Direct Synthesis of *N*-Aryl Derivatives of Quinazolin-4(3*H*)-ones Employing Arylboronic Acids in the Presence of $Cu(OAc)_2$

Kintali Sreeramamurthy, Ettam Ashok, Velisoju Mahendar, Gourishetti Santoshkumar, Parthasarathi Das*

Discovery Research, Dr. Reddy's Laboratories Ltd., Bollaram Road, Miyapur, Hyderabad 500049, AP, India
Fax +91(40)23045438; E-mail: parthads@yahoo.com

Received 7 September 2009

Abstract: Copper-promoted N-arylation of quinazolin-4(3*H*)-ones with boronic acid at room temperature in the presence of air has been investigated. This method is general and can be applied to synthesizing derivatives of quinazolin-4(3*H*)-one with medicinal values.

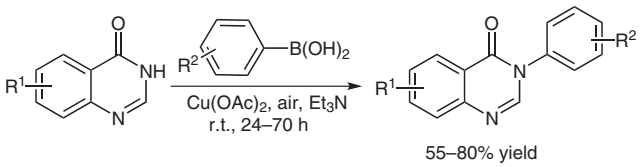
Key words: $Cu(OAc)_2$, boronic acid, quinazolin-4(3*H*)-one

Quinazolin-4(3*H*)-one derivatives are of considerable interest because of their broad spectrum of biological effects.[1] These include kinase inhibition,[2] anticancer,[3] anti-inflammatory,[4] antidiabetes, and anti-obesity activity.[5] In addition more than 40 alkaloids containing a quinazolin-4(3*H*)-one moiety have been isolated from natural source.[6] Some of these also have interesting biological features such as antimalarial activity[7], biofungicide,[8] and diuretic properties.

The most common methods for the preparation of quinazolinones involve the amidation of 2-aminobenzonitrile or 2-aminobenzoic acid or its derivatives followed by oxidative ring closure under basic conditions.[9] Other methods involve cycloaddition of anthranilic acid derivatives with a diverse range of substrates including imidates and iminohalides.[10] Recent reports reveal that quinazolin-4(3*H*)-ones have been prepared by using silica sulfuric acid,[11] PCl_3,[12] low-valent titanium,[13] and under microwave irradiation.[14] However, there is still a need to develop efficient, mild, and direct methods for the synthesis of *N*-aryl quinazolin-4(3*H*)-one derivatives.

Copper-promoted carboncnitrogen (C–N) and carbon–oxygen (C–O) oxidative coupling reactions of NH/OH-containing substrates with arylboronic acids have emerged as a powerful synthetic methodology.[15] This novel methodology is characterized by the mild reaction conditions (r.t., weak base, in air) and extensions and applications of this new methodology have been reported.[16,17] In connection with a drug discovery program, we recently required an efficient protocol for *N*-aryl substitution of quinazolin-4(3*H*)-ones and herein we report copper(II) acetate promoted C–N bond formation with arylboronic acids under mild, room-temperature conditions (Scheme 1).

Initial studies investigated reaction between 7-fluoroquinazolin-4(3*H*)-one[1c] and phenylboronic acid in the presence of $Cu(OAc)_2$ (1 equiv) at room temperature under air.[18] The desired *N*-aryl quinazolinone was isolated in good yield and, with this encouraging result, we investigate the scope with different boronic acids and quinazolin-4(3*H*)-ones, the results of which are listed in Table 1.



Scheme 1

Arylboronic acids with chloro-, fluoro-, and trifluoromethyl substitution gave good yields in shorter reaction times (Table 1, entries 2, 4, and 6) compared to the methoxy derivative (Table 1, entry 10). Reaction with benzodioxolboronic acid (Table 1 entry 3) and benzodioxinboronic acid (Table 1 entry 7) proceeded more slowly and in moderate yield. Having demonstrated the generality of this reaction, we explore the possibility in synthesizing kinase inhibitor analogues by following the same methodology. For this purpose 6-methoxy-7-(3-morpholinopropoxy)-quinazolin-4(3*H*)-one[19] was synthesized and treated with various arylboronic acids in the presence of $Cu(OAc)_2$ at ambient temperature to yield N-substituted quinazolin-4-(3*H*)-one derivatives (Table 2). As expected chloro- and fluoro-substituted arylboronic acids resulted in good yields (Table 2, entries 2 and 3) in shorter reaction times compared to the methoxy-substituted arylboronic acid (Table 2, entries 4 and 5).[20]

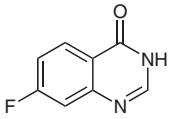
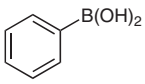
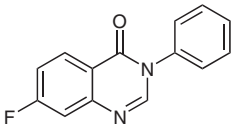
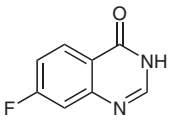
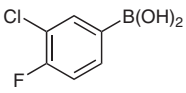
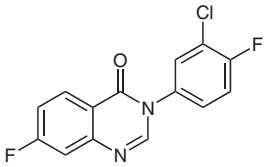
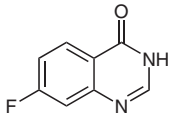
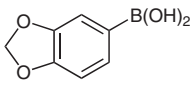
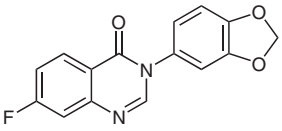
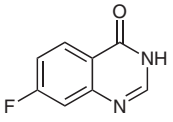
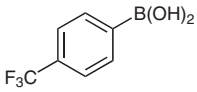
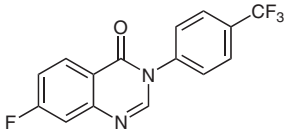
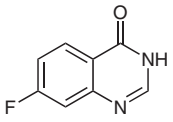
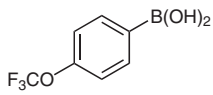
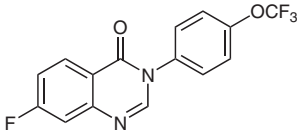
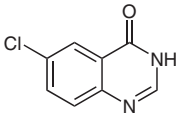
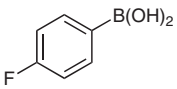
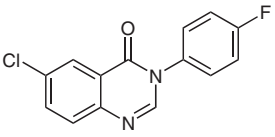
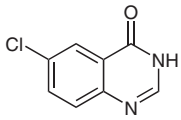
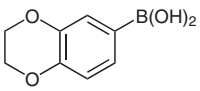
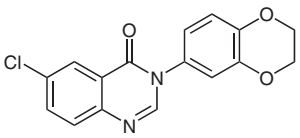
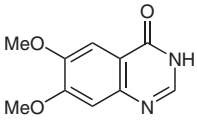
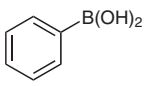
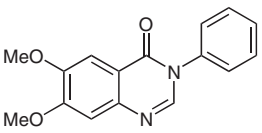
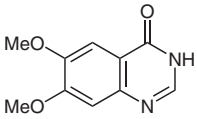
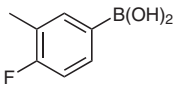
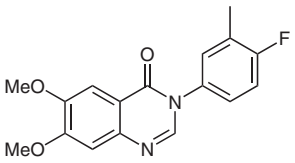
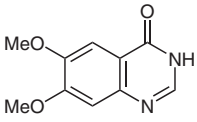
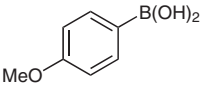
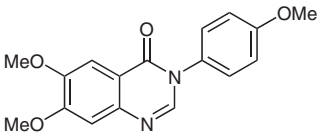
In summary, we have developed a general mild, efficient, and direct method for synthesizing the *N*-aryl derivatives of quinazolin-4(3*H*)-ones, and this method has been applied to the synthesis of quinazolinone derivatives of pharmaceutical interest.

Acknowledgment

We thank Dr. Reddy's Laboratories Ltd. for financial support and encouragement. Help from the analytical department in recording spectroscopic data is highly appreciated.

SYNLETT 2010, No. 5, pp 0721–0724
Advanced online publication: 10.02.2010
DOI: 10.1055/s-0029-1219385; Art ID: D24609ST

Table 1 Reactions between 7-Fluoroquinazolin-4(3*H*)-ones and Phenylboronic Acids in the Presence of $Cu(OAc)_2$

Entry	Substrate	Boronic acid	Product[a]	Time (h)	Yield (%)[b]
1				26	68
2				25	74
3				72	56
4				24	80
5				26	72
6				24	75
7				68	60
8				26	72
9				35	68
10				60	60

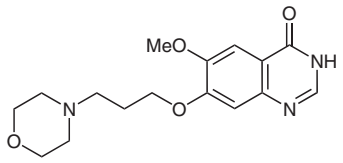
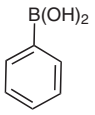
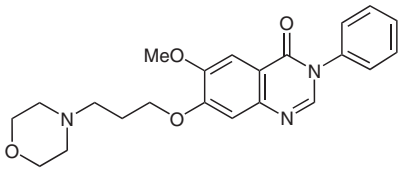
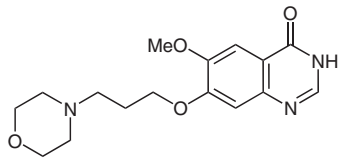
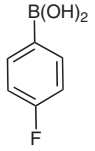
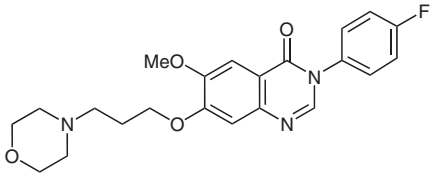
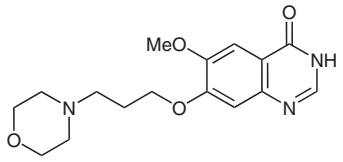
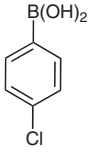
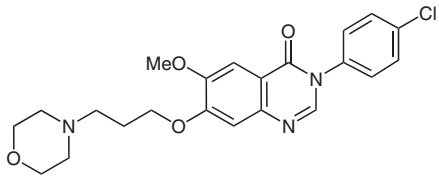
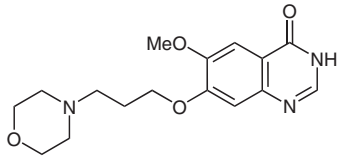
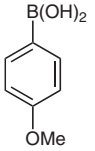
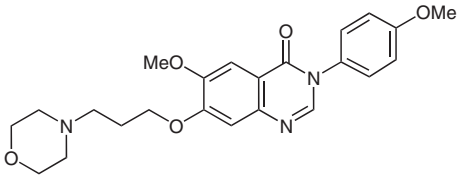
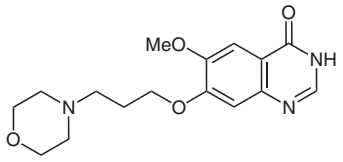
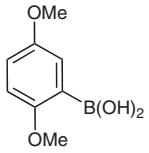
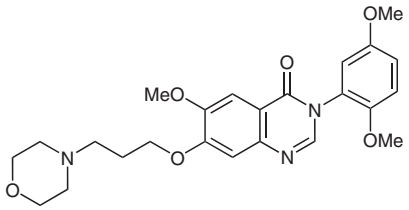
[a] Characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS.
[b] Isolated yield.

References and Notes

(1) (a) Armarego, W. L. F. *Quinazolines*; Brown, D. J., Ed.; John Wiley and Sons: London, **1967**. (b) Ellis, G. P. *Synthesis of Fused Heterocycles*, Vol. 47; John Wiley and Sons: Chichester, **1987**. (c) Hermecz, I.; Kokosi, J.; Podanyi, B.; Szasz, G. *Heterocycles* **1994**, 37903. (d) For review on quinazolinone, see: Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787.

(2) Fowler, K. W.; Huang, D.; Kesicki, E. A.; Ooi, H. C.; Oliver, A. R.; Ruan, F.; Treiberg, J. WO 2005113556, 2005-6, US 16778, **2005**; *Chem. Abstr.***2006**, *144*, 22759.

Table 2 Reactions between 6-Methoxy-7-(3-morpholinopropoxy)-uinazolin-4(3*H*)-ones with Various Arylboronic Acids in the Presence of $Cu(OAc)_2$

Entry	Substrate	Boronic acid	Product[a]	Time (h)	Yield (%)[b]
1				30	65
2				28	70
3				28	72
4				65	60
5				70	55

[a] Characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS.
[b] Isolated yield.

(3) Jiang, J. B.; Hesson, D. P.; Dusak, B. A.; Dexter, D. L.; Kang, G. J.; Hamel, E. *J. Med. Chem.* **1990**, *33*, 1721.

(4) Lowe, J. A. III.; Archer, R. L.; Chapin, D. S.; Cheng, J. B.; Helweg, D.; Johnson, J. L.; Koe, B. K.; Lebel, L. A.; Moore, P. F.; Nielsen, J. A.; Russo, L. L.; Shirley, J. T. *J. Med. Chem.* **1991**, *34*, 624.

(5) Rudolph, J.; Esler, W. P.; O'Connor, S.; Coish, P. D. G.; Wickens, P. L.; Brands, M.; Bierer, D. E.; Bloomquist, B. T.; Bondar, G.; Chen, L.; Chuang, C.-Y.; Claus, T. H.; Fathi, Z.; Fu, W.; Khire, U. R.; Kristie, J. A.; Liu, X.-G.; Lowe, D. B.; McClure, A. C.; Michels, M.; Ortiz, A. A.; Ramsden, P. D.; Schoenleber, R. W.; Shelekhin, T. E.; Vakalopoulos, A.; Tang, W.; Wang, L.; Yi, L.; Gardell, S. J.; Livingston, J. N.; Sweet, L. J.; Bullock, W. H. *J. Med. Chem.* **2007**, *50*, 5202.

(6) (a) Katritzky, A. R.; Rees, C. W. *The Structure, Reaction, Synthesis and Uses of Heterocyclic Compounds,* In *Comprehensive Heterocyclic Chemistry*, Part 2B, Vol. 3; Pergamon Press: New York, **1984**. (b) Pelletier, S. W. *Alkaloids: Chemical and Biological Prospective*, Vol. 1; John Wiley and Sons: New York, **1983**.

(7) Takeuchi, Y.; Koike, M.; Azuma, K.; Nishioka, H.; Abe, H.; Kim, H.-S.; Wataya, Y.; Harayama, T. *Chem. Pharm.* **2001**, *49*, 721.

(8) (a) Tsantrizos, Y. S.; Xu, X.-J. *Can. J. Chem.* **1993**, *71*, 1362. (b) Wang, H.; Genesan, A. *J. Org. Chem.* **1998**, *63*, 2432. (c) He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1397. (d) Sugimori, T.; Okawa, T.; Egushi, S.; Kakehi, A.; Yashima, E.; Okamoto, Y. *Tetrahedron* **1998**, *54*, 7997.

(9) (a) Kotsuki, H.; Sakai, H.; Morimoto, H.; Suenaga, H. *Synlett* **1999**, 1993. (b) Khosropour, A. R.; Mohammafpoor-Baltork, I.; Ghorbankhani, H. *Tetrahedron Lett.* **2006**, *47*, 3561. (c) Narasimhulu, M.; Mahesh, K. C.; Reddy, T. S.; Rajesh, K.; Venkateswarlu, Y. *Tetrahedron Lett.* **2006**, *47*, 4381.

(10) (a) Kametani, T.; Loc, C. V.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1997**, *99*, 2306,. (b) Connolly, D. J.; Guiry, P. J. *Synlett* **2001**, 1707. (c) Wang, L.; Xia, J.; Qin, F.; Qin, C.; Sun, J. *Synthesis* **2003**, 1241.

(11) Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Bahgbanzadeh, M. *Tetrahedron Lett.* **2004**, *46*, 7151.

(12) Xue, S.; McKenna, J.; Shieh, W. C.; Repi, O. *J. Org. Chem.* **2004**, *69*, 6474.
(13) Shi, D.; Rong, L.; Wang, J.; Zhuang, Q.; Wang, X.; Hu, H. *Tetrahedron Lett.* **2003**, *44*, 3199.
(14) (a) Kamal, A.; Reddy, K. S.; Prasad, B. R.; Babu, A. H.; Ramana, A. V. *Tetrahedron Lett.* **2004**, *45*, 6–517. (b) Kalusa, A.; Chessum, N.; Jones, K. *Tetrahedron Lett.* **2008**, *49*, 5840.
(15) (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941. (c) Chan, D. M. T.; Lam, P. Y. S. *Recent Advances in Copper-Promoted C-Heteroatom Bond Cross-Coupling Reaction with Boronic Acids and Derivatives,* In *Boronic Acids: Preparation and Application in Organic Synthesis and Medicine*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, **2005**, 205.
(16) (a) Lam, P. Y. S.; Deudon, S.; Averil, K. M.; Li, R.; He, M.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600. (b) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2002**, *43*, 3091. (c) Chan, D. M. T.; Monaco, K. L.; Li, R.; Bonne, D.; Clark, C. G.; Lam, P. Y. S. *Tetrahedron Lett.* **2003**, *44*, 3863.
(17) (a) Evans, D. A.; Katz, J. L.; Peterson, G. S.; Hinterman, T. *J. Am. Chem. Soc.* **2001**, *123*, 12411. (b) Collman, J. P.; Zhong, M.; Zhang, C.; Costanzo, S. *Org. Lett.* **2001**, *66*, 7892. (c) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 4309. (d) Bakkestuen, A. K.; Gundersen, L.-L. *Tetrahedron Lett.* **2003**, *44*, 3359. (e) Strouse, J. J.; Jeselnik, M.; Tapaha, F.; Jonsson, C. B.; Parker, W. B.; Arterburn, J. B. *Tetrahedron Lett.* **2005**, *46*, 5699. (f) Benard, S.; Neuville, L.; Zhu, J. *J. Org. Chem.* **2008**, *73*, 6441. (g) Guy, C. S.; Jones, T. C. *Synlett* **2009**, 2253.
(18) **General Procedure for N-Arylation of 4 (3*H*)-Quinazolinone**
A mixture of the requisite 4 (3*H*)-quinazolinone (1.0 mmol), phenylboronic acid (1.5 mmol), anhyd $Cu(OAc)_2$ (1.0 mmol) and Et_3N (2.0 mmol) in dry CH_2Cl_2 (10–15 mL) was stirred at ambient temperature under air for 24–70 h. Progress of the reaction was monitored by TLC. The reaction mixture was filtered through Celite, the filtrate concentrated in vacuo, and the resulting mixture purified by chromatography on silica gel (CH_2Cl_2–MeOH) to yield the corresponding N-substituted quinazolin-4 (3*H*)-one.
Selected Spectroscopic Data
Table 1, Entry 6
Brown solid; mp 221–223 °C. IR (KBr): 3105, 3043, 2976, 2495, 1928 1614 cm–1. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.37 (s, 1 H), 8.14–8.12 (m, 1 H,), 7.95–7.93 (m, 1 H), 7.80–7.78 (m, 1 H), 7.62–7.60 (m, 2 H), 7.42–7.45 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.0, 147.6, 146.4, 134.6, 131.6, 129.8, 129.6, 125.2, 116.2, 115.7. ESI-MS: 275 [M + H]$^+$. ESI-HRMS: *m/z* calcd for $C_{14}H_9ClFN_2O$ [M + H]$^+$: 275.0387; found: 275.0383.
Table 1, Entry 7
Brown solid; mp 194–196 °C. IR (KBr): 3066, 2981, 2939, 2727, 1681, 1556 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.32 (s, 1 H), 8.17–8.15 (m, 1 H), 7.97–7.95 (m, 1 H) 7.76–7.73 (m, 1 H), 7.12–7.10 (m, 1 H), 7.03–6.98 (m, 2 H), 4.30 (s, 4 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.0, 147.7, 146.3, 143.7, 143.2, 134.5, 131.4, 130.2, 129.4, 125.2, 123.1, 120.1, 117.0, 116.3, 64.0. ESI-MS: 315 [M + H]$^+$. ESI-HRMS): *m/z* calcd for $C_{16}H_{12}ClN_2O_3$ [M + H]$^+$: 315.0536; found: 315.0529.
Table 1, Entry 8
Brown solid; mp 190–192 °C. IR (KBr): 3086, 3026, 2962, 2654, 1739, 1610 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.24 (s, 1 H), 7.58–7.48 (m, 6 H,), 7.20–7.18 (m, 1 H), 3.94 (s, 3 H), 3.89 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.2, 154.6, 148.9, 145.6, 143.8, 137.7, 129.1, 128.5, 127.4, 114.8, 108.0, 105.4, 56.0, 55.7. ESI-MS: *m/z* = 283 [M + H]$^+$. ESI-HRMS: *m/z* calcd for $C_{16}H_{15}N_2O_3$ [M + H]$^+$: 283.1083; found: 283.1081.
Table 1, Entry 9
Brown solid; mp 243–245 °C. IR (KBr): 3433, 3060, 2962, 2837, 1683, 1610, 1502 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.22 (s, 1 H), 7.49–7.47 (m, 1 H), 7.46–7.44 (m, 1 H), 7.39–7.37 (m, 2 H), 7.19–7.17 (m, 1 H), 3.94 (s, 3 H), 3.88 (s, 3 H), 2.30 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 161.4, 159.2, 154.68, 148.99, 145.64, 143.84, 133.65, 130.68, 126.9, 125.3, 115.6, 114.7, 108.0, 105.3, 56.02, 55.75, 14.07. ESI-MS: *m/z* 315 [M + H]$^+$. ESI-HRMS: *m/z* calcd for $C_{17}H_{16}FN_2O_3$ [M + H]$^+$: 315.1145; found: 315.1143.
(19) Ple, P. A.; Green, T. P.; Hennequin, L. F.; Curwen, J.; Fennel, M.; Allen, J.; van der Brempt, C. L.; Costello, G. *J. Med. Chem.* **2004**, *47*, 871.
(20) **Selected Spectroscopic Data**
Table 2, Entry 2
Brown solid; mp 125–127 °C. IR (KBr): 3429, 3076, 2954, 2495, 2854 2445, 1678 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.22 (s, 1 H), 7.60–7.58 (m, 2 H,), 7.56–7.54 (m, 1 H), 7.40–7.36 (m, 2 H), 7.20–7.18 (m, 1 H), 4.20–4.18 (m, 2 H), 3.85 (s, 3 H), 3.60–3.58 (m, 4 H), 2.46–2.38 (m, 6 H), 1.96–1.94 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.0, 159.0, 153.9, 149.0, 145.5, 143.7,134.0, 133.8, 129.7, 129.5, 116.0, 115.6, 114.6, 108.6, 105.5, 66.9, 64.8, 55.7, 54.6, 53.0, 25.4. ESI-MS: 414 [M + H]$^+$. ESI-HRMS: *m/z* calcd for $C_{22}H_{25}FN_3O_4$ [M + H]$^+$: 414.1829; found: 414.1830.