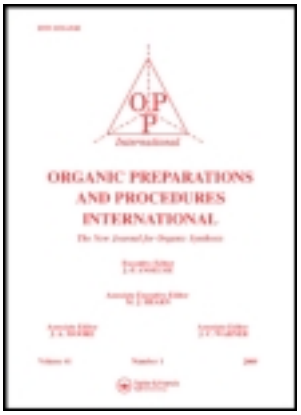

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Microwave-assisted Heck Synthesis of Substituted 2,4-Diaminopyrimidine-based Antibiotics

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Microwave-assisted organic synthesis is an area of increasing interest for promoting clean, reproducible, high-yielding reactions under mild conditions.[1,2] This is evident from the large number of papers and reviews that have appeared on this topic in the recent literature.[3–8] In the current work, microwave irradiation was employed to facilitate the intermolecular formation of C–C bonds using a palladium-catalyzed Heck coupling reaction. Microwave conditions have previously been used to accelerate this type of reaction[9,10] as well as other metal-catalyzed processes such as the Suzuki, Sonogashira and Negishi couplings.[11,12] However, the use of microwave irradiation to induce reactions of highly functionalized molecules has not been studied in detail. We, therefore, wish to report our work on a microwave-assisted Heck reaction to prepare a series of antibacterials bearing a variety of functional groups.

The goal of the current project is the synthesis 2,4-diaminopyrimidine antibiotics **3a–h**, which have potential for the treatment of inhalation anthrax, a bioterror threat. The most important aspect of these drugs is that they selectively inhibit the activity of *Bacillus anthracis* dihydrofolate reductase (DHFR) but not human DHFR.[13,14] DHFR plays a critical role in folate metabolism and is a good target for antibiotic drug candidates. Furthermore, since our compounds incorporate several structural units common to drugs that inhibit DHFR, it is less likely that bacteria exposed to these agents will readily develop a resistance to them.

The synthesis involves a Heck reaction of 2,4-diamino-5-(5-iodo-3,4-dimethoxybenzyl)pyrimidine (**1**) with a series of (±)-1-(1-substituted-1*H*-phthalazin-2-yl)prop-2-en-1-ones **2**, both of which are available by known methods.[13,15] Earlier syntheses of certain examples of **3** by conventional Heck procedures[13,15] gave yields of 10%–37%. The products obtained by this method, however, were difficult to purify from the reaction mixture

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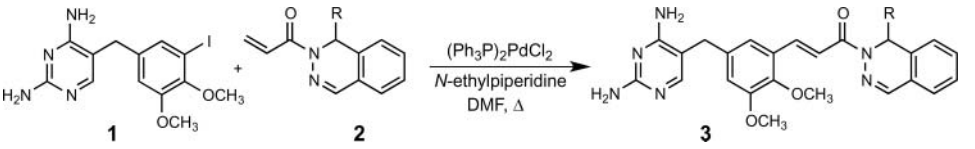
due to extensive side-product formation. We have successfully improved the synthesis by employing microwave irradiation to assist the Heck coupling process.



The conventional reactions were carried out using 2.07 mmol each of **1** and **2**, 2.27 mmol of *N*-ethylpiperidine and 0.026 mmol (1.24 mol % relative to substrates **1** and **2**) of bis(triphenylphosphine)palladium(II) dichloride catalyst in 8 mL of DMF under argon at 140°C–150°C for 18 h.[13,15] This procedure generally afforded the coupled product in low yield (10%–37%) with substantial side-product formation. In an effort to improve this outcome, substrate concentrations and temperatures were varied, but neither of these changes resulted in significant improvement. Attempts to adjust the catalyst loading for this transformation were also examined. An increase in catalyst loading to 2.00 mol % decreased the yield of the product and added to the impurity profile, making isolation of the product more difficult. A decrease in catalyst loading to 0.96 mol % led to incomplete reaction and recovery of starting material along with the desired product. Thus, a catalyst loading of 1.24 mol % proved optimum for the complete conversion to the product with a minimum of side reactions. Finally, the use of other catalysts (e.g. $Pd(OAc)_2$, $PdCl_2$, $(Ph_3P)_4Pd$, Pd/C and CuI)[13] and bases (e.g. Et_3N, DBU, K_2CO_3 and Cs_2CO_3)[13] failed to improve the conversion to product.

Reactions were also carried out on the same molar scale in sealed tubes. This resulted in slightly improved yields (42%–65%), but side-reactions were still problematic. It is conceivable that prolonged heating under conventional and sealed tube conditions caused degradation of the substrates and the catalyst, leading to a more complex product mixture. Thus, a method was sought to decrease the reaction time, which led us to the use of microwave irradiation.

Microwave-assisted reactions were run on the same scale as above at 400 W and 150°C under argon for 60–80 min and gave superior conversions to products with far fewer impurities. A comparison of yields obtained using conventional, sealed tube and microwave conditions is shown in *Table 1*. Microwave irradiation as an alternative source of heating expedited the reaction, decreased the required catalyst loading by 20% (to 0.96 mol %) and reduced the amount of solvent needed by 25%. A series of reactions was carried out with R = propyl, isobutyl, isobutenyl, phenyl, 4-fluorophenyl, benzyl, 4-methylbenzyl and 4-trifluoromethoxybenzyl to establish the generality of the method. Products prepared in this manner were conveniently purified by placing the crude reaction mixture directly onto a silica gel column and eluting with increasing concentrations of methanol in dichloromethane. The target molecules were isolated as hydrates or solvates[16] and were characterized by elemental and spectral analysis.

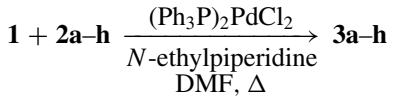


Table 1

Yields of **3** Using Conventional, Sealed Tube and Microwave Conditions

Product	R	Yields		
		Conventional	Sealed Tube[a]	Microwave[b]
3a	*n*-C_3H_7	37	42	74
3b	*i*-C_4H_9	30	65	76
3c	*i*-C_4H_7	36	65	70
3d	C_6H_5	26	60	78
3e	4-FC_6H_4	28	55	72
3f	$C_6H_5CH_2$	22	56	72
3g	4-$CH_3C_6H_4CH_2$	18	48	68
3h	4-$CF_3OC_6H_4CH_2$	10	25	58

[a]Sealed tube, 2.07 mmol each of **1** and **2**, 2.27 mmol of *N*-ethylpiperidine, 0.026 mmol of $(Ph_3P)_2PdCl_2$, 8 mL DMF, 140°C–150°C, 18 h; [b]Greenchem Plus glass microwave tube, 2.07 mmol each of **1** and **2**, 2.27 mmol of *N*-ethylpiperidine, 0.020 mmol of $(Ph_3P)_2PdCl_2$, 6 mL of DMF, 400 W, 150°C, 60–80 min.

We have successfully developed a synthesis of 2,4-diaminopyrimidine-based antibiotics that utilizes a microwave-assisted Heck reaction on highly functionalized substrates in the final step. The reaction is superior to reactions performed under conventional or sealed tube conditions, requiring less solvent and catalyst. More importantly, the use of microwave conditions reduced reaction times and provided higher coupling yields with fewer side products.

Experimental Section

Commercial anhydrous *N,N*-dimethylformamide (DMF) was stored under dry nitrogen and transferred by syringe into reactions where it was used. All other commercial reagents were used as received. Unless otherwise specified, all reactions were run under dry argon in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech No. 21521). Preparative separations were performed by column chromatography in quartz columns using silica gel (grade 62, 60–200 mesh) mixed with UV-active phosphor (Sorbent Technologies, No. UV-5) and band elution was followed using a hand-held UV lamp. Melting points were uncorrected. FT-IR spectra were run as thin films on sodium chloride disks. ^{1}H- and ^{13}C-NMR spectra were measured in DMSO-d_6 on a Varian GEMINI 300 instrument at 300 MHz (^{1}H) and 75 MHz (^{13}C) or a Varian INOVA 400 instrument at 400 MHz and 100 MHz, respectively, and referenced to internal tetramethylsilane. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

General Procedure for the Synthesis of 3a–h.[11]

A solution of 2,4-diamino-5-(5-iodo-3,4-dimethoxybenzyl)pyrimidine (**1**) (800 mg, 2.07 mmol),[11] the corresponding phthalazine derivative **2a–h** (2.07 mmol),[11] *N*-ethylpiperidine

(257 mg, 0.30 mL, 2.27 mmol) and *bis*(triphenylphosphine)palladium(II) dichloride (14 mg, 0.020 mmol) in 6 mL of dry DMF was prepared in a 125 mm × 30 mm id Greenchem Plus glass microwave reactor tube. The solution was purged with dry argon for 1 min, and the tube was closed. The sample was then placed inside a CEM (Mars Model 230/60) microwave unit and irradiated at 400 W and 150°C for 1–1.3 h. After cooling, the crude reaction mixture was transferred directly to a 30 cm × 2 cm silica gel column slurry packed in dichloromethane. Impurities were eluted using dichloromethane, and the coupled product was eluted using 4% methanol in dichloromethane. Evaporation of the solvent gave a pale yellow solid which was chromatographed a second time using a 15-cm × 2-cm silica gel column, packed with 5% triethylamine in dichloromethane and eluted with 4% methanol in dichloromethane. This second chromatography removed traces of catalyst as well as several other minor impurities. The products obtained were recrystallized from methanol to give pure **3a–h**.

(±)-(E)-3-{5-[(2,4-Diaminopyrimidin-5-yl)methyl]-2,3-dimethoxyphenyl}-1-[1-propylphthalazin-2(1H)-yl]prop-2-en-1-one (3a)

This compound was obtained as described above using 472 mg (2.07 mmol) of **2a** to give 745 mg (74%) of **3a** as a white powder, mp. 121°C–124°C (shrinks to a glass-like bead). IR: 3474, 3341, 3182, 1645 cm^{-1}; ^{1}H-NMR (300 MHz): δ 8.07 (d, 1 H, $J = 16.1$ Hz), 7.80 (s, 1 H), 7.66 (s, 1 H), 7.64 (d, 1 H, $J = 16.1$ Hz), 7.45 (td, 1 H, $J = 7.3$, 1.5 Hz), 7.36 (td, 1 H, $J = 7.5$, 1.3 Hz), 7.28 (dd, 1 H, $J = 7.5$, 1.5 Hz), 7.18 (dd, 1 H, $J = 7.3$, 1.5 Hz), 7.13 (d, 1 H, $J = 1.9$ Hz), 6.66 (d, 1 H, $J = 1.9$ Hz), 5.91 (t, 1 H, $J = 6.8$ Hz), 4.84 (br s, 2 H), 4.66 (br s, 2 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.68 (s, 2 H), 1.64 (m, 2 H), 1.27 (m, 2 H), 0.87 (t, 3 H, $J = 7.1$ Hz); ^{13}C-NMR (75 MHz): δ 166.5, 162.6, 162.3, 156.8, 153.5, 147.3, 142.3, 137.1, 134.2, 134.0, 131.4, 129.7, 128.0, 126.5, 125.6, 124.0, 118.7, 118.6, 112.9, 106.3, 61.4, 55.9, 51.3, 37.3, 34.4, 18.3, 13.8.

Anal. Calcd for $C_{27}H_{30}N_6O_3 \cdot 2.0\,H_2O \cdot 0.5\,CH_3OH$: C, 61.32; H, 6.32; N, 15.92. Found: C, 61.56; H, 6.12; N, 15.81.

(±)-(E)-3-{5-[(2,4-Diaminopyrimidin-5-yl)methyl]-2,3-dimethoxyphenyl}-1-[1-isobutylphthalazin-2(1H)-yl]prop-2-en-1-one (3b)

This compound was obtained as described above using 501 mg (2.07 mmol) of **2b** to give 790 mg (76%) of **3b** as an off-white powder, mp. 127°C–129°C. IR: 3443, 3352, 3173, 1644 cm^{-1}; ^{1}H-NMR (300 MHz): δ 8.00 (s, 1 H), 7.86 (d, 1 H, $J = 16.5$ Hz), 7.58 (d, 1 H, $J = 16.5$ Hz), 7.57 (s, 1 H), 7.55 (overlapping d and t, 2 H, $J \approx 7.7$ Hz), 7.46 (t, 1 H, $J = 7.4$ Hz), 7.38 (d, 1 H, $J = 7.1$ Hz), 7.27 (s, 1 H), 7.02 (s, 1 H), 6.87 (br s, 2 H), 6.38 (br s, 2 H), 5.89 (t, 1 H, $J = 6.6$ Hz), 3.80 (s, 3 H), 3.74 (s, 3 H), 3.62 (s, 2 H), 1.38 (m, 3 H), 0.93 (d, 3 H, $J = 4.9$ Hz), 0.88 (d, 3 H, $J = 4.9$ Hz); ^{13}C-NMR (75 MHz): δ 165.4, 162.8, 159.3, 152.5, 150.1, 146.1, 143.3, 136.6, 135.5, 134.0, 131.8, 128.3, 127.9, 126.2 (2 C), 123.6, 118.6, 117.9, 114.9, 106.9, 60.8, 55.8, 48.8, 43.3, 32.1, 23.5, 22.9, 22.2.

Anal. Calcd for $C_{28}H_{32}N_6O_3 \cdot 1.5\,H_2O$: C, 63.85; H, 6.69; N, 15.93. Found: C, 63.85; H, 6.44; N, 15.94.

(±)-(E)-3-{5-[(2,4-Diaminopyrimidin-5-yl)methyl]-2,3-dimethoxyphenyl}-1-[1-isobutenylphthalazin-2(1H)-yl]prop-2-en-1-one (3c)

This compound was obtained as described above using 497 mg (2.07 mmol) of **2c** to give 720 mg (70%) of **3c** as an off-white powder, mp. 130°C–132°C. IR: 3474, 3339, 3172, 1642 cm^{-1}; ^{1}H-NMR (400 MHz): δ 7.91 (s, 1 H), 7.86 (d, 1 H, $J = 16.0$ Hz), 7.59 (d, 1 H, $J = 16.0$ Hz), 7.57 (s, 1 H), 7.52 (m, 2 H), 7.42 (t, 1 H, $J = 7.4$ Hz), 7.31 (d, 1 H, $J = 7.7$ Hz), 7.25 (s, 1 H), 7.01 (s, 1 H), 6.72 (br s, 2 H), 6.50 (d, 1 H, $J = 8.8$ Hz), 6.24 (br s, 2 H), 5.24 (d, 1 H, $J = 8.8$ Hz), 3.80 (s, 3 H), 3.74 (s, 3 H), 3.61 (s, 2 H), 1.96 (s, 3 H), 1.60 (s, 3 H); ^{13}C-NMR (100 MHz): δ 165.3, 162.7, 159.9, 155.9, 152.5, 151.2, 146.1, 142.0, 136.7, 135.7, 133.8, 133.5, 132.1, 128.2, 127.9, 126.1 (2 C), 123.0, 122.1, 118.5, 118.0, 114.8, 106.6, 60.8, 55.8, 49.2, 25.2, 18.4.

Anal. Calcd for $C_{28}H_{30}N_6O_3 \cdot 1.5\ H_2O$: C, 64.32; H, 6.33; N, 15.99. Found: C, 64.67; H, 6.35; N, 16.07.

(±)-(E)-3-{5-[(2,4-Diaminopyrimidin-5-yl)methyl]-2,3-dimethoxyphenyl}-1-[1-phenylphthalazin-2(1H)-yl]prop-2-en-1-one (3d)

This compound was obtained as described above using 542 mg (2.07 mmol) of **2d** to give 840 mg (78%) of **3d** as a light pink powder, mp. 142°C–144°C. IR: 3478, 3340, 3178, 1653 cm^{-1}; ^{1}H-NMR (300 MHz): δ 7.98 (s, 1H), 7.87 (d, 1 H, $J = 15.9$ Hz), 7.70 (d, 1 H, $J = 15.9$ Hz), 7.64–7.50 (complex m, 3 H), 7.60 (s, 1 H), 7.45 (t, 1 H, $J = 7.1$ Hz), 7.33-7.18 (complex m, 7 H), 6.99 (s, 1 H), 6.19 (br s, 2 H), 5.74 (br s, 2 H), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.59 (s, 2 H); ^{13}C-NMR (75 MHz): δ 165.8, 162.3, 162.1, 155.8, 152.4, 146.0, 142.0, 141.7, 137.1, 136.6, 132.9, 132.2, 128.58, 128.51, 127.6, 127.5, 127.2, 126.4, 126.0, 122.9, 118.4, 117.6, 114.9, 105.7, 60.8, 55.7, 53.8, 32.4.

Anal. Calcd for $C_{30}H_{28}N_6O_3 \cdot 0.5\ H_2O$: C, 68.31; H, 5.50; N, 15.87. Found: C, 68.41; H, 5.49; N, 15.93.

(±)-(E)-3-{5-[(2,4-Diaminopyrimidin-5-yl)methyl]-2,3-dimethoxyphenyl}-1-[1-(4-fluorophenyl)-phthalazin-2(1H)-yl]prop-2-en-1-one (3e)

This compound was obtained as described above using 582 mg (2.07 mmol) of **2e** to give 800 mg (72%) of **3e** as an off-white powder, mp. 143°C–145°C. IR: 3479, 3347, 3180, 1649 cm^{-1}; ^{1}H-NMR (300 MHz): δ 8.00 (s, 1 H), 7.88 (d, 1 H, $J = 15.9$ Hz), 7.69 (d, 1 H, $J = 15.9$ Hz), 7.61-7.56 (complex m, 3 H), 7.60 (s, 1 H), 7.46 (m, 1 H), 7.27 (complex m, 3 H), 7.12 (t, 2 H, $J = 8.8$ Hz), 7.02 (s, 2 H), 6.19 (br s, 2 H), 5.75 (br s, 2 H), 3.79 (s, 3 H), 3.73 (s, 3 H), 3.59 (s, 2 H); ^{13}C-NMR (75 MHz): δ 165.8, 162.3, 162.2, 161.4 (d, $J = 243.9$ Hz), 155.8, 152.5, 146.0, 142.1, 137.9 (d, $J = 2.9$ Hz), 137.3, 136.6, 132.7, 132.3, 128.7, 128.3 (d, $J = 8.3$ Hz), 127.6, 127.2, 126.5, 122.9, 118.4, 117.5, 115.4 (d, $J = 21.5$ Hz), 114.4, 105.7, 60.8, 55.7, 53.0, 32.4.

Anal. Calcd for $C_{30}H_{27}FN_6O_3 \cdot 0.5\ H_2O$: C, 65.81; H, 5.12; N, 15.36. Found: C, 65.88; H, 5.14; N, 15.24.

(±)-(E)-1-(1-Benzylphthalazin-2(1H)-yl)-3-{5-[(2,4-diaminopyrimidin-5-yl) methyl]-2,3-dimethoxyphenyl}prop-2-en-1-one (3f)

This compound was obtained as described above using 571 mg (2.07 mmol) of **2f** to give 800 mg (72%) of **3f** as an off-white powder, mp. 143°C–145°C. IR: 3479, 3336, 3179, 1658 cm^{-1}; ^{1}H-NMR (400 MHz): δ 7.83 (d, 1 H, $J = 16.0$ Hz), 7.78 (s, 1 H), 7.61 (s, 1 H), 7.60 (d, 1 H, $J = 16.0$ Hz), 7.47-7.37 (complex m, 3 H), 7.24 (s, 1 H), 7.17 (m, 3 H), 7.00 (d, 1 H, $J = 1.2$ Hz), 6.96 (m, 1 H), 6.86 (m, 2 H), 6.19 (br s, 2 H), 6.04 (t, 1 H, $J = 6.4$ Hz), 5.73 (br s, 2 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 3.60 (s, 2 H), 2.90 (dd, 1 H, $J = 13.0$, 7.6 Hz), 2.83 (dd, 1 H, $J = 13.0$, 5.7 Hz); ^{13}C-NMR (100 MHz): δ 165.6, 162.3, 162.2, 155.8, 152.5, 146.0, 142.3, 136.64, 136.57, 136.2, 132.4, 131.3, 129.6, 128.4, 127.9, 127.8, 126.6, 126.5, 125.9, 123.8, 118.3, 117.8, 114.7, 105.7, 60.8, 55.7, 52.3, 48.6, 32.4.

Anal. Calcd for $C_{31}H_{30}N_6O_3 \cdot 1.0\ CH_3OH$: C, 67.96; H, 5.84; N, 14.86. Found: C, 68.13; H, 5.86; N, 15.12.

(±)-(E)-3-{5-[(2,4-Diaminopyrimidin-5-yl)methyl]-2,3-dimethoxyphenyl}-1-[1-(4-methylbenzyl)phthalazin-2(1H)-yl]prop-2-en-1-one (3g)

This compound was obtained as described above using 571 mg (2.07 mmol) of **2g** to give 770 mg (68%) of **3g** as an off-white powder, mp. 135°C–137°C. IR: 3477, 3338, 3176, 1657 cm^{-1}; ^{1}H-NMR (400 MHz): δ 7.83 (d, 1 H, $J = 16.1$ Hz), 7.78 (s, 1 H), 7.61 (s, 1 H), 7.60 (d, 1 H $J = 16.1$ Hz), 7.44 (m, 1 H), 7.41 (dd, 2 H, J = 5.6, 3.4 Hz), 7.24 (d, 1 H $J = 1.6$ Hz), 6.99 (s, 1 H), 6.98 (d, 2 H, $J = 8.0$ Hz), 6.96 (m, 1 H), 6.73 (d, 2 H, $J = 8.0$ Hz), 6.18 (br s, 2 H), 6.00 (t, 1 H, $J = 6.4$ Hz), 5.73 (br s, 2 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 3.60 (s, 2 H), 2.85 (dd, 1 H, $J = 13.2$, 7.6 Hz), 2.78 (dd, 1 H, $J = 13.2$, 5.5 Hz), 2.23 (s, 3 H); ^{13}C-NMR (100 MHz): δ 165.5, 162.3, 162.2, 155.8, 152.5, 146.0, 142.2, 136.6, 136.5, 135.4, 133.1, 132.5, 131.3, 129.5, 128.6, 128.3, 127.8, 126.7, 125.9, 123.8, 118.3, 117.8, 114.7, 105.7, 60.8, 55.7, 52.4, 48.6, 32.4, 20.7.

Anal. Calcd for $C_{31}H_{30}N_6O_3 \cdot 1.0\ CH_3OH$: C, 68.26; H, 6.25; N, 14.47. Found: C, 68.27; H, 6.11; N, 14.78.

(±)-(E)-3-{5-[(2,4-Diaminopyrimidin-5-yl)methyl]-2,3-dimethoxyphenyl}-1-[1-(4-trifluoromethoxybenzyl)phthalazin-2(1H)-yl]prop-2-en-1-one (3h)

This compound was obtained as described above using 716 mg (2.07 mmol) of **2h** to give 740 mg (58%) of **3h** as an off-white powder, mp. 125°C–127°C. IR: 3481, 3335, 3183, 1657 cm^{-1}; ^{1}H-NMR (400 MHz): δ 7.81 (d, 1 H, $J = 16.1$ Hz), 7.80 (s, 1 H), 7.60 (s, 1 H), 7.58 (d, 1 H, $J = 16.1$ Hz), 7.44 (m, 3 H), 7.24 (s, 1 H), 7.17 (d, 2 H, $J = 8.0$ Hz), 7.08 (m, 1 H), 6.99 (s, 1 H), 6.98 (d, 2 H, $J = 8.0$ Hz), 6.18 (br s, 2 H), 6.08 (t, 1 H, $J = 6.3$ Hz), 5.73 (br s, 2 H), 3.79 (s 3 H), 3.73 (s, 3 H), 3.59 (s, 2 H), 2.95 (dd, 1 H, $J = 13.2$, 7.0 Hz), 2.85 (dd, 1 H, $J = 13.2$, 6.1 Hz); ^{13}C-NMR (100 MHz): δ 165.6, 162.3, 162.2, 155.7, 152.5, 147.1, 146.0, 142.4, 136.6, 135.8, 132.3, 131.5, 131.4, 128.5, 127.7, 126.6, 126.0, 123.8, 120.5, 120.0 (q, $J = 256.2$ Hz), 118.8, 118.3, 117.7, 114.8, 105.7, 60.8, 55.7 (2 C), 52.0, 32.4.

Anal. Calcd for $C_{32}H_{29}F_3N_6O_4 \cdot 2.5\ H_2O$: C, 57.91; H, 4.86; N, 12.66. Found: C, 57.74; H, 4.51; N, 12.37.

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