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# A Novel Methodology for Efficient Removal of Residual Palladium from a Product of the Suzuki−Miyaura Coupling with Polymer-Supported Ethylenediamine Derivatives

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## Abstract:

**In our investigation to efficiently remove residual palladium from a drug candidate prepared via the Suzuki−Miyaura coupling reaction, it was found that polymer-bound ethylenediamines can absorb both Pd(0) and Pd(II). This property was applied to the removal of residual palladium from the crude 2′-cyanobiphenyl product (*R*)-2 obtained by the Suzuki−Miyaura coupling of an optically active bromobenzene derivative (*R*)-1 with a boronate 3. Treatment with the polymer-bound ethylenediamines reduced the palladium content of the crude product from 2000−3000 to 100−300 ppm. Subsequent purification by salt formation with di-*p*-toluoyl-D-tartaric acid (DTTA) attained a low palladium content of less than 10 ppm.**

For the past decade, palladium-catalyzed organic syntheses such as the Mizoroki−Heck, the Sonogashira and the Suzuki−Miyaura reactions have been utilized more frequently in C−C bond formation between aromatic rings.[1−3] However, during the course of their use for industrial preparation of active pharmaceutical ingredients (APIs), a serious problem was often encountered in that residual palladium remained in the final products. To our best knowledge, few efficient methods to remove the residual palladium have been reported.[4] In 1997, Rosso reported that trimercaptotriazine (TMT) works as an effective agent for removing the residual palladium as insoluble TMT−Pd complexes.[5] This method seems unsuitable to prepare compounds that have poor solubility in organic solvents, because TMT−Pd complexes also precipitate to prevent isolation of the target compounds in a pure form.

In the industrial production of E2040 that is a potent antagonist of $D_3$/$D_2$/5-$HT_2$ receptors,[6] we had the same problem of removal of residual palladium from a crude product. Rosso's method mentioned above was not effective (vide post). We found that various derivatives of ethylenediamine work effectively as reagents for our purpose. In this contribution, we wish to report that polymer-supported derivatives of ethylenediamine can be employed for efficient and convenient removal of residual palladium.

We synthesized the biphenyl moiety of E2040 by the Suzuki−Miyaura reaction. An optically active bromobenzene derivative **(*R*)-1** was subjected to the Suzuki−Miyaura coupling with a boronate **3** using 1 mol % of $PdCl_2(PPh_3)_2$, as shown in Scheme 1, to give a coupling product **(*R*)-2**. As expected, the crude **(*R*)-2** contained a large amount (more than 2000 ppm) of palladium after the usual workup. This value at this stage is too high to attain acceptable residual metal content (less than 10 ppm) in the final **E2040** as an API. Therefore, we turned to efforts to reduce the palladium content of crude **(*R*)-2**.

Activated carbon and activated clay were shown not to effectively remove the residual palladium from our crude **(*R*)-2**. Filtration of solutions of **(*R*)-2** through 0.22 μm filters cannot reduce the residual palladium level. Washing the organic layer with 25% aqueous ammonia showed a slight effect on the reduction of palladium, but it was not enough

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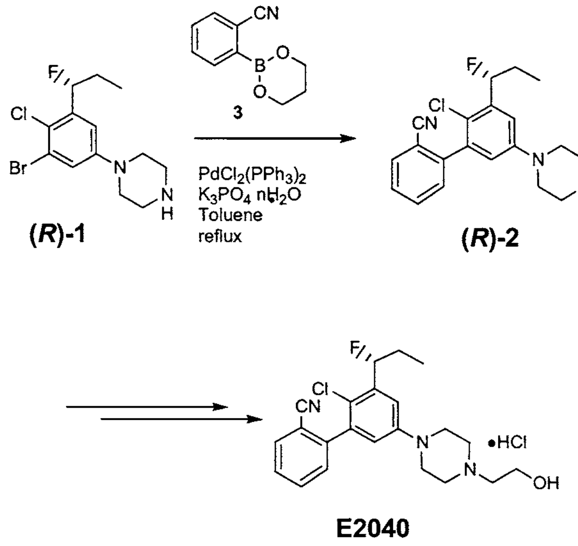
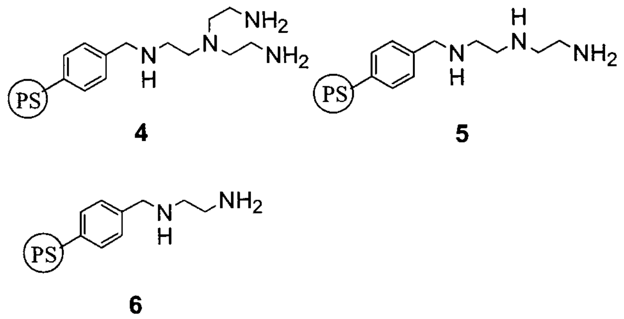
***Scheme 1.*** **Synthetic route of E2040 via the Suzuki–Miyaura cross coupling**



to reduce the residual palladium to an acceptable limit (<10 ppm) in the final API. Since (***R***)-**2** is unstable under acidic conditions, washing with diluted HCl cannot be employed. When ethylenediamine was added to make a complex with the residual palladium, an insoluble oil was deposited. The organic layer was separated and then treated with (+)-di-*p*-toluoyl-D-tartaric acid (DTTA) to give a salt that was shown to contain 11 ppm of residual palladium (Table 1). This value is acceptable because residual palladium can be decreased to an undetectable level (<1 ppm) in the final production step of E2040 by crystallization.

In the aforementioned treatment with ethylenediamine, the separation of the oil was troublesome. Hence, we examined the use of polymer-supported ethylenediamines for the removal of the residual palladium. The polymer-bound ethylenediamine derivatives shown in Chart 1 are commercially available. They are stable in organic solvents and have been employed as quenchers in combinatorial chemistry.[7]

***Chart 1.*** **Commercially available polymer-bound ethylenediamine derivatives**

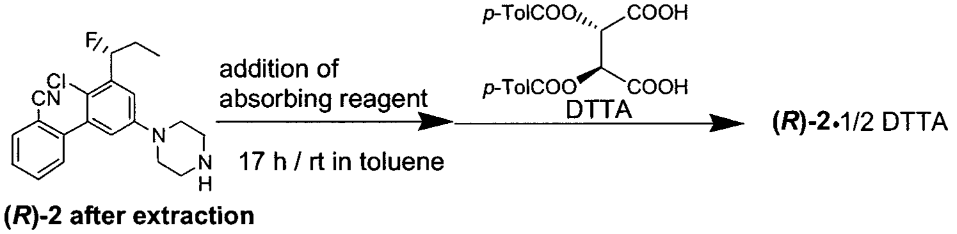


The ability of these polymer-supported ethylenediamines (**4**, **5**, and **6**) to remove palladium was examined.

Preliminarily, the crude ***(R)*-2** was treated with these reagents in toluene, acetone, or methanol for 65 h. As shown in Table 2 (entries 2–6), these reagents showed high ability to reduce the palladium content. Hence, we decided to employ **4** in further experiments using practical conditions (entries 7–14), because it is the most easily available resin. Since it was employed as an extraction solvent, toluene was selected as a reaction solvent in these examinations.

Although polymer **4** and PS-Trisamine are both resins with the ethylenediamine moiety, their ability to remove palladium is different (entries 7 and 13). Generally, the addition of the resin brought about the gradual decolorization of the (***R***)-**2** solution, accompanied by color of the surface of the resin turning black. However, PS-Trisamine neither changed its surface color nor the color of the solution (entry 13). Efficiency of the resin depends on its amount and the treatment time. Prolonged treatment reduced the palladium content in the presence of a small amount of resin (entry 11), but an amount of the resin equal in weight to that of the starting material is necessary to complete the reaction in a short time (entry 7). Although a plug-flow system is expected to reduce the necessitated amount of the resins, our experiments at the present time were carried out in a batch system because of the limitation of facilities.

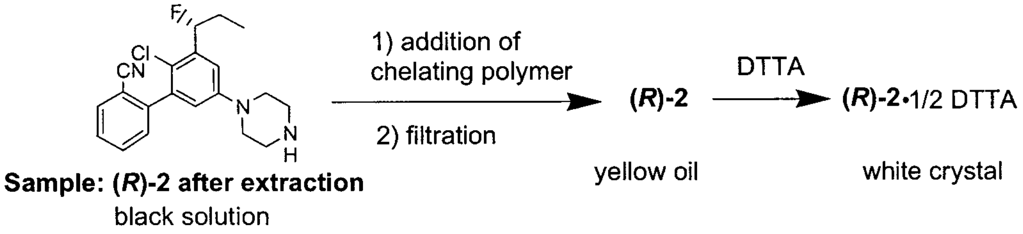
***Table 1.*** **Removal effect for (*R*)-2 by absorbing reagents**



| entry | sample[a] | absorbing reagents | mol equiv ratio against (***R***)-**1** | residual Pd (ppm) |
|---|---|---|---|---|
| 1 | A | none | | 903 |
| 2[b] | A | TMT[c] | 0.1 | 410 |
| 3 | B | TMT[c] | 1 | *e* |
| 4 | B | ethylenediamine[d] | 0.1 | 6 |
| 5 | B | ethylenediamine[d] | 1 | 11 |

[a] Sample is concentrated residue of crude ***(R)*-2** after extraction. Pd content of A is 2445 ppm. and Pd content of B is 2683 ppm. [b] Toluene/acetonitrile (1:9) was used as solvent. [c] Pd complex with TMT is separated by filtration as an insoluble solid from the solvent. [d] Pd complex with ethylenediamine is separated as a highly viscous oil by decantation from toluene. [e] The value was not determined, since recovery of (***R***)-**2** in the step of separation from TMT is very low (<30%).

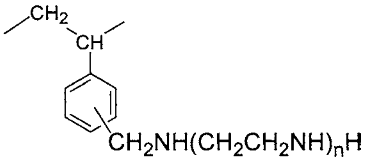
***Table 2.*** **Removing effect for (*R*)-2 by polymer-bound ethylenediamines**



| entry | polymer | sample[a] | solvent | loading amount | time (h) | residual Pd (ppm) (*R*)-2 | residual Pd (ppm) (***R***)-**2**·1/2DTTA |
|---|---|---|---|---|---|---|---|
| 1 | none | A | | | | – | 903 |
| 2 | **4** | A | toluene | 1 | 65 | – | 2 |
| 3 | **4** | A | acetone | 1 | 65 | – | 4 |
| 4 | **4** | A | methanol | 1 | 65 | – | 2 |
| 5 | **5** | A | toluene | 1 | 65 | – | <2 |
| 6 | **6** | A | toluene | 1 | 65 | – | <2 |
| 7 | **4** | B | toluene | 1 | 17 | 103 | 18 |
| 8 | **4** | B | toluene | 1 | 31 | 136 | 7 |
| 9 | **4** | B | toluene | 0.5 | 17 | 354 | 62 |
| 10 | **4** | B | toluene | 0.5 | 31 | 179 | 37 |
| 11 | **4** | A | toluene | 0.2 | 168 | 189 | 15 |
| 12 | **4** | A | toluene | 0.1 | 168 | 986[d] | – |
| 13 | **4**[b] | B | toluene | 1 | 15 | 516[d] | – |
| 14 | ethylenediamine[c] | B | toluene | 1 | 17 | 370 | 11 |

[a] Sample is concentrated residue of crude (***R***)-**2** after extraction. Pd content of A is 2445 ppm and Pd content of B is 2683 ppm. [b] PS-trisamine is used as tris(2-aminoethyl)amine polystyrene that is available from Argonaut Technologies, Inc. as a scavenging resin. [c] Ethylenediamine was used instead of **4**. [d] The solution was not decolorized after treatment with polymer.

***Chart 2.*** **DiAION CR20 (7)**



DIAION CR20 (**7**),[8] a chelating resin (Chart 2), is commercially supplied with constant quality and suitability for production in a large scale. Therefore **7** was also tested, and the results are summarized in Table 3. Treatment of the crude (***R***)-**2** with an excess amount (6 or 4:1 weight ratio) of **7** (entries 2 or 4, respectively) could remove the residual palladium to the same level as the aforementioned polymer-bound ethylenediamines. The use of an equal amount of **7** required a longer period of time (entry 1). It should be noted that treatment with twice amount of **7** for a day gave an insufficient result (entry 5), probably because of the small contact area of **7**. Indeed, milled **7** showed an improvement (entry 6). It is noteworthy that heating of the system brought about a dramatic effect to achieve a satisfactorily reduced content of residual palladium (entries 7 and 8).[9] Slow agitation (<100 rpm on magnetic stirrer) is enough for the polymer to adsorb residual palladium. Therefore, there was little attrition of the polymer beads in all experiments.

In aqueous organic solvents, polymer-bound ethylenediamines have less ability than under anhydrous conditions, although the polymers **4** were more effective than **7** (Table 4).

Since heating the system in toluene was most effective in our studies, this methodology was applied to the crude product containing palladium at a higher level. When the crude product (Pd content: 6126 ppm) obtained by the coupling reaction using an increased amount (2 mol %) of the catalyst was treated with **7** at 60 °C, the residual palladium was sufficiently removed (Pd content: 363 ppm). Subsequent treatment with DTTA afforded (***R***)-**2·1/2DTTA** which could be derived to the final API containing palladium less than 10 ppm.

The present method was successfully scaled up to 4.47 kg. As outlined in Scheme 2, 4.47 kg of (***R***)-**1** was subjected to the reaction with **3**. The present method was applied to give 3.95 kg of (***R***)-**2.** After salt formation with DTTA, 5.19 kg of (***R***)-**2·1/2DTTA** was obtained as a white powder containing 35 ppm of palladium.

Finally, we examined the ability of TMT and polymer-supported ethylenediamine to remove Pd(0) and Pd(II). As summarized in Table 5, TMT exhibited high ability to remove Pd(0) specifically, and Pd(II) was moderately removed by TMT. On the other hand, the reverse result was obtained by the use of the polymer-supported ethylenediamine. These results suggest that an effective approach to remove Pd(0) and Pd(II) at the same time is the use of a combination system of a resin-bound version of TMT with **4**.

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(8) Particle size distribution: >1180 $\mu$m, <5%; <300 $\mu$m, <1%.

(9) After being rinsed with toluene, **7** was heated in toluene at 80 °C over 31 h without substrate. Weight of the concentrated filtrate of the solution was negligible (<0.015% against **7**). This residue is detectable by HPLC and easily soluble in acetone that is the solvent in the next step. Actually, no corresponding peaks were detected in the obtained DTTA salt of (***R***)-**2**.

***Table 3.*** **Removing effect for (*R*)-2 by resin 7**

| entry | sample[a] | solvent | wt ratio **7/(*R*)-1** | temp | time (h) | residual Pd (ppm) **(*R*)-2** |
|---|---|---|---|---|---|---|
| 1 | A | toluene | 1 | rt | 65 | 119 |
| 2 | A | toluene | 6 | rt | 3 | 348 |
| 3 | B | toluene | 4 | rt | 2 | −(438)[b] |
| 4 | B | toluene | 4 | rt | 17 | 124 (18)[b] |
| 5 | B | toluene | 2 | rt | 17 | 1185 (553)[b] |
| 6 | A | toluene | 2(milled) | rt | 17 | 522 |
| 7 | B | toluene | 2 | 50 °C | 17 | 212 |
| 8 | B | toluene | 2 | 75 °C | 17 | 163 |
| 9 | A | acetone | 1 | rt | 3 | 445 (39)[b] |

[a] Sample is concentrated residue of crude **(*R*)-2** after extraction. Pd content of A is 2445 ppm and Pd content of B is 2683 ppm. [b] The value in parentheses shows residual Pd in DTTA salt that is induced from the corresponding **(*R*)-2**.

***Table 4.*** **Removing effect for (*R*)-2 by polymer-bound ethylenediamines in aqueous solvent systems at room temperature**

| entry | polymer | sample[a] | solvent (ratio) | wt. ratio **7/(*R*)-1** | time (days) | residual Pd (ppm) **(*R*)-2** |
|---|---|---|---|---|---|---|
| 1 | **4** | C | acetone/$H_2O$ (10/6) | 2 | 1 | 273 |
| 2 | **4** | D | EtOH/$H_2O$ (10/5) | 2 | 1 | 268 |
| 3 | **4** | E | MeOH/$H_2O$(10/2) | 2 | 1 | 203 |
| 4 | **7** | C | acetone/$H_2O$(10/6) | 1 | 3 | 868 |
| 5 | **7** | D | EtOH/$H_2O$(10/5) | 1 | 3 | 840 |
| 6 | **7** | E | MeOH/$H_2O$(10/2) | 1 | 3 | 685 |

[a] Sample is concentrated residue of crude **(*R*)-2** after extraction. Pd content of C is 3281 ppm, D is 3080 ppm, and E is 3898 ppm.

***Scheme 2.*** **Scaled-up experiment using 7**

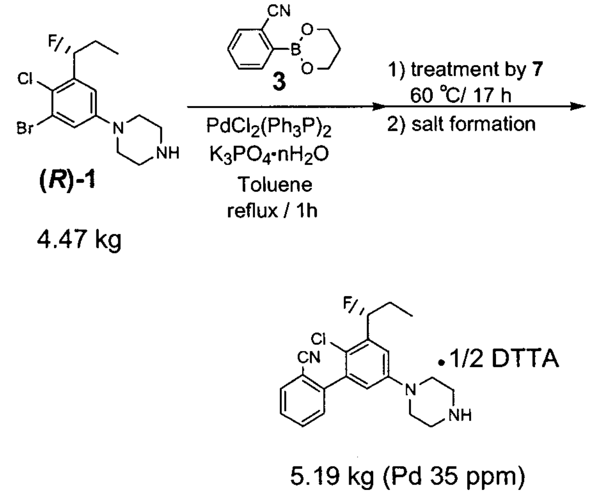

***Table 5.*** **Removing capacity of absorbing reagents for Pd(0) or Pd(II)**

| Pd source | additive | mol | residual Pd in filtrate (ppm) |
|---|---|---|---|
| $Pd(OAc)_2$ | TMT | 3 | 37.5 |
| $Pd_2(dba)_3$ | TMT | 3 | <0.1 |
| $Pd(OAc)_2$ | 4 | 3 | <0.1 |
| $Pd_2(dba)_3$ | 4 | 3 | 28.3 |

In summary, efficient removal of residual palladium from the cyanobiphenyl compound **(*R*)-2** that has high affinity for palladium was achieved with polymer-bound ethylenediamine derivatives. The present result promises that these derivatives can be used as powerful reagents for the removal of residual palladium, even in cases wherein TMT works inefficiently.

## Experimental Section

Polymer-supported ethylenediamines (**4**, **5**, and **6**) were purchased from Aldrich, and PS-Trisamine is available from Argonaut Technologies, Inc. Their catalog specifications are as follows.

**4**: tris(2-aminoethyl)amine, polymer-bound, swelling volume 8 mL/g dry resin, contains 4.0−5.0 mmol N/g. **5**: diethylenetriamine, polymer-bound, product comments: 1% cross-linked, 200−400 mesh, typical loading 2.5−3.0 mmol N/g. **6**: ethylenediamine, polymer-bound, product comments: 1% cross-linked, 200−400 mesh, typical loading 2.5−3.0 mmol N/g. **PS-Trisamine**: tris(2-aminoethyl)amine polystyrene; capacity: 3−5 mmol/g (based on benzoyl chloride uptake), resin type: 1% cross-linked poly(styrene-*co*-divinylbenzene). **7**: DIAION CR20 was purchased from Mitsubishi Chemical Corporation. 1-{3-bromo-4-chloro-5-[1-(*R*)-fluoropropyl]}phenylpiperazine **(*R*)-1** and 2-(1,3,2-dioxaborinan-2-yl)benzonitrile **3** were prepared by a previously reported method.[6]

Other solvents and reagents were used as received from commercial suppliers and used without further purification. All ICP experiments were done on a Perkin Elmer Optima 3300 DV.

**Typical Procedure in Experiments for Removal of Palladium.** To a solution of 31.9 g (assay: 92.5%, 95.0 mmol) of 1-{3-bromo-4-chloro-5-[1-(*R*)-fluoropropyl]}-phenylpiperazine **(*R*)-1**, 670 mg (0.95 mmol) of dichlorobis-(triphenylphosphine)palladium, and 26.7 g (143 mmol) of 2-(1,3,2-dioxaborinan-2-yl)benzonitrile **3** in 160 mL of toluene at room temperature was added 35.34 g (143 mmol) of tripotassium phosphate hydrate. Under nitrogen atmosphere, the reaction mixture was then heated under reflux for 1 h to consume most of **(*R*)-1**. The mixture was cooled to room temperature, and then 160 mL of water to conduct partition was added. The organic layer was separated and washed with 160 mL of water. The organic layer was evaporated to afford 45.23 g (assay: 72.9%) of 1-{3-(2-cyanophenyl)-4-chloro-5-[1-(*R*)-fluoropropyl]}phenylpiperazine as a viscous black oil (initial value of Pd; 2445 ppm in the residue).

In 10 mL of toluene was dissolved 0.50 g (1.0 mmol as **(*R*)-2**) of the oil, and to this at room temperature was added 0.54 g of resin **4** and then stirred 3 days. The mixture was filtered and evaporated to afford 0.49 g of crude 1-{3-(2-cyanophenyl)-4-chloro-5-[1-(*R*)-fluoropropyl]}phenyl piperazine **(*R*)-2** as a viscous yellow oil. (Residual Pd of the obtained residue was determined by ICP as crude **(*R*)-2**.) To a stirred solution of 0.24 g (0.6 mmol) of (+)-di-*p*-toluoyl-D-tartaric acid in 3.6 mL of acetone containing 1.1 mL of water was added a solution of 0.49 g of crude **(*R*)-2** in 3.6 mL of acetone containing 1.1 mL of water over 30 min at room temperature. The mixture was then heated at 60 °C and maintained at the same temperature while stirring for 5 h and allowed to cool to room temperature. After the mixture was stirred for further 16 h, the precipitates were collected by filtration, washed with aqueous acetone, and dried to a constant weight in an oven (60 °C) to give 0.41 g of **(*R*)-2·1/2DTTA** as white crystals (residual Pd: 2 ppm ).

**Preparation of 1-{3-(2-Cyanophenyl)-4-chloro-5-[1-(*R*)-fluoropropyl]}phenyl piperazine (*R*)-2 and Its (+)-Di-*p*-toluoyl-D-tartaric Acid Salt (*R*)-2·1/2DTTA.** To a solution of 4.47 kg (13.3 mol) of 1-{3-bromo-4-chloro-5-[1-(*R*)-fluoropropyl]}phenylpiperazine **(*R*)-1**, 100 g (0.14. mol) of dichlorobis(triphenylphosphine)palladium and 3.80 kg of 2-(1,3,2-dioxaborinan-2-yl)benzonitrile **3** in 23 L of toluene at room temperature was added 4.86 kg of tripotassium phosphate hydrate. Under nitrogen atmosphere, the reaction mixture was then heated under reflux for 1 h to consume most of **(*R*)-1**. The mixture was cooled to room temperature, and then 23 L of water to conduct partition was added. The organic layer was separated and washed with 23 L of water. To this organic layer was added 9.10 kg of DIAION CR20 and was stirred for 17 h at 60 °C. DIAION CR20 was removed by filtration, and the filtrate was concentrated to give crude **(*R*)-2** as a viscous yellow oil (content 3.95 kg, yield: 83%).

To a stirred solution of 2.56 kg (6.62 mol) of (+)-di-*p*-toluoyl-D-tartaric acid in 40 L of acetone containing 12 L of water was added a solution of the concentrated residue of crude **(*R*)-2** in 40 L of acetone containing 12 L of water over 30 min at room temperature. The mixture was then heated at 60 °C and maintained at the same temperature while stirring for 2.5 h and allowed to cool to room temperature. After the mixture was stirred for further 1.3 h, the precipitates were collected by filtration, washed with aqueous acetone, and dried in an oven (60 °C)to a constant weight to give 5.19 kg of **(*R*)-2·1/2DTTA** as white crystals (yield: 85% from crude **(*R*)-2**, residual Pd: 35 ppm).

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.07 (t, $J = 7.6$ Hz, 3H), 1.80−2.10 (m, 2H), 2.21 (s, 3H), 3.00−3.20 (m, 8H), 5.50 (s, 1H), 5.77 (ddd, $J = 3.2$, 8.4 and 47.2 Hz, 1H), 6.64 (d, $J = 2.8$ Hz, 1H), 6.89 (d, $J = 2.8$ Hz, 1H), 6.98 (d, $J = 8.4$ Hz, 2H), 7.32−7.44 (m, 4H), 7.79 (d, $J = 8.4$ Hz, 2H). Mp 197−199 °C dec. Anal. Calcd for $C_{30}H_{30}ClFN_3O_4$: C, 65.39; H, 5.49; N, 7.63%, Found: C, 65.19; H, 5.54; N, 7.61%.

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