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Synthesis of 6- or 4-functionalized indoles via a reductive cyclization approach and evaluation as aromatase inhibitors

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ABSTRACT

Two new series of benzonitrile derivatives on position 6 or 4 of indole ring were successfully synthesized via a Leimgruber–Batcho reaction. All the compounds were evaluated in vitro on the inhibition of aromatase (CYP19) and 17α-hydroxylase-C17,20-lyase (CYP17). The racemate, 4-[(1*H*-imidazol-1-yl)(1*H*-indol-4-yl)methyl]benzonitrile **9**, showed high level of inhibitory activity towards CYP19 (IC_{50} = 11.5 nM).

About two-thirds of breast cancers are dependent on estrogens for growth, so endocrine therapies are widely used for the treatment of hormone-dependent breast cancer (HDBC).[1] Amongst endocrine therapies available today, we find (i) selective estrogen receptor modulators (SERMs), (ii) estrogen deprivation therapy using LHRH agonists and aromatase inhibitors, and (iii) estrogen receptor downregulators and complete antagonists.[2] Recent studies[3–5] have shown that aromatase inhibitors (AIs) are superior to SERMs, such as tamoxifen in terms of survival and side effects. So, the reduction or blockade of estradiol (E2) biosynthesis becomes an important strategy of treatment. The efficacy of AIs can be explained by the fact that they block both genomic and non genomic activities of the estrogen receptor.[2] Then aromatase (CYP19) is a prime target and many researchers intensively worked to find selective AIs.[6] Two non steroidal AIs, letrozole and anastrozole, are daily used in postmenopausal women with HDBC (Fig. 1).

In previous works,[7,8] we presented diverse synthetic routes to 5 or 7-aroylindoles. In series 5, racemic compound **1** and chloro derivative **2** exerted aromatase inhibitory activity at nanomolar level.

In this letter, we describe a synthetic route to access to 6- and 4-aroylindoles, key intermediates in the synthesis of 4-[(azol-1-yl)(indol-6 or 4-yl)methyl)]-benzonitriles. All target compounds were evaluated in vitro for inhibitory activity against CYP19 and CYP17 enzymes.

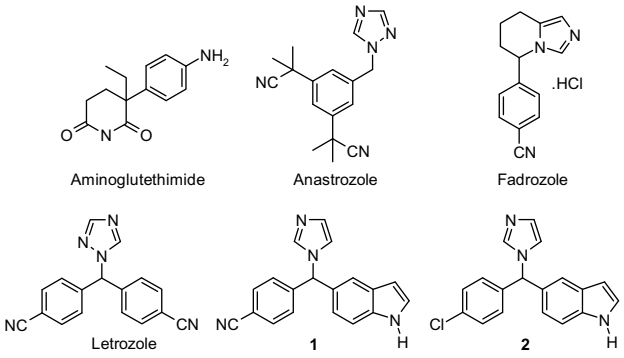

Figure 1. Non steroidal aromatase inhibitors (NSAIs).

As outlined in Scheme 1, the key intermediate **7** was prepared in three steps. First, an acylation of bromobenzene followed by a Leimgruber–Batcho reaction involving *(i)* the formation of enamine **6** and *(ii)* the catalytic reduction of the nitro group followed by spontaneous cyclization to provide the 6-aroylindole **7**.

For the Friedel-Crafts acylation, the bromobenzene **3** was treated with the 4-methyl-3-nitrobenzoyl chloride **4** in the presence of aluminium chloride at 80–85 °C to afford the benzophenone derivative **5** in 66% yield.[9,10] The condensation of **5** with *N,N*-

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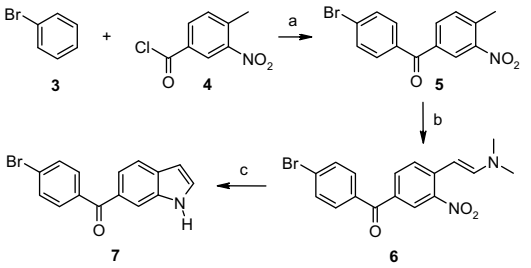


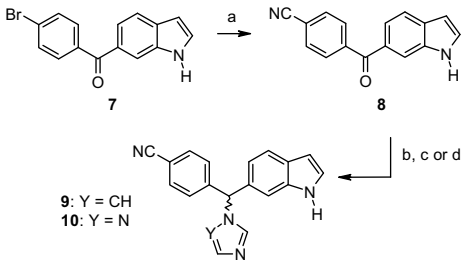
Scheme 1. Reagents and conditions: (a) $AlCl_3$, 80–85 °C, 17 h, 66%; (b) DMFDMA, DMF, 110 °C, 15 h, 73%; (c) Raney-Ni, H_2, EtOH, rt, 3 h, 32%.

dimethylformamide dimethyl acetal at 110 °C provided the corresponding enamine **6** in 73% yield.[11,12] The latter was subjected to reductive cyclization with catalytic hydrogenation using Raney nickel in ethanol to afford the key intermediate **7** in 32% yield.[13,14] Other reducing agents, such as zinc dust in acetic acid[15] or aqueous titanium (III) chloride in ammonium acetate,[16] were used unsuccessfully. Contrary to palladium on carbon, Raney Nickel is the catalyst of choice to avoid hydrogenolysis of bromine atom.

The compound **7** was used as a precursor to afford the nitrile derivative **8** by a bromine/cyano exchange reaction in the presence of zinc cyanide and $Pd(PPh_3)_4$ as catalyst under microwave irradiation (Scheme 2).[17,18]

The synthesis of target compounds **9** and **10** (Scheme 2) was carried out by reduction of the ketone derivative **8** in the presence of sodium borohydride in methanol,[19] followed by the fixation of imidazole or triazole moiety using 1,1′-carbonyldiimidazole (CDI, 61% yield) or 1,1′-carbonyldi(1*H*-1,2,4-triazole) (CDT, 10% yield) in dry acetonitrile or tetrahydrofuran.[20,21]

The same approach, via a Leimgruber–Batcho reaction, was employed to synthesize parent compounds in series 4 (Scheme 3). The commercially available acid **11** was treated with thionyl chloride to afford the corresponding acid chloride **12** in 98% yield.[22,23] Then, the bromobenzene **3** was acylated by compound **12** in the presence of aluminium chloride at 85 °C to afford the benzophenone derivative **13** in 70% yield.[9] The condensation of **13** with *N*,*N*-dimethylformamide dimethyl acetal at 110 °C provided the crude enamine **14** which was directly used in the catalytic hydrogenation using Raney Nickel in ethanol to afford the key intermediate **15** in 15% yield.[11,13] The latter was subjected to a bromine/cyano exchange reaction in the presence of zinc cyanide and $Pd(PPh_3)_4$ as catalyst under microwave irradiation to afford nitrile derivative **16** in 79% yield.[17] As described above, the target compounds **17**, **18** were obtained after reduction of ketone derivative **16** and fixation of azole moieties using CDI (48% yield) or CDT (13% yield).[20,24]



Scheme 2. Reagents and conditions: (a) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, microwaves, 60 W, 153 °C, 4 min, 67%; (b) $NaBH_4$, CH_3OH, 1 h, rt; (c) CDI, CH_3CN, rt, 24 h, 61%; (d) CDT/THF/N_2/rt, 43 h, 10%.

Determination of the in vitro anti-aromatase activity of **9**, **10** and **17**, **18** was carried out using microsomal fraction of human placental tissue,[25] according to a previously described procedure.[26] [1β − ^{3}H]Androstenedione (0.08 μCi, 15 nM), unlabeled androstenedione (485 nM), NADPH-generating system, and inhibitor (0–100 μM, DMSO as solvent) in phosphate buffer (pH 7.4) were preincubated for 5 min at 30 °C in a shaking water bath. Microsomal protein was added to start the enzymatic reaction. After incubation for 14 min at 30 °C, a cold $HgCl_2$ 1 mM solution and a Norit A 2% suspension were added. After shaking and centrifugations, aliquots of the supernatant were assayed for ^3H_2O by counting in a scintillation mixture using LKB-Wallac β-counter. The IC_{50} values were determined by plotting the percent inhibition *versus* the concentration of inhibitor on a semilog plot.

The CYP17 assay was performed in vitro using membrane fractions of recombinant *E. coli* pJL17/OR coexpressing human CYP17/rat NADPH-P450 reductase and progesterone as a substrate.[27] Results are summarized in Table 1.

All target compounds were inactive towards CYP17. The highest inhibition was 26% at 2.5 μM.

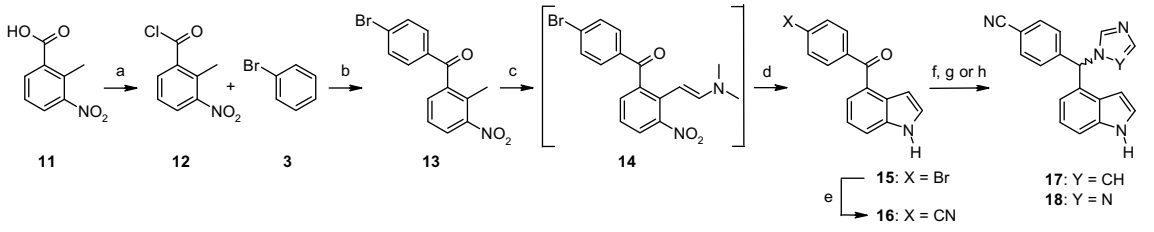
In the aromatase inhibition assay, the triazole derivatives **10** and **18** were less active than the corresponding imidazole analogues **9** and **17**. This results confirmed our previous studies.[7,8,28]

The fixation site of (benzonitrile)(4-cyanophenyl)(1H-imidazol-1-yl)methyl chain on indole ring influenced the pharmacological activities. Thus, the compound **9** in series 6 (IC_{50} = 11.5 nM) was 1.6-fold more potent than its analogue **17** in series 4 (IC_{50} = 18.7 nM). In the same way, compound **9** is more active than the benzonitrile derivative **1** in series 5 (IC_{50} = 19.3 nM).[8]

Table 1
In vitro CYP19 and CYP17 inhibitions by benzonitrile derivatives

Compound	Series	Y	CYP19		CYP17
			IC_{50} (μM)[a]	RP[b]	% Inhibition[c]
9	6	CH	0.0115 (±0.0006)	2587	026
10	6	N	0.0938 (±0.0066)	0317	na
17	4	CH	0.0187 (±0.0021)	1591	018
18	4	N	1.6200 (±0.1800)	0018	<10
AG	—	—	29.75	0001	—
Fadrozole	—	—	00.03	992	na

[a] Values are the mean of at least two experiments performed in duplicate, standard deviation is given in parentheses.
[b] Relative potency RP=IC_{50}(AG)/IC_{50} (tested compound).
[c] Progesterone: 25 μM, inhibitor: 2.5 μM. Values are the mean of two experiments performed in duplicate (na, not active).



Scheme 3. Reagents and conditions: (a) $SOCl_2$, 60 °C, 24 h, 98%; (b) $AlCl_3$, 85 °C, 17 h, 70%; (c) DMFDMA, DMF, 110 °C, 39 h; (d) Raney-Ni, H_2, EtOH, rt, 2.25 h, 15%; (e) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, microwaves, 60 W, 153 °C, 4 min, 79%; (f) $NaBH_4$, CH_3OH, rt; 1 h (g) CDI, CH_3CN, rt, 19 h, 48%; (h) CDT/THF/N_2/rt, 17 h, 13%.

In comparison to our lead racemate inhibitor **2** (IC_{50} = 15.3 nM),[8] the compound **9** showed the highest anti-aromatase activity, with an IC_{50} of 11.5 nM.

All tested molecules were more active than standard compound aminoglutethimide AG (IC_{50} = 29.75 μM). The imidazole derivatives **9** and **17** exhibited an inhibitory activity superior to that of fadrozole (IC_{50} = 30 nM) whereas triazole analogues **10** and **18** were inferior. Furthermore, letrozole and anastrozole, third generation of NSAIs, exhibited inhibition of aromatase activity with IC_{50} values from 10 to 15 nM.[29] So our compound **9** displayed in vitro anti-aromatase activity comparable to that of letrozole (IC_{50} = 11.5 nM).

In summary, the introduction of (benzonitrile)(4-cyanophenyl)(1H-imidazol-1-yl)methyl chain at position 6 or 4 of the indole ring led to potent and selective CYP19 inhibitors. We confirmed that the imidazole core was more favourable than triazole moiety in vitro. Further investigations are required in due course to confirm these above results. We have to separate enantiomers to test them on CYP19 inhibition and to study their in vivo potency.

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10. *Preparation of 4′-bromo-4-methyl-3-nitrobenzophenone* **5**. Aluminium choride (2.23 g, 18.20 mmol) was added portionwise to a stirred solution of 4-methyl-3-nitrobenzoyl chloride (2.55 mL, 17.50 mmol) and bromobenzene (2.90 mL, 27.47 mmol). The reaction mixture was stirred for 17 h at 80–85 °C prior to quenching with H_2O and ethyl acetate. The mixture was poured onto crushed ice, water and ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic fractions were washed with brine and dried over Na_2SO_4. The solvent was removed and the residue was purified on silica gel (hexane-ethylacetate, 8:2 v/v) to afford a beige solid **5** in 66% overall yield. Mp 107–108 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.66 (s, 3H, CH_3), 7.74 (d, J = 7.60 Hz, 1H, H-5), 7.75 (d, J = 8.20 Hz, 2H, H-3′, H-5′), 7.84 (d, J = 8.20 Hz, 2H, H-2′, H-6′), 8 (dd, J = 1.58 Hz, J = 7.60 Hz, 1H, H-6), 8.29 (d, J = 1.58 Hz, 1H, H-2); IR (KBr): 3084 (CH_{arom}), 2957 (CH_{alkane}), 1652 (C=O), 1578 (C=C_{arom}, NO_2), 1340 (NO_2) cm^{-1}.
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12. *Preparation of 4′-bromo-4-[(E)-2-(dimethylamino)vinyl]-3-nitrobenzophenone* **6**. A solution of **5** (2.50 g, 7.80 mmol) and DMFDMA (2.07 mL, 16.60 mmol) in 10 mL of DMF was stirred for 15 h at 110 °C. After cooling, the reaction mixture was filtered. The precipitate **6** was washed with diethyl ether and dried. The filtrate was washed with water and dried over Na_2SO_4. The solvent was removed and the residue was recrystallized from diethyl ether to afford a purple powder **6** in 73% overall yield. Mp 140–141 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.04 (s, 6H, CH_3), 5.86 (d, J = 13.10 Hz, 1H, CH=CHN), 7.69 (d, J = 8.10 Hz, 2H, H-3′, H-5′), 7.77 (d, J = 8.85 Hz, 1H, H-6), 7.81 (d, J = 8.10 Hz, 2H, H-2′, H-6′), 7.87 (d, J = 8.85 Hz, 1H, H-5), 7.89 (d, J = 13.10 Hz, 1H, CH=CHN), 8.15 (s, 1H, H-2); IR (KBr): 3034 (CH_{arom}), 2900 (CH_{alkane}), 1612 (C=O), 1261 (NO_2) cm^{-1}.
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14. Preparation of (4-bromophenyl)(1*H*-indolyl-6-yl)methanone **7**. Raney nickel (catalytic amount, 1/2 spatula) was added to a stirred solution of **6** (2.50 g, 2.12 mmol) in 50 mL of ethanol. The reaction mixture was stirred during 3 h at rt under hydrogen atmosphere. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and the organic layer was washed with H_2O, brine and dried over Na_2SO_4. The solvent was removed and the residue was purified on silica gel (hexane-ethylacetate, 7:3 v/v) to afford a brown solid **7** in 32% overall yield. Mp 183–184 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.61 (d, J = 2.84 Hz, 1H, indolyl H-3), 7.51 (dd, J = 1.58 Hz, J = 8.20 Hz, 1H, indolyl H-5), 7.68 (dd, J = J = 2.84 Hz, 1H, indolyl H-2), 7.71 (d, J = 8.51 Hz, 2H, 4-bromophenyl H-3, H-5), 7.72 (d, J = 8.20 Hz, 1H, indolyl H-4) 7.81 (d, J = 8.51 Hz, 2H, 4-bromophenyl H-2, H-6), 7.86 (s, 1H, indolyl H-7), 11.53 (s, 1H, NH); IR (KBr): 3226 (NH), 3050 (CH_{arom}), 1607 (C=O), 1560 (C=C_{arom}) cm^{-1}.
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18. Characteristics of 4-(1*H*-indol-6-ylcarbonyl)benzonitrile **8**. The residue was purified on silica gel (CH_2Cl_2) to afford compound **8** in 67% overall yield. Mp 198–199 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.62 (d, J = 2.84 Hz, 1H, indolyl H-3), 7.53 (dd, J = 1.51 Hz, J = 8.51 Hz, 1H, indolyl H-5), 7.71 (dd, J = J = 2.84 Hz, 1H, indolyl H-2), 7.74 (d, J = 8.51 Hz, 1H, indolyl H-4), 7.85 (s, 1H, indolyl H-7), 7.90 (d, J = 8.20 Hz, 2H, benzonitrile H-2, H-6), 8.08 (d, J = 8.20 Hz, 2H, benzonitrile H-3, H-5), 11.57 (s, 1H, NH); IR (KBr): 3290 (NH), 3070 (CH_{arom}), 2233 (C≡N), 1632 (C=O), 1560, 1504 (C=C_{arom}) cm^{-1}.
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21. Preparation of 4-[(1*H*-indol-6-yl)(1*H*-1,2,4-triazol-1-yl)methyl]benzonitrile **10**. Sodium borohydride (262 mg, 6.92 mmol) was added portionwise to a stirred solution of **8** (427 mg, 1.73 mmol) in 30 mL of methanol. The reaction mixture was stirred for 1 h at rt prior to quenching with H_2O. The aqueous layer was extracted with Et_2O. The organic layer was dried over Na_2SO_4 and the solvent was evaporated to give a light white oil. The corresponding alcohol (381 mg, 1.54 mmol) and CDT (554 mg, 3.08 mmol) in 30 mL THF were stirred for 43 h at rt under N_2 atmosphere. The solvent was removed and the residue was dissolved in H_2O and CH_2Cl_2. The layers were separated, the organic layer was washed with H_2O, and dried over Na_2SO_4. The solvent was evaporated and the residue was purified on silica gel (ethyl acetate-hexane, 7:3 v/v) to afford a beige powder **10** in 10% overall yield. Mp 68–69 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.43 (d, J = 2.21 Hz, 1H, indolyl H-3), 6.97 (dd, J = 1.26, J = 8.20 Hz, 1H, indolyl H-5), 7.30 (s, 1H, indolyl H-7), 7.33 (s, 1H, CH), 7.42-7.44 (m, 3H, indolyl H-2, benzonitrile H-3, H-5), 7.58 (d, J = 8.20 Hz, 1H, indolyl H-4), 7.89 (d, J = 8.51 Hz, 2H, benzonitrile H-2, H-6), 8.13 (s, 1H, triazolyl H), 8.64 (s, 1H, triazolyl H), 11.19 (s, 1H, NH); ^{13}C NMR (500 MHz, DMSO-d_6): δ 65.75 (CH), 101.17 (C-3), 110.72 (benzonitrile C-1), 111.69 (C-7), 118.73 (C≡N), 119.5 (C-5), 120.5 (C-4), 126.71 (C-2), 127.64 (C-4a), 128.97 (2C, benzonitrile C-3, C-5), 130.71 (C-6), 132.64 (2C, benzonitrile C-2, C-6), 135.82 (C-7a), 144.75 (triazolyl C), 145.42 (benzonitrile C-4), 152.18 (triazolyl C); IR (KBr): 3370 (NH), 3123 (CH_{arom}), 2229 (C≡N), 1502 (C=C_{arom}, C=N), 1245 (C–N) cm^{-1}. Anal. calcd for $C_{18}H_{13}N_5$: C, 72.23; H, 4.38; N, 23.40. Found: C, 72.20; H, 4.37; N, 23.44.
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23. Preparation of 2-methyl-3-nitrobenzoyl chloride **12**. A solution of 2-methyl-3-nitrobenzoic acid **11** (1 g, 5.52 mmol) in thionyl chloride (8.8 mL, 0.12 mmol) was stirred for 24 h at 60 °C. After cooling, thionyl chloride was evaporated under reduced pressure to afford a beige powder **12** in 98% overall yield. Mp 158–159 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.60 (s, 3H, CH_3), 7.70 (dd, J = J = 8.0 Hz, 1H, H-5), 8.18 (d, J = 8.0 Hz, 1H, H-6), 8.45 (d, J = 8.0 Hz, 1H, H-4); IR (KBr): 3094 (CH_{arom}), 2964 (CH_{alkane}), 1748 (C=O), 1522 (C=C_{arom}, NO_2), 1357 (NO_2) cm^{-1}.
24. Preparation of 4-[(1*H*-imidazol-1-yl)(1*H*-indol-4-yl)methyl]benzonitrile **17**. Sodium borohydride (92 mg, 2.44 mmol) was added portionwise to a stirred solution of **16** (150 mg, 0.61 mmol) in 20 mL of methanol. The reaction mixture was stirred for 1 h at rt prior to quenching with H_2O. The aqueous layer was extracted with Et_2O. The organic layer was dried over Na_2SO_4 and the solvent was evaporated to give a light white oil. The corresponding alcohol (151 mg, 0.61 mmol) and CDI (168 mg, 1.04 mmol) in 15 mL CH_3CN were stirred for 19 h at rt. The solvent was removed and the residue was dissolved in H_2O and CH_2Cl_2. The layers were separated, the organic layer was washed with H_2O, and dried over Na_2SO_4. The solvent was evaporated and the residue was purified on silica gel (ethyl acetate-hexane, 8:2 v/v) to afford a white powder **17** in 48% overall yield. Mp 107–108 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.21 (d, J = 2.84 Hz, 1 H, indolyl H-3), 6.59 (d, J = 7.25, 1H, indolyl H-5), 6.99 (s, 1H, imidazolyl H), 7.12 (dd, J = 7.25, J = 7.88 Hz, 1H, indolyl H-6), 7.14 (s, 1H, imidazolyl H), 7.34 (s, 1H, CH), 7.35 (d, J = 8.20 Hz, 2H, benzonitrile H-3, H-5), 7.37 (dd, J = J = 2.84 Hz, 1H, indolyl H-2), 7.46 (d, J = 7.88 Hz, 1H, indolyl H-7), 7.71 (s, 1H, imidazolyl H), 7.89 (d, J = 8.20 Hz, 2H, benzonitrile H-2, H-6), 11.34 (s, 1H, NH); ^{13}C NMR (500 MHz, DMSO-d_6): δ 61.60 (CH), 99.45 (C-3), 110.74 (benzonitrile C-1), 112.13 (C-7), 118.25 (C-5), 118.70 (C≡N), 119.53 (imidazolyl C), 121.03 (C-6), 126.05 (C-2), 126.46 (C-4a), 128.66 (2C, benzonitrile C-3, C-5), 128.75 (imidazolyl C), 130 (C-4), 132.75 (2C, benzonitrile C-2, C-6), 136.22 (C-7a), 137.47 (imidazolyl C), 145.69 (benzonitrile C-4); IR (KBr): 3107 (NH), 3060 (CH_{arom}), 2229 (C≡N), 1501 (C=C_{arom}, C=N), 1281 (C–N) cm^{-1}. Anal. calcd for $C_{19}H_{14}N_4$: C, 76.49; H, 4.73; N, 18.78. Found: C, 76.51; H, 4.71; N, 18.79.
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