Chapter 6

*t*ert-Butyl Nitrite Mediated Conversion of Alcohols to Amides: Application in Synthesis of Anti-Alzheimer Compounds

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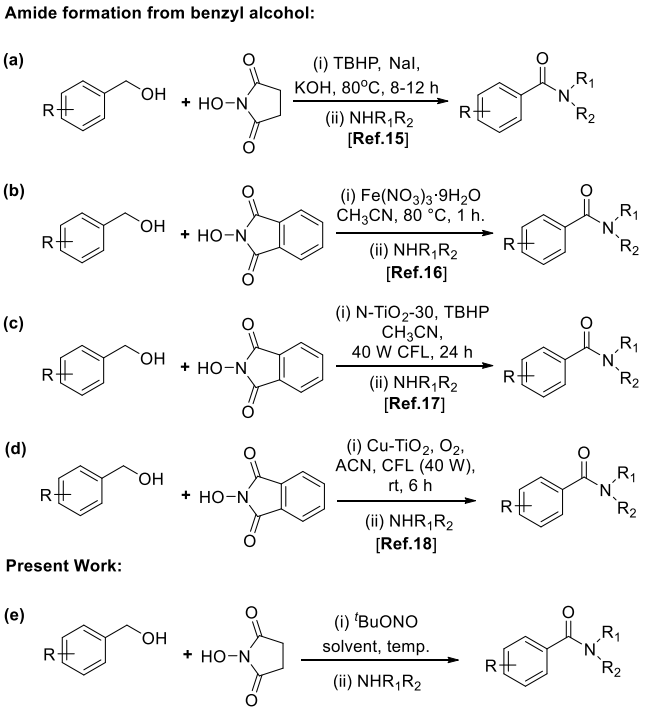
6.1 Introduction

Amide functionality is widely distributed in natural products, biopolymers, and pharmaceuticals.[1–4] They are often synthesized by acylating amines with activated carboxylic acid, specifically using *N*-hydroxyimide esters.[5] The *N*-hydroxyimide esters involve direct coupling of aroyl(heteroaroyl) chloride employing a base or by reacting aryl(heteroaryl) carboxylic acids using carbodiimide as coupling reagents, thereby producing urea as the byproduct, often posing difficulties during purification.[6–10] Several researches in this direction resulted in substantial advancement in the field of amidation using *N*-hydroxyimides. Yamamoto *et al.* reported oxidative amidation from aldehydes using catalytic amounts of cobalt(II) acetate and *N*-hydroxysuccinimide (NHS). NHS acts as a bifold promoter of aldehyde oxidation as well as amine displacement.[11] Barbas III groups reported amidation reaction of aldehyde using *N*-hydroxyphthalimide (NHPI), tetrabutylammonium iodide (*n*Bu_4NI), and *tert*-butyl hydrogen peroxide (TBHP).[12] Qu, Kang, and the group demonstrated the role of *tert*-butyl nitrite (^{t}BuONO) in the coupling of aldehydes and oxo(phenyl)acetaldehyde with *N*-hydroxyimides.[13] Based on this work, Laha *et al.* used ^{t}BuONO and NHS for decarboxylative amidation of aryl/heteroarylacetic acids.[14]

Taking into account the stability and accessibility of alcohols, various research groups focused on the conversion of alcohols into amides via *N*-hydroxyimide ester. Yu group performed NaI-catalyzed esterification of *N*-hydroxyphthalimide (NHPI) using KOH and super stoichiometric amounts of TBHP in acetonitrile in 18 h (scheme 6.1a).[15] Xie groups performed oxidative esterification of alcohols with NHPI using iron-nitrate (scheme 6.1b).[16] Panda *et al.* reported an *N*-doped TiO_2-catalyzed reaction of alcohols with TBHP as an external oxidant for

yielding *N*-hydroxylamine active ester (scheme 6.1c).[17] The same group reported the amide synthesis using heterogeneous photocatalyst Cu-N-TiO_2 from alcohols and amines via *N*-hydroxy phthalimide active ester under 40 W CFL light (scheme 6.1d).[18] As evident from literature reports, most of these methods involve transition metals. Thus, a simple, mild, and metal-free method of yielding amides from alcohol is highly prudent. Recently, we have demonstrated metal-free oxidative coupling of alcohols with indoles and 1,2-diaminobenzene to synthesize bisindolylmethane and benzimidazole, respectively.[19,20] Herein, we describe developing a novel approach towards synthesizing amides via activated esters from alcohols in the presence of ^{t}BuONO.

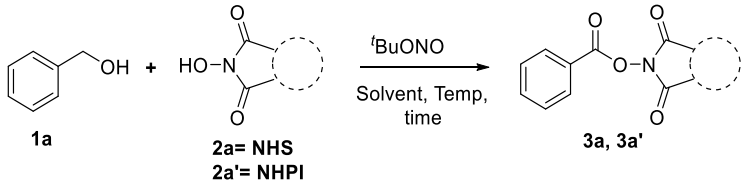


Scheme 6.1: [a-d] Previous reported methods, and [e] Our current approach for the synthesis of amides synthesis from alcohols.

6.2 Results and Discussion

The reaction condition was optimized using benzyl alcohol (**1a**) and NHS (**2**) as model substrates (Table 6.1). **1a** (1 mmol) was reacted with **2** (1 mmol) using ^{t}BuONO (1 equiv.) in dichloroethane at 80 ^{o}C for 3 h (entry 1), which resulted in the formation of 2,5-dioxopyrrolidine benzoate (**3a**) in 72% isolated yield. However, performing the same reaction under room temperature conditions for 12 h resulted in no product formation (entry 2). The solvent effect, including EtOAc, DMSO, water, and acetonitrile, was explored (entries 3-6), and acetonitrile was the optimal solvent (entry 6). Increasing the amount of ^{t}BuONO produced no significant improvement in the yield **3a** (entry 7). The reaction was also performed in the absence of ^{t}BuONO, and no product formation (entry 8) suggested the indispensable importance of ^{t}BuONO in the progression of the reaction. Replacing imide **2a** with *N*-hydroxyphthalimide (**2a'**) gave **3a'** an 81% yield under optimal conditions (entry 9).

Table 6.1: Optimization of reaction condition.[a]



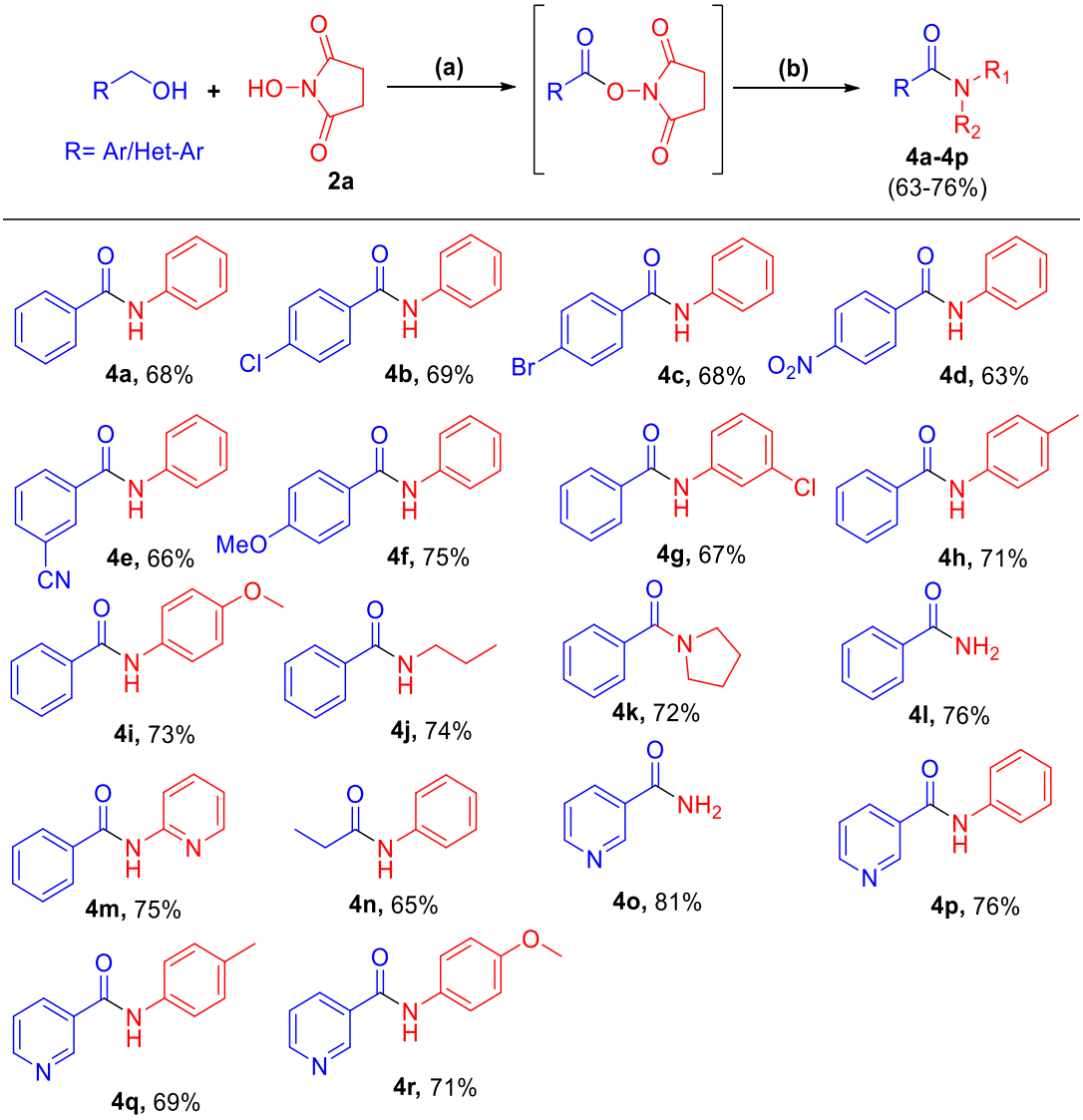
Entry	^{t}BuONO (equiv.)	Solvent	Temp	Time (h)	Yield
1[c]	1	DCE	80 ^{o}C	3	72[e]
2[c]	1	DCE	r.t.	12	N.R.[b]
3[c]	1	EtOAc	80 ^{o}C	3	62[e]
4[c]	1	DMSO	80 ^{o}C	3	66 [e]

5[c]	1	H_2O	80 °C	3	N.R.[b]
6[c]	1	CH_3CN	80 °C	3	85[e]
7[c]	2	CH_3CN	80 °C	3	87[e]
8[c]	-	CH_3CN	80 °C	3	N.R.[b]
9[d]	1	CH_3CN	80 °C	3	81[f]

[a]Reaction conditions: **1a** (1 mmol), **2a** or **2b** (1 mmol), solvent (2 mL). [b] N.R.= no reaction. [c] **2a** was used. [d] **2a'** was used. [e] isolated yield of **3a**. [f] isolated yield of **3a'**.

After successfully synthesizing activated aryl ester of NHS (**3a**) in good yield, we probed the scope of formation of amide product **4a** in one pot (scheme 6.2). First, we reacted **1a** and **2a** with optimized reaction conditions (Table 6.1, entry 6). After completion of reaction, aniline was added to the reaction mixture and stirred at ambient temperature for another 2 h, affording **4a** in 68% yield (scheme 6.2). Further, we investigated the scope of different benzyl alcohols. Coupling of benzyl alcohols functionalized with electron-withdrawing (-Cl, -Br, NO_2, and -CN), as well as electron-donating groups (-OMe) with aniline, effortlessly afforded one-pot amide products **4b**-**4f** in good yields of 69%, 67%, 73%, and 75%, respectively. Next, we examined the scope of both aromatic and aliphatic amines. Aromatic amines, such as electron-rich and electron-deficient. Anilines were found to be well tolerated to give the desired amides **4g**-**4i** in good yields (67–73%). Aliphatic, alicyclic and hetero aryl amines underwent the reaction smoothly and gave the corresponding amides **4j**, **4k** and **4m** in 74%, 72 % and 75% yields respectively. Aqueous ammonia was also well tolerated, and benzamide (**4l**) was obtained in 76% yield. This method was further extended to alkyl and heteroaryl alcohols affording corresponding amide products (**4n**-**4r**) in 65-81% yields, respectively

Scheme 6.2: Reaction scope with alcohols and amines.

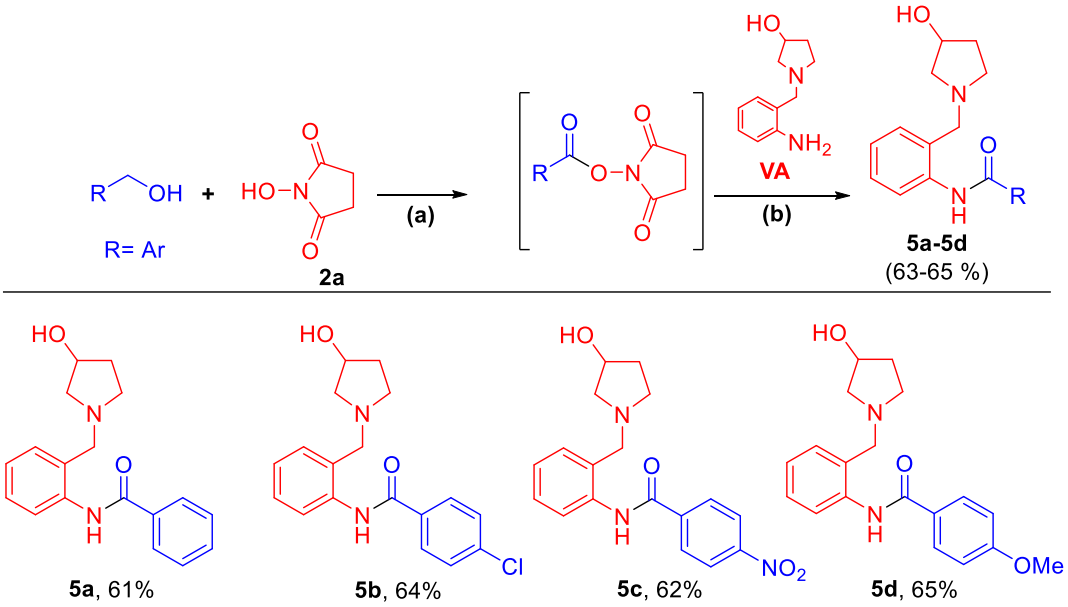


[a] Reaction conditions: alcohols (1 mmol), **2a** (1 mmol), ^{t}BuONO (1 mmol), CH_3CN (2 mL), 80 ^{o}C, 3 h. [b]1.2 equiv. of amine source, rt, 2 h.

1-(2-amino benzyl) pyrrolidine-3-ol (**VA**) is formed by scission of imidine bond of vasicine employing sodium borohydride in H_2O/CH_3OH (1:1).[21] Recently, it is reported that amide derivatives of **VA** showed anti-Alzheimer activity.[22] To check the applicability of our developed methodology for amide bond formation with **VA**, we treated alcohols with **VA**

under the optimized reaction condition (scheme 6.3). The desirable amide derivatives **5a-5d** were obtained in fair yields.

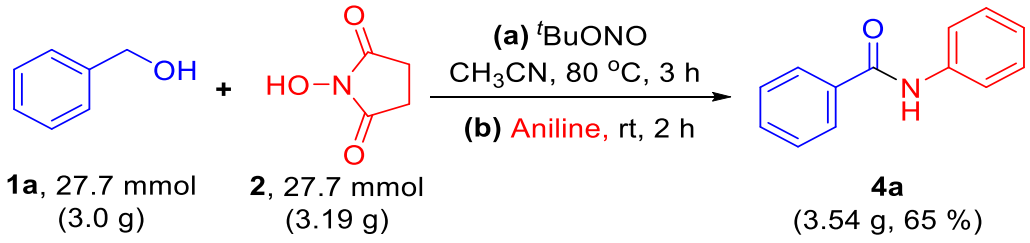
Scheme 6.3: Reaction scope with alcohols and 1-(2-amino benzyl) pyrrolidine-3-ol.



[a]Reaction conditions: alcohols (1 mmol), **2a** (1 mmol), ^{t}BuONO (1 mmol), CH_3CN (2 mL), 80 ^{o}C, 3 h. [b] 1.2 equiv. of **VA**, rt, 2 h.

To evaluate the scalability of our developed method, we performed a multi-gram-scale reaction for the synthesis of **4a**. Compound **4a** was isolated with a 65% yield, proving the method's robustness (scheme 6.4).

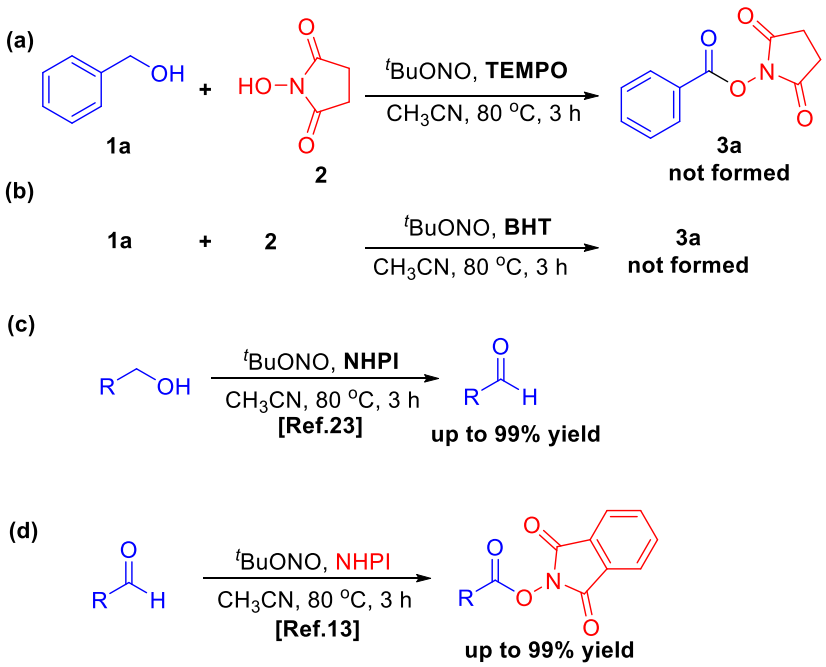
Scheme 6.4: Gram scale synthesis.



Reaction conditions: (a) ^{t}BuONO (1 mmol), CH_3CN (10 mL), 80 ^{o}C, 3 h, (b) 1.2 mmol aniline, rt, 2 h.

Control experiments were carried out to investigate the reaction pathway. Compound **3a** was not formed in the presence of an excess of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) or 2,6-*ditert*-butyl-4-methylphenol (BHT) under standard conditions (schemes 6.5a and 6.5b). Li *et al.* reported the conversion of alcohols to ketones and aldehydes using a catalytic amount of ^{t}BuONO and N-hydroxyimide (scheme 6.5c).[23] Qu, Kang, and co-workers reported that ^{t}BuONO catalyzed synthesis of NHS-coupled activated ester using aldehydes with *N*-hydroxyimides (scheme 6.5d). [13]

Scheme 6.5: Control experiments.

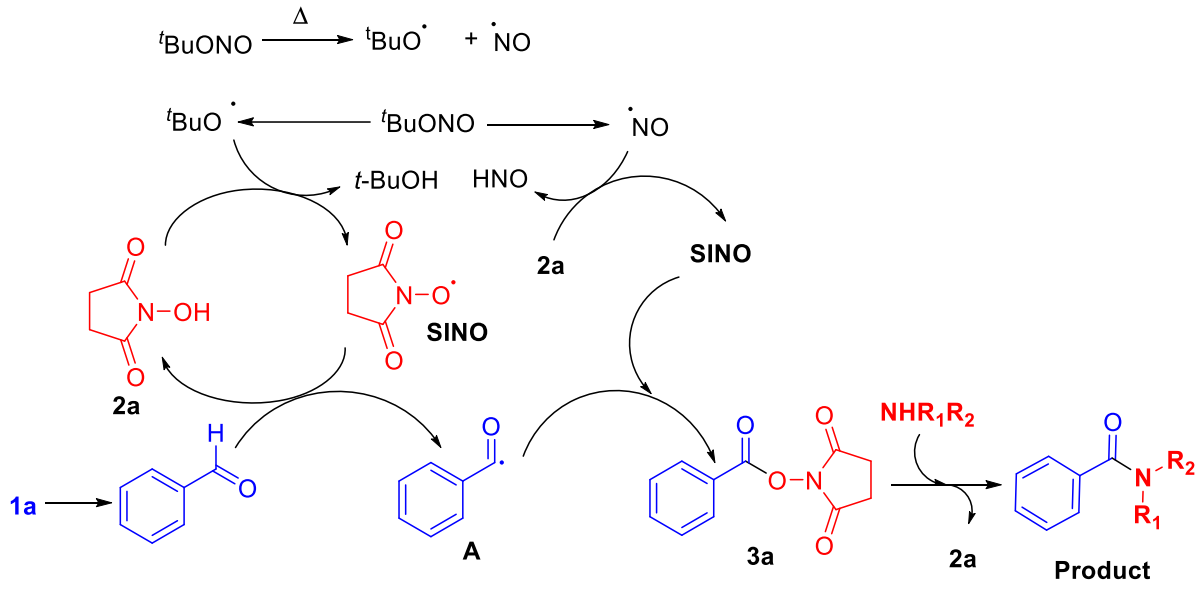


[a]Reaction conditions: **1a** (1 mmol), **2** (1 mmol), ^{t}BuONO (1 mmol), TEMPO (2.5 mmol), CH_3CN (2 mL), 80 °C, 3 h. [b] **1a** (1 mmol), **2** (1 mmol), ^{t}BuONO (1 mmol), BHT (2.5 mmol), CH_3CN (2 mL), 80 °C, 3 h. [c and d] literature reports

Based on control experiments and reported methods (Scheme 6.5)[13,14,23], we have drawn a plausible reaction mechanism, as depicted in Scheme 6.6. Upon heating, the ^{t}BuONO undergoes homolytic cleavage to form *tert*-butyloxy (^{t}BuO·) and nitrite (NO·) radicals. Each

radical abstracts a hydrogen atom from NHS (**2a**) to produce SINO. According to the literature, the benzyl alcohol is converted to benzaldehyde by a catalytic amount of ^{t}BuONO and *N*-hydroxyimide. Further conversion of benzaldehyde to benzoyl radical (**A**) may occur by SINO and ^{t}BuO· Radicals. Intermediate **A** and SINO undergo homolytic fusion to produce the activated NHS ester (**3a**), which then reacts with amines to produce the final desired amide-containing product.

Scheme 6.6: Plausible reaction mechanism



6.3 Conclusion

We have described a synthetic protocol for the generation of aryl amides from benzyl alcohols and various amines using *N*-hydroxysuccinimide (NHS) and *tert*-butyl nitrite. The proposed method demonstrates fair substrate tolerability and robustness without transition metal or halogen-containing reagents. The application of an amidation reaction has been successfully demonstrated for synthesizing anti-Alzheimer compounds. Control experiments proved the occurrence of a free radical in the course of a reaction. Mechanistic pathway studies have revealed the involvement of benzoyl radicals in the formation of an activated ester in the

presence of NHS and ^{t}BuONO. This ester then reacts with amines to form the corresponding amides.

6.4 Experimental section

6.4.1 Extraction and isolation of vasicine from Adhatoda vasica: The dried powdered leaves of Adhatoda vasica (Family: Acanthaceae) were purchased from Vedic vatica private limited, Chhattisgarh, India. In this process, 1 kg of leaves powder was transferred into maceration chamber and methanol (3 L) was added. This mixture was kept at room temperature and stirred every 4 h. After 72 h, the mixture was filtered using a muslin cloth/filter paper. The process was repeated for 3 times at a time interval of 72 h. The obtained methanolic extract was concentrated under reduced pressure.

The obtained semi-solid extract (100 g) was dissolved into water (1L). Followed by an aqueous mixture that was treated with hexane (1L) for 3 times to remove the chlorophyll and highly nonpolar compound (fatty acids and oils etc.). The obtained aqueous mixture was basified with aqueous ammonia to get a pH of 12–13. The basified solution was further extracted with DCM/chloroform (1L) for 3 times. The resulting DCM extract was evaporated under reduced pressure. Next, column was loaded with silica gel (60–120 mesh) slurry prepared using hexane. The mobile phase was used as dichloromethane and methanol by gradually increasing polarity (gradient method). The column started with DCM (100%) and end with DCM: methanol (95:5). The obtained fractions were monitored by TLC, for this mobile phase used as dichloromethane: methanol (9:1) and stationary phased used as precoated silica gel 60 F_{254} (Merck KGaA, Germany). The resulting TLC plates were observed by keeping them in an iodine chamber, under UV light, and Dragendorff's reagent for detection of vasicine and its analogs.

6.4.2. Procedure for synthesis of VA: The isolated vasicine (VAS) (1 equiv.) was taken into 100 mL RBF and dissolve in water: methanol (1:1) 20 mL. The RBF was placed on magnetic stirrer for stirring at 5–10 °C (10 min). Then, $NaBH_4$ (3 equiv.) was added slowly up to 30 min and reaction was kept at room temperature for 4 h. Reaction was monitored by TLC until reaction was completed. The reaction was stopped by quenching ethyl acetate into reaction mixture, followed by washing with water (3 × 20 ml). Then obtained ethyl acetate fraction was treated with sodium sulfate, filtered, and dried under reduced pressure. The residue was purified by column chromatography using silica gel (60–120 mesh) and mobile phase [ethyl acetate: methanol (98:2)] to afford the desired compound.

6.4.3 General procedure for the one pot synthesis of amides (4a-5d): In an oven-dried screw capped vial equipped with a magnetic stir bar, a solution of benzyl alcohols (1 mmol, 1 equiv.), N-hydroxysuccinimide (1 mmol, 1 equiv.), *tert*-butyl nitrite (1 mmol, 1 equiv.) and ACN (4 mL) was heated at 80 ˚C for 3 h. After the complete consumption of the starting material, monitored through TLC, 1.2 mmol, of aq. ammonia or aliphatic or aromatic amine was added to the same vial and the mixture was allowed to stir at room temperature for another 2 h. The reaction mixture was then extracted using dichloromethane. Organic layers were collected and dried over Na_2SO_4, concentrated under reduced pressure, and purified using column chromatography (100–200 mesh silica) to obtain the desired product.

6.4.5 Gram-scale procedure for the synthesis of compound 4a

A round bottom flask was charged with benzyl alcohol (1.08 g, 10 mmol), NHS (1.15 g, 10 mmol), *tert*-butyl nitrite (1 equiv.) in ACN (20 mL). The resulting solution was stirred at 80 °C for 3 h. After the complete consumption of the starting material, monitored through TLC, 1.2 mmol, of aniline was added to the same vial and the mixture was allowed to stir at room temperature for another 2 h. The reaction mixture was then extracted using dichloromethane.

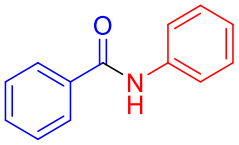
Organic layers were collected and dried over Na_2SO_4, concentrated under reduced pressure, and purified using column chromatography (100–200 mesh silica) to obtain the desired product **4a** (1.21g, 66%).

6.5 Control experiments

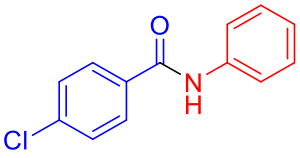
6.5.1 TEMPO addition in the general procedure: An oven-dried screw cap vial was charged with benzyl alcohol (1 mmol), NHS (1 equiv.), ^{t}BuONO (1 equiv.), TEMPO (3 equiv.) in ACN (4 mL). The resulting solution was stirred at 80 °C for 3 h. We have not observed formation of product **3a**.

6.5.2 BHT addition in the general procedure: An oven-dried screw cap vial was charged with benzyl alcohol (1 mmol), NHS (1 equiv.), ^{t}BuONO (1 equiv.), in ACN (4 mL). BHT (3 equiv.) in ACN (5 mL). The resulting solution was stirred at 80 °C for 3 h. We have not observed formation of product **3a**.

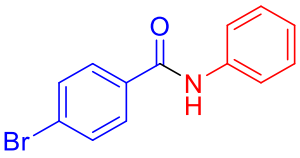
6.6 Analytical Data of synthesized compounds



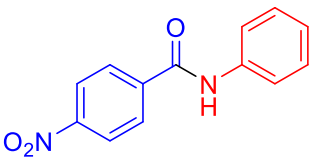
N-phenylbenzamide (4a): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 25% ethyl acetate:hexane. Compound **4a** was obtained as white solid with 68% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.84 (d, *J* = 7.8 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.14 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.0, 137.9, 134.9, 131.8, 129.1, 128.8, 127.0, 124.6, 120.4. HRMS ESI $[M+H]^+$ Calculated for $C_{13}H_{12}NO$ 198.0919, found 198.0916.



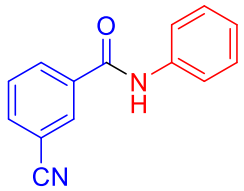
4-chloro-N-phenylbenzamide (4b): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 25% ethyl acetate: hexane. Compound **4b** was obtained as a white solid with a 69% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.78 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.47 – 7.46 (m, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.17 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 138.2, 137.6, 133.3, 129.2, 129.1, 128.4, 124.8, 120.2. HRMS ESI $[M+H]^+$ Calculated for $C_{13}H_{11}ClNO$ 232.0529 found 232.0531.



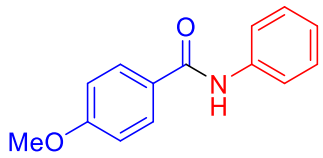
4-bromo-N-phenylbenzamide (4c): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 25% ethyl acetate:hexane. Compound **4c** was obtained as white solid with 68% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.77 -7.75 (m, 2H), 7.66 – 7.63 (m, 4H), 7.40 (t, *J* = 6.0 Hz, 2H), 7.19 (t, *J* = 6.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 137.6, 133.8, 132.0, 129.1, 128.6, 126.6, 124.8, 120.3. HRMS ESI $[M+H]^+$ Calculated for $C_{13}H_{11}BrNO$ 276.0024 found 2176.0021.



4-nitro-N-phenylbenzamide (4d): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 25% ethyl acetate: hexane. Compound **4d** was obtained as a white solid with a 63% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 -8.36 (m, 2H), 8.07 (d, *J* = 8.5 Hz, 2H), 7.87 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.45 – 7.42 (m, 2H), 7.25 – 7.22 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 149.8, 140.5, 137.2, 129.3, 128.2, 125.3, 124.0, 120.4. HRMS ESI $[M+H]^+$ Calculated for $C_{13}H_{10}N_2O_3$ 242.0691,found 242.0695

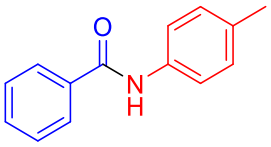


3-cyano-N-phenylbenzamide (4e): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 25% ethyl acetate:hexane. Compound **4e** was obtained as white solid with 66% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (t, *J* = 1.2 Hz, 1H), 8.20 -8.13 (m, 1H), 7.98 (s, 1H), 7.86 - 7.84 (m, 1H), 7.67 – 7.63 (m, 3H), 7.43 -7.40 (m, 2H), 7.23 – 7.20 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 137.3, 136.2, 134.9, 131.4, 130.8, 129.8, 129.2, 125.2, 120.4, 117.9, 113.1. HRMS ESI $[M+H]^+$ Calculated for $C_{14}H_{11}N_2O$ 223.0871 found 223.0873.

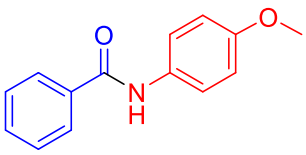


4-methoxy-N-phenylbenzamide (4f): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 25% ethyl

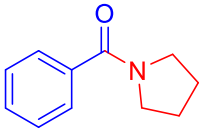
acetate: hexane. Compound **4f** was obtained as a white solid with a 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.85 (m, 2H), 7.83 (s, 1H), 7.65 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.00 – 6.97 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 162.5, 138.1, 129.0, 128.9, 127.1, 124.3, 120.1, 114.0, 55.4. HRMS ESI $[M+H]^+$ Calculated for $C_{14}H_{14}NO_2$ 228.1025 found 228.1027.



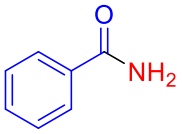
N-(p-tolyl)benzamide (4h): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 25% ethyl acetate: hexane. Compound **4h** was obtained as a white solid with a 71% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81-7.85 (m, 3H), 7.57-7.53 (m, 3H), 7.51-7.47 (m, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 135.3, 135.1, 134.2, 131.7, 129.6, 128.7, 127.0, 120.3, 20.9. HRMS ESI $[M+H]^+$ Calculated for $C_{14}H_{14}NO$ 212.1075 found 212.1079.



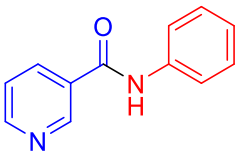
N-(4-methoxyphenyl)benzamide (4i): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 25% ethyl acetate:hexane. Compound **4i** was obtained as white solid with 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.85-7.83 (m, 2H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.95-6.94 (m, 2H), 3.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 162.4, 138.1, 129.0, 128.9, 127.1, 124.3, 120.2, 113.9, 55.4. HRMS ESI $[M+H]^+$ Calculated for $C_{14}H_{14}NO_2$ 228.1025 found 228.1027.



phenyl(pyrrolidin-1-yl)methanone (4k): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 25% ethyl acetate:hexane. Compound **4k** was obtained as yellowish orange oil, yield with 72% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43-7.41 (m, 2H), 7.31-7.28 (m, 3H), 3.55 (t, *J* = 6.6 Hz, 2H), 3.32 (t, *J* = 6.6 Hz, 2H), 1.86 (quint, *J* = 6.6 Hz, 2H), 1.77 (quint, *J* = 6.6 Hz, 2H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.7, 138.1, 128.7, 127.2, 126.0, 48.5, 45.1, 25.3, 23.4. HRMS ESI $[M+H]^+$ Calculated for $C_{11}H_{13}NO$ 175.0997, found 175.0996.

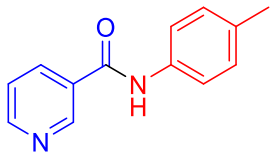


Benzamide (4l): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 25% ethyl acetate: hexane. Compound **4l** was obtained as a white solid with a 76% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82-7.81 (m, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 6.25 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 133.4, 132.0, 128.6, 127.3.

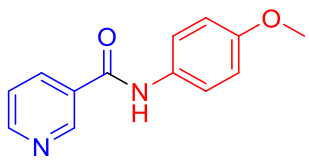


N-phenylnicotinamide (4n): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 25% ethyl acetate: hexane. Compound **4n** was obtained as a brown solid with a 76% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 6.6 Hz, 1H), 7.96-7.95 (m, 2H), 7.86 (s, 1H),7.66 (d, *J* = 9 Hz, 1H),

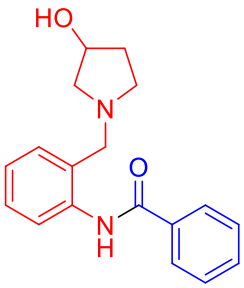
7.43 (t, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.19-7.16 (m, 1H), 6.78 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.4, 133.4, 128.7, 128.1, 126.1, 125.6, 124.9, 117.4, 112.6, 108.1. HRMS ESI $[M+H]^+$ Calculated for $C_{12}H_{11}N_2O$ 199.0871 found 199.0870.



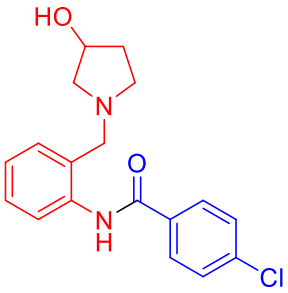
N-(p-tolyl)nicotinamide (4o): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 25% ethyl acetate: hexane. Compound **4o** was obtained as a white solid with a 69% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.0 (s, 1H), 8.69-8.68 (m, 1H), 8.44 (s,1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.38-7.34 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 152.2, 147.9, 135.4, 134.9, 134.7, 130.9, 129.6, 123.6, 120.7, 20.9.



N-(4-methoxyphenyl)nicotinamide (4p): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 25% ethyl acetate: hexane. Compound **4p** was obtained as a white solid with a 71% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.0 (s, 1H), 8.74-8.73 (m, 1H), 8.20-8.19 (m, 2H), 7.54 (d, *J* = 8.33 Hz, 2H), 7.42-7.40 (m, 1H), 6.91 (d, *J* = 4.5 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 156.9, 152.3, 147.8, 135.3, 130.8, 130.5, 123.6, 122.4, 114.3, 55.5.

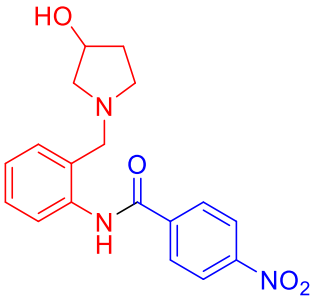


N-(2-((3-hydroxypyrrolidin-1-yl)methyl)phenyl)benzamide (5a): The representative general procedure mentioned above was followed. The compound was purified using 5% (methanol: ethyl acetate) by column chromatography. Compound **5a** was obtained as a pale brown solid with a 61% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.63 (s, 1H), 8.43-8.42 (m, 1H), 8.03 (d, *J* = 7 Hz, 2H), 7.55-7.47 (m, 3H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 4.53-4.51 (m, 1H), 3.82-3.75 (m, 2H), 2.96-2.94 (m, 1H), 2.77-2.66 (m, 2H), 2.45 (s, 1H), 2.32-2.26 (m, 1H), 1.89- 1.83 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 138.7, 135.2, 131.6, 129.1, 128.6, 128.5, 127.3, 126.4, 123.4, 120.8, 71.1, 62.6, 59.5, 52.4, 35.0. HRMS (ESI) m/z was calculated for $C_{18}H_{21}N_2O_2$ $[M+H]^+$ as 297.1603, found 297.1578.

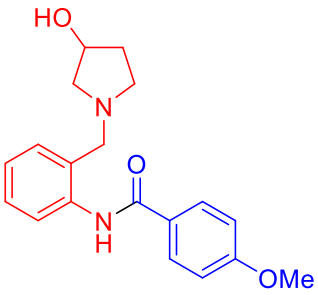


4-chloro-N-(2-((3-hydroxypyrrolidin-1-yl)methyl)phenyl)benzamide (5b): The representative general procedure mentioned above was followed. The compound was purified using 5% (methanol: ethyl acetate) by column chromatography. Compound **5b** was obtained as a pale yellow solid with a 64% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.73 (s, 1H), 8.41-8.39 (m, 1H), 8.0 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.16

(d, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 4.55-4.53 (m, 1H), 3.81-3.73 (m, 2H), 2.82-2.80 (m, 1H), 2.42-2.37 (m, 1H), 2.32-2.25 (m, 1H), 2.01 (bs, 1H), 1.89-1.83 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 138.6, 137.8, 133.5, 129.1, 128.8, 128.8, 126.4, 123.5, 120.8, 71.1, 62.6, 59.6, 52.5, 34.9. HRMS (ESI) m/z was calculated for $C_{18}H_{20}ClN_2O_2$ $[M+H]^+$ as 331.1213, found 331.1273.

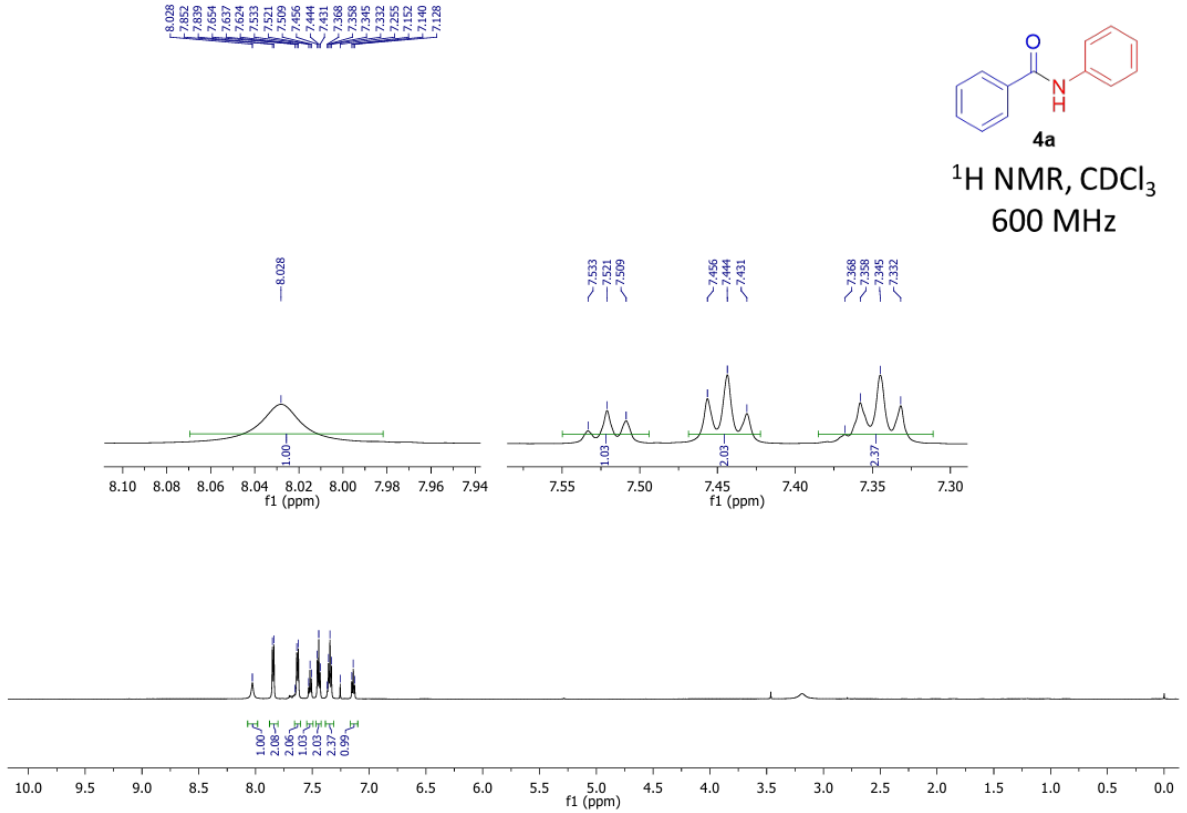


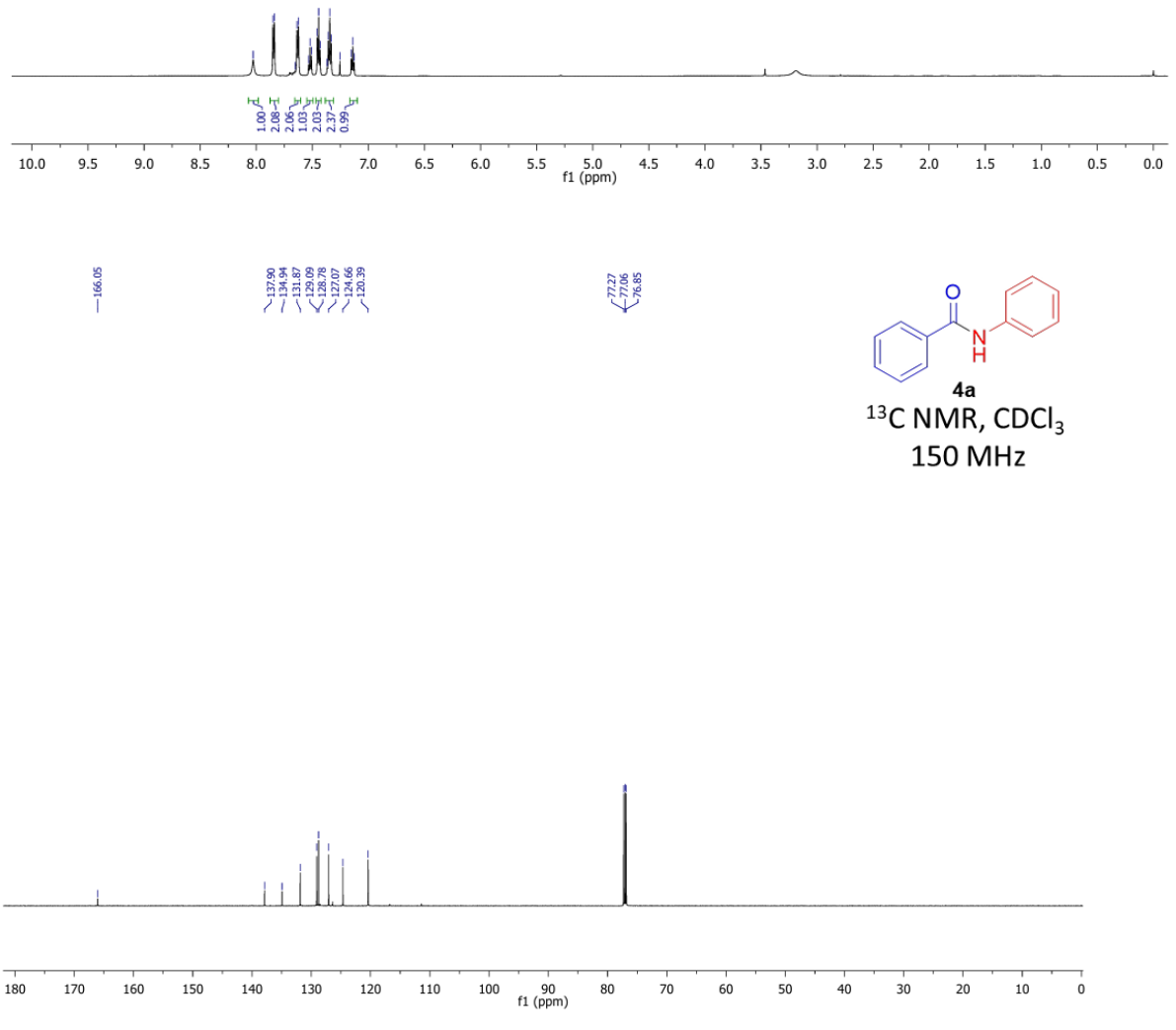
N-(2-((3-hydroxypyrrolidin-1-yl)methyl)phenyl)-4-nitrobenzamide (5c): The representative general procedure mentioned above was followed. The compound was purified using 5% (methanol: ethyl acetate) by column chromatography. Compound **5c** was obtained as a brown solid with 62% yield, m.p: 206 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.14 (s, 1H), 8.33 (s, 1H), 8.24 (s, 4H), 7.33-7.31 (m, 1H), 7.16-7.15 (m, 1H), 7.07-7.04 (m, 1H), 4.55 (s, 1H), 3.80-3.73 (m, 2H), 3.01 (s, 1H), 2.90-2.76 (m, 2H), 2.52 (s, 1H), 2.31-2.28 (m, 2H), 1.90-1.89 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 149.5, 140.5, 138.1, 129.2, 128.7, 128.4, 126.6, 124.1, 123.8, 120.7, 70.9, 62.6, 59.4, 52.5, 34.8. HRMS (ESI) m/z was calculated for $C_{18}H_{20}N_3O_4$ $[M+H]^+$ as 342.1454, found 342.1505.

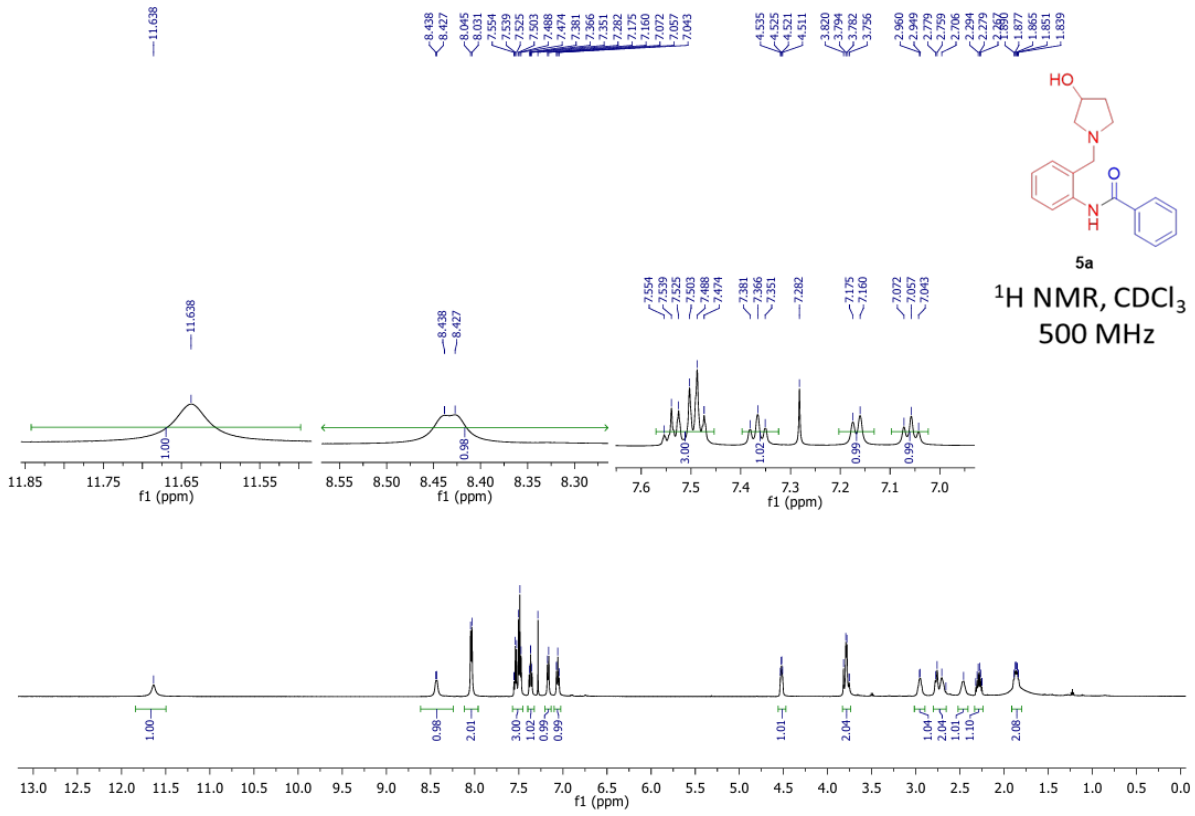


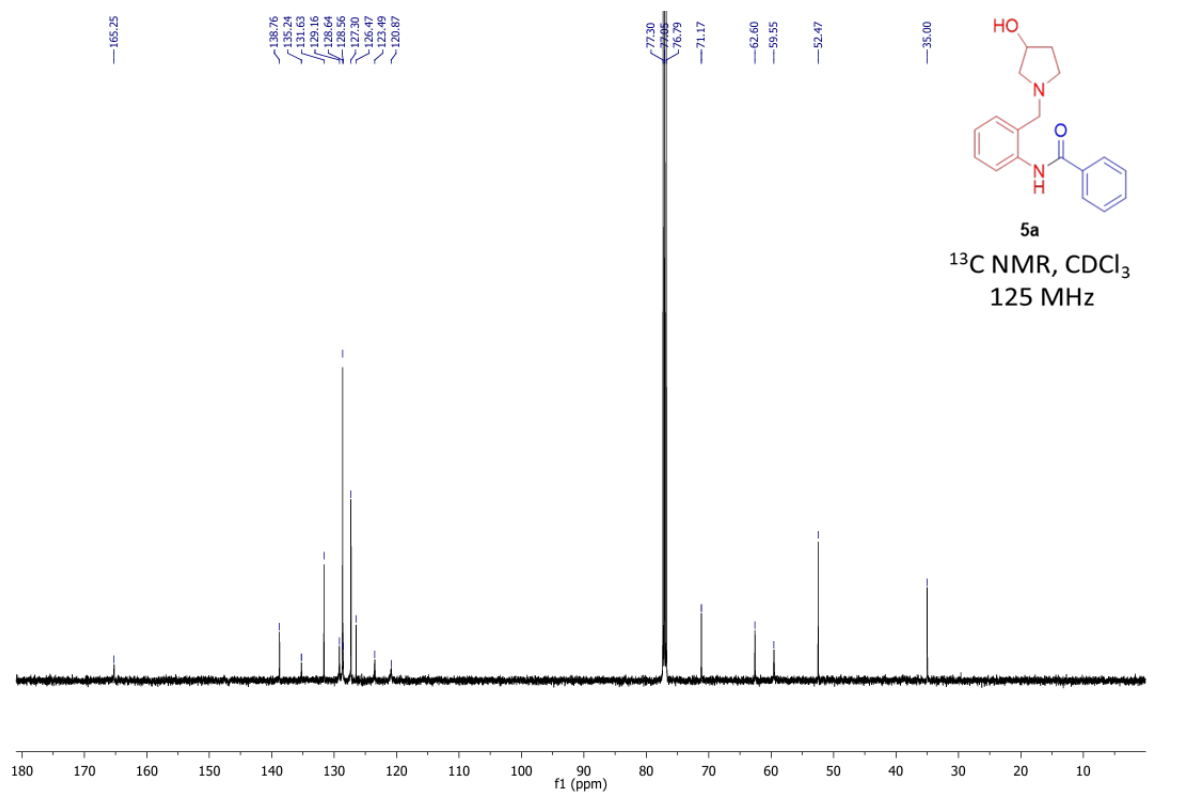
N-(2-((3-hydroxypyrrolidin-1-yl)methyl)phenyl)-4-methoxybenzamide (5d): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 5% (methanol: ethyl acetate). Compound **5d** was obtained as pale yellow solid with 65% yield, m.p :172 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.49 (s, 1H), 8.40 (d, *J* = 8 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.17-7.14 (m, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8 Hz, 2H), 4.54-4.51 (m, 1H), 3.87 (s, 3H), 3.81-3.73 (m, 2H), 2.98-2.93 (m, 1H), 2.79-2.67 (m, 1H), 2.70-2.67 (m, 1H), 2.46-2.44 (m, 1H), 2.32-2.25 (m, 1H), 2.06- 2.0 (m, 1H). 1.89- 1.83 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 162.3, 138.9, 129.2, 129.1, 128.5, 127.5, 126.3, 120.9, 113.8, 71.1, 62.6, 59.6, 55.4, 52.4, 35.0.

6.7 Spectral Data of Synthesized Products






HO
N
O
N
H
5a
^{1}H NMR, $CDCl_3$
500 MHz
f1 (ppm)


HO
N
O
N
H
5a
^{13}C NMR, $CDCl_3$
125 MHz
f1 (ppm)

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