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Efficient synthesis of amino-quinolinium and amino-quinazolinium salt series: Amination or *N*-Alkylation first?

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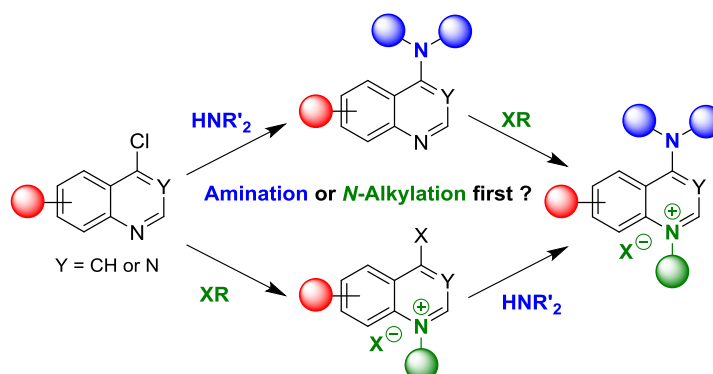
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Abstract The pharmacokinetic properties, particularly the poor solubility of lead drug compounds, are often a major impediment to their future clinical development. One common and effective solution is generally to use salt forms. Efficient strategies for the synthesis of quinolinium and quinazolinium salt series with promising therapeutic activities are thus of major interest. This study compares different synthetic routes for the rapid preparation of monomeric and dimeric amino-quinolinium and amino-quinazolinium salts. The advantages and limitations of the different processes, especially the importance of step order, are discussed.

Key words Amino-quinolinium salt, amino-quinazolinium salt, *N,N'*-bridging alkylation, amination, nucleophilic aromatic substitution.

Introduction

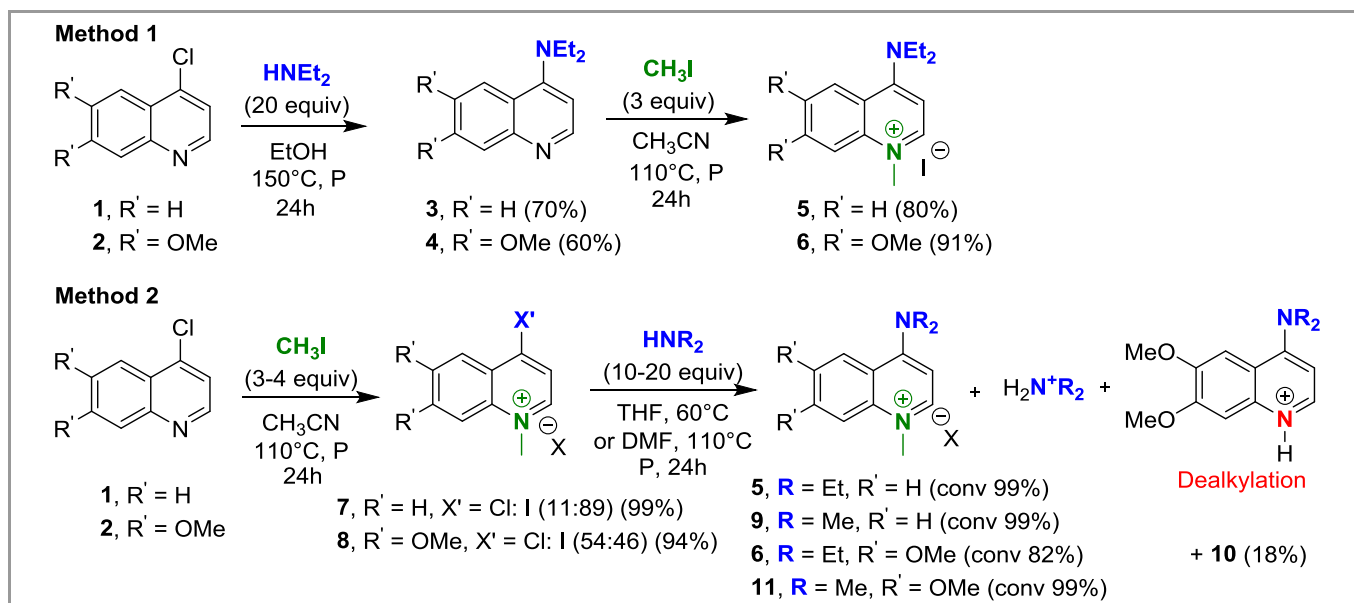
Most drugs available on the market or pharmacologically active molecules in development have heterocyclic pharmacophoric structures, often with quinoline and quinazoline nuclei.¹⁻³ These polyvalent compounds have aroused strong interest for numerous applications due to their wide range of pharmacological properties including, inter alia, anticancer, antibacterial, antiviral, or antihypertensive activities.⁴⁻⁵ Several FDA-approved quinoline and quinazoline compounds act on new therapeutic targets, affecting key cellular metabolic processes such as apoptosis, angiogenesis, cell proliferation and migration.^{4,6} Gefitinib and Lapatinib (4-aminoquinazolines), or Tivozanib and Foretinib (6,7-alkoxyquinolines) play, for instance, an essential role in the inhibition of tumor growth, targeting protein kinases.⁷ Amodiaquine or Primaquine are aminoquinolines used to treat infections caused by *Plasmodium falciparum* malaria parasites.⁸ Primaquine and Trimetrexate (aminoquinazoline) are also used as antipneumocystic medication. Several clinical trials involving quinoline and quinazoline drugs are underway, particularly for the treatment of incurable diseases.⁹ Nevertheless, the pharmacokinetic properties and in particular the poor solubility of these lead drug compounds are often a major impediment to their future clinical development. High

solubility is particularly desirable given the increasing number of drugs administered by small or large volume parenteral injection or through implants for rapid systemic effects.¹⁰⁻¹¹ In such situations, using quinazolinium and quinolinium salt forms is one common and effective approach to increase drug water-solubility, dissolution rates and bioavailability. To meet this need, efficient synthetic strategies and simple purification processes are required for the preparation of quinolinium and quinazolinium cationic scaffolds with promising therapeutic activities.

As part of our research on antimalarial candidates,¹²⁻¹⁴ we recently prepared more than forty *N*-heterocyclic iminium salts with good antiparasmodial activities and a promising mechanism of action.¹⁵ The extensive synthetic work carried out for this project enabled us to identify interesting strategies for the efficient and rapid preparation of amino-quinolinium and amino-quinazolinium salt series. This paper compares these different synthetic routes. The advantages and limitations of the different processes, especially the importance of step order, are discussed.

1. Results

We first evaluated a synthetic pathway for the preparation of quinolinium salts in two steps (**Method 1**, Scheme 1). Starting from the commercially available 4-chloroquinoline **1** or 4-chloro-6,7-dimethoxyquinoline **2**, a nucleophilic aromatic substitution (S_NAr) was first performed to introduce *N*-substituted amine groups on the *para* position of the pyridine moiety. Despite excess diethylamine (20 equiv.), chloride substitution was laborious, requiring to launch the reaction at high temperature (150°C) in a pressure sealed flask. With quinoline **2**, the electron-donating effect of the methoxy groups made the substitution even more difficult, reaching 60% of 4-(diethylamino)-6,7-dimethoxyquinoline **4**.

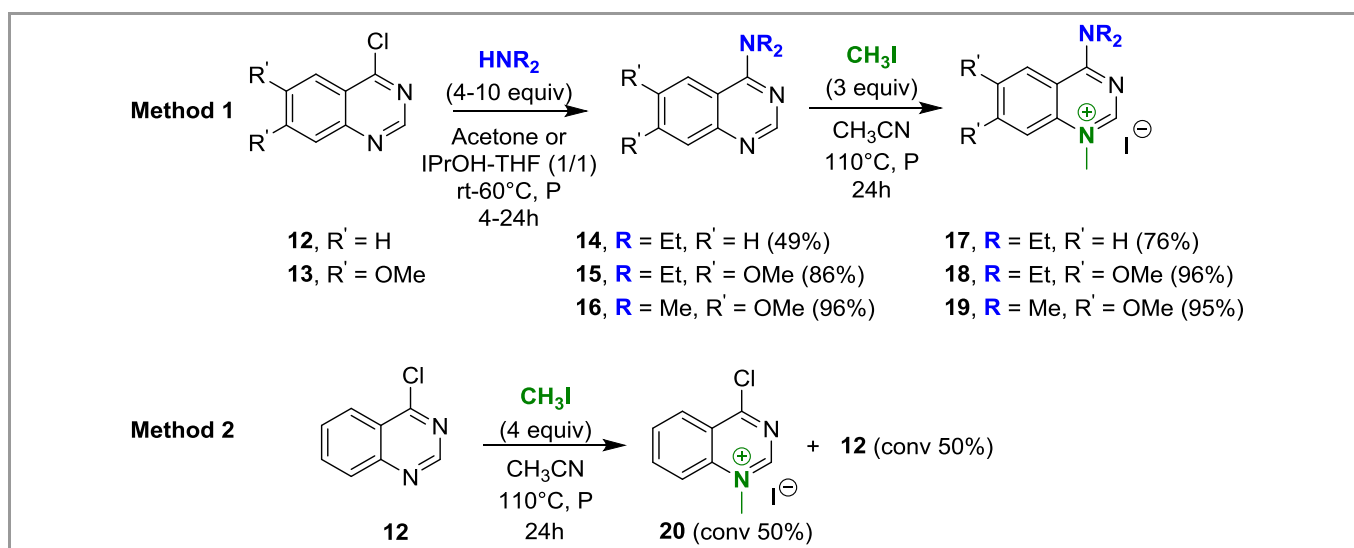


Scheme 1: Synthetic pathways for the preparation of amino-quinolinium salts (P = pressure sealed flask).

Moreover, the purifications by column chromatography of both quinolamines **3** and **4** to remove the remaining starting material were fastidious. The final *N*-methylation step to obtain the amino-quinolinium salts **5** and **6** also had to be performed in a pressure sealed flask to guarantee high yields. Finally, amino-quinolinium salts **5** and **6** were obtained in moderate overall yields, 56% and 54% respectively.

In the light of these drawbacks, we considered an alternative synthetic pathway that could improve overall yields (**Method 2**, Scheme 1). The strategy was to first perform the *N*-alkylation leading directly to the *N*-alkyl cationic salt form, and thus to facilitate S_NAr substitutions on the electron-deficient 4-chloropyridinium ring. Hence, 4-chloroquinoline **1** and 4-chloro-6,7-dimethoxyquinoline **2** were totally converted into the corresponding *N*-methylated salts **7** or **8** (94-99%). Note that during the process part of the chlorine substituent was replaced by the iodide released by the nucleophilic substitution, leading to a mixture of 4-chloro and 4-iodo-1-

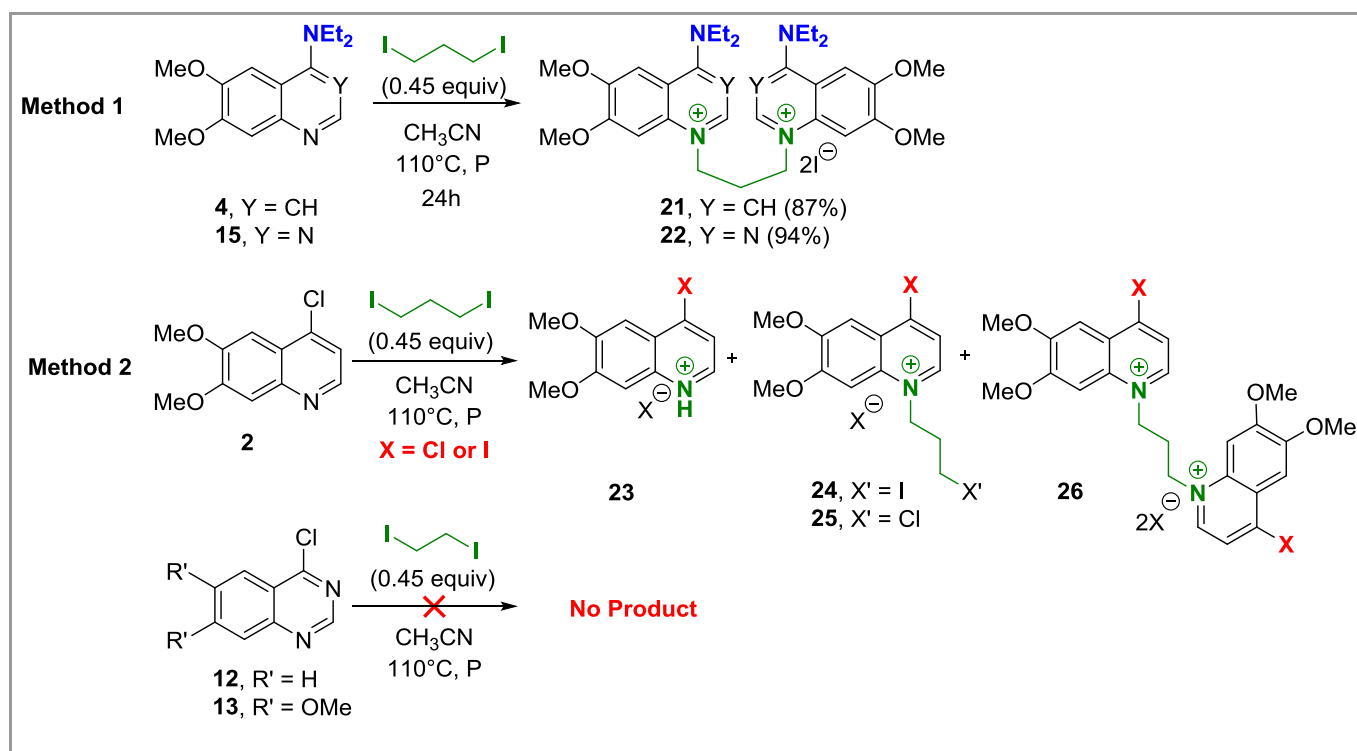
methylquinolin-1-ium iodide or chloride salts. While a quasi-equimolar mixture of chloro and iodo-quinolinium (54/46) was obtained for methoxy-substituted derivative **8**, the counterpart **7** was almost exclusively obtained as the iodo form (89%). The mixtures were used as is for the next amination step. As predicted, the S_NAr of the halogens by diethylamine or dimethylamine efficiently provided the expected amino-quinolinium salts **5**, **9** and **11** in excellent conversions (99%), after simple filtration. Interestingly, some dealkylation was observed for salt **6** leading to the amino-quinolinium **10** (18%). This dealkylation was attributed to a S_N2 on the methyl substituent of the iminium by the diethylamine.¹⁶ Note that all salts were isolated in mixture with the corresponding protonated dialkyl amine. Hopefully, the amine was easily removed during the next anion-exchange step (Scheme 4). Hence, the overall conversions and treatment processes were much better with this **method 2** than with **method 1**.



Scheme 2: Synthetic pathways for the preparation of amino-quinazolinium salts (P = pressure sealed flask).

We then evaluated the same two-step synthetic strategy for the preparation of quinazolinium salts (**Method 2**, Scheme 2). Unfortunately, this method proved unsuitable for the alkylation of the quinazoline core, giving a mixture of the expected methylated quinazolinium salt **20** and starting material **12** (ratio 50/50). Our different attempts to separate **20** from **12** failed. **Method 1**, consisting first of the amination step and then the alkylation step, was therefore applied again. Interestingly, **method 1** was well suited to the functionalization of the quinazoline core. Nucleophilic aromatic

substitutions on the 4-chloro-**12** and 4-chloro-6,7-dimethoxyquinazoline **13** were facilitated by the presence of this second nitrogen closer to the chlorine and gave the expected amino-quinazolines **14-16** in good to excellent yields (49-98%). This time, the presence of the electron-donating methoxy groups was no longer a problem. Finally, *N*-methylation of the amino-quinazolines **14-16** gave the corresponding amino-quinolinium salts **17-19** in excellent yields (76-96%) (overall yields of 37, 83 and 91%, respectively).

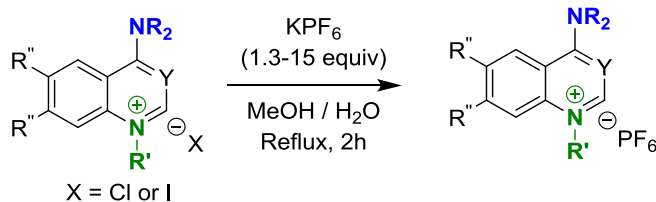


Scheme 3: Synthetic pathways for the preparation of *N,N'*-bridged bis-quin(az)olinium salts (P = pressure sealed flask).

Finally, we sought to determine which method would be more appropriate for the preparation of dimeric *N,N'*-bridged bis-quin(az)olinium salts **21** and **22**. Despite the better results provided by **method 2** on the synthesis of monomeric quinolinium salt (Scheme 1), starting with the *N*-alkylation step for the *N,N'*-tethering of two chloroquinoline cycles was unfavourable (Scheme 3, **method 2**). An attempted *N,N'*-alkylation of two molecules of 4-chloro-6,7-dimethoxyquinoline **2** with a propyl-bridge resulted in an inseparable mixture of expected dimer **26**, mono-substituted *N*-halopropane quinolinium salts **24** or **25**, and protonated 4-halo-6,7-dimethoxyquinolinium salt **23**, in addition to halogen exchanges. When diiodoethane was used to form an ethyl-bridge, no alkylation was detected at all on 4-chloroquinazolines **12** and **13**. We suspected that the diiodoethane underwent halogen eliminations under the high temperature

conditions. Therefore, **method 1** was the only possible route for the synthesis of *N,N'*-propyl-bridged bis-quinolinium salt **21**, even though yields were moderate using this pathway (overall yield = 52%) (Scheme 3). As with the preparation of monomeric quinazolinium salts, **method 1** was also the most efficient route for the synthesis of *N,N'*-propyl-bridged bis-quinazolinium salt **22**, through first amination and then bis-alkylation (overall yield = 81%) (Scheme 3).

To adjust the solubility of these quin(az)olinium salts and facilitate their storage, the halide counterion could be exchanged for a hexafluorophosphate ion, making it less hygroscopic. This also avoided mixtures of halide counterions, ensuring a single hexafluorophosphate anion. Anion exchanges performed smoothly under reflux, leading to the hexafluorophosphate salts **5**-, **6**-, **9**-, **11**-, **17**-, **18**-, **19**-, **21**- and **22-PF₆** in good to excellent yields (Scheme 4, 38-88%).



Scheme 4: Anion exchange on quinazolinium salts

- 5-PF₆, Y = CH, R = Et, R' = Me, R'' = H (61%)
 6-PF₆, Y = CH, R = Et, R' = Me, R'' = OMe (65%)
 9-PF₆, Y = CH, R = Me, R' = Me, R'' = H (46%)
 11-PF₆, Y = CH, R = Me, R' = Me, R'' = OMe (53%)
 17-PF₆, Y = N, R = Et, R' = Me, R'' = H (77%)
 18-PF₆, Y = N, R = Et, R' = Me, R'' = OMe (88%)
 19-PF₆, Y = N, R = Me, R' = Me, R'' = OMe (38%)
 21-PF₆, Y = CH, R = Et, R' = -(CH₂)₃, R'' = OMe (59%)
 22-PF₆, Y = N, R = Et, R' = -(CH₂)₃, R'' = OMe (75%)

Conclusion

This study demonstrated the advantages and limitations of different synthetic routes for the preparation of monomeric and dimeric amino-quinolinium and -quinazolinium salt series with promising anti-plasmodial properties. Method 1, consisting first in amination followed by *N*-alkylation step to form the final salt, was the most versatile procedure, allowing the synthesis of a large range of compounds. However, it required large excess of amine reagents (up to 20 equivalents) and successive purification steps resulting in lower overall yields. Method 2, consisting first in *N*-alkylation to form an iminium salt intermediate that then facilitated the amination step, allowed a drastic increase of the overall yield in some cases. However, this method was not applicable to the synthesis of several salts, notably quinazolinium salts, leading to partial conversions during the alkylation step.

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Supporting Information

YES

Conflict of Interest

The authors declare no conflict of interest.

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- 1,3-Bis(4-(diethylamino)-6,7-dimethoxy-quinolinium)propane diiodide, **21**: In a sealed microwave vial, a solution of *N,N'*-diethyl-6,7-dimethoxyquinolin-4-amine **4** (50 mg, 0.19 mmol, 1 equiv) and 1,3-diiodopropane (10 µl, 0.086 mmol, 0.45 equiv.) was stirred 24h in anhydrous acetonitrile (5 mL) at 110°C. Diethyl ether (25 mL) was then added to the cooled suspension to favour the precipitation of the solid. The suspension was then filtered, washed with diethyl ether (3 x 10 mL) and dried under vacuum. The solid was recrystallized from ethanol to give the desired 1,3-bis(4-(diethylamino)-6,7-dimethoxy-quinolin-1-ium)propane diiodide **21** as a pale-yellow solid (61 mg, 87%). ¹H NMR: (400 MHz, DMSO-d₆) δ 1.38 (12H, t, J = 6.9 Hz, 4 CH₃), 2.44-2.46 (2H, m, CH₂), 3.72 (8H, q, J = 6.9 Hz, 4 NCH₂), 3.96 (6H, s, 2 OCH₃), 3.98 (6H, s, 2 OCH₃), 4.79 (4H, broad t, J = 7.2 Hz, 2 N⁺CH₂), 7.02 (2H, d, J = 7.5 Hz, 2 H³), 7.27 (2H, s, 2 H⁸), 7.31 (2H, s, 2 H⁵), 8.45 (2H, d, J = 7.5 Hz, 2 H²). ¹³C APT NMR: (100 MHz, DMSO-d₆) δ 12.4 (CH₃), 27.9 (CH₂), 46.8 (NCH₂), 51.2 (N⁺CH₂), 55.9 (OCH₃), 56.7 (OCH₃), 98.7 (CH³), 103.7 (CH⁵), 106.0 (CH⁸), 113.7 (C^{4a}), 135.8 (C^{8a}), 142.8 (CH²), 147.4 (C⁶), 154.3 (C⁷), 157.4 (C⁴). HRMS (ESI): m/z 281.1752 [M]²⁺ calcd for C₃₃H₄₆N₄O₄²⁺ 281.1754.
- 1,3-Bis(4-(diethylamino)-6,7-dimethoxy-quinolinium)propane dihexafluorophosphate **21-PF₆**: A solution of 1,3-bis(4-(diethylamino)-6,7-dimethoxy-quinolin-1-ium)propane diiodide **21** (40 mg, 0.048 mmol, 1 equiv.) and potassium hexafluorophosphate (0.135 g, 0.73 mmol, 15 equiv) was stirred 2 h in a MeOH/H₂O solution (5 mL, 1:1) at 60°C under reflux. Water (20 mL) was then added to the cooled suspension to favour the precipitation of the solid. The suspension was filtered and

washed with water (3 x 10 mL) and dried under vacuum to give the desired 1,3-bis(4-(diethylamino)-6,7-dimethoxyquinolinium)propane dihexafluorophosphate **21-PF₆** as a pale-yellow solid (24 mg, 59%). **¹H NMR**: (400 MHz, DMSO-*d*⁶) δ 1.37 (12H, t, *J* = 6.9 Hz, 4 CH₃), 2.41-2.49 (2H, m, CH₂), 3.72 (8H, q, *J* = 6.9 Hz, 4 NCH₂), 3.95 (6H, s, 2 OCH₃), 3.96 (6H, s, 2 OCH₃), 4.74 (4H, broad t, *J* = 7.2 Hz, 2 N⁺CH₂), 7.01 (2H, d, *J* = 7.6 Hz, 2 H³), 7.25 (2H, s, 2 H⁸), 7.31 (2H, s, 2 H⁵), 8.41 (2H, d, *J* = 7.6 Hz, 2 H²). **¹³C APT NMR**: (100 MHz, DMSO-*d*⁶) δ 12.4 (CH₃), 27.8 (CH₂), 46.8 (NCH₂), 51.2 (N⁺CH₂), 55.9 (OCH₃), 56.6 (OCH₃), 98.7 (CH³), 103.7 (CH⁵), 106.0 (CH⁸), 113.7 (C^{4a}), 135.8 (C^{8a}), 142.9 (CH²), 147.4 (C⁶), 154.3 (C⁷), 157.5 (C⁴). **¹⁹F NMR** (DMSO-*d*⁶) δ -70, *d*, *J* =

711 Hz. **³¹P NMR** (162 MHz, DMSO-*d*⁶) δ -144, sept, *J* = 711 Hz. **HRMS (ESI)**: *m/z* 281.1754 [M]²⁺, calcd for C₃₃H₄₆N₄O₄²⁺ 281.1754; *m/z* 707.3153 [M²⁺+PF₆]⁺, calcd for C₃₃H₄₆F₆N₄O₄P⁺ 707.3155. **Decomposition point** = 240-245°C.
