

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ABSTRACT

We have developed a general one-pot method to provide highly functionalized tryptamine derivatives, via a Fischer indole type pathway. In this article, we demonstrate optimal conditions for a one-pot indole synthesis, allowing for the synthesis of a broad scope of 2-methyl tryptamine derivatives and a precursor for the synthesis of the core structure of some akuammiline alkaloids. Additionally, further modification of the indole products is described.

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1. Introduction

Tryptamine and associated analogues possess a variety of important biological activities.[1–4] For example, 5-hydroxytryptamine (**1**, Fig. 1) is a key signalling molecule found in a wide variety of species, playing an important role in numerous fundamental processes, including the regulation of mood, sleep and muscle contraction.[2] Furthermore, melatonin (**2**, Fig. 1) is another natural product that has a variety of functions in humans, such as regulation of sleep, interactions with immune system, and antioxidant.[3] Synthetic tryptamine derivatives bearing substitutions at the C_2-position of the indole have been reported as agonists of serotonine or melatonine receptors.[4] In addition, tryptamine comprises a main structural unit in many indole alkaloid natural products. For example, both the vinca alkaloids (e.g., vindoline **3**, Fig. 1) and the akuammiline alkaloids (e.g., minfiensine **4**, Fig. 1) contain tryptamine as a core component. Hence, tryptamine and related derivatives have been used widely in both bio- and chemical syntheses of complex indole alkaloids.[5,6]

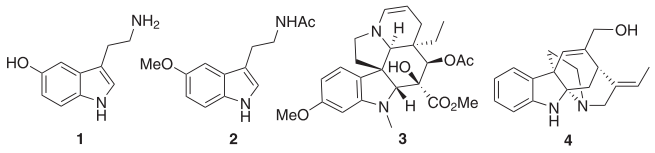

Fig. 1. Tryptamine-containing natural products.

Currently, there are several major approaches for the chemical synthesis of tryptamine derivatives. The first method begins with functionalization of indoles via carbon–carbon bond formation.[7] The second mode of construction assembles tryptamine by a palladium-catalyzed reaction from *o*-haloanilines.[8] Recent studies by Nicolaou and co-workers describe an alternative approach, which employs readily available *N*-Boc-protected anilines and provides a variety of highly functionalized tryptamines in three steps.[9] Another tactic is perhaps the most familiar; a Fischer indole synthesis utilizing functionalized aminoaldehyde or the equivalent provides a breadth of tryptamine derivatives.[10] Facile syntheses of complex tryptamine derivatives from commercially available materials are still in demand. The Fischer indole synthesis shows promise as an avenue for the efficient synthesis of tryptamine derivatives. However, the necessary isolation or preparation of reactive intermediates, such as ketones leaves room for improvement.

2. Results and discussion

As part of our ongoing efforts to synthesize both simple and complex indole alkaloids, we have developed a one-pot, three-component synthesis for the rapid assembly of highly functionalized tryptamine derivatives.[11] Herein, we report our optimized conditions, scope and applications of this one-pot process.

We propose a one-pot, cascade-based strategy for the construction of tryptamine derivatives (Scheme 1). As it has been demonstrated, cyclic imines, such as **5a**, can be activated by acyl

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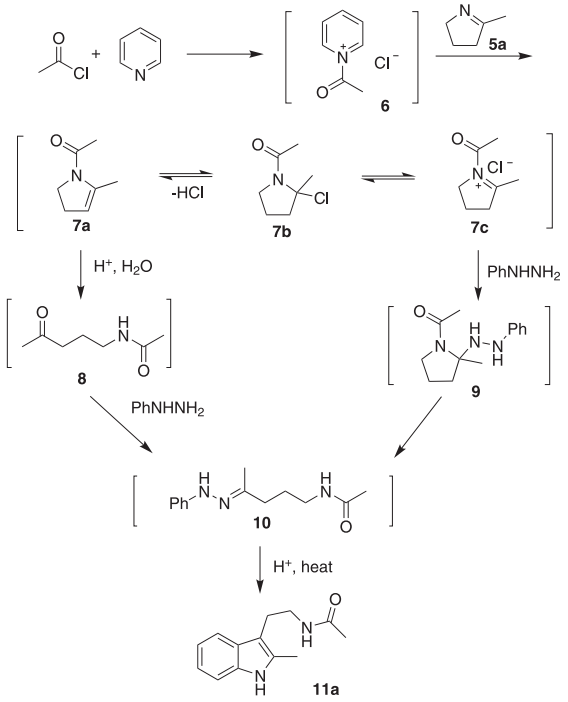
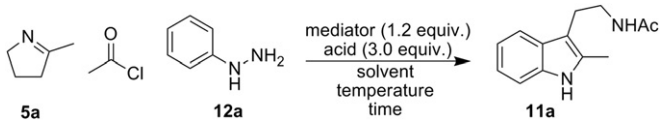
chloride in the presence of a mediator.[10e] Pyridine or other mediator forms intermediate **7a**, **7b**, or **7c** presumably in equilibrium. From enamine **7a** or *N*-acyliminium ion **7c**, there are two possible pathways to the desired product **11a**. Under acidic conditions, **7a** may be hydrolyzed to amidoketone **8**, the precursor to hydrazone **10**. Alternatively, addition of phenylhydrazine to **7c** might yield hydrazone **10** through intermediate **9**. As **10** is a standard intermediate in Fischer indole syntheses, it should be readily transformed to produce tryptamine derivative **11a** under acidic conditions. Therefore, we hypothesized that this ketone **8** and/or intermediate **9** can be generated in situ from the cyclic imine and afford tryptamine derivative **11a** under standard Fischer indole synthesis condition in one-pot.



Scheme 1. Proposed one-pot indole synthesis pathway.

We selected commercially available 2-methyl-1-pyrroline **5a**, acetyl chloride, phenylhydrazine, pyridine and HCl for the initial attempt. This combination gave 62% yield of the desired product (entry 1, Table 1). This primary result indicates that the phenylhydrazone can be formed without isolation of the ketone intermediate **8** towards the synthesis of tryptamine derivatives.

Table 1
Optimization of one-pot indole synthesis conditions



Entry	Mediator	Acid	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	Pyridine	HCl	DMF	82	3	62
2	—	HCl	DMF	82	3	14
3	DMAP	HCl	DMF	82	3	73
4	DMAP	HCl	DMF	82	3	23[b]
5	DMAP	TsOH·H_2O	DMF	82	3	73
6	DMAP	AcOH	DMF	82	3	62
7	DMAP	TsOH·H_2O	CH_3CN	82	20	100[c]
8	DMAP	TsOH·H_2O	CH_3CN	82	20	100[d]

[a] ^{1}H NMR yield determined using an internal standard.
[b] DMAP (0.1 equiv) was used.
[c] The isolated yield was 97%.
[d] Stirred for 3 h after the addition of imine. Acid was added before $PhNHNH_2$. The isolated yield was 99%.

With the initial result in hand, a variety of optimization studies were conducted. First, we optimized the mediator (e.g., DMAP, Et_3N and 2,6-lutidine) for the reaction. Without the mediator, the reaction proceeds in only 14% yield (entry 2, Table 1). DMAP was found to be the most effective mediator and stoichiometric amounts are required (entries 3 and 4, Table 1). We then screened numerous acids, such as HCl, TsOH·H_2O and HOAc. Both HCl and TsOH·H_2O gave high yields with DMF as a solvent. During the solvent optimization, it was found that TsOH·H_2O performs better in a variety of solvents. As a result, TsOH·H_2O and acetonitrile (entry 7, Table 1) were chosen as the optimal acid and solvent. With optimized reagents, we also varied temperatures and reaction times (see Supplementary data for detailed conditions). We found that the best yield can be obtained when the reaction is conducted using DMAP (1.2 equiv) and TsOH·H_2O (3 equiv) in CH_3CN at 82 °C for 20 h (entry 8, Table 1).

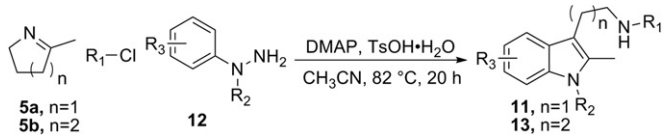
During optimization studies, we found that addition of acid, followed by phenylhydrazine, gave higher isolated yields. This suggests that reaction equilibrium lies towards intermediate **7a**, compared to **7b** or **7c** (Scheme 1). Additionally, we found that 70% of the enamide **7a** along with 20% of ketone **8** can be isolated without aqueous workup before the addition of acid and phenylhydrazine. Based on these experimental results, we assume that the acid would open the enamide ring in the presence of water to yield ketone **8**, which reacts with phenylhydrazine to form indole product. To clarify the detailed reaction process, under standard conditions and without the addition of phenylhydrazine, we succeeded in the isolation of the ketone intermediate in nearly a quantitative yield, further supporting our initial hypothesis. It is also worth mentioning that compared with our one-pot process that yielded 99% of **11a** from imine **5**, a traditional two-step approach using the same substrates has previously been reported. The yields for these two steps are 75% and 77%, respectively;[10e] therefore, the total yield for the two-step approach was 58%.

Optimization of reaction conditions for the one-pot method opened an avenue to synthesize numerous tryptamine derivatives. Our method allows for variation of three different functional groups on the tryptamine skeleton: functionalization of amine (R_1, Table 2), derivatization on the indole nitrogen (R_2, Table 2) and substitution on indole backbone (R_3, Table 2).

Initially, we used 2-methyl-1-pyrroline **5a** (entries 1–20, Table 2) as the cyclic imine to produce tryptamine derivatives. By using commercially available acyl chlorides, sulfonyl chlorides, anhydrides and methyl chloroformate, we synthesized a number of tryptamine derivatives with different functional groups on the amines in excellent yields (entries 1–9, Table 2). Next, we changed phenylhydrazines with different functional groups on nitrogens to achieve substitutions on the indole nitrogen and the yields remained satisfactory (entries 10–12, Table 2). Additional modifications of the phenyl rings of phenylhydrazine introduced functionality on the indole backbone to generate more complex products (entries 13–20, Table 2). Also, we were able to utilize a readily available six-membered cyclic imine **5b**[12] to produce homotryptamine derivatives in good yields (entries 21 and 22, Table 2). In these cases, slower reaction rates were observed in the acyl transfer step. Overall, we prepared a variety of highly functionalized tryptamine derivatives in good to excellent yields, from commercially available materials in a single step.

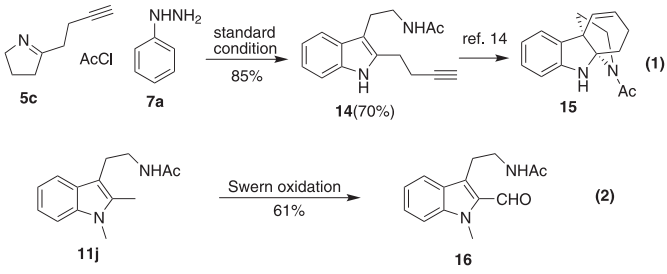
Next, we applied this method for the synthesis of alkynyl indole **14** (Eq. 1, Scheme 2) using a readily available alkynyl imine **5c**.[13] To our delight, the desired product **14** was isolated in 70% yield, together with 14% of its regioisomer. Compound **14** can be readily converted to the core structure of the akuammiline alkaloids, such as minfiensine, using a previously developed gold(I)-catalyzed tandem cyclization reaction.[14]

Table 2
Scope of tryptamine derivatives synthesis



Entry	*n*	R_1	R_2/R_3	**12**	Yield (%)	Product
1	1	Ac	H/H	**12a**	99	**11a**
2	1	4-F–Bz	H/H	**12a**	96	**11b**
3	1	Ts	H/H	**12a**	88	**11c**
4	1	Butyryl	H/H	**12a**	85	**11d**
5	1	MeOCO	H/H	**12a**	82	**11e**
6	1	Ms	H/H	**12a**	83	**11f**
7	1	TFA	H/H	**12a**	92	**11g**
8	1	Tf	H/H	**12a**	92[a]	**11h**
9	1	Ns	H/H	**12a**	75[a,b]	**11i**
10	1	Ac	Me/H	**12b**	90	**11j**
11	1	Ac	allyl/H	**12c**	85	**11k**
12	1	Ac	^{m}FBn/H	**12d**	82	**11l**
13	1	Ac	H/2-Cl	**12e**	83[c]	**11m**
14	1	Ac	H/4-MeO	**12f**	87	**11n**
15	1	Ac	H/4-Br	**12g**	71	**11o**
16	1	Ac	allyl/4-MeO	**12h**	96	**11p**
17	1	Ts	4-FBn/4-MeO	**12i**	73	**11q**
18	1	Tf	Me/H	**12b**	66	**11r**
19	1	4-F–Bz	Me/4-Br	**12j**	90	**11s**
20	1	TFA	H/4-MeO	**12f**	70	**11t**
21	2	Ac	H/H	**12a**	71[d]	**13a**
22	2	Ac	Me/H	**12b**	70[d]	**13b**

[a] Stirred for 2 h after adding acid.
[b] DMF was used as solvent.
[c] DMF was used as solvent. Stirred at 140 °C.
[d] DMF was used as solvent. Stirred for 12 h after the addition of imine.



Scheme 2. Applications of one-pot indole synthesis process.

Furthermore, we demonstrated that the 2-methyl group of the tryptamine derivative **11j** can be selectively oxidized to aldehyde **16** under mild Swern oxidation conditions (Eq. 2, Scheme 2),[15] a more versatile chemical handle for further elaborations.[5b,16] A variety of well-documented methods for the functionalization of 2-methyl group of indoles have also been reported by others,[17,18] which make the 2-methyl tryptamine derivative a useful synthon for complex molecule synthesis.

3. Conclusion

In summary, we describe the development of a facile synthesis of highly functionalized tryptamine derivatives using a one-pot, three-component process via Fischer indole type pathway. Using this method, we were able to assemble a wide range of tryptamine derivatives with good to excellent yields in a single step. A regioselective oxidation of the 2-methyl group allows for transformation of the products into more useful synthons. Further applications of this approach to the syntheses of complex indole alkaloids are in progress and will be reported in due course.

4. Experimental section

4.1. General experimental section

Unless otherwise noted, reagents were obtained commercially from Sigma, Aldrich, GFS and used without further purification. Thin-layer chromatography (TLC) analysis of reaction mixtures was performed on Dynamic adsorbents silica gel F-254 TLC plates. Flash chromatography was carried out on Cilicycle 60 ECO silica gel. ^{1}H and ^{13}C NMR in $CDCl_3$ spectra were recorded with Varian INOVA 400, and Bruker Avance-III 300 spectrometers. Mass spectral and analytical data were obtained via the PE SCIEX/ABI API QSTAR Pulsar i Hybrid LC/MS/MS, or SYNAPT G2 High Definition Mass Spectrometry System From Waters, Applied Biosystems operated by the Central Analytical Laboratory, University of Colorado at Boulder. Infrared (IR) spectra were recorded on a Thermo Nicolet Avatar 370 FT-IR spectrometer. Melting point (mp) determinations were performed by using a Thomas Hoover capillary melting point apparatus and are uncorrected.

4.2. Typical procedure for the preparation of tryptamine derivatives (11a–t)

Acyl chloride (1.2 mmol, 1.2 equiv) was added to a solution of 4-dimethylaminopyridine (DMAP) (1.2 mmol, 1.2 equiv) in acetonitrile (1.0 mL) at 0 °C. The reaction was stirred at room temperature for 15 min. A solution of the 5-methyl-3,4-dihydro-2*H*-pyrrole (1.0 mmol) in acetonitrile (1.0 mL) was added and the reaction was stirred at room temperature for 3 h. *p*-Toluenesulfonic acid monohydrate (3.0 mmol, 3.0 equiv) was added at 0 °C under inert atmosphere. The reaction was then stirred at room temperature for 2 h. Arylhydrazine (1.5 mmol, 1.5 equiv) was added and stirred for an addition 5 min at room temperature. The reaction was then heated to 82 °C for 20 h. The reaction cools down to room temperature. The residue was then dissolved in ethyl acetate and washed with brine and a saturated aqueous solution of $NaHCO_3$. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a crude solid, which was purified by column chromatography on silica gel.

*4.2.1. 4-Methyl-N-(2-(2-methyl-1H-indol-3-yl)ethyl)benzenesulfonamide (**11c**).* Yield 88%; brown black solid; R_f 0.25 (hexanes/EtOAc 3:1); mp 135–137 °C; IR (thin film): ν 3397, 3055, 2920, 1597, 1462, 1320, 1157, 1093, 910 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.65–7.59 (m, 2H), 7.32–7.27 (m, 2H), 7.22 (dd, *J*=8.6, 0.7 Hz, 2H), 7.14–7.07 (m, 1H), 7.05–6.98 (m, 1H), 4.27 (t, *J*=6.3 Hz, 1H), 3.22 (q, *J*=6.6 Hz, 2H), 2.90 (t, *J*=6.7 Hz, 2H), 2.42 (s, 3H), 2.36 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ143.4, 136.9, 135.46, 132.7, 129.8, 128.3, 127.2, 121.4, 119.6, 117.7, 110.6, 107.2, 43.4, 24.8, 21.7, 11.8 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{18}H_{21}N_2O_2S$ $[M+H]^+$ 329.1318, Found 329.1330.

*4.2.2. N-(2-(2-Methyl-1H-indol-3-yl)ethyl)butyramide (**11d**).* Yield 85%; yellowish oil; R_f 0.20 (hexanes/EtOAc 3:1); IR (thin film): ν 3400, 3283, 3058, 2962, 2873, 1721, 1649, 1527, 1463, 909 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.53–7.47 (m, 1H), 7.32–7.27 (m, 1H), 7.11 (m, 2H), 5.46 (s, 1H), 3.52 (dd, *J*=12.8, 6.6 Hz, 2H), 2.92 (t, *J*=6.7 Hz, 2H), 2.39 (s, 3H), 2.09–2.03 (m, 2H), 1.67–1.53 (m, 2H), 0.90 (t, *J*=7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 135.4, 132.3, 128.5, 120.8, 119.0, 117.6, 110.6, 108.0, 40.0, 38.6, 24.2, 19.1, 13.8, 11.4 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{15}H_{21}N_2O$ $[M+H]^+$ 245.1637, Found 245.1637.

*4.2.3. Methyl 2-(2-methyl-1H-indol-3-yl)ethylcarbamate (**11e**).* Yield 82%; brown oil; R_f 0.30 (hexanes/EtOAc 3:1); IR (thin film): ν 3400, 2940, 1702, 1524, 1462, 1257, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.80 (s, 1H), 7.50 (d, *J*=7.0 Hz, 1H), 7.31–7.28 (m, 1H), 7.17–7.04 (m, 2H), 4.69 (s, 1H), 3.66 (s, 3H), 3.50–3.35 (m, 2H), 2.91 (t, *J*=6.7 Hz, 2H), 2.38 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 135.5, 132.3, 128.6, 121.2, 119.4, 117.9, 110.5, 108.3, 52.2, 41.6, 24.7, 11.6 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{13}H_{17}N_2O_2$ $[M+H]^+$ 233.1285, Found 233.1280.

*4.2.4. N-(2-(2-Methyl-1H-indol-3-yl)ethyl)methanesulfonamide (**11f**).* Yield 83%; brown oil; R_f 0.25 (hexanes/EtOAc 3:1); IR (thin film): ν 3393, 2929, 1463, 1313, 1147, 971 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.48 (dd, *J*=8.2, 0.8 Hz, 1H), 7.32–7.27 (m, 1H), 7.16–7.05 (m, 2H), 4.20–4.11 (br, 1H), 3.42 (q, *J*=6.5 Hz, 2H), 3.00 (t, *J*=6.5 Hz, 2H), 2.81 (s, 3H), 2.43 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.4, 132.8, 128.3, 121.2, 119.4, 117.7, 110.7, 107.2, 43.5, 39.8, 25.2, 11.6 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{12}H_{17}N_2O_2S$ $[M+H]^+$ 253.1005, Found 253.0995.

*4.2.5. 2,2,2-Trifluoro-N-(2-(2-methyl-1H-indol-3-yl)ethyl) acetamide (**11g**).* Yield 92%; dark-brown solid; R_f 0.25 (hexanes/EtOAc 3:1); mp 98–102 °C; IR (thin film): ν 3398, 2922, 1705, 1553, 1463, 1437, 1181, 910 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.49 (d, *J*=7.4 Hz, 1H), 7.34–7.27 (m, 1H), 7.21–7.08 (m, 2H), 6.50–6.35 (br, 1H), 3.62 (q, *J*=6.5 Hz, 2H), 3.00 (t, *J*=6.7 Hz, 2H), 2.37 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 158.2, 157.7, 157.2, 156.7, 135.5, 132.6, 128.3, 121.5, 119.6, 117.6, 110.7, 107.2, 40.46, 23.6, 11.4 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{13}H_{14}F_3N_2O$ $[M+H]^+$ 271.1053, Found 271.1064.

*4.2.6. 1,1,1-Trifluoro-N-(2-(2-methyl-1H-indol-3-yl)ethyl) methanesul fonamide (**11h**).* Yield 92%; dark-brown oil; R_f 0.30 (hexanes/EtOAc 3:1); IR (thin film): ν 3407, 3300, 2922, 1463, 1367, 1193, 1145, 1060 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90–7.85 (br, 1H), 7.47 (dd, *J*=8.1, 0.9 Hz, 1H), 7.32–7.27 (m, 1H), 7.21–7.09 (m, 2H), 4.85–4.70 (br, 1H), 3.55 (q, *J*=6.4 Hz, 2H), 3.01 (t, *J*=6.6 Hz, 2H), 2.41 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 133.0, 128.1, 121.8, 120.0, 117.7, 117.7, 110.8, 106.4, 44.6, 25.7, 11.8 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{12}H_{14}F_3N_2O_2S$ $[M+H]^+$ 307.0723, Found 307.0721.

*4.2.7. N-(2-(2-Methyl-1H-indol-3-yl)ethyl)-2-nitrobenzenesulfonamide (**11i**).* Yield 75%; brown oil; R_f 0.25 (hexanes/EtOAc 2:1); mp 125–127 °C; IR (thin film): ν 3399, 2921, 1538, 1302, 1242, 1063 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03–7.94 (m, 1H), 7.76 (s, 1H), 7.68–7.53 (m, 3H), 7.22–7.15 (m, 2H), 7.07–7.02 (m, 1H), 6.92–6.87 (m, 1H), 5.26 (t, *J*=5.5 Hz, 1H), 3.39 (dd, *J*=12.3, 6.7 Hz, 2H), 2.96 (t, *J*=6.7 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 133.4, 132.9, 132.7, 131.0, 128.0, 125.6, 121.4, 119.6, 117.6, 110.5, 106.9, 100.2, 44.0, 24.6, 11.9 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{17}H_{18}N_3O_4S$ $[M+H]^+$ 360.1013, Found 360.1008.

*4.2.8. N-(2-(1,2-Dimethyl-1H-indol-3-yl)ethyl)acetamide (**11j**).* Yield 90%; pink solid; R_f 0.25 (hexanes/EtOAc 1:2); mp 101–104 °C; IR (thin film): ν 3289, 2932, 1650, 1553, 1370, 1294, 1184 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J*=7.7 Hz, 1H), 7.27 (d, *J*=8.0 Hz, 1H), 7.22–7.15 (m, 1H), 7.14–7.06 (m, 1H), 5.80–5.73 (br, 1H), 3.66 (s, 3H), 3.54–3.35 (m, 2H), 2.95 (t, *J*=6.8 Hz, 2H), 2.38 (s, 3H), 1.90 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 136.7, 133.9, 127.8, 120.8, 119.1, 117.8, 108.8, 107.8, 40.4, 29.6, 24.5, 23.4, 10.3 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{14}H_{19}N_2O$ $[M+H]^+$ 231.1492, Found 231.1494.

*4.2.9. N-(2-(1-Allyl-2-methyl-1H-indol-3-yl)ethyl)acetamide (**11k**).* Yield 85%; black solid; R_f 0.20 (hexanes/EtOAc 1:2); mp 90–93 °C; IR (thin film): ν 3288, 2928, 1650, 1553, 1469, 1367, 1293, 1181, 922 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.51 (m, 1H), 7.26–7.22 (m, 1H), 7.20–7.02 (m, 2H), 5.94 (ddt, *J*=17.0, 10.3, 4.7 Hz, 1H), 5.77–5.50 (br, 1H), 5.16–5.07 (m, 1H), 4.89–4.73 (m, 1H), 4.69 (dt, *J*=4.6, 1.8 Hz, 2H), 3.56–3.43 (m, 2H), 2.95 (t, *J*=6.7 Hz, 2H), 2.34 (s, 3H), 1.90 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 136.3, 133.7, 133.6, 128.0, 121.1, 119.3, 117.9, 116.3, 109.2, 108.3, 45.6, 40.4, 24.6, 23.6, 10.2 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{16}H_{21}N_2O$ $[M+H]^+$ 257.1648, Found 257.1645.

*4.2.10. N-(2-(1-(3-Fluorobenzyl)-2-methyl-1H-indol-3-yl)ethyl)acetamide (**11l**).* Yield 82%; black oil; R_f 0.25 (hexanes/EtOAc 3:1); IR (thin film): ν 3291, 3056, 2930, 1650, 1555, 1487, 1468, 1367, 1250, 1134, 925 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.53 (m, 1H), 7.25–7.16 (m, 2H), 7.16–7.08 (m, 2H), 6.97–6.87 (m, 1H), 6.78–6.73 (m, 1H), 6.64–6.58 (m, 1H), 5.52–5.42 (br, 1H), 5.30 (s, 2H), 3.51 (q, *J*=6.6 Hz, 2H), 2.98 (t, *J*=6.7 Hz, 2H), 2.30 (s, 3H), 1.90 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 164.8, 161.6, 140.8, 140.7, 136.5, 133.5, 130.5, 130.4, 128.0, 121.6, 121.3, 119.5, 118.0, 114.4, 113.1, 109.0, 109.0, 46.1, 46.1, 40.3, 24.5, 23.3, 10.2 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{22}FN_2O$ $[M+H]^+$ 325.1711, Found 325.1713.

*4.2.11. N-(2-(7-Chloro-2-methyl-1H-indol-3-yl)ethyl)acetamide (**11m**).* Yield 83%; yellowish solid; The reaction was heated to 140 °C for 20 h in DMF; R_f 0.25 (hexanes/EtOAc 3:1); mp 119–121 °C; IR (thin film): ν 3272, 2923, 1651, 1557, 1450, 1297, 1199, 1130, 1082, 1048, 949 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.39 (d, *J*=7.8 Hz, 1H), 7.12 (dd, *J*=7.7, 1.0 Hz, 1H), 7.02 (t, *J*=7.7 Hz, 1H), 5.54–5.40 (br, 1H), 3.48 (dd, *J*=12.9, 6.6 Hz, 2H), 2.90 (t, *J*=6.7 Hz, 2H), 2.42 (s, 3H), 1.91 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 133.0, 132.7, 130.3, 120.8, 120.5, 116.7, 116.1, 110.1, 40.2, 24.5, 23.6, 11.9 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{13}H_{16}ClN_2O$ $[M+H]^+$ 251.0946, Found 251.0957.

*4.2.12. N-(2-(5-Bromo-2-methyl-1H-indol-3-yl)ethyl)acetamide (**11o**).* Yield 71%; yellowish oil; R_f 0.25 (hexanes/EtOAc 3:1); IR (thin film): ν 3273, 2928, 1651, 1536, 1433, 1364, 1304, 1097, 1047, 909 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.62–7.54 (m, 1H), 7.22–7.05 (m, 2H), 5.63 (s, 1H), 3.44 (q, *J*=6.7 Hz, 2H), 2.84 (t, *J*=6.8 Hz, 2H), 2.39–2.31 (m, 3H), 1.92 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 134.1, 133.8, 130.6, 123.9, 120.5, 112.7, 112.0, 108.4, 40.3, 24.2, 23.6, 11.8 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{13}H_{16}BrN_2O$ $[M+H]^+$ 295.0441, Found 295.0450.

*4.2.13. N-(2-(1-Allyl-5-methoxy-2-methyl-1H-indol-3-yl)ethyl)acetamide (**11p**).* Yield 96%; black oil; R_f 0.30 (hexanes/EtOAc 3:1); IR (thin film): ν 3292, 3083, 2933, 2831, 1650, 1484, 1419, 1300, 1229, 1229, 1184, 1036, 923 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J*=8.8 Hz, 1H), 6.98 (d, *J*=2.4 Hz, 1H), 6.80 (dd, *J*=8.8, 2.4 Hz, 1H), 5.91 (ddt, *J*=17.0, 10.3, 4.6 Hz, 1H), 5.60 (s, 1H), 5.16–5.06 (m, 1H), 4.79 (ddd, *J*=17.0, 3.0, 1.8 Hz, 1H), 4.64 (dt, *J*=4.5, 1.8 Hz, 2H), 3.85 (s, 3H), 3.47 (q, *J*=6.6 Hz, 2H), 2.91 (t, *J*=6.7 Hz, 2H), 2.31 (s, 3H), 1.90 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 154.2, 134.2, 133.7, 131.5, 128.3, 116.2, 110.7, 109.9, 108.0, 100.3, 56.2, 45.7, 40.3, 24.6, 23.6, 10.2 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{17}H_{22}N_2O_2$ $[M+H]^+$ 287.1755, Found 287.1762.

*4.2.14. N-(2-(1-(4-Fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl)ethyl)-4-methylbenzenesulfonamide (**11q**).* Yield 73%; white solid; R_f 0.25 (hexanes/EtOAc 3:1); mp 130–132 °C; IR (thin film): ν 3284, 2936, 2832, 1603, 1509, 1484, 1325, 1229, 1157, 1094, 907 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.56 (m, 2H), 7.25–7.17 (m, 2H), 7.06 (dd, *J*=8.8, 0.4 Hz, 1H), 6.99–6.87 (m, 4H), 6.84 (d, *J*=2.2 Hz, 1H), 6.76 (dd, *J*=8.8, 2.4 Hz, 1H), 5.20 (s, 2H), 4.45 (t, *J*=6.2 Hz, 1H), 3.80 (s, 3H), 3.20 (q, *J*=6.7 Hz, 2H), 2.93 (t, *J*=6.8 Hz, 2H), 2.40 (s, 3H), 2.24 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 160.6, 154.3, 143.5, 137.0, 134.7, 133.7, 133.7, 131.8, 129.8, 128.0, 127.8, 127.7, 127.2, 116.0, 115.7, 111.1, 110.0, 107.1, 100.3, 56.1, 46.3, 43.4, 25.2, 21.7, 10.6 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{26}H_{28}N_2O_3S$ $[M+H]^+$ 467.1800, found 467.1790.

*4.2.15. N-(2-(1,2-Dimethyl-1H-indol-3-yl)ethyl)-1,1,1-trifluoromethan esulfonamide (**11r**).* Yield 66%; brown oil; R_f 0.30 (hexanes/EtOAc

4:1); IR (thin film): ν 3300, 3054, 2944, 1614, 1567, 1063, 1013, 922 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49–7.45 (m, 1H), 7.32–7.27 (m, 1H), 7.24–7.17 (m, 1H), 7.15–7.07 (m, 1H), 4.67 (s, 1H), 3.69 (s, 3H), 3.56 (q, J=6.3 Hz, 2H), 3.05 (t, J=6.5 Hz, 2H), 2.40 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 134.8, 127.2, 122.0, 121.5, 119.7, 117.7, 117.6, 109.2, 105.5, 44.8, 29.9, 26.0, 10.5 ppm; HRMS (ESI): m/z: calcd for $C_{13}H_{16}F_3N_2O_2S$ $[M+H]^+$ 321.0880, found 321.0883.

*4.2.16. N-(2-(5-Bromo-1,2-dimethyl-1H-indol-3-yl)ethyl)-4-fluorobenzamide (**11s**).* Yield 90%; white solid; R_f 0.25 (hexanes/EtOAc 4:1); mp 120–122 °C; IR (thin film): ν 3379, 2937, 1643, 1541, 1501, 1372, 1319, 1234, 1162, 1099, 851 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–7.61 (m, 3H), 7.21 (dd, J=8.6, 1.9 Hz, 1H), 7.14–6.97 (m, 3H), 6.35 (s, 1H), 3.66–3.52 (m, 5H), 2.98 (t, J=6.7 Hz, 2H), 2.33 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 166.4, 163.1, 135.5, 135.4, 130.9, 130.9, 129.6, 129.4, 129.3, 123.6, 120.3, 115.8, 115.6, 112.5, 110.4, 107.7, 41.1, 29.9, 24.3, 10.5 ppm; HRMS (ESI): m/z: calcd for $C_{19}H_{18}BrFN_2ONa$ $[M+Na]^+$ 411.0479, found 411.0476.

*4.2.17. 2,2,2-Trifluoro-N-(2-(5-methoxy-2-methyl-1H-indol-3-yl) ethyl)acetamide (**11t**).* Yield 70%; white solid; R_f 0.30 (hexanes/EtOAc 3:1); mp 130–131 °C; IR (thin film): ν 3395, 2943, 1707, 1558, 1485, 1215, 1180, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.19 (dd, J=8.7, 0.4 Hz, 1H), 6.92 (d, J=2.4 Hz, 1H), 6.81 (dd, J=8.7, 2.4 Hz, 1H), 6.33 (s, 1H), 3.85 (s, 3H), 3.62 (q, J=6.4 Hz, 2H), 2.96 (t, J=6.6 Hz, 2H), 2.36 (s, 3H) ppm; ^{13}C NMR (75 MHz, CD_3OD) δ 159.8, 159.4, 158.9, 158.4, 155.1, 134.4, 132.4, 130.3, 112.1, 112.1, 111.3, 108.1, 101.0, 56.4, 41.7, 24.7, 11.5 ppm; HRMS (ESI): m/z: calcd for $C_{14}H_{16}F_3N_2O_2$ $[M+H]^+$ 301.1159, found 301.1157.

4.3. Typical procedure for the preparation of tryptamine derivatives (13a, 13b)

Acetyl chloride (1.2 mmol, 1.2 equiv) was added to a solution of 4-dimethylaminopyridine (DMAP) (1.2 mmol, 1.2 equiv) in DMF (1.0 mL) at 0 °C. The reaction was stirred at room temperature for 15 min. A solution of the 6-methyl-2,3,4,5-tetrahydropyridine (1.0 mmol) in DMF (1.0 mL) was added and the reaction was stirred at room temperature for 20 h. *p*-Toluenesulfonic acid monohydrate (3.0 mmol, 3.0 equiv) was added at 0 °C under inert atmosphere. The reaction was then stirred at room temperature for 2 h. Arylhydrazine (1.5 mmol, 1.5 equiv) was added and stirred for an addition 5 min at room temperature. The reaction was then heated to 82 °C for 20 h. The reaction was cooled down to room temperature. The residue was then dissolved in ethyl acetate and washed with brine and a saturated aqueous solution of $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude solid, which was purified by column chromatography on silica gel.

*4.3.1. N-(3-(2-Methyl-1H-indol-3-yl)propyl)acetamide (**13a**).* Yield 71%; brown oil; R_f 0.25 (hexanes/EtOAc 1:2); IR (thin film): ν 3398, 2932, 2855, 1651, 1462, 4598, 1239, 1185, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.51–7.41 (m, 1H), 7.26–7.22 (m, 1H), 7.16–6.99 (m, 2H), 5.46 (s, 1H), 3.30–3.19 (m, 2H), 2.73 (t, J=7.2 Hz, 2H), 2.33 (s, 3H), 1.91–1.77 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 135.5, 131.3, 128.6, 121.2, 119.3, 118.0, 110.9, 110.5, 39.8, 30.3, 23.5, 21.8, 11.8 ppm; HRMS (ESI): m/z: calcd for $C_{14}H_{19}N_2O$ $[M+H]^+$ 231.1492 found 231.1491.

*4.3.2. N-(3-(1,2-Dimethyl-1H-indol-3-yl)propyl)acetamide (**13b**).* Yield 70%; brown oil; R_f 0.25 (hexanes/EtOAc 1:2); IR (thin film): ν 3287, 3053, 2933, 2854, 1650, 1472, 1370, 1331, 1294, 1247, 1199 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J=7.7 Hz, 1H), 7.25 (d, J=6.7 Hz, 1H), 7.16 (t, J=7.0 Hz, 1H), 7.08 (t, J=7.4 Hz, 1H), 5.71 (s, 1H), 3.63 (s, 3H), 3.24 (dd, J=13.5, 6.7 Hz, 2H), 2.76 (t, J=7.3 Hz, 3H), 2.34 (s, 3H), 1.96–1.75 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 136.7, 133.0, 127.6, 120.7, 118.8, 117.9, 110.2, 108.7, 39.7, 30.5, 29.6, 23.3, 22.0, 10.3 ppm; HRMS (ESI): m/z: calcd for $C_{15}H_{21}N_2O$ $[M+H]^+$ 245.1649, found 245.1651.

4.4. Typical procedure for the preparation of substituted arylhydrazines

Arylhydrazine (10.0 mmol), fluorobenzyl bromide (10.5 mmol) and triethylamine (1.5 mL, 11.0 mol) in toluene (30 mL) were heated at 100 °C for 3 h. The solution was cooled, diluted with ether (50 mL), and the solid was removed by filtration through Celite. After removal of the solvent, the residue was taken up in EtOAc (100 mL) and washed with a saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a crude solid, which was purified by column chromatography on silica gel to afford the product.

*4.4.1. 1-(3-Fluorobenzyl)-1-phenylhydrazine (**12d**).* Yield 55%; brown solid; R_f 0.20 (hexanes/EtOAc 10:1); mp 48–50 °C; IR (thin film): ν 3335, 3059, 3036, 2893, 2836, 2585, 1935, 1858, 1600, 1485, 1448, 1355, 1249, 1131, 1026, 955 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.24 (m, 3H), 7.14–6.93 (m, 5H), 6.86–6.80 (m, 1H), 4.60 (s, 2H), 3.65–3.61 (br, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.5, 130.3, 129.7, 129.4, 123.5, 123.4, 119.0, 115.0, 114.7, 114.6, 114.3, 113.6, 113.1, 60.2, 60.2 ppm; HRMS (ESI): m/z: calcd for $C_{13}H_{14}FN_2$ $[M+H]^+$ 217.1136, found 217.1133.

*4.4.2. 1-(4-Fluorobenzyl)-1-(4-methoxyphenyl)hydrazine (**12i**).* Yield 81%; brown oil; R_f 0.25 (hexanes/EtOAc 10:1); IR (thin film): ν 3346, 3041, 2933, 2834, 1602, 1506, 1441, 1358, 1242, 1155, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.26 (m, 2H), 7.08–6.99 (m, 4H), 6.88–6.82 (m, 2H), 4.41 (s, 2H), 3.78 (s, 3H), 3.46–3.41 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 160.8, 153.7, 146.4, 133.4, 133.4, 130.2, 130.1, 116.7, 115.8, 115.5, 114.6, 61.9, 55.9 ppm; HRMS (ESI): m/z: calcd for $C_{14}H_{16}FN_2O$ $[M+H]^+$ 247.1242, found 247.1243.

*4.4.3. Allyl-1-(4-methoxyphenyl)hydrazine (**12h**).* To a solution of 4-methoxyphenyl-hydrazine hydrochloride (1.75 g, 10 mmol) in THF (20 mL) was added a solution of LiHMDS (11 mL, 11 mmol, 1.0 M in THF) at 0 °C. The resulting mixture was stirred at 0 °C to room temperature for 30 min, the reaction was cooled to 0 °C, and then allyl bromide (0.95 mL, 11 mmol) was added. The resulting mixture was stirred at room temperature for 2 h. A saturated aqueous solution of NH_4Cl was added and the aqueous layer was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a crude oil, which was purified by column chromatography on silica gel (hexanes/ethyl acetate=10:1) to afford the product (1.15 g, 6.45 mmol) as a colourless oil in 65% yield. IR (thin film): ν 3339, 3075, 2997, 2832, 1857, 1603, 1506, 1294, 1180, 1037, 882 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.08–6.98 (m, 2H), 6.90–6.79 (m, 2H), 5.97–5.78 (m, 1H), 5.35–5.29 (m, 1H), 5.27–5.23 (m, 1H), 3.92 (dt, J=6.2, 1.3 Hz, 2H), 3.77 (s, 3H), 3.55–3.46 (br, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 146.2, 133.2, 119.3, 116.5, 114.6, 60.9, 55.9 ppm; HRMS (ESI): m/z: calcd for $C_{10}H_{15}N_2O$ $[M+H]^+$ 179.1179, found 179.1175.

4.5. *N*-(2-(3-(but-3-ynyl)-1*H*-indol-2-yl)ethyl)acetamide (14′)

Yield 15%; brown oil; R_f 0.20 (hexanes/EtOAc 1:5); IR (thin film): ν 3291, 3088, 2932, 1651, 1538, 1461, 1370, 1295, 1245, 1181, 909 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.63 (d, J=7.7 Hz, 1H), 7.37 (d, J=7.6 Hz, 1H), 7.16–7.09 (m, 2H), 3.64 (d, J=2.7 Hz, 2H), 3.34 (dd, J=12.4, 6.3 Hz, 3H), 2.85–2.77 (m, 2H), 2.03 (t, J=2.7 Hz, 1H), 1.99 (s, 3H), 1.86–1.76 (m, 2H) ppm; ^{13}C NMR

(101 MHz, $CDCl_3$) δ 171.6, 135.4, 127.8, 121.4, 119.3, 118.1, 111.1, 105.5, 83.4, 68.2, 38.6, 30.1, 23.5, 22.4, 13.9 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{16}H_{19}N_2O$ $[M+H]^+$ 255.1492, found 255.1491.

4.6. *N*-(2-(2-Formyl-1-methyl-1*H*-indol-3-yl)ethyl)acetamide (16)

To a solution of oxalyl chloride (0.038 mL, 0.434 mmol) in dry CH_2Cl_2 (1 mL), at −78 °C under a nitrogen atmosphere, was added DMSO (0.044 mL, 0.608 mmol). The solution was stirred for ca. 10 min, until effervescence ceased. A solution of indole (20 mg, 0.086 mmol) in dry CH_2Cl_2 (0.3 mL) was added dropwise, and the red solution was stirred for 10 min at −78 °C. Triethylamine (0.122 mL, 0.868 mmol) was then added and the solution was left to warm to room temperature for 20 min. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous solution of NH_4Cl. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated, and the residue was purified by column chromatography on silica gel, eluting with 1:2 hexanes/ethyl acetate to provide the product with a yield of 61%; mp 125–127 °C; IR (thin film): ν 3274, 2923, 1652, 1555, 1471, 1431, 1297, 1065 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.10 (s, 1H), 7.74 (d, *J*=7.6 Hz, 1H), 7.44 (t, *J*=7.5 Hz, 1H), 7.37 (d, *J*=8.4 Hz, 1H), 7.18 (t, *J*=7.0 Hz, 1H), 5.67 (s, 1H), 4.07 (s, 3H), 3.65–3.55 (br, 2H), 3.35–3.30 (br, 2H), 1.93 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.0, 170.7, 139.9, 131.9, 127.7, 127.2, 126.5, 121.5, 120.9, 110.6, 41.6, 31.8, 24.0, 23.8 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{14}H_{17}N_2O_2$ $[M+H]^+$ 245.1285, found 245.1281.

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Supplementary data

Full table of condition screening and the spectroscopic data of all new compounds are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.11.032.

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