Tetrahedron 73 (2017) 6393–6400

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis and identification of metabolite biomarkers of 25C-NBOMe and 25I-NBOMe

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ARTICLE INFO

Article history:
Received 14 June 2017
Received in revised form
30 August 2017
Accepted 13 September 2017
Available online 18 September 2017

Keywords:
Biomarker
25C-NBOMe
25I-NBOMe
Metabolite
Urinary detection

ABSTRACT

Synthetic routes have been developed for synthesis of potential metabolites of 25C-NBOMe and 25I-NBOMe. Nine potential metabolites have been synthesized, among which compounds **8** and **20a** could be used as metabolite biomarkers of 25C-NBOMe and **20b** of 25I-NBOMe in urinary detection at forensic laboratories to prove intake.

1. Introduction

It is estimated that a total of 246 million people, or 1 out of 20 people between the ages of 15 and 64 years, used an illicit drug in 2014 according to the *World Drug Report 2016*. Although drug abuse may lead to many health and social problems,[1] new psychoactive substances (NPS) that are produced by clandestine laboratories and purchased *via* the internet head shops, keep being pumped into the market with 66 new psychoactive substances firstly reported to the EU early warning system in 2017.[2]

The NBOMes (*N*-Benzyl-oxy-methyl derivatives of 2C phenylethylamines), a new group of NPS, have strong hallucinogenic effects and have been reportedly sold as a legal alternative to lysergic acid diethylamide (LSD). More than 39 NBOMes and analogues have been reported.[3,4] The most commonly abused NBOMes are 25I-NBOMe, 25C-NBOMe and 25B-NBOMe (Fig. 1), which are now scheduled as controlled substances in many countries. Ingestion of these substances can cause tachycardia, agitation, hallucination, hypertension, confusion and mydriasis.[5,6] Cases of fatal intoxication associated with the use of NBOMes have been reported around the world, e.g. in the US, Europe, and Australia.[6–8]

It can be challenging to detect NPS because the parent drugs are not always found in urine specimens. Metabolites can be a more suitable target and can also extend the time window of detection.

Therefore, metabolite identification studies to determine NPS biomarkers are important. There are only a few reports on NBOMe metabolism although fatal intoxication cases caused by using NBOMes have been reported in several countries. Studies on the metabolism of 25I-NBOMe and 25B-NBOMe using LC-HR-MS etc. analytical methods have been carried out by Caspar and Boumrah in 2015.[9,10] In the same year, Poklis et al. reported the identification of metabolite biomarkers of 25I-NBOMe as well as the synthesis of two major metabolites with 8 and 9 steps respectively.[11] With synthetic reference standards, the metabolites with monodemethylation of the 2,5-dimethoxyphenyl ring can now be distinguished. Since the synthetic route is long, there is need for optimization or identification of other metabolite biomarkers, which could be synthesized in fewer steps.

25C-NBOMe is one of the most abused NBOMes; to the best of our knowledge, there are no reports on the synthesis of its metabolite biomarkers. In collaboration with the National Board of Forensic Medicine of Sweden we synthesized several potential

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https://doi.org/10.1016/j.tet.2017.09.024
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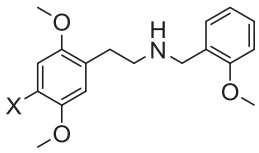


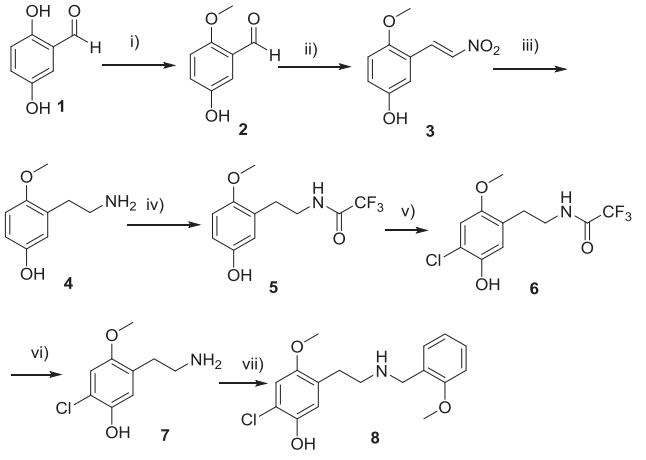
Fig. 1. Structures of 25I-NBOMe, 25B-NBOMe and 25C-NBOMe.

metabolites of 25C-NBOMe and 25I-NBOMe for comparison.

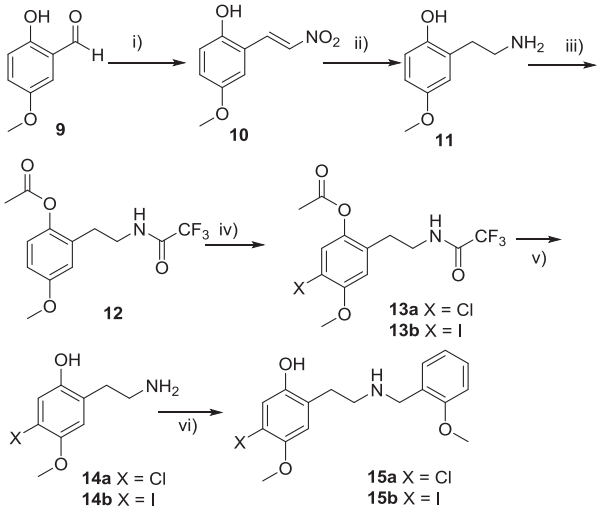
2. Results and discussion

Aldehyde **2** is commercially available. It can also be synthesized from compound **1** using MeI under basic conditions.[12] The methylation is selective, which might be due to the acidic difference of the two phenol groups. The yield was moderate due to incomplete conversion. Henry reaction between compound **2** and nitromethane gave **3** in high yield. When a higher amount of nitromethane was used with starting material of **9**, a lower yield was obtained and dialkylation side product was increased. The reduction of **3** to **4** with $LiAlH_4$ was straightforward, but the work-up was problematic and led to lower yield than expected. Protection of **4** using trifluoroacetic anhydride gave **5**, which could undergo chlorination with NCS without protection of the phenol. The chlorination selectively occurred at the ortho position of phenol to give compound **6** as the major product. After deprotection and reductive amination, compound **8** was obtained. The yield was low. Full conversion was not achieved with $NaCNBH_3$, although an excess amount of reagent was added. $NaBH_4$ was then added. The lower yield might be caused by the poor quality of $NaCNBH_3$. The synthetic route of **8** was two steps shorter than its metabolite analogue of 25I-NBOMe, which was reported by Poklis et al.[11] The overall yield might be increased with reagents of better quality (Scheme 1).

Following a similar procedure **15a**, another potential metabolite of 25C-NBOMe, was synthesized (Scheme 2). The difference was that the phenol had to be protected with an acyl group to increase the selectivity of chlorination at the ortho position of the methoxy



Scheme 1. i) MeI, K_2CO_3, DMF, 57%; ii) CH_3NO_2 (14 equiv.), NH_4OAc (0.65 equiv.), AcOH, 94%; iii) $LiAlH_4$, THF, 59%; iv) TFAA, DCM, 52%; v) NCS, acetonitrile, 75 °C, 30 min, 73%; vi) 5% NaOH, EtOH, rt, vii) 2-methoxybenzaldehyde, $NaCNBH_3$ and $NaBH_4$, EtOH, rt, 26%.



Scheme 2. i) CH_3NO_2 (30 equiv.), NH_4OAc (1 equiv.), AcOH, 120 °C, 70 min, 68%; ii) $LiAlH_4$, THF, 65 °C, 4 h, 71%; iii) a) TFAA, TEA, THF, rt; b) acetyl chloride, TEA, $CHCl_3$, rt, 51%; iv) **13a**: NCS, acetonitrile, rt, 65%; **13b**: NIS, conc. H_2SO_4, acetonitrile, rt, 65%; v) 5% NaOH, EtOH, rt, 100% for both **14a** and **14b**; vi) 2-methoxybenzaldehyde, $NaCNBH_3$, DCE, rt, 36% and 35% for **15a** and **15b**, respectively.

group. Instead of protecting with an acyl group, excess amount of trifluoroacetic anhydride was also tested to give a di-trifluoroacyl protected intermediate to reduce one step, unfortunately it failed. Both protective groups could be removed under basic conditions in the same procedure. A similar metabolite of 25I-NBOMe, compound **15b**, was synthesized using a similar procedure (Scheme 2). Compared to the synthesis reported in the literature, our procedure required one step less and replaced 2-bromo propane for protection and BCl_3 for deprotection by more common reagents.

Both metabolites of 25C-NBOMe, compound **8** and **15a,** were used as reference standards in the analysis of two authentic forensic urine specimens (Fig. 2A). It was found that compound **8**, 5′-desmethyl-25C-NBOMe, was more abundant than **15a**, 2′-desmethyl-25C-NBOMe, suggesting that compound **8** is a good metabolite biomarker of 25C-NBOMe. Moreover, it was found that **15b,** 2′-desmethyl-25I-NBOMe, was not a good metabolite biomarker for analysis of intake of 25I-NBOMe either (Fig. 2C).[13] Although the synthesis of **8** and **15** was carried out successfully with improvement, the synthetic route was still long. However other metabolites that can be synthesized with shorter synthetic routes could be identified and used as biomarkers too. 25B/I/C-NBOMes were metabolized by O-demethylation, O-di-demethylation and hydroxylation.[11,13] Metabolites with a hydroxyl group on the benzyl ring of 25C/I-NBOMe were then synthesized.

The position of the hydroxyl group of a major metabolite of NBOMes at the benzyl ring was controversial in literature.[13,15–17] Therefore, it is imperative to have all four possible metabolites to address the problem. Here we have synthesized all of them, **20a**, **21a**, **22** and **23** (Scheme 3).

Compound **17** was synthesized using a Curtius rearrangement from **16** with Boc_2O/NaN_3 under catalysis of $Zn(TfO)_2$.[14] The amino group was protected at the same time. The resulting product **17** was then halogenated, deprotected using TFA, followed by reductive amination to give compounds **20**–**23**, with hydroxylation at 6, 5, 4 or 3 position of the benzyl ring of NBOMe, respectively. Compound **19** was also synthesized for comparison with metabolite **15b**. It was found that it is not a proper metabolite biomarker (Fig. 2B). Therefore, we refrained from synthesizing its chloro analogue. The synthesis of **20**–**23** was straightforward (Scheme 3). The

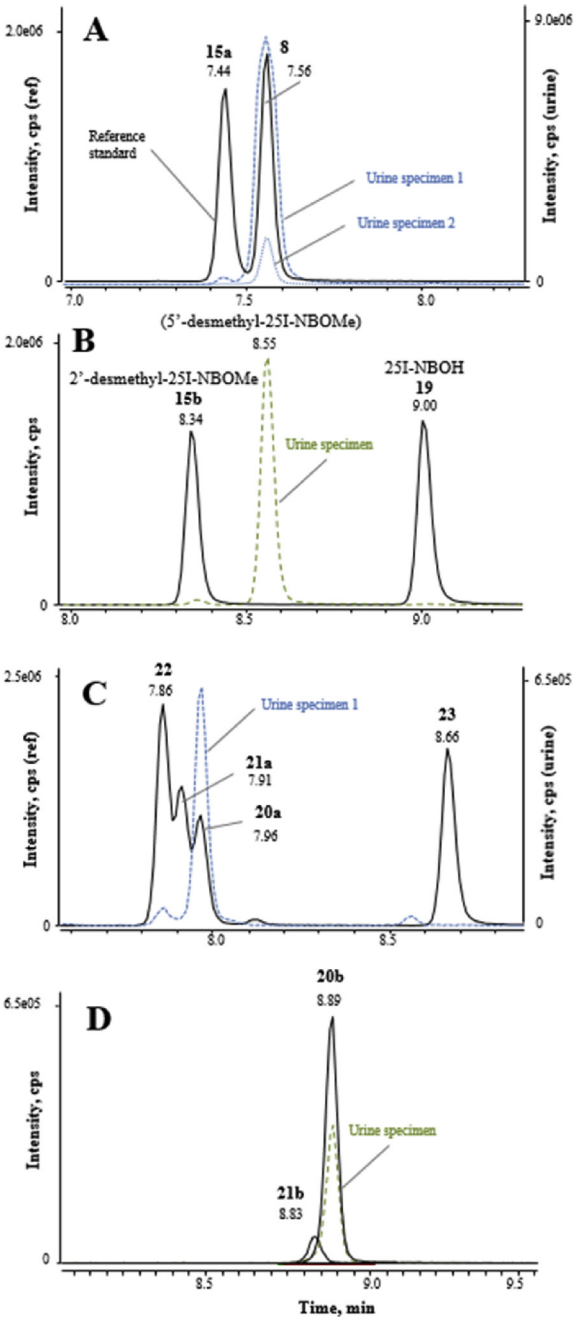
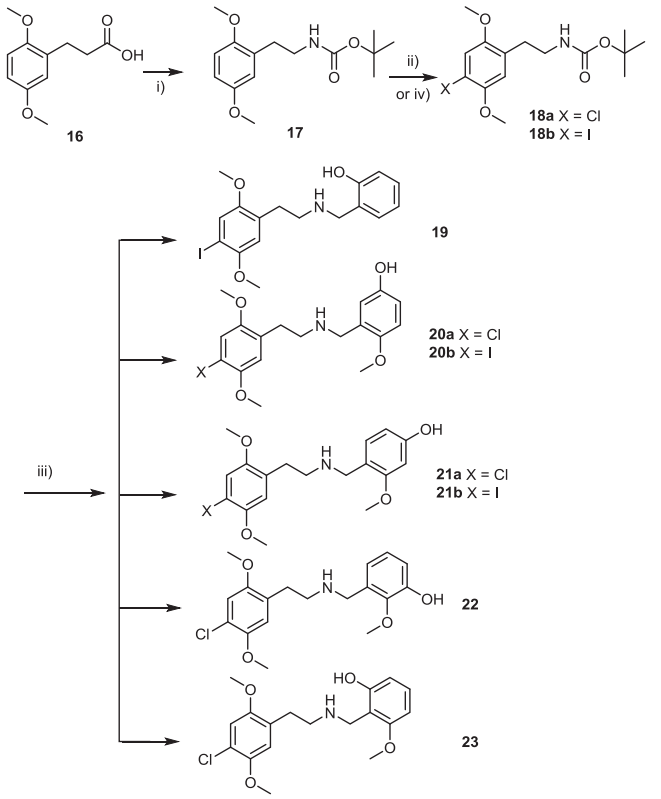


Fig. 2. Analysis of synthesized potential metabolites of NBOMes (solid line) and authentic humman urine cases (dashed line) using LC-QTOF with an ACE Excel 2 C18-AR column and an extended gradient.

rearrangement worked but was sensitive. The yield of **17** varied from 45 to 72% under similar conditions by different chemists. Chlorination of **17** gave full conversion at 75 °C using either MW irradiation or conventional heating. The selectivity was good, but product with chloro group at position 6 was still found. Compound **21a** was not stable and decomposed during concentration under heating at 50 °C after LC purification. The fractions from preparative LC turned red and the bond between the amine group and the benzyl ring was broken to give 2-(4-chloro-2,5-dimethoxyphenyl) ethan-1-amine according to LC-MS. Its stability was much better at room temperature. Freeze-drying was then used for removing solvent. It was found that compound **21b** was not stable either and gave a similar side product together with another *N,N*-



Scheme 3. i) NaN_3, Bu_4NBr, $Zn(OTf)_2$, Boc_2O, THF, 72%; ii) **18a:** NCS, acetonitrile, MW, 75 °C, 84%; **18b**: NIS, AcOH, rt, 65%; iii) a) TFA, DCM; b) **21b**: $NaBH_4$, EtOH, 49%; iv) a) NCS, acetonitrile, MW, 75 °C; b) TFA, DCM, rt; c) aldehyde, $NaBH_4$ or $Na(OAc)_3BH$ or $NaCNBH_3$, overall yield from **17** or **18b**: **20a**: 76%; **20b**: 50%; **21a**: 60%; **22**: 27%; **23**: 56%.

dibenzylation side product under heating after LC preparation. The stabilities of **20a**, **22** and **23** were better.

After analysis of the human urine samples and comparison with these references, it was found that compound **20a** was the correct mono-hydroxy metabolite of 25C-NBOMe and can be used as another suitable metabolite biomarker (Fig. 2C). The result was consistent with the metabolite study of 25B-NBOMe by Kristersen et al.[16] Interestingly, Nielsen et al. reported that the 4-hydroxy metabolite, compound **21b**, was identified as one of the major metabolites of 25I-NBOMe using human liver microsomes. In the same paper, the authors also reported that, instead of the 4-hydroxy metabolite, the 5-hydroxy metabolite at the benzyl ring was the major mono-hydroxy metabolite of 25I-NBOH, which is an analogue of 25I-NBOMe.[17] During our study it was found that the four metabolites of 25C-NBOMe had very close retention times and required optimized conditions to improve separation. This may be also true for 25I-NBOMe. Compound **20b** was then synthesized using a similar method (Scheme 3). It was found that instead of **21b**, compound **20b** was more likely to be the major mono-hydroxy metabolite of 25I-NBOMe in authentic human urine sample in our analysis (Fig. 2D).

3. Conclusion

Straightforward synthetic routes have been developed for the synthesis of potential metabolites of 25C-NBOMe and 25I-NBOMe. The yield might be improved if further optimization is carried out. Analysis of authentic urine species and human hepatocyte samples showed that 5′-desmethyl-25C-NBOMe (compound **8**) and 5-OH-25C-NBOMe (compound **20a**) are two metabolite biomarkers,

which can be used as targets in urine analysis for 25C-NBOMe. Further study on the metabolites of 25I-NBOMe suggested that 5-OH-25I-NBOMe (**20b**), not 4-OH-25I-NBOMe (**21b**), was the major mono-hydroxy metabolite of 25I-NBOMe in our human urine specimen. All the three most commonly abused NBOMes, 25I/C/B-NBOMe, showed similar metabolites suggesting that other NBOMes might follow a similar metabolic pattern. Therefore, after considering the synthetic route, we found that the 5-OH-NBOMe metabolite has a potential to be developed as a general metabolite biomarker for detection of NBOMe intake from human urine.

4. Experimental section

4.1. General information

TLC was performed using 0.25 mm precoated silica-gel plates (Merck 60 F_{254}), detection by UV-abs at 254 nm. ^{1}H and ^{13}C-NMR spectra were recorded on a Varian Mercury 300 MHz instrument (25 °C in $CDCl_3$ or methanol-d_4). HPLC-MS was performed on a Waters system Column: XSELECT Phenyl-Hexyl, 5 μm, 250 × 19 mm and Waters X-Bridge C-18 3.5 μm, 50 × 4.6 mm for preparative and analytical experiments respectively; Mobile phase: organic phase: acetonitrile:water 90:10, with 10 mM NH_4OAc; water phase: acetonitrile:water 5:95, with 10 mM NH_4OAc. Flash chromatography was performed using the following silica gel: High purity grade (Merck Grade 9385), pore size 60 Å, 230–240 mesh particle size. The results of the high-resolution mass measurements using LC-QTOF-MS by National Board of Forensic Medicine, Sweden, can be found in the experimental.

4.2. Synthesis

4.2.1. 5-hydroxy-2-methoxybenzaldehyde (**2**)

A mixture of 2,5-dihydroxybenzaldehyde (1 g, 7.24 mmol) and K_2CO_3 (1 g, 7.24 mmol) was dissolved in DMF (10 mL) and stirred at room temperature for 30 min before methyl iodide (0.679 mL, 10.9 mmol) was added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuum* and the crude was purified using flash-column chromatography (n-heptane/EtOAc 2:1) to gain compound **2**[12] (621 mg, 57% yield) as a yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.33 (s, 1H), 7.30 (d, J = 3.2 Hz, 1H), 7.10 (dd, J = 9.0, 3.2 Hz, 1H), 6.84 (d, J = 8.9 Hz, 1H), 6.70 (broad s, 1H), 3.84 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.6, 156.6, 150.2, 125.0, 124.1, 113.9, 113.5, 56.2.

4.2.2. (E)-4-methoxy-3-(2-nitrovinyl)phenol (**3**)

A mixture of compound **2** (303 mg, 1.99 mmol), nitromethane (1.5 mL, 27.7 mmol) and ammonium acetate (99.5 mg, 1.29 mmol) in AcOH (6.15 mL) in a microwave vial was irradiated under MW at 120 °C for 20 min. Water was added (5 mL) and the reaction mixture was extracted using DCM (3 × 15 mL) and evaporated *in vacuum* to gain compound **3** (367 mg, 94% yield) as an orange solid. ^{1}H-NMR (300 MHz, MeOD) δ 8.11 (d, J = 13.6 Hz, 1H), 7.87 (d, J = 13.6 Hz, 1H), 6.98–6.95 (m, 1H), 6.95–6.93 (m, 2H), 3.88 (s, 3H). ^{13}C-NMR (75 MHz, MeOD) δ 154.7, 152.6, 139.3, 136.1, 121.8, 120.8, 118.1, 114.0, 56.8.

4.2.3. 3-(2-aminoethyl)-4-methoxyphenol phenol (**4**)

Compound **3** (385 mg, 1.97 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. $LiAlH_4$ (7.9 mL, 1 M in THF solution) was added and the reaction mixture was left to stir under nitrogen gas flow at 65 °C for 4 h. Cold water was added to the reaction along with 15% NaOH (aq.) in excess and some additional THF. The solution was vacuum filtered and the filtrate was evaporated *in vacuum* and pre-absorbed on to silica gel before purification using flash-column chromatography (DCM/MeOH/Et_3N 90:10:1) to gain compound **4**[18] (194 mg, 59% yield). ^{1}H-NMR (300 MHz, MeOD) δ 6.78–6.71 (m, 1H), 6.65–6.54 (m, 2H), 3.73 (s, 3H), 2.91–2.74 (m, 2H), 2.69 (t, J = 6.6 Hz, 2H). ^{13}C-NMR (75 MHz, MeOD) δ 151.0, 150.9, 128.5, 117.2, 113.1, 111.5, 55.0, 41.3, 33.4.

4.2.4. 2,2,2-trifluoro-N-(5-hydroxy-2-methoxyphenethyl) acetamide (**5**)

Compound **4** (194 mg, 1.16 mmol) was dissolved in THF (4 mL) and trifluoroacetic anhydride (193 μL, 1.39 mmol) and Et_3N (194 μL, 1.39 mmol) was added to the solution. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuum*, water was added to the crude and then extracted using DCM (3 × 15 mL). The crude was purified using flash-column chromatography (n-heptane/EtOAc 2:1) to gain compound **5** (158 mg, 52% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.46 (broad s, 1H), 6.78–6.69 (m, 2H), 6.65 (d, J = 2.2 Hz, 1H), 3.78 (s, 3H), 3.57–3.44 (m, 2H), 2.86–2.77 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 157.7 (q, J_{CF} = 36.8 Hz, 1C), 151.1, 150.2, 127.7, 117.9, 116.0 (q, J_{CF} = 283.9 Hz, CF_3), 114.6, 111.9, 55.9, 41.5, 29.2. ^{19}F-NMR (282.2 MHz, $CDCl_3$) −76.2 (s, 3F).

4.2.5. N-(4-chloro-5-hydroxy-2-methoxyphenethyl)-2,2,2-trifluoroacetamide (**6**)

Compound **5** (89.5 mg, 0.34 mmol) was dissolved in ACN (2 mL) and NCS (45.5 mg, 0.34 mmol) was added. The reaction mixture was stirred at 75 °C for 30 min and left to cool to room temperature. The solvent was evaporated *in vacuum* and the crude was purified using preparative LC to gain compound **6** (74.3 mg, 73% yield) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.82 (s, 1H), 3.79 (s, 3H), 3.59–3.49 (m, 2H), 2.86–2.81 (m, 2H).

4.2.6. 5-(2-aminoethyl)-2-chloro-4-methoxyphenol (**7**) and 2-chloro-4-methoxy-5-(2-((2-methoxybenzyl)amino)ethyl)phenol (**8**)

NaOH (aq.) (86 μl, 0.998 mmol, 5 M) was added to a solution of compound **6** (74.3 mg, 0.25 mmol) in EtOH (1.5 mL) and the reaction mixture was stirred at room temperature for 2 h. The pH was adjusted to around 10 using HCl (aq.) and the solution was extracted using DCM (5 × 10 mL). The solvent was evaporated *in vacuum* and the resulting product (compound **7**) was re-dissolved in EtOH (2 mL). 2-methoxy benzaldehyde (33 μL, 0.275 mmol) and sodium cyanoborohydride (31.4 mg, 0.499 mmol) was added to the solution that was left to stir at room temperature overnight. Finally sodium borohydride (9.44 mg, 0.25 mmol) was added to the solution and left to stir for about 1 h. The solvent was evaporated *in vacuum* and the crude purified using preparative LC to gain product **8** (20.5 mg, 26% yield) as colorless syrupy. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.21 (td, J = 8.0, 1.7 Hz, 1H), 7.14 (dd, J = 8.0, 1.7 Hz, 1H), 6.85 (td, J = 8.0, 1.0 Hz, 1H), 6.77 (dd, J = 8.0, 1.0 Hz, 1H), 6.73 (s, 1H), 6.68 (s, 1H), 3.80 (s, 2H), 3.65 (s, 3H), 3.58 (s, 3H), 2.85 (t, J = 5.9 Hz, 2H), 2.75 (t, J = 5.9 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 157.7, 150.9, 146.8, 130.8, 129.1, 127.1, 125.6, 120.5, 118.5, 118.1, 112.3, 110.2, 56.0, 55.2, 49.1, 46.6, 30.2. ESI-HRMS positive mode (m/z): calcd. for $C_{17}H_{21}^{35}ClNO_3$ ($[M+H]^+$): 322.1210. Found: 322.1217; calcd. for $C_{17}H_{21}^{37}ClNO_3$ ($[M+H]^+$): 324.1180. Found: 324.1182.

4.2.7. (E)-4-methoxy-2-(2-nitrovinyl)phenol (**10**)

A mixture of 2-hydroxy-5-methoxybenzaldehyde **9** (76.1 mg, 0.5 mmol), nitromethane (0.82 mL, 15.3 mmol) and ammonium acetate (38.5 mg, 0.5 mmol) in a microwave vial was irradiated under MW at 120 °C for 70 min. The reaction mixture was cooled to room temperature, water was added and extracted using EtOAc (3 × 10 mL). The solvent was evaporated *in vacuum* and the crude was purified using flash-column chromatography (n-heptane/EtOAc 1:1) to gain compound **10**[19] (67.4 mg, 68% yield). ^{1}H-NMR

(300 MHz, $CDCl_3$) δ 8.11 (d, J = 13.6 Hz, 1H), 7.90 (d, J = 13.6 Hz, 1H), 6.96–6.88 (m, 2H), 6.82–6.74 (m, 1H), 5.33 (broad s, 1H), 3.80 (s, 3H). ^{13}C-NMR (75 MHz, MeOD) δ 154.4, 153.9, 139.0, 136.8, 121.5, 118.8, 118.1, 115.9, 56.4.

4.2.8. 2-(2-aminoethyl)-4-methoxyphenol (**11**)

Compound **10** (247 mg, 1.27 mmol) was dissolved in THF (8 mL) and cooled to 0 °C. $LiAlH_4$ (5.1 mL, 1 M in THF solution) was added dropwise and the reaction mixture was left to stir under nitrogen gas flow at 65 °C for 4 h. Cold water was added to the reaction along with 15% NaOH (aq.) in excess and some additional THF. The solution was vacuum filtered and the filtrate was evaporated *in vacuum* and pre-absorbed on to silica gel before purification using flash-column chromatography (DCM/MeOH/Et_3N 90:10:1) to gain compound **11**[20] (150 mg, 71% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.84 (d, J = 8.7 Hz, 1H), 6.67 (dd, J = 8.7, 3.0 Hz, 1H), 6.58 (d, J = 3 Hz, 1H), 3.73 (s, 3H), 3.10–3.03 (m, 2H), 2.80–2.72 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 152.8, 150.6, 128.8, 118.1, 116.7, 113.0, 55.9, 42.6, 36.2.

4.2.9. 4-methoxy-2-(2-(2,2,2-trifluoroacetamido)ethyl)phenyl acetate (**12**)

Compound **11** (75.2 mg, 0.45 mmol) was dissolved in THF (1 mL) and trifluoroacetic anhydride (125 μL, 0.899 mmol) and Et_3N (125 μL, 0.899 mmol) was added to the solution. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuum*, water was added to the crude and then extracted using DCM (3 × 15 mL). The solvent was once again evaporated *in vacuum* and the crude product was re-dissolved in $CHCl_3$ (2 mL). Acetyl chloride (47 μL, 0.54 mmol) and Et_3N (81 μL, 0.58 mmol) were added to the solution and stirred at room temperature overnight. Saturated $NaHCO_3$ (aq.) was added to the solution and the organic phase was removed and evaporated *in vacuum*. The crude was purified using flash-column chromatography (n-heptane/EtOAc 2:1) to gain compound **12** (70.6 mg, 51% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.96 (d, J = 8.8 Hz, 1H), 6.80 (dd, J = 8.8, 3.0 Hz, 1H), 6.74 (d, J = 3.0 Hz, 1H), 6.66 (broad s, 1H), 3.78 (s, 3H), 3.62–3.50 (m, 2H), 2.77 (t, J = 6.9 Hz, 2H), 2.32 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.5, 157.8, 142.8, 130.9, 123.6, 115.9 (q, J_{CF} = 284.1 Hz, CF_3), 115.5, 113.6, 55.7, 40.3, 29.4, 20.9.

4.2.10. 5-chloro-4-methoxy-2-(2-(2,2,2-trifluoroacetamido)ethyl) phenyl acetate (**13a**)

Compound **12** (53.3 mg, 0.175 mmol) was dissolved in ACN (1 mL) and NCS (25.7 mg, 0.192 mmol) was added at 0 °C. The reaction mixture was then left to reach room temperature and stirred overnight. The solvent was evaporated *in vacuum* and the crude was purified using flash-column chromatography (n-heptane/EtOAc 2:1) to gain compound **13a** (38.4 mg, 65% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.10 (s, 1H), 6.74 (s, 1H), 6.60 (broad s, 1H), 3.87 (s, 3H), 3.61–3.50 (m, 2H), 2.78 (t, J = 6.9 Hz, 2H), 2.32 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.0, 153.4, 142.3, 129.2, 124.5, 121.6, 115.7 (q, J_{CF} = 284.7 Hz, CF_3), 113.0, 56.5, 39.9, 29.1, 20.7.

4.2.11. 5-iodo-4-methoxy-2-(2-(2,2,2-trifluoroacetamido)ethyl) phenyl acetate (**13b**)

N-iodosuccinimide (24.2 mg, 0.108 mmol) was added to a solution of compound **12** (26.4 mg, 0.086 mmol) in AcOH (1 mL) and. After 4 h, the conversion was about 50% according to LC-MS. Additional *N*-iodosuccinimide (9.70 mg, 0.043 mmol) was added along with H_2SO_4 (2.4 μL, 18 M, 0.043 mmol) and the reaction mixture was stirred overnight. An excess of $Na_2S_2O_3$ (aq.) and Et_2O was added to the reaction mixture and the water phase was removed. The solvent was evaporated in *vacuum* and the crude purified using flash-column chromatography (n-heptane/EtOAc 2:1) to gain compound **13b** (24 mg, 65% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.46 (s, 1H), 6.63 (s, 1H), 6.56 (broad s, 1H), 3.85 (s, 3H), 3.62–3.52 (m, 2H), 2.77 (t, J = 6.8, 2H), 2.32 (s, 3H).

4.2.12. 2-(2-aminoethyl)-5-chloro-4-methoxyphenol (**14a**) and 5-chloro-4-methoxy-2-(2-((2-methoxybenzyl)amino)ethyl)phenol (**15a**)

NaOH (aq.) (40 μL, 0.223 mmol, 5 M) was added to a solution of compound **13a** (38.4 mg, 0.113 mmol) in EtOH (1 mL) and the reaction mixture was stirred at room temperature overnight. The pH was adjusted to around 8–9 using 1 N HCl (aq.) and the solution was extracted using DCM (3 × 10 mL). The solvent was evaporated and part of the resulting compound **14a** (11.7 mg, 0.0582 mmol) was re-dissolved in DCE (1 mL). 2-methoxy benzaldehyde (7.7 μL, 0.0640 mmol), sodium cyanoborohydride (7.3 mg, 0.116 mmol) and one drop of AcOH were added to the solution, which was stirred at room temperature overnight. The solvent was evaporated *in vacuum* and the crude purified using flash-column chromatography (DCM/MeOH/Et_3N 96:4:1) and preparative LC to gain product **15a** (6.8 mg, 36% yield) as colorless syrupy. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29 (td, J = 7.7, 1.1 Hz, 1H), 7.21 (dd, J = 7.7, 1.7 Hz, 1H), 6.98 (s, 1H), 6.96–6.85 (m, 2H), 6.57 (s, 1H), 3.90 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 2.97–2.87 (m, 2H), 2.85–2.72 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 157.7, 151.5, 147.9, 130.8, 129.6, 126.4, 121.5, 120.8, 120.4, 119.4, 115.6, 110.6, 57.2, 55.5, 49.0, 48.9, 33.3. ESI-HRMS positive mode (m/z): calcd. for $C_{17}H_{21}^{35}ClNO_3$ ($[M+H]^+$): 322.1210. Found: 322.1211; calcd. for $C_{17}H_{21}^{37}ClNO_3$ ($[M+H]^+$): 324.1180. Found: 324.1180.

4.2.13. 2-(2-aminoethyl)-5-iodo-4-methoxyphenol (**14b**) and 5-iodo-4-methoxy-2-(2-((2-methoxybenzyl)amino)ethyl)phenol (**15b**)

NaOH (aq.) (20 μL, 0.111 mmol, 5 M) was added to a solution of compound **13b** (24 mg, 0.0557 mmol) in EtOH (0.5 mL) and water (0.5 mL) and the reaction mixture was stirred at room temperature overnight. The pH was adjusted to around 8–9 using 1 N HCl (aq.) and the solution was extracted using DCM (3 × 10 mL). The solvent was evaporated *in vacuum* and the resulting compound **14b** (15.8 mg, 0.0539 mmol) was re-dissolved in DCE (1 mL). 2-methoxy benzaldehyde (7.2 μL, 0.0593 mmol), sodium cyanoborohydride (6.8 mg, 0.108 mmol) and one drop of AcOH were added to the solution that was left to stir at room temperature for about 2 h. The solvent was evaporated *in vacuum* and the crude purified using flash-column chromatography (DCM/MeOH/Et_3N 98:2:1) and preparative LC to gain product **15b** (5.8 mg, 25% yield) as pale yellow syrupy. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.18 (dd, J = 7.4, 1.7 Hz, 1H), 6.96–6.86 (m, 2H), 6.48 (s, 1H), 3.85 (s, 5H), 3.78 (s, 3H), 2.91–2.82 (m, 2H), 2.79–2.71 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 157.9, 152.4, 151.3, 130.7, 129.4, 128.7, 128.2, 125.8, 120.8, 114.1, 110.5, 84.1, 57.4, 55.4, 49.1, 49.0, 34.2. ESI-HRMS positive mode (m/z): calcd. for $C_{17}H_{21}INO_3$ ($[M+H]^+$): 414.0566. Found: 414.0569.

4.2.14. Tert-butyl 2,5-dimethoxyphenethylcarbamate (**17**)

A mixture of 3-(2,3-dimethoxyphenyl) propionic acid **16** (200 mg, 0.950 mmol), sodium azide (216 mg, 3.33 mmol), tetrabutylammonium bromide (45.6 mg, 0.143 mmol), zinc triflate (11.4 mg, 31.4 μmol) and di-*tert*-butyldicarbonate (228 mg, 1.05 mmol) in dry THF (9.5 mL) was stirred at 40 °C under nitrogen overnight. When the reaction was completed according to LC-MS, a 10% $NaNO_2$ aq. solution (6 mL) was added along with EtOAc (6 mL) and the reaction mixture was left stir at room temperature for 20 min. The water phase was extracted using additional EtOAc (3 × 6 mL) and the organic phases were combined and washed with saturated aq. NH_4Cl (6 mL), saturated Na_2SO_4 (6 mL) and saturated $NaHCO_3$ (6 mL). The solvent was evaporated *in vacuum* and the

crude product purified using flash-column chromatography (n-heptane/EtOAc 3:1). The fractions containing the product were concentrated *in vacuum* to afford compound **17**[21] (192 mg, 72% yield) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.79–6.68 (m, 3H), 4.68 (broad s, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.39–3.26 (m, 2H), 2.77 (t, J = 6.8 Hz, 2H), 1.42 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.0, 153.6, 151.9, 128.7, 116.9, 111.9, 111.4, 79.0, 55.9, 55.7, 40.7, 31.0, 28.5.

4.2.15. 2-(2-((tert-butoxycarbonyl)amino)ethyl)-5-chloro-4-methoxyphenyl acetate (**18a**)

The mixture of **17** (50.2 mg, 0.178 mmol) and NCS (25.0, 0.187 mmol) in acetonitrile (1 mL) was irradiated under microwave at 75 °C for 30 min. The mixture was purified directly using preparative LC to give compound **18a** (47 mg, 84% yield) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.74 (s, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.38–3.25 (m, 2H), 2.76 (d, J = 6.6 Hz, 2H), 1.42 (s, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 156.1, 151.8, 149.1, 127.0, 120.5, 115.4, 113.1, 79.2, 57.0, 56.1, 40.6, 30.8, 28.5.

4.2.16. 2-(2-((tert-butoxycarbonyl)amino)ethyl)-5-iodo-4-methoxyphenyl acetate (**18b**)

A mixture of compound **17** (434 mg, 1.54 mmol) and *N*-iodosuccinimide (434 mg, 1.93 mmol) in AcOH (12 mL) was stirred at room temperature for 4 h. When the reaction was completed according to LC-MS an excess amount of saturated Na_2SO_3 (aq.) was added to the reaction mixture and the water phase was then extracted using DCM (3 × 10 mL). The solvent was evaporated *in vacuum* and the crude product was purified using flash-column chromatography twice i) n-heptane/EtOAc 2:1; ii) DCM/MeOH (98.4:0.6) to give compound **18b**[22] (411 mg, 65% yield) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.21 (s, 1H), 6.64 (s, 1H), 4.61 (broad s, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.36–3.25 (m, 2H), 2.76 (t, J = 6.9 Hz, 2H), 1.41 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.0, 152.6, 152.5, 128.9, 121.7, 114.0, 82.9, 79.3, 57.2, 56.2, 40.6, 31.2, 28.5.

4.2.17. 2-(((4-iodo-2,5-dimethoxyphenethyl)amino)methyl)phenol (**19**)

4.2.17.1. Deprotection of ***18b****.* TFA (1.35 mL) was added dropwise to a solution of compound **18b** (367 mg, 0.902 mmol) in DCM (1.5 mL). The reaction mixture was left to stir at room temperature for about 1 h. When the reaction was completed according to LC-MS the solvent was evaporated *in vacuum* and saturated $NaHCO_3$ (aq.) was added to adjust the pH to around 8–9. The product was then extracted using DCM (3 × 10 mL) and the solvent was removed *in vacuum* to give the amine (275 mg, 99% yield). The amine was used further for the synthesis of compound **19** and **21b**.

4.2.17.2. Reductive amination. Et_3N (28.4 μL, 0.204 mmol) was added to a solution of resulting amine (62.6 mg, 0.204 mmol) in EtOH (2 mL). The reaction was monitored by TLC and after 2 h a full conversion of the starting material had occurred and an imine had formed. $NaBH_4$ (15.4 mg, 0.407 mmol) was added and the mixture was stirred for 30 min. The solvent was evaporated and the pH of the crude mixture was adjusted to around 8–9 using K_2CO_3 (aq.). The mixture was extracted using DCM (3 × 10 mL) and the crude was then purified using flash-column chromatography twice (i) DCM/MeOH/Et_3N 92:8:1; ii) n-heptane/EtOAc/Et_3N 99:1:1) and preparative LC to gain the final product **4** (16.3 mg, 19% yield) as pale yellow syrupy. The low yield was due to the problem of purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.22 (s, 1H), 7.16 (td, J = 7.8, 1.5 Hz, 1H), 6.97 (dd, J = 7.8 Hz, 1.5 Hz, 1H), 6.82 (br d, J = 7.8 Hz, 1H), 6.76 (br t, J = 7.8 Hz, 1H), 6.65 (s, 1H), 3.98 (s, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 2.91 (t, J = 6.1 Hz, 2H), 2.82 (t, J = 6.1 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.4, 152.7, 152.5, 128.9, 128.8, 128.4, 122.6, 121.8, 119.1, 116.5, 113.8, 83.1, 57.3, 56.2, 52.6, 48.3, 30.9. ESI-HRMS positive mode (m/z): calcd. for $C_{17}H_{21}INO_3$ ($[M+H]^+$): 414.0566. Found: 414.0576.

4.2.18. 4-(((4-iodo-2,5-dimethoxyphenethyl)amino)methyl)-3-methoxyphenol (**21b**)

To the resulting amine (33.4 mg, 0.109 mmol) in EtOH (1.5 mL), which was achieved from **18b after** deprotection in the synthesis of compound **19**, 4-hydroxy-2-methoxybenzaldehyde (18.2 mg, 0.12 mmol) was added. The reaction was monitored by TLC and after 2 h a full conversion of the starting material had occurred and an imine had formed. $NaBH_4$ (14.4 mg, 0.381 mmol) was then added and the mixture was stirred overnight. The solvent was evaporated and the pH of the crude mixture was adjusted to around 8–9 using K_2CO_3 (aq.). The mixture was extracted using DCM (3 × 10 mL) and the crude was then purified first using flash-column chromatography (DCM/MeOH/Et_3N 95:5:1) and recrystallization by dissolving the crude in MeOH (0.5 mL), adding HCl (28 μL, 2 M in ether solution) and then dilute with Et_2O until crystallization and then recrystallize the product using i-PrOH and Et_2O. The product was dissolved in water (3 mL), adjusted pH to about 9 using K_2CO_3 (aq.), extracted with DCM (3 × 5 mL), concentrated to give the product **21b** (23.6 mg, 49% yield) as pale yellow syrupy. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.21 (s, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.69 (s, 1H), 6.20 (d, J = 2.0 Hz, 1H), 6.05 (dd, J = 8.0, 2.0 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.69 (s, 2H), 3.59 (s, 3H), 2.96–2.84 (m, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.6, 158.1, 152.7, 152.6, 131.2, 129.1, 121.9, 114.1, 107.6, 99.6, 82.9, 57.2, 56.3, 55.2, 49.2, 48.4, 30.6. ESI-HRMS positive mode (m/z): calcd. for $C_{18}H_{23}INO_4$ ($[M+H]^+$): 444.0672. Found: 444.0668.

4.3. General procedure for synthesis of ***20, 21a, 22 and 23***

4.3.1. Chlorination

The mixture of **17** (102 mg, 0.363 mmol) and NCS (50.9 mg, 0.381 mmol) in acetonitrile (2 mL) was irradiated under microwave at 75 °C for 30 min or under conventional heating at 75 °C for 1 h. The reaction was analyzed using LC-MS. The mixture was concentrated followed by adding 3 mL water. The mixture was extracted with DCM (3 × 3 mL) and concentrated to give the crude product for next step without further purification.

4.3.2. Deprotection

To the crude product (0.363 mmol) in DCM (2 mL), TFA (277.8 μL, 3.63 mmol) was added. The mixture was stirred overnight at rt. The mixture was concentrated, co-evaporated with DCM three times to remove excess amount of TFA. The crude product was about 140 mg, suggesting the amount of TFA is 0.526 mmol, 1.5 equiv. of the free amine because the reaction gave full conversion. The mixture was dissolved in 5 mL 1,2-dichloroethane (DCE) and divided into two parts for reductive amination.

4.3.3. Reductive amination

To the crude product (0.182 mmol) in DCE (2.5 mL) from last step, TEA (38.1 μL, 0.273 mmol) was added and the mixture was stirred at rt for about 15 min. Aldehyde (30.4 mg, 0.200 mmol) was then added to the mixture and stirred at rt. The reaction was monitored using LC-MS. The imine formation was not completed after 3 h for **20, 22** and **23**. Reducing reagent (0.363 mmol, $NaCNBH_3$ for **20b**, **22** and **23**, or $Na(OAc)_3BH$ for **20a**) and EtOH (1.5 mL) were then added to the mixture and stirred at rt for 2 h (**20a**) or overnight (**20b**, **22** and **23**). The imine formation was completed after 3 h for **21a**, $NaBH_4$ (1.09 mmol) and 1.5 mL EtOH were added and stirred at rt for 2 h. The reaction mixture was then concentrated at 30 °C, re-dissolved in MeOH and purified using

preparative LC and freeze-drying to give the desired product as white solid. The solid became sticky under air atmosphere. Chemical shifts of NMR can be slightly different for the same compound but containing different amount of solvent residue from the preparative LC. Compound **20a** was used as an example to show the difference. Its chemical shifts were different when the solvent was removed using freeze-drying or extraction using DCM followed by concentration at about 25 °C.

4.3.4. 3-(((4-chloro-2,5-dimethoxyphenethyl)amino)methyl)-4-methoxyphenol (**20a**)

The synthesis was started from **18a** (30 mg, 0.0950 mmol), following the general procedure from the step of deprotection. The reaction mixture was purified using preparative LC. The fractions containing **20a** were dried using freeze-drying to give compound **20a** (16.4 mg, 49% yield) as a white solid. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.86 (s, 1H), 6.79 (s, 1H), 6.71 (dd, J = 8.7, 2.8 Hz, 1H), 6.65 (d, J = 8.7 Hz, 1H), 6.62 (d, J = 2.8 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 2H), 3.71 (s, 3H), 3.63 (s, 3H), 2.99–2.91 (m, 2H), 2.91–2.83 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 151.8, 151.0, 150.97, 149.2, 125.8, 123.7, 121.0, 118.3, 116.3, 115.6, 113.3, 111.7, 57.0, 56.2, 55.8, 48.0, 47.2, 29.2. ESI-HRMS positive mode (m/z): calcd. for $C_{18}H_{23}^{35}ClNO_4$ ($[M+H]^+$): 352.1316. Found: 352.1316; calcd. for $C_{18}H_{23}^{37}ClNO_4$ ($[M+H]^+$): 354.1286. Found: 354.1288.

The synthesis was started from compound **17** (51.0 mg, 0.182 mmol), following the general procedure step from chlorination. The reaction mixture was purified using preparative LC. To the fractions containing desired product from preparative LC added water (3 mL) and extracted with DCM (4 mL x 8), combined and concentrated to give compound **20a** (48.7 mg, 76% yield) as pale yellow syrupy. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.86 (s, 1H), 6.77 (s, 1H), 6.65–6.61 (m, 2H), 6.51–6.47 (m, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.66 (s, 2H), 3.63 (s, 3H), 2.94–2.81 (m, 4H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 151.9, 151.2, 150.7, 149.0, 127.4, 127.2, 120.5, 118.9, 115.7, 115.5, 113.2, 111.5, 57.0, 56.2, 55.7, 49.5, 48.7, 30.3. ESI-MS positive mode (m/z): calcd. for $C_{18}H_{23}^{35}ClNO_4$ ($[M+H]^+$): 352.13. Found: 352.42; calcd. for $C_{18}H_{23}^{37}ClNO_4$ ($[M+H]^+$): 354.13. Found: 354.17.

4.3.5. 3-(((4-iodo-2,5-dimethoxyphenethyl)amino)methyl)-4-methoxyphenol (**20b**)

The synthesis was started from **18b** (40 mg, 0.098 mmol), following the general procedure for the synthesis of **20**–**23** from the step of deprotection, the reaction mixture was purified using preparative LC and the fractions containing **20b** were dried using freeze-drying to give compound **20b** (21.8 mg, 50% yield) as a white solid. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.19 (s, 1H), 6.77–6.61 (m, 4H), 3.84 (s, 2H), 3.78 (s, 3H), 3.69 (s, 3H), 3.60 (s, 3H), 2.99 (t, J = 6.2 Hz, 2H), 2.90 (t, J = 6.2 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 152.7, 152.4, 151.03, 150.97, 127.7, 123.8, 121.9, 118.3, 116.3, 114.1, 111.6, 83.5, 57.2, 56.2, 55.8, 48.3, 47.0, 29.6. ESI-HRMS positive mode (m/z): calcd. for $C_{18}H_{23}INO_4$ ($[M+H]^+$): 444.0672. Found: 444.0660.

4.3.6. 4-(((4-chloro-2,5-dimethoxyphenethyl)amino)methyl)-3-methoxyphenol (**21a**)

The synthesis was started from compound **17** (51.0 mg, 0.182 mmol), following the general procedure step from chlorination. The reaction mixture was purified using preparative LC. The LC fractions containing desired product were dried using freeze-drying to give compound to give **21a** (38.4 mg, 60% yield) as a white solid. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.90–6.84 (m, 3H), 6.15–6.02 (m, 2H), 3.83 (s, 3H), 3.77 (s, 2H), 3.76 (s, 3H), 3.56 (s, 3H), 3.04 (t, J = 6.2 Hz, 2H), 2.94 (t, J = 6.2 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 159.0, 158.5, 151.8, 149.2, 131.3, 126.1, 121.0, 115.8, 114.4, 113.3, 107.8, 99.4, 57.0, 56.2, 55.2, 48.7, 47.8, 29.5. ESI-HRMS positive mode (m/z): calcd. for $C_{18}H_{23}^{35}ClNO_4$ ($[M+H]^+$): 352.1316. Found: 352.1315; calcd. for $C_{18}H_{23}^{37}ClNO_4$ ($[M+H]^+$): 354.1286. Found: 354.1287.

4.3.7. 3-(((4-chloro-2,5-dimethoxyphenethyl)amino)methyl)-2-methoxyphenol (**22**)

The synthesis was started from compound **17** (51.0 mg, 0.182 mmol), following the general procedure step from chlorination. The reaction mixture was purified using preparative LC. The LC fractions containing desired product were dried using freeze-drying to give compound **22** (17.3 mg, 27% yield) as a white solid. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.91 (dd, J = 8.1, 7.5 Hz, 1H), 6.86 (s, 1H), 6.82 (dd, J = 8.1, 1.8 Hz, 1H), 6.77 (s, 1H), 6.75 (dd, J = 7.5, 1.8 Hz, 1H), 3.85 (s, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 2.96–2.81 (m, 4H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 151.8, 149.3, 149.1, 145.8, 131.2, 127.0, 125.0, 121.4, 120.6, 116.2, 115.3, 113.2, 61.3, 57.0, 56.2, 48.6, 48.3, 30.3. ESI-HRMS positive mode (m/z): calcd. for $C_{18}H_{23}^{35}ClNO_4$ ($[M+H]^+$): 352.1316. Found: 352.1329; calcd. for $C_{18}H_{23}^{37}ClNO_4$ ($[M+H]^+$): 354.1286. Found: 354.1294.

4.3.8. 2-(((4-chloro-2,5-dimethoxyphenethyl)amino)methyl)-3-methoxyphenol (**23**)

The synthesis was started from compound **17** (51.0 mg, 0.182 mmol), following the general procedure step from chlorination. The reaction mixture was purified using preparative LC. The LC fractions containing desired product were dried using freeze-drying to give compound **23** (35.9 mg, 56% yield) as a white solid. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.09 (t, J = 8.4 Hz, 1H), 6.87 (s, 1H), 6.75 (s, 1H), 6.50 (dd, J = 8.4, 0.9 Hz, 1H), 6.36 (dd, J = 8.4, 0.9 Hz, 1H), 4.09 (s, 2H), 3.83 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 3.01–2.80 (m, 4H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 159.3, 158.0, 151.7, 149.1, 129.3, 126.0, 120.9, 115.3, 113.3, 109.9, 109.0, 101.6, 57.0, 56.1, 55.7, 47.8, 43.9, 29.8. ESI-HRMS positive mode (m/z): calcd. for $C_{18}H_{23}^{35}ClNO_4$ ($[M+H]^+$): 352.1316. Found: 352.1322; calcd. for $C_{18}H_{23}^{37}ClNO_4$ ($[M+H]^+$): 354.1286. Found: 354.1288.

Acknowledgements

Financial support from the National Board of Forensic Medicine in Sweden is gratefully acknowledged.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2017.09.024.

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