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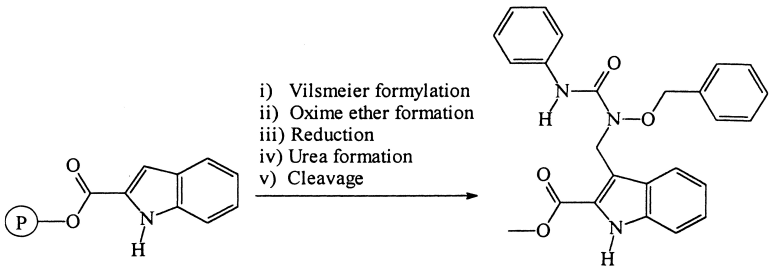

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Vilsmeier Formylation of 2-Carboxyindoles and Preparation of *O*-Benzylhydroxyureas on Solid Phase

Jan Tois,*,† Robert Franzèn,‡ Olli Aitio,† Into Laakso,§ and Irene Kylänlahti||

Department of Pharmacy, Division of Pharmaceutical Chemistry, University of Helsinki, P.O. Box 56, FIN-00014, Helsinki, Finland, Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-Ku, Tokyo 113-0033, Japan, Department of Pharmacy, Division of Pharmacognosy, University of Helsinki, P.O. Box 56, FIN-00014, Helsinki, Finland, and Department of Pharmacy, Viikki Drug Discovery Technology Center, P.O. Box 56, FIN-00014 University of Helsinki, Finland

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The Vilsmeier formylation has been introduced for the solid-phase functionalization of five different 2-carboxyindoles. The aldehyde functionality has been utilized in the preparation of *O*-benzylhydroxyureas.

Introduction

Interest in the application of solid-phase synthesis in drug research has increased rapidly in the past 5 years.[1,2] Undoubtedly, there is a growing need to expand the repertoire of efficient organic reactions on solid phase.

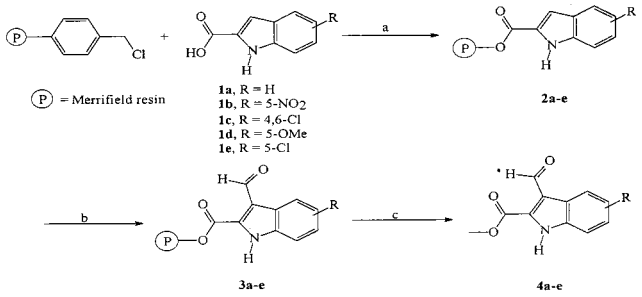
Usually in combinatorial solid-phase chemistry the aromatic ring systems are built from smaller molecules, and several publications have reported the formation of pyrroles,[3,4] pyridines,[5,6] indoles,[7] and other aromatic ring systems.[8] On the other hand, there are only a few examples where the aromatic systems have been modified directly by introducing a new functionality to the resin-bound moiety.[9−11]

Vilsmeier formylation is a classical organic name reaction.[12] The reaction was first used only for activated aromatics and heteroaromatics, but more recently this reaction has shown its compatibility for aliphatic substrates.[13] Until today, according to our knowledge, the reaction has not been used for the modifications of any solid-supported substrates.

Results and Discussion

In an ongoing project on the modifications of pharmaceutically interesting 2-carboxyindoles,[14] we needed a versatile functionality at the C-3 position for combinatorial purposes. As mentioned by Hermkens and Hamersma,[15] the aldehyde group was listed as a functionality suitable for chemical transformations and for giving access to a new region in chemical diversity space. We decided to try the Vilsmeier reaction[16] to provide a facile way for introducing a CHO group to 2-carboxyindoles on solid phase. The synthetic route and formylating conditions are illustrated in Scheme 1 and Table 1, respectively.

Scheme 1[a]



[a] Reagents and conditions: (a) Cs_2CO_3 or DIPEA, CsI, DMF, 60 °C; (b) see Table 1; (c) NaOMe, THF/MeOH 4:1, room temp.

Table 1. Attempted Reaction Conditions in Our Experiments

resin	formylating agent[a]	conversion **2**/**3**[b] (%)	*T* (°C)
2a	$POCl_3$/NMFA	0/100	room temp
2a	$POCl_3$/DMF	0/100	60
2a	$POCl_3$/NMFA	0/100	60
2b	$POCl_3$/DMF	85/15	60
2b	$POCl_3$/NMFA	60/40	60
2b	$POCl_3$/NMFA	15/85	reflux
2b	$SOCl_2$/DMF	90/10	60
2c	$POCl_3$/DMF	85/15	60
2c	$POCl_3$/NMFA	70/30	60
2c	$POCl_3$/NMFA	10/90	reflux
2c	$SOCl_2$/DMF	90/10	60
2d	$POCl_3$/NMFA	0/100	room temp
2d	$POCl_3$/DMF	0/100	room temp
2e	$POCl_3$/NMFA	0/100	room temp
2e	$POCl_3$/DMF	0/100	room temp

[a] NMFA: *N*-methylformanilide. DMF: *N*,*N*-dimethylformamide. [b] Determined by mass percentages of isolated column-purified yields.

In all experiments (Table 1) the formylating agent was prepared in a separate vessel and resins **2a**−**e** were added to the mixture after 20 min with 1,2-dichloroethane. The reaction time and the equivalents of formylating agent were kept constant in each attempt (16 h and 10 equiv, respectively). The hydrolysis of the prime product (iminium salt) was performed with 50% NaOAc in all cases except the entries where DMF/$POCl_3$ was used as the formylating

* To whom correspondence should be addressed. E-mail: Jan.Tois@helsinki.fi.
† Division of Pharmaceutical Chemistry, University of Helsinki.
‡ University of Tokyo.
§ Division of Pharmacognosy, University of Helsinki.
|| Viikki Drug Discovery Technology Center.

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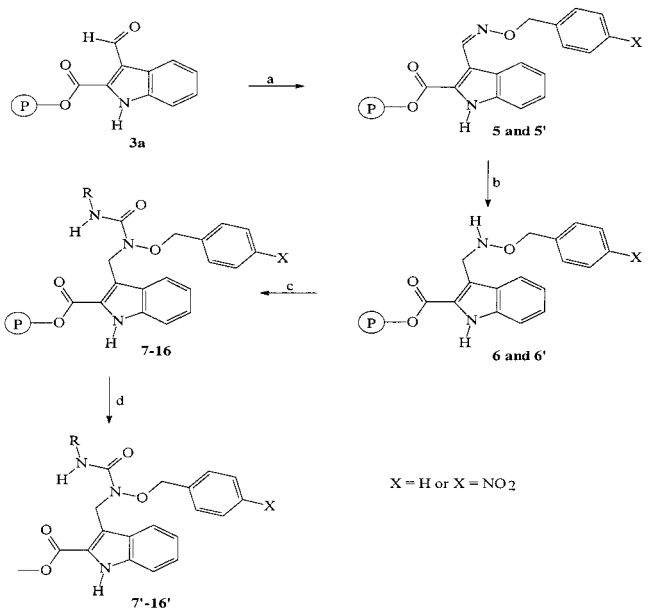
Scheme 2[a]



[a] Reagents and conditions: (a) *O*-benzylhydroxylamine hydrochloride, pyridine/EtOH 1:1, room temp; (b) BH_3/pyridine, dichloroacetic acid, DCM, 0 °C to room temperature; (c) isocyanates (see Table 2), DMF, room temp; (d) NaOMe, THF/MeOH 4:1, room temp.

complex. In these cases, water was used instead of NaOAc. Reaction worked smoothly for resins **2a**, **2d**, and **2e** (quantitative conversion at room temperature), but resins **2b** and **2c** needed more drastic conditions (reflux).

The attachment of **1a**, **1d**, and **1e** to Merrifield resin worked well when Cs_2CO_3 was used as a base. However, we noticed that **1b** and **1c** were attached to the polymer through a C−N bond also.[17] This was probably due to an electronic effect of the R substituent. The C−N bond formation during the attachment was avoided when DIPEA was used as a base instead of Cs_2CO_3. The Boc protection[18] was also an alternative, but we found it to be much more convenient to change the attachment conditions.

Next we treated **3a** with *O*-benzylhydroxylamine hydrochloride or 4-nitro-*O*-benzylhydroxylamine hydrochloride, affording **5** or **5′**, respectively. Reduction of the *O*-benzyloxime ether **5** and **5′** with a borane−pyridine complex in the precence of dichloroacetic acid[19] gave **6** and **6′**. *O*-Benzylhydroxylamines **6** and **6′** were reacted with isocyanates and cleaved[20] from the resin, providing *O*-benzylhydroxyureas **7′**−**16′** (Scheme 2, Table 2).

In summary, we have demonstrated that Vilsmeier formylation is an efficient and simple method for C−C bond formation on solid support. Although the total yields of six steps were only moderate (30−75%, calculated on the basis of the commercially announced loading), the purity of the compouds were high (>90%). There was no need for chromatographic purification after cleavage. We are now in the process of extending our studies toward using different carboxyindoles, making this route more useful for preparation of combinatorial libraries.

Experimental Section

General Methods. Reagents were obtained from Aldrich, and Merrifield resin was purchased from NovaBiochem. Thin-layer chromatography was performed on 0.25 mm E. Merck silica gel 60 F_{254} plates and visualized by UV (254 nm). Purity analyses were performed on an HP 1100 liquid chromatography system using UV detection (254 nm). NMR spectra were recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C on a Varian Unity 500 spectrometer, and DMSO-d_6 was used as solvent in all experiments. HRMS data were recorded on a ZABSPEC-oa TOF/Fisons instrument. After each reaction step, a small amount of product was cleaved from the resin and the complete conversion was checked by TLC.

Typical Procedure for 3a. The attachment of **1a** to Merrifield resin (commercially announced loading of 0.63 mmol/g) followed the procedure by Frenette and Friesen.[19] The derivatized resin **2a** was washed and dried properly before the next step. A mixture of *N*-methylformanilide (NMFA) (0.44 mL) and $POCl_3$ (0.33 mL) was stirred for 20 min under nitrogen, providing a yellow solid salt. Resin **2a** (0.4 g) was added to the salt, followed by dichloroethane (DCE, 7 mL). The mixture was stirred overnight at room temperature. After 16 h, 50% NaOAc solution (3 mL) was added to the reaction mixture and the slurry was stirred for 2 h at room temperature. After the hydrolysis, resin **3a** was filtered and washed with DCE, DMF, DMF/H_2O, THF, MeOH, and DCM and dried.

Typical Procedure for 5. Polymer **3a** (0.4 g) was suspended in 8 mL of pyridine/EtOH (1:1). *O*-Benzylhydroxylamine hydrochloride (0.4 g) was added to the mixture, and the mixture was stirred overnight at room temperature. Resin **5** was filtered and washed with pyridine, EtOH, DMF, MeOH, and DCM.

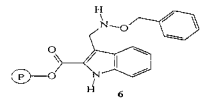
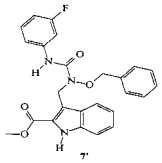
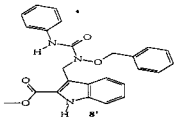
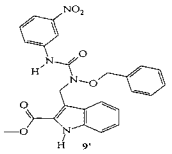
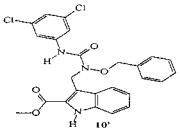
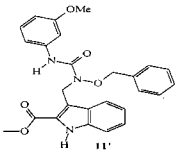
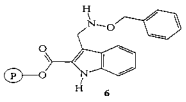
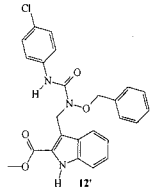
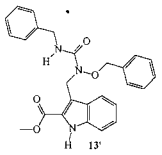
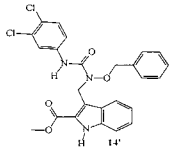
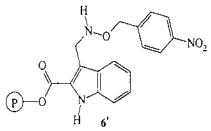
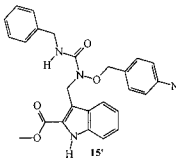
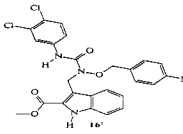
Typical Procedure for 6. Resin **5** (0.4 g) was suspended in DCM (4 mL) and treated with BH_3/pyridine (0.35 mL). The mixture was cooled to 0 °C, and dichloroacetic acid (0.7 mL) was added dropwise. The vessel was capped, and the mixture was stirred overnight with occasional venting during the first hour. Resin **6** was filtered and washed with DCM, MeOH, DMF, MeOH, and DCM.

Typical Procedure for 7. Polymer **6** (0.2 g) was suspended in DMF (3 mL), and 3-fluorophenyl isocyanate (0.145 mL) was added to the mixture. The slurry was stirred overnight at room temperature. Polymer **7** was filtered and washed with DMF, MeOH, DMF, and DCM.

Typical Procedure for 7′. Polymer **7** (0.2 g) was suspended in 5 mL of THF/MeOH (4:1). The mixture was treated with NaOMe (5 mg) and stirred overnight at room temperature. The resin was filtered and washed with THF and MeOH. The filtrate was evaporated to dryness, and 10 mL of water was added to the residue. The white powder was filtered with suction and washed with water. The yield of **7′** was 31.6 mg (67%).

Data for Compounds 7′−16′. 3-[1-Benzyloxy-3-(3-fluorophenyl)ureidomethyl]-1H-indole-2-carboxylic Acid Methyl Ester (7′). Purity was 93% by HPLC. ^{1}H NMR: δ 3.88 (s, 3 H), 4.78 (s, 2 H), 5.36 (s, 2 H), 6.79 (t, 1 H, J = 8 Hz), 7.05 (t, 1 H, J = 8 Hz), 7.28 (m, 7 H), 7.45 (m, 2 H), 7.81 (d, 2 H, J = 8 Hz), 8.89 (s, 1 H), 11.83 (s, 1 H). ^{13}C NMR: δ 40.60, 51.73, 75.74, 106.18 (d, J = 26 Hz), 108.87 (d, J = 21 Hz), 112.46, 115.34, 116.99, 120.02, 121.25, 124.97, 125.97 (d, J = 185 Hz), 127.97, 128.26, 129.36, 129.82 (d,

Table 2. Starting Materials, Products, and Yields Summarized

Entry	Polymer	Isocyanate	Product	Yield (%)
1				67
2				71
3				30
4				53
5				70
6				52
7				73
8				67
9				75
10				33

$J = 10$ Hz), 135.14, 136.21, 140.89 (d, $J = 11$ Hz), 156.13, 161.06, 162.13, 162.97. HRMS: *m/z* calcd for $C_{25}H_{22}N_3O_4F$, 447.1594; found, 447.1607.

3-(1-Benzyloxy-3-phenylureidomethyl)-1H-indole-2-carboxylic Acid Methyl Ester (8′). Purity was 90% by HPLC. ^{1}H NMR: δ 3.88 (s, 3 H), 4.76 (s, 2 H), 5.34 (s, 2 H), 6.98 (t, 1 H, $J = 7.5$ Hz), 7.04 (t, 1 H, $J = 7.5$ Hz), 7.28 (m, 8 H), 7.44 (m, 3 H), 7.83 (d, 1 H, $J = 8.5$ Hz), 8.63 (s, 1 H), 11.83 (s, 1 H). ^{13}C NMR: δ 40.83, 51.72, 75.78, 112.43, 117.19, 119.86, 119.96, 121.37, 122.68, 124.95, 125.20, 126.75, 128.00, 128.24, 128.32, 129.31, 135.30, 136.20, 138.85, 156.47, 162.15. HRMS: *m/z* calcd for $C_{25}H_{23}N_3O_4$, 429.1689; found, 429.1684.

3-[1-Benzyloxy-3-(nitrophenyl)ureidomethyl]-1H-indole-2-carboxylic Acid Methyl Ester (9′). Purity was 91% by HPLC. ^{1}H NMR: δ 3.87 (s, 3 H), 4.81 (s, 2 H), 5.38 (s, 2 H), 7.05 (t, 1 H, $J = 7.5$ Hz), 7.28 (m, 6 H), 7.44 (d, 1 H, $J = 8$ Hz), 7.52 (t, 1 H, $J = 8$ Hz), 7.81 (m, 2 H), 7.91 (d, 1 H, $J = 8$ Hz), 8.51 (s, 1 H), 9.25 (s, 1 H), 11.84 (s, 1 H). ^{13}C NMR: δ 40.47, 51.77, 75.71, 112.51, 113.64, 116.88, 116.97, 120.08, 121.15, 125.01, 125.23, 125.72, 126.67, 127.95, 128.24, 129.30, 129.63, 135.09, 136.21, 140.48, 147.80, 156.07, 162.11. HRMS: *m/z* calcd for $C_{25}H_{22}N_4O_6$, 474.1539; found, 474.1541.

3-[1-Benzyloxy-3-(3,5-dichlorophenyl)ureidomethyl]-1H-indole-2-carboxylic Acid Methyl Ester (10′). Purity was 91% by HPLC. ^{1}H NMR: δ 3.87 (s, 3 H), 4.79 (s, 2 H), 5.36 (s, 2 H), 7.06 (t, 1 H, $J = 7$ Hz), 7.16 (s, 1 H), 7.28 (m, 6 H), 7.44 (d, 1 H, $J = 8$ Hz), 7.63 (d, 2 H, $J = 1.5$ Hz), 7.77 (d, 1 H, $J = 8$ Hz), 9.08 (s, 1 H), 11.83 (s, 1 H). ^{13}C NMR: δ 40.35, 51.75, 75.70, 112.50, 116.79, 117.49, 120.09, 121.10, 121.50, 125.01, 125.22, 126.65, 127.93, 128.25, 129.33, 133.63, 134.99, 136.20, 141.68, 155.73, 162.09. HRMS: *m/z* calcd for $C_{25}H_{21}N_3O_4Cl_2$, 497.0909; found, 497.0906.

3-[1-Benzyloxy-3-(3-methoxyphenyl)ureidomethyl]-1H-indole-2-carboxylic Acid Methyl Ester (11′). Purity was 92% by HPLC. ^{1}H NMR: δ 3.70 (s, 3 H), 3.88 (s, 3 H), 4.76 (s, 2 H), 5.35 (s, 2 H), 6.56 (dd, 1 H, $J = 8$ Hz, $J = 2,5$ Hz), 7.06 (m, 2 H), 7.14 (m, 2 H), 7.27 (m, 6 H), 7.44 (d, 1 H, $J = 8$ Hz), 7.83 (d, 1 H, $J = 8$ Hz), 8.61 (s, 1 H), 11.83 (s, 1 H). ^{13}C NMR: δ 40.82, 51.73, 54.93, 75.79, 105.58, 108.09, 112.08, 112.44, 117.15, 119.98, 121.37, 124.96, 125.22, 126.75, 128.02, 128.26, 129.08, 129.30, 135.31, 136.21, 140.07, 156.37, 159.33, 162.15. HRMS: *m/z* calcd for $C_{26}H_{25}N_3O_5$, 459.1794; found, 459.1801.

3-[1-Benzyloxy-3-(4-chlorophenyl)ureidomethyl]-1H-indole-2-carboxylic Acid Methyl Ester (12′). Purity was 92% by HPLC. ^{1}H NMR: δ 3.87 (s, 3 H), 4.76 (s, 2 H), 5.34 (s, 2 H), 7.04 (t, 1 H, $J = 7.5$ Hz), 7.26 (m, 8 H), 7.43 (d, 1 H, $J = 8.5$ Hz), 7.51 (d, 2 H, $J = 8.5$ Hz), 7.80 (d, 1 H, $J = 8.5$ Hz), 8.82 (s, 1 H), 11.83 (s, 1 H). ^{13}C NMR: δ 40.68, 51.73, 75.71, 112.44, 117.05, 119.98, 121.26, 124.96, 125.21, 126.25, 126.70, 127.95, 128.16, 128.23, 129.33, 135.20, 136.19, 137.98, 156.29, 162.12. HRMS: *m/z* calcd for $C_{25}H_{22}N_3O_4Cl$, 463.1299; found, 463.1299.

3-(3-Benzyl-1-benzyloxyureidomethyl)-1H-indole-2-carboxylic Acid Methyl Ester (13′). Purity was 90% by HPLC.

^{1}H NMR: δ 3.83 (s, 3 H), 4.24 (d, 2 H, J = 5 Hz), 4.67 (s, 2 H), 5.27 (s, 2 H), 7.01 (t, 1 H, J = 7 Hz), 7.09 (d, 2 H, J = 7.5 Hz), 7.24 (m, 9 H), 7.37 (t, 1 H, J = 6 Hz), 7.43 (d, 1 H, J = 8 Hz), 7.81 (d, 1 H, J = 8 Hz), 11.79 (s, 1 H). ^{13}C NMR: δ 41.38, 42.94, 51.62, 75.66, 106.96, 112.306, 117.54, 119.82, 121.70, 124.87, 125.14, 126.37, 126.77, 127.93, 127.98, 128.06, 129.00, 135.46, 136.17, 140.20, 159.42, 162.15. HRMS: *m*/*z* calcd for $C_{26}H_{25}N_3O_4$, 443.1845; found, 443.1863.

3-[1-Benzyloxy-3-(3,4-dichlorophenyl)ureidomethyl]-1H-indole-2-carboxylic Acid Methyl Ester (14′). Purity was 93% by HPLC. ^{1}H NMR: δ 3.87 (s, 3 H), 4.78 (s, 2 H), 5.35 (s, 2 H), 7.05 (t, 1 H, J = 8 Hz), 7.28 (m, 6 H), 7.43 (d, 1 H, J = 8.5 Hz), 7.49 (m, 2 H), 7.78 (d, 1 H, J = 8 Hz), 7.83 (d, 1 H, J = 2 Hz), 9.02 (s, 1 H), 11.83 (s, 1 H). ^{13}C NMR: δ 40.50, 51.73, 75.70, 112.47, 116.87, 119.61, 120.04, 120.65, 121.15, 123.90, 124.98, 125.21, 126.66, 127.92, 128.24, 129.33, 130.14, 130.53, 135.06, 136.19, 139.34, 155.97, 162.09. HRMS: *m*/*z* calcd for $C_{25}H_{21}N_3O_4Cl_2$, 497.0909; found, 497.0916.

3-[3-Benzyl-1-(4-nitrobenzyloxy)ureidomethyl]-1H-indole-2-carboxylic Acid Methyl Ester (15′). Purity was 90% by HPLC. ^{1}H NMR: δ 3.80 (s, 3 H), 4.23 (d, 2 H, J = 5 Hz), 4.80 (s, 2 H), 5.24 (s, 2 H), 7.02 (t, 1 H, J = 7.5 Hz), 7.08 (d, 2 H, J = 6.5 Hz), 7.23 (m, 4 H), 7.42 (m, 3 H), 7.62 (t, 1 H, J = 6 Hz), 7.80 (d, 1 H, J = 8 Hz), 8.05 (d, 2 H, J = 8.5 Hz), 11.78 (s, 1 H). ^{13}C NMR: δ 41.89, 42.93, 51.61, 74.38, 112.30, 117.24, 119.82, 121.62, 122.78, 124.87, 125.08, 126.42, 126.75, 126.84, 127.92, 129.58, 136.13, 140.09, 143.47, 146.91, 159.61, 162.06. HRMS: *m*/*z* calcd for $C_{26}H_{24}N_4O_6$, 488.1696; found, 488.1682.

3-[3-(3,4-Dichlorophenyl)-1-(4-nitrobenzyloxy)ureidomethyl]-1H-indole-2-carboxylic Acid Methyl Ester (16′). Purity was 90% by HPLC. ^{1}H NMR: δ 3.81 (s, 3 H), 4.92 (s, 2 H), 5.32 (s, 2 H), 7.04 (t, 1 H, J = 7.5 Hz), 7.25 (t, 1 H, J = 7.5 Hz), 7.40 (d, 1 H, J = 8.5 Hz), 7.49 (m, 4 H), 7.75 (d, 1 H, J = 8.5 Hz), 7.84 (d, 1 H, J = 2 Hz), 8.08 (d, 2 H, J = 8.5 Hz), 9.20 (s, 1 H), 11.83 (s, 1 H). ^{13}C NMR: δ 40.74, 51.71, 74.63, 112.47, 116.61, 119.80, 120.05, 120.92, 121.06, 122.82, 124.15, 124.99, 125.12, 126.61, 129.65, 130.19, 130.56, 136.14, 139.21, 143.06, 146.97, 156.20, 161.96. HRMS: *m*/*z* calcd for $C_{25}H_{20}N_4O_6Cl_2$, 544.0760; found, 542.0759.

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