A Self-Assembled Foldamer Capsule: Combining Single and Double Helical Segments in One Aromatic Amide Sequence

Chunyan Bao,[a] Quan Gan,[b] Brice Kauffmann,[a] Hua Jiang,*[b] and Ivan Huc*[a]

Abstract: In this manuscript, we present supramolecular capsules based on a new design relying on both self-assembly and folding of oligomeric strands. We have designed an aromatic amide foldamer in which each monomer encodes three levels of information: a specific cavity size, recognition groups for guest binding, and a propensity to adopt a single or a double helical motif. Thus, a tetradecameric sequence based on four different monomers was encoded so that a wide double helical segment resulting from the hybridization of two strands creates a cavity in which guests, such as 1,10-decanediol, can be bound. Additionally two narrow single helical segments form end-caps and isolate the guest from the solvent. The design, synthesis, solid-state and solution-state characterization of duplex formation and guest binding are presented.

Keywords: chirality · helical structures · molecular recognition · supramolecular chemistry · X-ray diffraction

Introduction

Self-assembly has proven to be an efficient method to produce large supramolecular containers endowed with molecular-recognition properties. Despite their large size, such containers can be based on remarkably simple molecular building blocks and often feature high levels of symmetry.[1–10] In contrast, Nature achieves highly selective molecular recognition using receptors that are primarily based on the folding of long and complex peptide sequences into well-defined conformations having low symmetry, if any. In this manuscript we present a synthetic receptor based on a combination of both folding and self-assembly of an oligomeric sequence, and describe the first synthetic host for organic guests having a double helical architecture.

Inspired by Nature’s receptor design strategy, chemists have recently begun to explore the possibility to elicit molecular recognition within the cavities of oligomeric chains folded into single helices.[11–17] These objects have until now been much smaller and far less complex than proteic receptors. Nevertheless, they share with them a vast potential for tunability: they are based on sequences whose monomers can be changed one at a time and introduced by using the same synthetic methods. In principle, they are also amenable to larger and increasingly complex structures through the iterative elongation of their sequence. Along these lines, we have described helical capsules based on the folding of oligoamide sequences of various aromatic amino acids designed in order to create a large helix diameter at the center of the sequence and narrow diameters at the end, so as to define a closed space in which bound guest molecules are completely surrounded by the helix backbone.[17] A potential drawback of this design is that binding of an elongated guest would require a multiple turn helix comprised of numerous monomers: in other words, a difficult synthetic target. We assumed that a more straightforward route to helical containers having an elongated cavity may rest on the high propensity of some aromatic amide sequences to assemble into double-stranded helices twice as long as their single helical precursors.[18,19] As shown in the following, several potential hurdles had to be overcome to validate this concept, in particular the fact that none of these aromatic oligoamide double helices had been endowed with molecular recognition properties until now, and the fact that single helical seg-

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ments and double helical segments had never been combined in a single foldamer sequence and shown to each adopt their preferred folded conformation independently from one another.

**Results and Discussion**

**Design and synthesis**: Oligomers 1 and 2 were designed as candidates for double helical receptor formation (Scheme 1). Both are based on the same set of monomers.

The longer sequence of 2 comprises a trimer of 8-amino-2-quinoline carboxylic acid (Q), known to form a helix too narrow to accommodate any guest and thus to cap the helix cavity.[20] Both 1 and 2 comprise a trimer of 2,6-diaminopyridine and 2,6-pyridinedicarboxylic acid (P), which forms a helix with a polar hollow that binds to aliphatic hydroxyl or amino groups that can thus constitute hot spots to anchor guests within the helix cavity.[17] A tetrameric and an octameric amide sequence of 7-amino-8-fluoro-2-quinolinecarboxylic acid (Q F) were also included in 1 and 2, respectively. These oligomers fold into a helix the hollow of which is large enough to accommodate an alkyl chain, though it apparently does not engage in any attractive interactions with such moieties.[19]

Each segment of homologous monomer thus brings about a given helix diameter, and displays an array of functions that converge towards the helix hollow. In addition, the various monomers also differ in their preference for a single helical conformation or a hybridized double helix. Qₙ oligomers do not hybridize into multiple helices,[23] but oligomers can hybridize, and not sequences as short as a trimer.[18] The terminal Q₃P₃ sequence of 2 was thus expected to preferentially form a single helix. However, Q₉ oligomers form stable multiple helices; Boc-Q³₉₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋˓→

The longer sequence of 2 comprises a trimer of 8-amino-2-quinoline carboxylic acid (Q), known to form a helix too narrow to accommodate any guest and thus to cap the helix cavity.[20] Both 1 and 2 comprise a trimer of 2,6-diaminopyridine and 2,6-pyridinedicarboxylic acid (P), which forms a helix with a polar hollow that binds to aliphatic hydroxyl or amino groups that can thus constitute hot spots to anchor guests within the helix cavity.[17] A tetrameric and an octameric amide sequence of 7-amino-8-fluoro-2-quinolinecarboxylic acid (Q F) were also included in 1 and 2, respectively. These oligomers fold into a helix the hollow of which is large enough to accommodate an alkyl chain, though it apparently does not engage in any attractive interactions with such moieties.[19]

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parallel duplexes or quadruplexes, and Boc-Q⁹₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋˓→

The synthesis of 1 was achieved from monoamine mono-Boc-protected trimer 3 (Scheme 1). The amine group was coupled to pivaloyl chloride and the Boc group was subsequently removed with TFA to yield 4. Coupling with the acid chloride of Q⁹ afforded 6, which was deprotected with TFA and subjected again to the acid chloride of Q⁹ to give 8, which was converted into 1. The synthesis of 2 (Scheme 2) was achieved from amine intermediate 9 (Q₃P₃QF⁸) used in the preparation of the capsule Q₃P₃QF⁸⁻₋₋₋₋₋₋₋₋₋₋₋˓→

Hybridization of 1 and 2 into double helices: Unlike its precursor 8, oligomer 1 could be crystallized and its solid-state structure solved by X-ray crystallography (Figure 1). The results show that two strands associate through the formation of an antiparallel double helix of two Q₃₉ segments. The terminal pyridine trimer P₃ of each strand sits on one end of
this short duplex and adopts a crescent-like conformation that apparently could be extended to a single helix without perturbing the duplex structure. Two molecules of DMSO are included in the duplex structure, with their oxygen atom hydrogen bonded to the amide protons of the 2,6-pyridinedicarboxamide units. However, $^1$H NMR solution studies of 1 showed no evidence of stable duplex formation of guest binding in the helix hollow. In this respect, the behavior of 1 is consistent with that of Q F$_4$ the aggregates of which could be characterized only at 243 K and high concentration (40 mM).[19]

The validity of the design principles of 2 were compellingly demonstrated by its crystal structure (Figure 2a). Its architecture is unprecedented in that it comprises a wide central (QF$_8$)$_2$ double helical subunit each strand of which spans two turns with a pitch of 7 Å, and two narrower peripheral Q$_3$P$_3$ single helical subunits each spanning another two turns with a pitch of 3.5 Å. As a consequence of the hybridization, the bulky tert-butyl groups do not lie at the ends of the structure despite their position at the end of the sequence. Instead, they are found at the border between single helical and double helical segments. However, no steric hindrance or perturbation of the helical shape results because the diameter of the single helical segments is reduced; this avoids clashes with the tert-butyl groups. The central antiparallel double helix of 2 is superimposable to that of the (Boc-Q$_8$F$_8$-OMe)$_2$ duplex that we previously characterized.[19] In particular, the relative position of the two strands, that is, the extent to which they are entwined into one another, is the same in the two duplexes. This perfect conservation of the (Boc-Q$_8$F$_8$-OMe)$_2$ duplex architectures is remarkable and was not obvious a priori considering the size of the Q$_3$P$_3$ extensions. Hybridization in this series appears to be dominated by the propensity of QF units to arrange pairwise in a head-to-tail fashion.

Studies were carried out to assess the extent of hybridization of 2 in solution. At low concentration, $^1$H NMR spectra in CDCl$_3$ show one set of sharp lines. Upon increasing concentration (Figure 3) or lowering temperature (see the Supporting Information) a second set of signals emerges at
higher field; this indicates stronger ring current effects. This pattern is consistent with a slow exchange on the NMR timescale between a single helical and a double helical form of 2, as observed for other aromatic amide foldamers[18,19] and in particular for Boc-Q2p-O-Me[10]. Based on the proportions between single and double helices, a dimerization constant \( K_{\text{dimer}} = 250 \, \text{L/mol}^{-1} \) can be calculated. This value is notably smaller—by more than three orders of magnitude—than that of Boc-Q2p-O-Me, indicating that the large P2Q3 segment of 2 disfavors duplex formation.

**Host-guest properties of 2**: As explained above, the sequence of 2 was designed to bind to elongated diamine or diol guest molecules. This property was assessed both in the solid state and in solution. Two crystal structures of inclusion complexes of a guest within double helical 2 were obtained. The structure shown in Figure 2 is that of HO-(CH2)9OH, and shows an excellent match between the cavity size and the guest length: the terminal hydroxyl groups lie in the same plane as (and form two hydrogen bonds with) the 2,6-pyridinedicarboxamide units. These hydrogen bonds presumably represent the main driving force of guest complexation. The structure of HO(CH2)9OH-C(2)2 shows the complete surrounding of the host around the guest, which is completely isolated from the solvent once encapsulated. This structure must undergo substantial conformational changes to capture and release a guest, such as 1,10-decanediol. A possible pathway could involve the partial unfolding of the terminal Q2P single helical segment, which would create an opening at the end of the cavity. Alternatively, guest binding could occur while the host exists as a single helix and hybridization takes place with the guest prelocated in the binding pocket.

The structure of HO(CH2)9OH-C(2)2 was also obtained. It is very similar to the above as far as the conformation of (2) is concerned. However, it shows that the guest is slightly too short to simultaneously bind to the 2,6-pyridinedicarboxamide units at both its extremities. Instead, the guest has to slide in one direction or the other to form hydrogen bonds with the host, and disorder and partial occupancy factors are observed at the guest’s terminal (Figure 4).

Binding studies in solution confirmed the solid-state observations, but were complicated by relatively weak binding constants, multiple exchange phenomena and extensive overlap of \(^1\text{H}\) NMR signals belonging to different species. An NMR titration of 2 with 1,10-decanediamine (Figure 3) showed chemical-shift variations of the amide signals of the open ended single helix; this indicates binding in a fast-exchange regime. Broadening of these signals is also observed, which we have previously assigned to exchange between guest-amine and host-amine protons in other titrations with aliphatic amines of capsule Q2P2Q4AQ2xP2Q3[17a,31] The titration concomitantly revealed the emergence of a second set of signals very near to those of the empty duplex (2)2; we attributed these to the host-guest complex observed in the solid state in slow exchange with empty (2)2. A binding constant of the guest by the double helical capsule of the order of 200 \( \text{L/mol}^{-1} \) was estimated from the proportions of the two sets of signals. The saturation of both (2)2 (disappearance of the signals of the empty guest) and of single helical 2 (chemical shifts reach a limit value) was almost complete after the addition of 10 equivalents of guest. Saturation resulted in a slight increase of the proportion of strands involved in double helices from 25 to 40% with respect to the single helical monomer. This small variation indicates that guest binding is stronger in the duplex than with the single helix, but not much stronger despite the additional hydrogen bonds that occur at both ends of the guest in the duplex. It should be pointed out that the duplex (Boc-Q2p-O-Me)2, which constitutes the central section of (2)2, does not show any affinity for alkane diols or diamines. Binding enthalpy can thus be assigned to hydrogen bonding between the pyridine-carboxamide moieties and the guest’s polar functions.

Titrations of 2 (2 mM) with 1,9-nonanediol, 1,10-decanediol and 1,11-undecanediol led to similar results (see the Supporting Information) and gave rise to a final proportion...
of strands involved in double helices of 40, 70, and 30%, respectively. The stronger effect of decanediol with respect to nonanediol and undecanediol corroborates the better complementarity of decanediol with the host’s cavity observed in the solid state. Finally, titration of 2 was also carried out with Bu₂CO₂(CH₂)₄NH₂. Because it bears a bulky group, this guest was expected to bind to the single helical form of 2 and not to the duplex (2₆). This prediction proved to be correct (see the Supporting Information) but binding was weak (< 80 L·mol⁻¹) and did not result in a significant enhancement of the proportion of single helix.

Conclusions

For the purpose of designing synthetic capsules, self-assembly has the advantage of synthesis efficiency as it can be based on small and accessible building blocks. On the other hand, folding of oligomeric sequences provides access to complexity and tunability. We have shown here that these two approaches can be advantageously combined into one design. Double helical cages, as the one described here, represent unprecedented objects in terms of their architecture but also in terms of the opportunities that they offer for guest binding and release, which might proceed through duplex dissociation or through the unfolding of a single helical cap at one end of a duplex. This work also demonstrates that monomers in a foldamer sequence can be simultaneously encoded with several distinct properties: helix diameter for guest binding and release, which might proceed through single or double helical conformations. Aromatic amide foldamers thus offer a highly modular approach towards receptor design. Current efforts in our groups aim at further expanding the registry of available monomers and at improving synthesis methods to reach larger molecular containers with designed properties.

Experimental Section

General: All reactions were carried out under a dry nitrogen or argon atmosphere. Unless otherwise noted, the original materials were used directly from commercial suppliers without any purification. Dry THF was distilled from Na/benzophene, dry dichloromethane and diisopropyl-ether. All reactions were carried out under a dry nitrogen or argon atmosphere. 1H NMR (CDCl₃, 300 MHz): δ = 9.87 (s, 1H), 9.85 (s, 1H), 8.56 (d, J(H-H) = 7.8, 2H), 8.23–8.06 (m, 4H), 7.98 (s, 1H), 7.87–7.78 (m, 3H), 7.09 (s, 1H), 1.55 (s, 9H), 1.39 (s, 9H). 13C NMR (CDCl₃, 75 MHz): δ = 176.9, 161.4, 152.1, 150.1, 149.8, 148.3, 148.8, 150.6, 141.1, 139.6, 125.9, 102.3, 109.9, 108.7, 81.3, 39.9, 28.3, 27.5. MS (ESI): m/z: 534.2 [M+H⁺]. This compound (170 mg, 0.32 mmol) was dissolved in CH₂Cl₂ (10 mL) and excess TFA (1.5 mL) was added dropwise. The mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was dissolved in CH₂Cl₂ (20 mL), washed with saturated NaHCO₃, dried over Na₂SO₄ and then concentrated to give trimere 4 as a light yellow solid. This compound was used in the next step without further purification.

1H NMR (CDCl₃, 300 MHz): δ = 10.82 (s, 1H), 10.76 (s, 1H), 10.17 (s, 1H), 10.16 (s, 1H), 8.87 (t, J(H-H) = 7.2, 1H), 8.56–8.52 (m, 2H), 8.46 (t, J(H-H) = 7.2, 1H), 8.20–8.16 (m, 3H), 8.10 (d, J(H-H) = 7.8, 1H), 8.05–8.01 (m, 6H), 7.92 (d, J(H-H) = 8.1, 1H), 7.75 (d, J(H-H) = 8.1, 1H), 7.69 (s, 1H), 7.67 (s, 1H), 7.49 (t, J(H-H) = 7.8, 1H), 7.19 (s, 1H), 4.12 (t, J(H-H) = 6.3, 4H), 2.32–2.30 (m, 2H), 1.66 (s, 9H), 1.21–1.17 (m, 12H), 0.97 (s, 9H).

13C NMR (CDCl₃, 75 MHz): δ = 176.9, 163.1, 162.3, 162.1, 161.6, 161.2, 152.3, 151.0, 150.6, 150.1, 149.5, 143.9, 148.9, 140.6, 140.0, 139.9, 127.5, 127.4, 127.2, 125.9, 120.2, 119.4, 118.5, 117.5, 117.1, 110.4, 110.3, 110.2, 109.9, 109.8, 109.7, 97.0, 75.4, 75.3, 39.4, 28.3, 21.8, 20.9, 19.2. MS (ESI): m/z: 1054.5 [M+Na⁺].

Heptamere 8: Pentamer 6 (120 mg, 0.11 mmol) was dissolved in CH₂Cl₂ (10 mL) and TFA (1.5 mL) was added dropwise. The mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was dissolved in CH₂Cl₂ (20 mL), washed with saturated NaHCO₃, dried over Na₂SO₄ and then concentrated to give heptamer amine 1 as a light yellow solid, which was used without further purification. 1H NMR ([D₅]DMSO, 300 MHz): δ = 11.49 (s, 1H), 11.24 (s, 1H), 10.79 (s, 1H), 10.29 (s, 1H), 10.18 (s, 1H), 10.07 (s, 1H), 10.04 (s, 1H), 9.86 (s, 1H), 8.54 (d, J(H-H) = 7.8, 2H), 8.19 (m, 2H), 8.04 (d, J(H-H) = 8.1, 2H), 7.86–7.80 (m, 2H), 7.60 (t, J(H-H) = 7.8, 1H), 6.38 (d, J(H-H) = 7.8, 1H), 4.54 (s, 2H), 1.38 (s, 9H).

13C NMR (CDCl₃, 75 MHz): δ = 170.7, 161.3, 161.1, 157.3, 150.1, 149.0, 148.9, 148.6, 148.3, 141.1, 140.5, 139.6, 125.8, 125.7, 110.2, 109.7, 105.1, 103.6, 39.7, 37.3. MS (ESI): m/z: 434.4 [M+H⁺].
A Self-Assembled Foldamer Capsule

Decameter 1: A solution of acid chloride 8\[^{9}\] (70 mg, 0.1 mmol) in THF (10 mL) was added via a syringe to a solution of octamater aniline 9\[^{10}\] (70 mg, 0.10 mmol) in THF (20 mL) containing DIEA (0.04 mmol, 0.5 mmol). The reaction mixture was stirred at room temperature, overnight. The solution was evaporated and the crude was purified by flash chromatography (SiO\(_2\)) and eluted with cyclohexane/EtOAc (50:50 v/v) to obtain decameter 10 as a light yellow solid (140 mg, 63% yield).

\[^{1}\]H NMR (CDCl\(_3\), 300 MHz): \(\delta = 11.90\) (s, 1H), 11.33 (s, 1H), 10.90 (s, 1H), 10.78 (s, 1H), 10.72 (s, 1H), 10.37 (s, 1H), 10.11 (s, 1H), 9.84 (s, 1H), 9.15 (s, 1H), 9.04 (t, \(J = 7.8\) Hz, 8.80), 8.80 (d, \(J = 7.2\) Hz, 8.29), 8.29 (d, \(J = 7.2\) Hz, 2.11), 8.21 (d, \(J = 7.8\) Hz, 7.81), 8.15–8.11 (m, 3H), 7.98–7.92 (m, 6H), 7.64 (m, 2H), 7.58–7.54 (m, 2H), 7.43–7.38 (m, 4H), 7.38 (m, 2H), 7.38–7.34 (m, 4H), 7.23 (m, 1H), 7.12–7.08 (m, 1H), 6.97 (t, \(J = 7.8\) Hz, 2.11).

\(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta_{c} = 163.58, 163.1, 162.9, 162.8, 162.7, 162.2, 162.1, 161.6, 161.3, 160.8, 154.2, 152.0, 151.2, 150.8, 150.5, 150.3, 149.8, 141.5, 141.0, 141.4, 139.3, 139.0, 138.9, 138.5, 137.4, 134.9, 134.4, 128.3, 127.2, 127.1, 126.8, 126.7, 126.5, 125.9, 125.5, 124.7, 123.7, 123.5, 123.7, 123.3, 121.6, 120.4, 120.3, 119.8, 119.7, 119.6, 118.7, 118.4, 118.2, 118.0, 117.8, 117.6, 117.2, 116.6, 116.2, 116.0, 111.3, 109.4, 108.9, 108.9, 99.5, 99.1, 98.2, 98.1, 97.9, 97.5, 81.3, 75.8, 75.7, 75.5, 75.2, 75.0, 28.7, 28.6, 28.4, 19.9, 19.8, 19.7, 19.6, 18.5, 18.4, 18.3, MS (ESI): m/z = 2248.80 [M+2H\(^{+}\)]\(^{2}\), 2259.0 [M+4H\(^{+}\)]\(^{2}\), 2270.0 [M+2ZNa\(^{+}\)]\(^{2}\).

Capsule 2: Decameter 10 (120 mg, 0.05 mmol) was dissolved in CH\(_{2}\)Cl\(_{2}\) (10 mL) and excess TFA (1.5 mL) was added dropwise. The mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was dissolved in CH\(_{3}\)CN (20 mL), washed with saturated NaHCO\(_{3}\) solution to remove TFA and then concentrated to give decameter 11 as a yellow solid, which was used without further purification.

\[^{1}\]H NMR (CDCl\(_{3}\), 300 MHz): \(\delta = 11.85\) (s, 1H), 11.29 (s, 1H), 10.84 (s, 1H), 10.74 (s, 1H), 10.74 (m, 1H), 10.73 (s, 1H), 10.23 (s, 1H), 9.77 (s, 1H), 9.36 (s, 1H), 8.92 (s, \(J = 7.8\) Hz, 7.21), 8.76 (d, \(J = 7.5\) Hz, 8.25) (d, \(J = 7.8\) Hz, 8.11), 8.71–8.74 (m, 4H), 7.88–7.79 (m, 4H), 7.61 (d, \(J = 7.2\) Hz, 7.21), 7.55 (d, \(J = 7.5\) Hz, 7.47), (d, \(J = 7.5\) Hz, 7.12), 7.38–7.31 (m, 6H), 7.21–7.12 (m, 4H), 6.89 (s, \(J = 7.8\) Hz, 1H), 6.83 (s, 1H), 6.75 (d, \(J = 7.2\) Hz, 7.11), 6.65–6.54 (m, 2H), 6.37 (d, \(J = 7.8\) Hz, 1.12), 4.26–4.03 (m, 9H), 3.83–3.78 (m, 1H), 3.70–3.58 (m, 4H), 3.27 (s, 2H), 3.17–2.79 (m, 4H), 2.15–2.04 (m, 3H), 1.35–1.22 (m, 3H), 1.16–0.96 (m, 10H); MS (ESI): m/z = 1704.45 [M+2H\(^{+}\)]\(^{2}\), 1654.5 [M+4H\(^{+}\)]\(^{2}\).