Synthesis of 2,7-Naphthyridine-Containing Analogues of Luotonin A

Xiangqian Dai,[a] Chen Cheng,[a] Chunyong Ding,[b] Qizheng Yao,[b] Ao Zhang*[a]

[a] Synthetic Organic & Medicinal Chemistry Laboratory (SOMCL), Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, P. R. of China
Fax +86(21)50806035; E-mail: aozhang@mail.shcnc.ac.cn

[b] School of Pharmacy, China Pharmaceutical University, Nanjing 210009, P. R. of China

Received 26 June 2008

Abstract: A series of luotonin A analogues **7a–d** with the N-14 atom moved to position 18 was prepared using an intramolecular aza-hetero-Diels–Alder reaction.

Key words: luotonin A, 2,7-naththyridine, anticancer, intramolecular aza-hetero-Diels–Alder reaction

Camptothecin (**1**), a natural product isolated from Chinese tree *Camptotheca acuminate* in 1966,[1] is one of the lead molecules for the development of clinically effective anticancer drugs. It exerts its biological effects by stabilizing the covalent binary complex formed between DNA and topoisomerase I during DNA relaxations.[2] It has been long accepted that the E-lactone ring, although not physicochemically stable, is a key structural determinant for camptothecin's topoisomerase I inhibition and its antineoplastic properties. In this regard, the majority of the structure–activity relationship studies of **1** have been focused on the optimization of rings A–C in the last two decades,[3–5] leading to two drugs (topotecan[6] and irinotecan[7]) which have reached the market and with dozens still remain in clinical trials.[8–10] Such strategy has changed since another natural product, luotonin A (**3**)[11–13] with an aromatic E-ring, was identified and possessed a similar cellular activity[14] by interacting with DNA and topoisomerase I. Although slightly lower than **1** in activity, luotonin A (**3**) opens a new avenue for the development of clinically effective, chemically stable anticancer drugs.[15]

In our recent studies, we have successfully established a method[16] for the construction of the 2,7-naphthyridine scaffold and synthesized several 2,7-naphthyridine-containing natural products, for example, lophocladine A (**4**) which was reported to possess anticancer activities.[17] As a continuation of this study, we decided to develop hybridized compounds by incorporation of the 2,7-naphthyridine core into luotonin A, resulting in a class of new analogues **7** (Figure 1). Such a design strategy can be viewed as a N-walking approach through which the N-14 atom moves to C-18 in luotonin A.

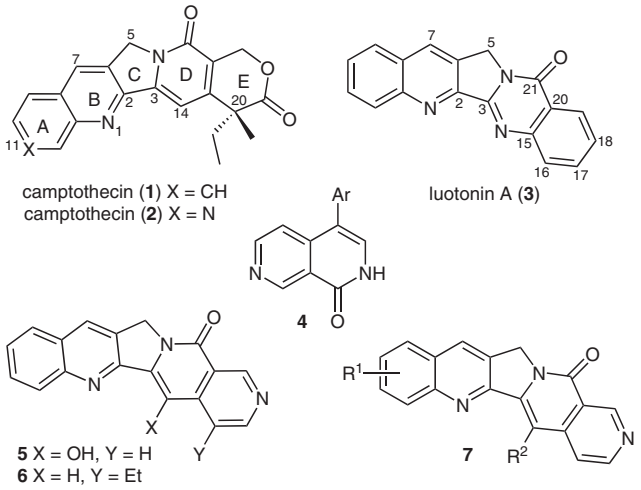
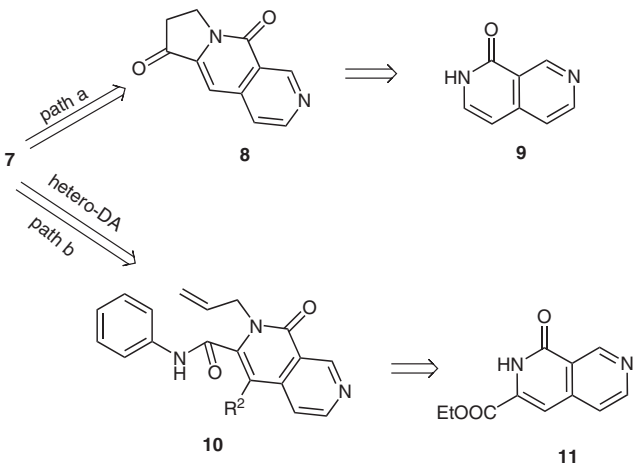


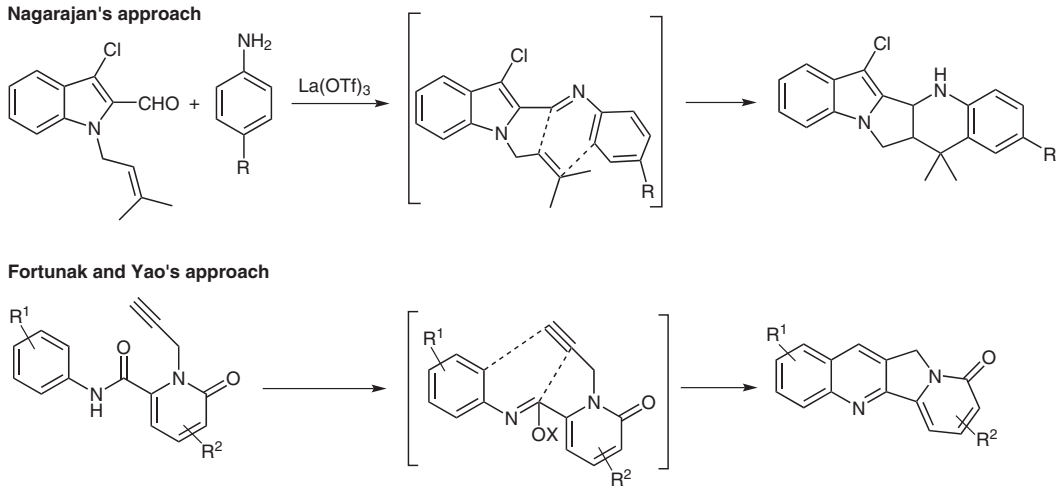
Figure 1 Camptothecin, luotonin A, and their analogues



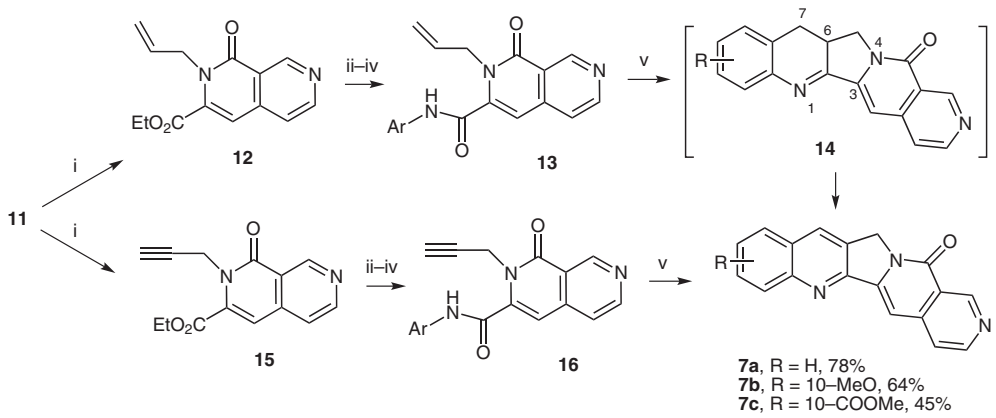
Scheme 1 Retrosynthesis of naphthyridine analogues **7**

A search of the literature disclosed that two compounds (**5**,[18] **6**[19]) have been reported as camptothecin analogues with a 2,7-naphthyridine fragment. Although no biological data have been reported for these E-ring-modified compounds of luotonin A, a 1,7-naphthyridine analogue (**2**) has been described with slightly higher activity than **1** in the topoisomerase I cleavable complex assay.[20] In addition, the reported synthesis of the 2,7-naphthyridine analogues (**5**, **6**) was primarily based on the key intermediate naphthyridine-fused 3-pyrrolidinone **8** (Scheme 1, path a), which was highly unstable.[18,19] Therefore, it would be

SYNLETT 2008, No. 19, pp 2989–2992
Advanced online publication: 23.10.2008
DOI: 10.1055/s-0028-1087299; Art ID: W10208ST



Scheme 2 Nagarajan's and Fortunak's intramolecular hetero-Diels–Alder reactions



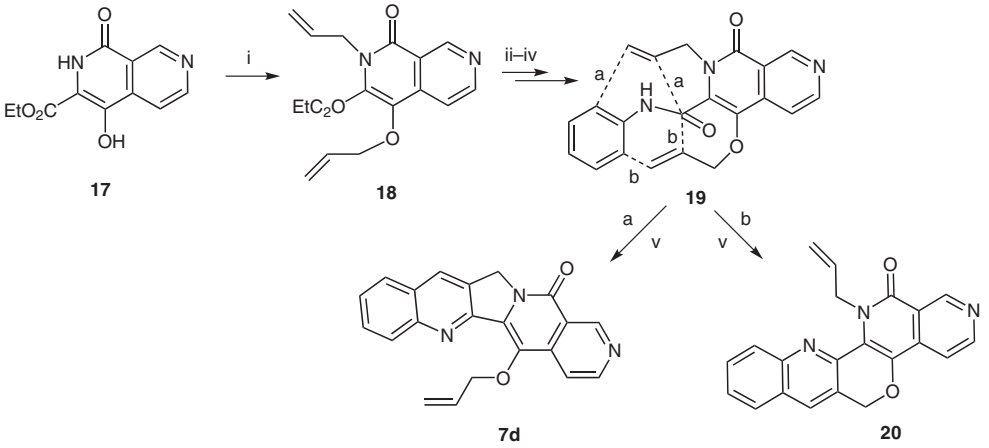
Scheme 3 *Reagents and conditions*: i) allyl bromide for compound **12**, propargyl bromide for compound **15**, K_2CO_3, 90%; ii) LiOH, THF–H_2O, reflux; iii) oxalic chloride, CH_2Cl_2, 0 °C; iv) aniline, CH_2Cl_2, 50–60% for step ii–iv; v) Ph_3PO (3.0 equiv), Tf_2O (1.5 equiv), r.t.

of great importance to develop a versatile methodology to efficiently construct such N-walking analogues **7** of luotonin A.

Our synthesis was based on a modified intramolecular imino hetero-Diels–Alder (DA) reaction (Scheme 1, path b) which was validated recently by Nagarajan[21] on the synthesis of indolopyrroloquinolines. This approach is also similar to the intramolecular aza-DA reaction initially developed by Fortunak[22a] and Batey,[22b] and further improved by Yao[23] recently in the synthesis of **1** and **3** (Scheme 2). In this regard, the key step in our synthesis is to prepare the intermediate **10** where the allyl moiety acts as the dienophile, and the *N*-aryl-amido moiety serves as the diene.

To validate the proposed intramolecular aza-hetero-DA reaction on the 2,7-naphthyridine model, we synthesized 3-ethoxycarbonyl-2,7-naphthyridin-1-one (**11**) from 4-methyl-3-cyanopyridine by using a similar procedure to the one we reported recently.[16] N-Allylation of **11** with allyl bromide and K_2CO_3 yielded naphthyridone **12** in 90% yield (Scheme 3). Saponification with LiOH followed by treating with oxalyl chloride and then an appropriate aniline gave the key precursor **13** in 50–60% overall yield. However, the proposed intramolecular aza-DA cyclization of **13a** (Ar = Ph) did not occur by using Nagarajan's catalytic conditions [$La(OTf)_3$, dioxane, 140 °C].[21] Extending the reaction time, elevating the temperature, or increasing catalyst loading of Lewis acid [$La(OTf)_3$] did not trigger this reaction. Fortunately, after several trials, we found that bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate, formed in situ from Ph_3PO and Tf_2O (reported by Yao),[23] could readily initiate this reaction at 0 °C and yielded a major product in 78% yield. However, the spectroscopic data[24] of this cycloadduct did not support the structure of **14a** (R = H), instead the 6,7-dehydro product – quinoline **7a** – was obtained. The formation of compound **7a** can be rationalized by the stability of aromatic system of **7a**, which was driven by the acidity of the catalytic system. Similarly, cyclization of compound **13b** under the same catalytic conditions gave compound **7b** in 64% yield.[24,25]

It is of interest to note that using the same catalytic conditions, cyclization of *N*-propargyl-2,7-naphthyridines gave the same products. Thus, cyclization of **16** (Ar = 4-$MeO_2CC_6H_4$) provided **7c** in 45% yield. Similar yield of **7a** was obtained for cyclization of **16** (Ar = Ph).



Scheme 4 *Reagents and conditions*: i) allyl bromide, K_2CO_3, 45%; ii) LiOH, THF–H_2O, reflux; iii) oxalic chloride, CH_2Cl_2, 0 °C; iv) anilin CH_2Cl_2, 20% step ii–iv; v) Ph_3PO (3.0 equiv), Tf_2O (1.5 equiv), r.t.

This result was in complete agreement with Yao's report on isoquinolin-1-one.[23] The somewhat lower yields of the cycloadducts **7a–c** were probably due to the lower reactivity of the 2,7-naphthyridine core compared to that of isoquinolin-1-ones.

To examine the selectivity of the intramolecular aza-DA reaction, we prepared compound **18** using a similar procedure,[16] and then converted it to the cyclization precursor **19** in 20% overall yield. The low yield of this conversion may be ascribed to the contamination of bis-O-alkylation product. Since both *N*- or *O*-propargyl moiety in **19** can serve as the dienophile, two cycloadducts **7d** and **20** could be produced through intramolecular aza-DA reaction (path a or path b) as described in Scheme 4. However, using the catalyst formed in situ from Ph_3PO and Tf_2O, only one compound **7d**[26] was isolated in 30% yield, and compound **20** was not observed. The production of compound **7d** may be due to the less ring strain in forming the five-membered C-ring in **7d** than that in forming six-membered pyran ring in **20**.

In summary, we have demonstrated a procedure of intramolecular aza-hetero-Diels–Alder reaction on the 3-(*N*-aryl-amido)-2-allyl-2,7-naphthyridin-1-ones as the substrate, by combining Nagarajan's and Yao's reaction conditions. A small series of luotonin A analogues **7a–d**, where the N-14 atom walked to position 18, was prepared in moderate yields.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was supported by a Hundred Talent Project of the Chinese Academy of Sciences, and grants from Chinese National Science Foundation (30672517, 30772625), Shanghai Commission of Science and Technology (06ZR14102, 07pj14104), and grants from Shanghai Institute of Materia Medica.

References and Notes

(1) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888.
(2) Moertel, C. G.; Schutt, A. J.; Reitemeier, R. J.; Hahn, R. G. *Cancer Chemother. Rep.* **1977**, *56*, 649.
(3) Li, Q. Y.; Zu, Y. G.; Shi, R. Z.; Yao, L. P. *Curr. Med. Chem.* **2006**, *13*, 202.
(4) Driver, R. W.; Yang, L. X. *Mini-Rev. Med. Chem.* **2005**, *5*, 425.
(5) Du, W. *Tetrahedron* **2003**, *59*, 8649.
(6) Kingsbury, W. D.; Boehm, J. C.; Jakas, D. R. *J. Med. Chem.* **1991**, *34*, 98.
(7) Graul, A. I.; Prous, J. R. *Drug News Perspect.* **2005**, *1*, 21.
(8) Giovanella, B. C.; Stehlin, J. S.; Hinz, H. R.; Kozielski, A. J.; Harris, N. J.; Vardeman, D. M. *Int. J. Oncol.* **2002**, *20*, 81.
(9) Eckhardt, S. G.; Baker, S. D.; Eckardt, J. R. *Clin. Cancer Res.* **1998**, *4*, 595.
(10) Minami, H.; Fujii, H.; Igarashi, T.; Itoh, K.; Tamanoi, K.; Oguma, T.; Sasaki, Y. *Clin. Cancer Res.* **2001**, *7*, 3056.
(11) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1997**, *46*, 541.
(12) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1193.
(13) Ma, Z.-Z.; Hano, Y.; Nomura, T. *Heterocycles* **2005**, *65*, 2203.
(14) Cagir, A.; Jones, S. H.; Gao, R.; Eisenhauer, B. M.; Hecht, S. M. *J. Am. Chem. Soc.* **2003**, *125*, 13628.
(15) Most recent approaches: (a) Bowman, W. R.; Cloonan, M. O.; Fletcher, A. J.; Stein, T. *Org. Biomol. Chem.* **2005**, *3*, 1460. (b) Lee, E. S.; Park, J. G.; Kim, S. I.; Jahng, Y. *Heterocycles* **2006**, *68*, 151. (c) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787. (d) Servais, M.; Azzouz, A.; Lopes, D.; Courillon, C.; Malacria, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 576. (e) Bowman, W. R.; Elsegood, M. R. J.; Stein, T.; Weaver, G. W. *Org. Biomol. Chem.* **2007**, *5*, 103. (f) Mason, J. J.; Bergman, J. *Org. Biomol. Chem.* **2007**, *5*, 2486. (g) Nacro, K.; Zha, C.; Guzzo, P. R.; Herr, R. J.; Peace, D.; Friedrich, T. D. *Bioorg. Med. Chem. Lett.* **2007**, *15*, 4237.
(16) Zhang, A.; Ding, C.; Cheng, C.; Yao, Q. *J. Comb. Chem.* **2007**, *9*, 916.
(17) Gross, H.; Goeger, D. E.; Hills, P.; Mooberry, S. L.; Ballantine, D. L.; Murray, T. F.; Valeriote, F. A.; Gerwick, W. H. *J. Nat. Prod.* **2006**, *69*, 640.

(18) Shamma, M.; Novak, L. *Tetrahedron* **1969**, *25*, 2275.
(19) Wenkert, E.; Dave, K. G.; Lewis, R. G.; Sprague, P. W. *J. Am. Chem. Soc.* **1967**, *89*, 6741.
(20) Uehling, D. E.; Nanthakumar, S. S.; Croom, D.; Emerson, D. L.; Leitner, P. P.; Morton, B.; Profeta, S.; Vuong, A.; Besterman, J. M. *J. Med. Chem.* **1995**, *38*, 1106.
(21) Gaddam, V.; Nagarajan, R. *Tetrahedron Lett.* **2007**, *48*, 7335.
(22) (a) Fortunak, J. M. D.; Mastrocola, A. R.; Mellinger, M.; Sisti, N. J.; Wood, J. L.; Zhuang, Z.-P. *Tetrahedron Lett.* **1996**, *37*, 5679. (b) Twin, H.; Batey, R. A. *Org. Lett.* **2004**, *6*, 4913.
(23) (a) Zhou, H.-B.; Liu, G.-S.; Yao, Z.-J. *J. Org. Chem.* **2007**, *72*, 6270. (b) Zhou, H.-B.; Liu, G.-S.; Yao, Z.-J. *Org. Lett.* **2007**, *9*, 2003.
(24) **General Procedure for the Intramolecular Aza-Diels–Alder Cyclization**
To a solution of Ph_3PO (837 mg, 2.98 mmol) in anhyd CH_2Cl_2 (20 mL) at 0 °C was added dropwise a solution of Tf_2O (0.25 mL, 1.5 mmol) in CH_2Cl_2 (2 mL). After the mixture was stirred for 15 min at 0 °C, a solution of 2-allyl-1-oxo-*N*-aryl-2,7-naphthyridin-3-carboxamide (**13**, 1.0 mmol) or 2-propargyl-1-oxo-*N*-aryl-2,7-naphthyridin-3-carboxamide (**16**, 1.0 mmol) in CH_2Cl_2 (20 mL) was dropped slowly. The reaction mixture was stirred at 0 °C for 0.5 h, and then at r.t. for 1–5 h. The completion of the reaction was detected by disappearance of the carboxamide substrate **13**. A solution of aq Na_2CO_3 (10%, 10 mL) was added to quench the reaction. The mixture was extracted with $CHCl_3$ (3 × 30 mL). The organic phases were combined, washed with brine, and dried over anhyd Na_2SO_4. After filtration, the solvent was removed, and the residue was subjected to column chromatography (CH_2Cl_2–MeOH, 10:1). The cyclization products **7a–c** were obtained.
Compound 7a (78%): white solid, mp >210 °C. MS (EI): *m/z* (%) =285(100) [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 5.17 (br s, 2 H), 7.47 (m, 3 H), 7.63 (m, 1 H), 7.75 (d, *J* = 8.4 Hz, 1 H), 7.99 (d, *J* = 8.7 Hz, 1 H), 8.27 (s, 1 H), 8.51 (d, *J* = 5.4 Hz, 1 H), 9.37 (s, 1 H). HRMS: *m/z* calcd for $C_{18}H_{11}ON_3$: 285.0902; found: 285.0890.
Compound 7b (45%): slightly yellow solid, mp >200 °C. MS (EI): *m/z* (%) = 343(100) [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 3.81 (s, 3 H), 5.21 (br s, 2 H), 7.46 (s, 1 H), 7.52 (d, *J* = 5.4 Hz, 1 H), 8.03 (d, *J* = 9.0 Hz, 1 H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.39 (s, 1 H), 8.48 (s, 1 H), 8.54 (d, *J* = 5.4 Hz, 1 H), 9.39 (s, 1 H). HRMS: *m/z* calcd for $C_{20}H_{13}O_3N_3$: 343.0957; found: 343.0959.
Compound 7c (64%): slightly yellow solid, mp >210 °C. MS (EI): *m/z* (%) = 315(100) [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 3.94 (s, 3 H), 5.31 (s, 2 H), 7.19 (s, 1 H), 7.45 (m, 1 H), 7.51 (s, 1 H), 7.58 (d, 1 H, *J* = 7.6 Hz), 8.06 (d, *J* = 12.4 Hz, 1 H), 8.25 (s, 1 H), 8.69 (s, 1 H), 9.60 (s, 1 H). HRMS: *m/z* calcd for $C_{19}H_{13}O_2N_3$: 315.1008; found: 315.1017.
(25) The cycloadducts **7a–c** showed extremely poor solubility in regular deuterated solvents ($CDCl_3$, CD_3OD, CD_3SOCD_3, D_2O). Their purity (>95%) was further confirmed by HPLC analysis on an Agilent 1100 series LC system (Agilent ChemStation Rev.A.10.02; ZORBAX Eclipse XDB-C8, 4.8 mm × 150 mm, 5 μM, 1.0 mL/min, UV: λ = 254 nm, r.t.) with two solvent systems (MeCN–H_2O, and MeOH–H_2O).
(26) **Compound 7d** (30%): yellow solid, mp 202–204 °C. MS (EI): *m/z* = 341 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 4.90 (d, *J* = 6.0 Hz, 1 H), 5.35 (s, 2 H), 5.36 (d, *J* = 6.6 Hz, 1 H), 5.50 (dd, *J* = 1.2, 17.1 Hz, 1 H), 6.37 (m, 1 H), 7.62 (t, *J* = 7.2 Hz, 1 H), 7.78 (t, *J* = 7.2 Hz, 1 H), 7.86 (m, 2 H), 8.23 (d, *J* = 8.7 Hz, 1 H), 8.28 (s, 1 H), 8.85 (d, *J* = 5.7 Hz, 1 H), 9.68 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 49.7, 76.0, 115.4, 118.9, 119.6, 127.0, 127.6, 127.8, 128.4, 129.8, 130.2, 133.3, 134.2, 134.9, 140.7, 148.8, 150.4, 150.5, 151.7, 158.6. HRMS: *m/z* calcd for $C_{21}H_{15}O_2N_3$: 341.1164; found: 341.1160.