Catechol Reactivity: Synthesis of Dopamine Derivatives Substituted at the 6-Position

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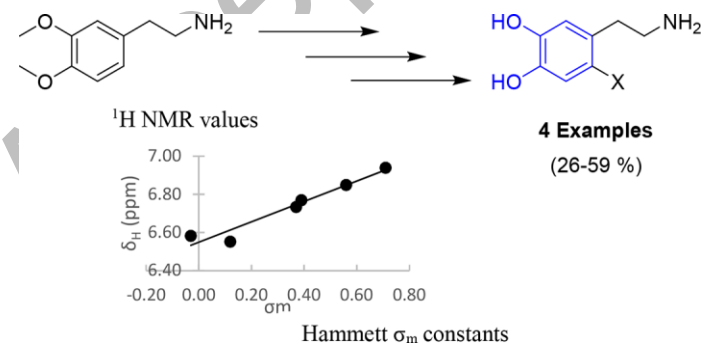
Abstract

Dopamine is a ubiquitous neurotransmitter essential in the proper functioning of the human body. In addition to this critical role, the catecholamine core has shown utility as a scaffold for numerous drugs and in other applications, like metal detection and adhesive materials. Substituents at the 6-position of dopamine's catechol core can modulate its stereoelectronic properties, the acidity of its phenolic hydroxyl groups, and the overall hydrophobicity of the molecule. Herein, we report the synthesis of a series of four novel dopamine analogues substituted at the 6-position of the catechol core. The ^{1}H NMR chemical shift of the aromatic proton *meta* to the substituent correlated strongly with the Hammett σ_m constant, confirming the electronic properties of the substituents.

Graphical Abstract



KEYWORDS: dopamine, Hammett constant, catecholamine, boron tribromide, *O*-demethylation

INTRODUCTION

4-(2-Aminoethyl)benzene-1,2-diol (dopamine, DA, Figure 1) is a neurotransmitter that plays a critical role in the proper functioning of the human body.[1] In the body, DA is synthesized from L-3,4-dihydroxyphenylalanine (L-DOPA).[2] In addition to its role as a neurotransmitter, DA is the precursor of norepinephrine and epinephrine, meaning that deficiencies in DA also result in decreased levels of norepinephrine and epinephrine. Furthermore, DA levels play a role in numerous diseases and disorders, including Parkinson's disease,[3] schizophrenia,[4] attention deficit disorders[5] and addiction.[6] The ubiquitous nature of DA in the body makes it crucial to understand its complex functions and the activity of the enzymes that modify it.

There are many enzymes that are integral to the metabolism of dopamine. The major pathway involves conversion of DA to the inactive metabolite homovanillic acid (HVA), through either 3,4-dihydroxyphenylacetic acid (DOPAC) or 3-methoxytyramine (3-MT) intermediates.[2] The enzymes responsible for these conversions are monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT).

Another enzyme important in the regulation of dopamine circulating in the body is the sulfotransferase, SULT1A3.[1] Cytosolic sulfotransferases (SULTs) transfer a sulfuryl moiety ($-SO_3$) from 3'-phosphoadenosine-5'-phosphosulfate (PAPS) to an alcohol or

monoamine group of phenolic-based compounds.[7] This sulfation renders the DA water-soluble and allows its excretion from the body. Although there is limited knowledge about the substrate selectivity of this class of enzymes, their utility is clear: greater than 90% of DA in the body is found as dopamine sulfate.[8]

Dopamine and other catechol derivatives have also been used for a broad range of applications. Gomes et al. reported the use of dopamine/catechol scaffolds to prevent biofilm formation through the inhibition of quorum sensing.[9] Belitsky et al. utilized catechol-based materials to detect metal ions in solution with the naked eye.[10] DOPA/catechol-tethered polymers have also been described in detail as biomimetic adhesive materials.[11] Recently, Hu and coworkers investigated the polymerization of dopamine analogues.[12]

Because of crucial role of dopamine in the body and the utility of the catechol core as a scaffold for broader applications, we have designed a series of 6-substituted dopamine derivatives (Figure 1). While the significance of the aminoethyl tail is evident in binding to various enzymes, the addition of electron donating and withdrawing substituents to the 6-position of the ring will affect the stereoelectronic properties of the catechol core. Many of the modifications of dopamine and related catechols in the body involve further functionalization of the hydroxyl groups. Therefore, these derivatives could serve as probes to determine mechanistic and structural details about the enzymes that modify them.

Recent computational work by Bigler et al. investigated this suite of 6-substituted dopamine analogues as substrates for SULT1A3.[13] In the most biologically-relevant model where the ligands were optimized with implicit solvation and relaxed amino acid side chains, 6-carboxydopamine provided a significant improvement in interaction energy compared to dopamine, whereas 6-cyanodopamine showed a modest improvement. Hatstat and colleagues reported the investigation of the same series of dopamine analogues as inhibitors of COMT.[14] Although the dopamine derivatives studied exhibited only a slight to modest improvement in total electronic binding energies, the series provides an interesting scaffold for designing improved inhibitors of COMT.

This paper describes the synthesis of four novel DA analogues (**2**-**5**, Figure 1). This series of molecules was prepared by diversifying the aromatic core of DA at the 6-position with substituents that vary in size, shape and polarity. The DA analogues were designed to have a range of steric and electronic properties. As a result, these modifications are expected to alter the electronic nature of both phenolic hydroxyl groups, the hydrogen-bonding ability and overall hydrophilic/hydrophobic nature of the catecholamine derivative. A correlational analysis was performed to examine the effect of the substituents.

RESULTS AND DISCUSSION

6-Nitrodopamine (**1**) was prepared according to the literature procedure[15] via nitration of dopamine. The product precipitated immediately upon addition of the acid as a bright yellow solid, which was collected by filtration and dried.

The remaining analogues were synthesized from commercially available 3,4-dimethoxyphenethylamine (3,4-DMPEA). The cyclic dopamine analogue (**2**) was prepared in an overall 36% yield using a Pictet-Spengler cyclization.[16] Starting from 3,4-DMPEA, paraformaldehyde and formic acid were used to first form the dimethoxy tetrahydroisoquinoline intermediate **6** (Scheme 1). It was found that **6** was much more stable as the ammonium salt and that decomposition occurred as the ammonium nitrogen became deprotonated. Therefore, immediately following purification, the methyl ethers were removed with boron tribromide[17] to give **2** as a white solid in 70% yield. Derivative **2** was obtained as a hydrobromide salt, which helped to stabilize the final product and prevent conversion to the corresponding isoquinoline.

6-Bromodopamine (**3**) was prepared by brominating 3,4-DMPEA using bromine and acetic acid[18] to produce intermediate **7** (Scheme 2). Although the reaction ran for 2 hours, an orange solid precipitated almost immediately and additional acetic acid had to be added to ensure stirring continued. Initial attempts at converting the hydrobromide salt of **7** directly to the final analogue **3** were unsuccessful due to solubility issues, and therefore, the hydrobromide salt was removed with a basic aqueous work-up. Intermediate **7** was subsequently deprotected using boron tribromide to yield **3** in a 75% yield.

The synthesis of 6-cyanodopamine (**4**) was accomplished according to Scheme 3 in an overall 43% yield from 3,4-DMPEA. Briefly, the amino group of 3,4-DMPEA was

protected with an acetyl group producing **8** in good yield, and the N-acetyl intermediate was then mono-iodinated at the 6-position using iodine monochloride in glacial acetic acid to produce **9** in a 91% yield.[19] Conversion to the cyano intermediate **10** was accomplished with copper cyanide.[20] Deacetylation of the amine was accomplished by first installing a Boc group (**11**) and removing the acetyl group under mild, basic conditions.[21] The final deprotection of the methyl ethers and removal of the Boc group with boron tribromide yielded **4** as an off-white solid in an 80% yield**.**

6-Carboxydopamine (**5**) was prepared according to Scheme 4 in an overall 29% yield from **8**. An acetyl group was added to the 6-position of the ring using acetic anhydride and polyphosphoric acid (PPA), yielding **13**.[22] Intermediate **13** was then Boc protected to produce **14**. Then, the 6-acetyl group in **14** was oxidized with potassium iodide and an 8.25 % sodium hypochlorite solution,[23] which also removed the acetyl group from the amino tail to give **15**. The oxidation of the 6-acetyl group in **14** was also attempted using mild, basic conditions.[24] However, success was achieved with the highest yield resulting from the use of sodium hypochlorite. This oxidation step was also attempted both before and after the addition of the Boc group. However, oxidization before fully protecting the amine tail of DA facilitated intramolecular cyclization and formation of a Schiff base between the nitrogen and the carbonyl of the acetyl substituent. The methyl ethers and Boc groups were subsequently removed from **15** using boron tribromide to produce compound **5** as a pale yellow solid in 47% yield.

The final derivatives (**2-5**) were precipitated as hydrobromide salts from a methanolic solution with diethyl ether or acetonitrile (**5**). All analogues were fully characterized by ^{1}H and ^{13}C NMR and HRMS, and purity was confirmed by HPLC. The derivatives showed significantly different retention times from each other and DA when separated by a reverse phase HPLC column, indicating the substitutions have an effect on the hydrophobicity of the molecule.

One indirect method to examine the electron donating and withdrawing ability of the substituent is to correlate the Hammett constants and NMR chemical shift values. Soerensen et al.[25] and Kara[26] observed a correlation between Hammett constants and ^{1}H, ^{13}C and ^{77}Se chemical shift values. A correlational analysis between Hammett constants and the ^{1}H NMR chemical shifts of the aromatic protons of the dopamine analogues **1-5** and 6-hydroxydopamine was performed. There are existing σ_m and σ_p values in the literature[27] for all substituents except the cyclic dopamine analogue (**2**). Therefore, the σ_m value (-0.03) for $-CH_2NH_2$ was used for **2**. The chemical shift of the proton at the *meta* position relative to the substituent correlates well with the σ_m values, giving an R^2 value of 0.94 (Figure 2), demonstrating the expected effect of the substituent. When the data point for **2** was removed, the R^2 value for the correlation was stronger (R^2 = 0.99; Figure S43), indicating that the value used is accurate. Since there is no proton at the *para* position, the ^{1}H NMR chemical shift of the proton at the *ortho* position was examined with respect to the σ_p values[27], resulting in a correlation of R^2 = 0.80 (Figure S44). It is likely that the interaction between the substituent and the *ortho* position is a combination of resonance, field and inductive effects and is not well

described by a single Hammett constant. Nonetheless, the strong linear correlation between the Hammett σ_m constant and the ^{1}H NMR chemical shift value illustrates the substituents are having the expected effect on the electronic properties of the molecule. These parameters, taken with other experimental data, will be important in establishing a complete structure-activity relationship in future work.

CONCLUSION

In summary, we report the synthesis of four dopamine derivatives with a variety of electron-donating or -withdrawing substituents at the 6-position. Novel analogues 6-bromodopamine, 6-cyanodopamine and 6-carboxydopamine were synthesized in overall 59%, 43% and 26% yields, respectively from the commercially available 3,4-dimethoxyphenethylamine. 1,2,3,4-Tetrahydroisoquinoline-6,7-diol was conveniently synthesized in two steps in an overall 36% yield. There was a significant correlation between the Hammett σ_m constant and the ^{1}H chemical shift value of the proton *meta* to the substituent. Given the different stereoelectronic properties induced by the substituents, this series will have important implications when used as substrates or potential inhibitors of DA enzymes or even in other non-biological applications. In addition, the intermediates may serve as precursors for other catecholamine derivatives.

EXPERIMENTAL

All reagents and solvents were purchased as the highest grade available from Acros or Sigma-Aldrich and were used without further purification. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian 400 MHz spectrometer.

General Method A: Addition Of Boc Group

To a stirring solution of the appropriate substituted N-(4,5-dimethoxyphenethyl)acetamide and 4-(dimethylamino)pyridine in anhydrous CH_3CN under argon, a solution of di-*tert*-butyl dicarbonate in anhydrous CH_3CN was added. The reaction was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with saturated ammonium chloride solution, and then concentrated under reduced pressure. The product was used as is or was purified by column chromatography.

General Procedure B: Method For *O*-Demethylation With Boron Tribromide

The dimethoxy intermediate was dissolved in anhydrous CH_2Cl_2 under an inert atmosphere (Ar) at -78 ˚C. To this solution, 1 M BBr_3 in CH_2Cl_2 was added dropwise and stirred for 10 minutes. The reaction mixture was stirred and allowed to reach room temperature for 2 h. The reaction was then quenched with MeOH and stirred for an additional 1.5 h. The mixture was then transferred to a conical vial and was concentrated under reduced pressure to yield the crude solid, which was subsequently precipitated as the final product.

ACKNOWLEDGEMENT

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SUPPLEMENTARY INFORMATION

Full experimental detail, characterization data and copies of ^{1}H NMR and ^{13}C NMR spectra for all compounds and HPLC traces of **1**-**5**. This material can be found via the "Supplementary Content" section of this article's webpage.

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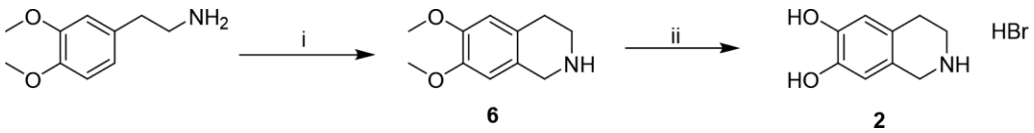
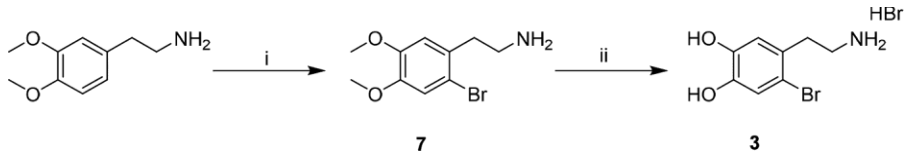
Scheme 1. Cyclization of the amino ethyl tail to give the tetrahydroisoquinoline derivative **2**. Reagents and conditions: i) HCO_2H, $(CH_2O)_n$, 50 °C, 15 h, 51%; ii) BBr_3, CH_2Cl_2, -78 °C to 0 °C, 3 h, 70%.



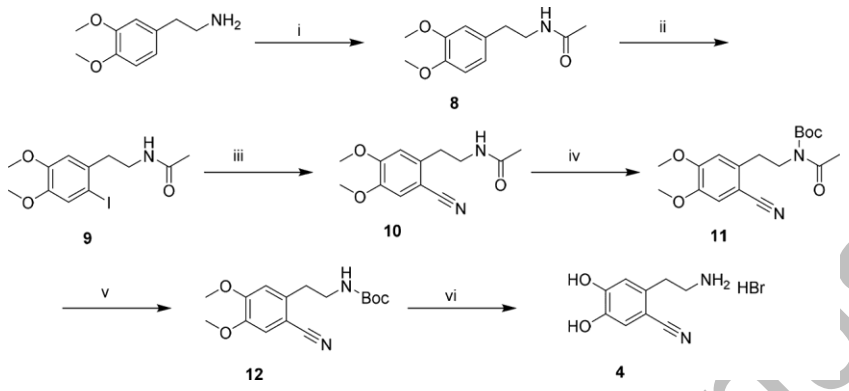
6 **2**

Scheme 2. Synthesis of 6-bromodopamine (**3**). Reagents and conditions: i) Br_2, AcOH, rt, 2 h, 78%; ii) BBr_3, CH_2Cl_2, -78 °C to rt, 3 h, 75%.



7 **3**

Scheme 3. Synthesis of 6-cyanodopamine (**4**). Reagents and conditions: i) AcCl, Et_3N, CH_2Cl_2, rt, 18 h, 89%; ii) ICl, AcOH, rt, 18 h, 91%; iii) CuCN, DMF, 130 °C, 5 h, 76%; iv) Boc_2O, DMAP, CH_3CN, rt, 17 h, 91%; v) K_2CO_3, CH_3OH, rt, 2 h, 95%; vi) BBr_3, CH_2Cl_2, -78 °C to rt, 3.5 h, 80%.



Scheme 4. Synthesis of 6-carboxydopamine (**5**). Reagents and conditions: i) Ac_2O, PPA, CH_2Cl_2, 60 °C, 19 h, 88%; ii) Boc_2O, DMAP, CH_3CN, rt, 19 h, 81%; iii) KI, NaOCl (8.25%), 1:1 1,4-dioxane/H_2O, rt, 19 h, 86%; iv) BBr_3, CH_2Cl_2, -78 °C to rt, 3.5 h, 4 h, 47%.

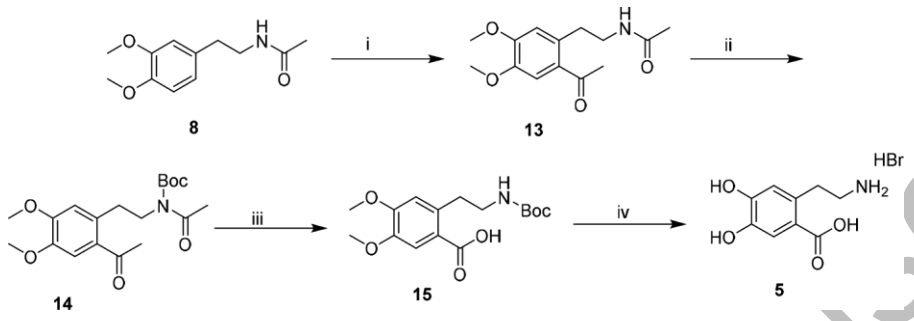


Figure 1. The structures of dopamine and the dopamine analogues synthesized in this work.

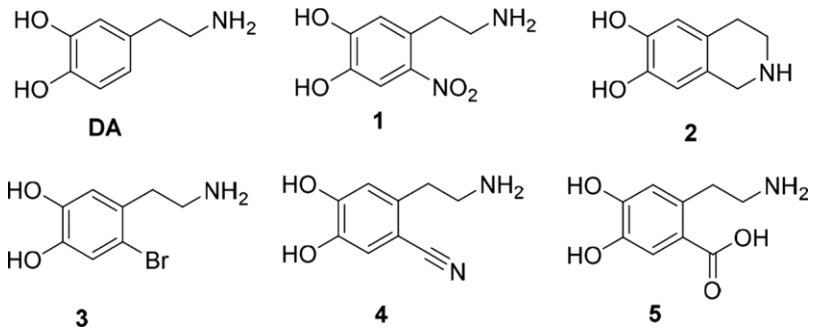


Figure 2. Plot of Hammett σ_m constant versus the ^{1}H NMR chemical shift (ppm) of the proton at the *meta*-position relative to the substituent. Data labels correspond to the chemical shift of the proton at the *meta*-position relative to the substituent in NO_2 = **1**, cyclic = **2**, Br = **3**, CN = **4**, CO_2H = **5** and OH = 6-hydroxydopamine.