A Concise and Cascade Synthesis of Batracylin and Substituted Isoindolo-[1,2-*b*]quinazolin-12(10*H*)-ones

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Received 28 October 2010

This paper is dedicated to Prof. H. Ila on the occasion of her 67th birthday

Abstract: A concise, highly convergent, and practical synthesis of the clinical-phase anticancer agent batracylin in a two-stage process in excellent yield is described. The B and C rings of this tetracyclic heterocycle are constructed by cascade cyclization of 5-nitro-2-aminobenzyl alcohol with 2-cyanomethyl benzoate in trifluoroacetic acid in good yield in a single-pot reaction. A plausible mechanism for the cascade reaction is also proposed. As part of these studies, a range of batracylin derivatives with different substituents on the C and D rings are synthesized.

Key words: batracylin, antineoplastic agents, cascade cyclization, 5-nitro-2-aminobenzyl alcohol

Batracylin (8-aminoisoindolo[1,2-b]quinazolin-12(10*H*)-one); NSC320846, **1**) is an anticancer agent synthesized by Kabbe in 1978.[1] It is currently undergoing clinical evaluation as an anticancer agent at the National Cancer Institute.[2] Batracylin exhibits in vivo antineoplastic activity against murine leukemia P-388, and is shown to inhibit tumor growth completely in 80–100% of mice with early-stage colon adenocarcinoma.[3] Animal studies have also shown that batracylin has effective oral activity against solid tumors (implanted colon adenocarcinomas, pancreatic ductal carcinomas, hepatoma 129) and adriamycin, cisplatin, and methotrexate-resistant P388 leukemia.[4] Structurally batracylin is a quinazoline fused onto an isoindolone moiety. Similar structures are present in several natural products of great pharmacological interest including (–)-vasicine (**2**)[5] and tryptanthrin (**3**)[6] which have anti-inflammatory activity, and lutonins **4a**–**c**[7] which has antitumoural activity (Figure 1). The major limitations to the chemotherapeutic potential of batracylin (**1**) are the high level of dose required for its antineoplastic activity and its systemic toxicity, especially in rats.

Batracyclin (**1**) is known to undergo reversible hydrolytic cleavage to produce ring-opened 2-(2,5-diaminobenzyl)isoindoline-1,3-dione (**5**) under acidic hydrolytic conditions.[8] Most of the reported synthetic approaches to batracylin thus utilize 2-(2,5-diaminobenzyl)isoindoline-1,3-dione (**5**) as the key intermediate, which is synthesized by the reaction of either phthalic anhydride (**6a**) or phthalimide (**6b**) with appropriately substituted benzyl

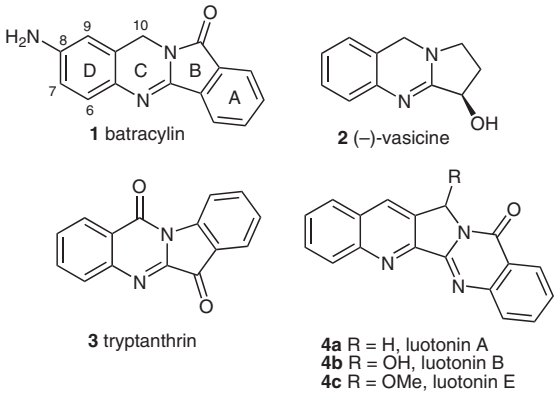


Figure 1

halides or benzyl amine **7**. This intermediate 2-(2,5-diaminobenzyl)isoindoline-1,3-dione (**5**) upon cyclodehydration under different reaction conditions results in batracylin in varying yields.[9] Malacria et al. utilized an amide-iminyl radical **8** cyclization protocol in their approach to the batracylin framework[10] (Figure 2).

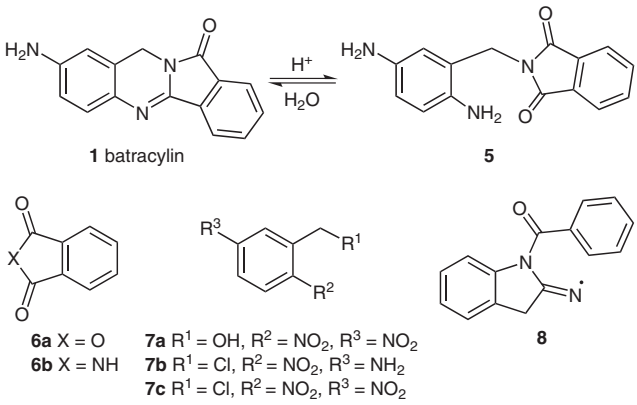
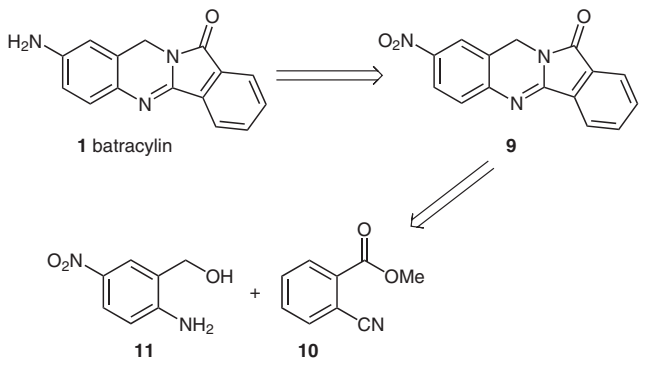


Figure 2

Herein we report a highly concise and convergent cascade synthesis of batracylin (**1**) in a two-step process in very high isolated yield. The methodology employed in our total synthesis of batracylin and its derivatives is depicted in the retrosynthetic scheme (Scheme 1). The reduction of nitro group in **9** to an amine functionality would yield batracylin (**1**). The (8-nitro-isoindolo[1,2-*b*]quinazolin-

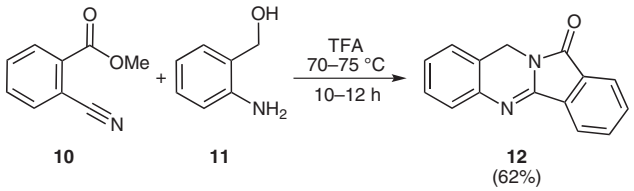
SYNLETT 2011, No. 6, pp 0844–0848
Advanced online publication: 16.03.2011
DOI: 10.1055/s-0030-1259921; Art ID: D29010ST

12(10*H*)-one (**9**) could be synthesized via the reaction of 2-methyl cyanobenzoate (**10**) with 2-amino-5-nitrophenyl methanol (**11**) under acidic conditions.



Scheme 1

To test the validity of our disconnection approach, the cascade cyclization reaction was attempted for the synthesis of de-amino batracylin, isoindolo[1,2-*b*]quinazolin-12(10*H*)-one (**12**, Scheme 2). 2-Methyl cyanobenzoate **10** was prepared by cyanation of commercially available methyl iodobenzoate with Cu(I)CN in acetonitrile as reported in the literature.[11] The cascade cyclization was attempted initially in various organic acids such as formic and acetic acid, under neat conditions, and also in combination with other solvents at elevate temperatures, but these attempts did not furnish the desired product. The reaction was also performed in PTSA/toluene combinations, and in various Lewis acids such as $BF_3{\cdot}OEt_2$, $SnCl_4$, and $TiCl_4$ in suitable solvents or under solvent-free conditions, but resulted in either unidentifiable product mixtures or unreacted or hydrolyzed starting materials. However, when the reaction was carried out in anhydrous trifluoroacetic acid at 70–75 °C, complete disappearance of starting materials was observed within 10–12 hours along with formation of a single major product and work-up and isolation gave pure product **12** in 62% yield.[12] The structure of isoindolo[1,2-*b*]quinazolin-12(10*H*)-one (**12**) was confirmed by means of IR and NMR spectroscopy and mass spectroscopy.[13]

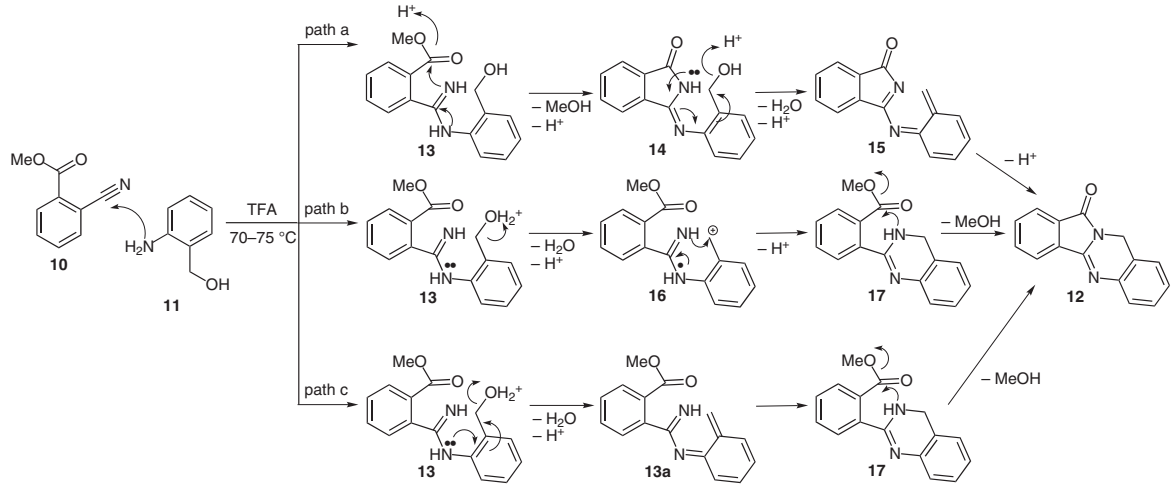


Scheme 2

The intermediate methyl 2-{*N*-[2-(hydroxymethyl)phenyl]carbamimidoyl}benzoate (**13**) is assumed to be formed by nucleophilic attack of amine **11** on the nitrile functionality of **10** under acidic reaction conditions (Scheme 3). In path a, the cycloamidation of the intermediate **13** via the elimination of methanol results in the formation of iminoisoindolinone derivative **14**. Intermediate **14** on loss of water yields the triene **15**, which on electrocyclization under thermal conditions can lead to the formation of isoindolo[1,2-*b*]quinazolin-12(10*H*)-one (**12**). Conversely, iminoamine **13** (path b) under S_N1 reaction conditions results in carbocation **16**, which further leads to the formation of methyl 2-(3,4-dihydroquinazolin-2-yl)benzoate (**17**). The cycloamidation of **17** along with concomitant elimination of methanol gives **12**. In path c, the triene **13a** is assumed to be the key intermediate, which on electrocyclization under thermal reaction conditions results in methyl 2-(3,4-dihydroquinazolin-2-yl)benzoate (**17**). The cycloamidation of **17** with loss of methanol yields **12**.

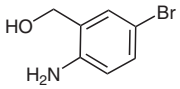
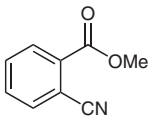
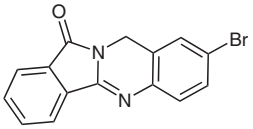
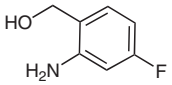
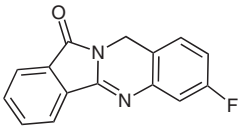
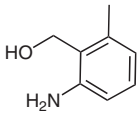
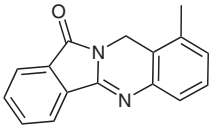
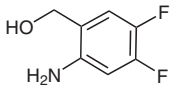
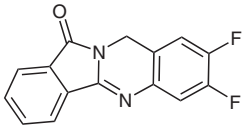
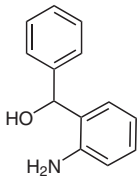
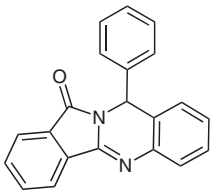
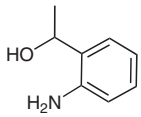
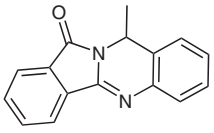
Encouraged by these results, batracylin derivatives **24**–**29** were synthesized (Table 1).[14] All the reactions are performed in a single-pot operation in trifluoroacetic acid at 70–75 °C over a period of 10–16 hours.

The isolated yields of these products provide some insight into the reaction mechanism, indicating that the reaction might have proceeded preferentially via path b. The amino alcohols **22** and **23** forms stable carbocations under



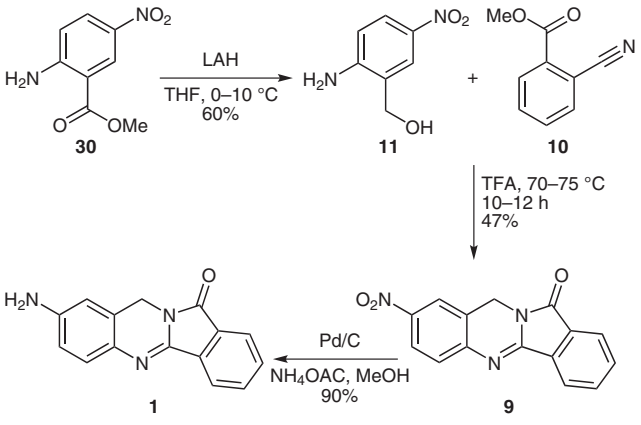
Scheme 3

Table 1 Synthesis of Isoindolo[1,2-*b*]quinazolin-12(10*H*)-one

Entry	Aminobenzyl alcohol	Cyanomethyl benzoate	Batracylin derivative	Yield (%)	Mp (°C)
1	 **18**	 **10**	 **24**	63	214
2	 **19**	**10**	 **25**	57	213
3	 **20**	**10**	 **26**	54	243
4	 **21**	**10**	 **27**	53	278
5	 **22**	**10**	 **28**	72	210
6	 **23**	**10**	 **29**	70	123

S_N1 reaction conditions, and this is consistent with the formation of isoindolo[1,2-*b*]quinazoline **28** and **29** in higher yields. The electron-withdrawing effect of the fluoro substituents would destabilize the carbocations derived from amino alcohols **21** and **19** and the isoindolo[1,2-*b*]quinazolines **27** and **25** are formed from these starting materials in comparatively lower yields.

For the synthesis of batracylin (Scheme 4), the required 2-aminonitrophenyl methanol (**11**) was synthesized by the reduction of corresponding benzoic acid methyl ester **30**.[15] The cascade reaction of **11** with 2-methyl cyanobenzoate (**10**) in the presence of trifluoroacetic acid at 70–75 °C resulted in 8-nitroisoindolo[1,2-*b*]quinazolin-12(10*H*)-one (**9**) in 47% yield of analytically pure product within 13–15 hours. Reduction of the nitro functionality in **9** was carried out with ammonium formate–Pd/C and afforded batracylin (**1**) in 90% yield as a yellow solid (mp 280–282 °C; lit. 287–288 °C[9b])[16] with spectroscopic and analytical data in agreement with the literature.[17]



Scheme 4

In summary, a highly convergent cascade process has been developed for the synthesis of batracylin and its analogues in excellent yield. The novel synthetic approach

involves assembly of the B and C rings of batracylin under acidic conditions. Compared with the known methods of batracylin synthesis, the present synthesis provides a new unique cascade route to batracylin and its substituted isoindolo[1,2-*b*]quinazolin-12(10*H*)-one derivatives from easily accessible precursors. This novel methodology appears to be well suited for preparation of simple congeners and several analogues that may prove useful in defining a pharmacological profile of this class of batracylin and its derivatives. We are further exploring the application of this cascade reaction sequence for the synthesis of other naturally occurring compounds having the isoindolo[1,2-*b*]quinazoline frame work.

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

Acknowledgment

The authors would like to thank Dr. Vilas H. Dahanukar for his constant encouragement and support. We also thank the analytical department, Dr. Reddy's Laboratories, for providing the analytical support.

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(12) A solution of methyl 2-cyanobenzoate (0.5 g, 0.003 mol), 2-aminophenylmethanol (0.57 g, 0.0047 mol) in TFA (10 mL) was refluxed for 10–12 h, and the progress of the reaction was monitored by TLC. After complete disappearance of the starting material, the reaction was quenched with ice water and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts washed with aq $NaHCO_3$ (10%, 25 mL) dried over anhyd Na_2SO_4, filtered, and concentrated under vacuum. The crude product was then purified by column chromatography using CH_2Cl_2 as an eluent; yield 0.43 g (62%).
(13) **Isoindolo [1,2-*b*]Quinazolin-12(10*H*)-one (12)**
Yield 62%; mp 186 °C (lit. 175–177 °C);[8] IR (KBr): 1724, 1650 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.6 Hz, 1 H, ArH), 7.90 (d, *J* = 6.7 Hz, 1 H, ArH), 7.74–7.63 (m, 2 H, ArH), 7.51 (d, *J* = 8.0 Hz, 1 H, ArH), 7.34–7.18 (m, 3 H, ArH), 5.00 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.2, 148.7, 140.0, 134.0, 133.2, 132.4, 130.1, 128.4, 127.4, 127.3, 127.2, 122.8, 121.9, 121.2, 40.2 ppm. MS: *m/z* (%) = 235.2 $[M + H]^+$. Anal. Calcd for $C_{15}H_{10}N_2O$ (234.2): C, 76.91; H, 4.30; N, 11.96; O, 6.83. Found: C, 76.83; H, 4.25, N, 4.26, O, 6.70.
(14) **8-Bromoisoindolo[1,2-*b*]quinazolin-12(10*H*)-one (24)**
Yield 63%; mp 214 °C. IR (KBr): 1731, 1645 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 8.02 (d, *J* = 7 Hz, 1 H, ArH), 7.90 (d, *J* = 7 Hz, 1 H, ArH), 7.84–7.77 (m, 2 H, ArH), 7.57 (s, 1 H, ArH), 7.51 (dd, *J* = 8.2, 1.5 Hz, 1 H, ArH), 7.34 (d, *J* = 8.5 Hz, 1 H, ArH), 4.93 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 149.2, 139.3, 133.7, 133.1, 132.4, 131.1, 129.8, 128.8, 124.4, 122.7, 121.9, 119.5, 40.7 ppm. MS: *m/z* (%) = 313.1 $[M + H]^+$. Anal. Calcd for $C_{15}H_9BrN_2O$ (311.99): C, 57.53; H, 2.90; N, 8.95; O, 5.11. Found: C, 57.48; H, 2.85; N, 8.85; O, 5.1.
7-Fluoroisoindolo[1,2-*b*]quinazolin-12(10*H*)-one (25)
Yield 57%; mp 213 °C. IR (KBr): 1729, 1646 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.2 Hz, 1 H, ArH), 7.92 (d, *J* = 6.8 Hz, 1 H, ArH), 7.75–7.69 (m, 2 H, ArH), 7.22 (dd, *J* = 2.4, 9.6 Hz, 1 H, ArH), 7.19–7.12 (m, 1 H, ArH), 6.98–6.93 (m, 1 H, ArH), 4.95 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 149.9, 142.1, 133.0, 132.6, 132.3, 131.6, 131.1, 130.4, 127.8, 127.7, 123.5, 123.2, 122.3, 40.3 ppm. MS: *m/z* (%) = 253.2 $[M + H]^+$. Anal. Calcd for $C_{15}H_9FN_2O$ (252.07): C, 71.42; H, 3.60; N, 11.11; O, 6.34. Found: C, 71.34; H, 3.50; N, 11.01; O, 6.29.
9-Methylisoindolo[1,2-*b*]quinazolin-12(10*H*)-one (26)
Yield 54% mp 243 °C. IR (KBr): 1721, 1650 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.04 (d, *J* = 6.8 Hz, 1 H, ArH), 7.92–7.78 (m, 3 H, ArH), 7.26–7.24 (m, 2 H, ArH), 7.14–7.10 (m, 1 H, ArH), 4.85 (s, 2 H, CH_2), 2.49 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 148.4, 139.8, 135.4, 134.1, 132.8, 132.0, 130.4, 129.3, 128.3, 125.7, 123.1, 122.3, 119.8, 39.4, 18.1 ppm. MS: *m/z* (%) = 249.2 $[M + H]^+$. Anal. Calcd for $C_{16}H_{12}N_2O$ (248.09): C, 77.40; H, 4.87; N, 11.28; O, 6.44. Found: C, 77.32; H, 4.78; N, 11.19; O, 6.35.
7,8-Difluoroisoindolo[1,2-*b*]quinazolin-12(10*H*)-one (27)
Yield 53%; mp 278 °C. IR (KBr): 1729, 1647 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 7.6 Hz, 1 H, ArH), 7.9 (d, *J* = 6.8 Hz, 1 H, ArH), 7.75–7.68 (m, 2 H, ArH), 7.34 (m, 1 H, ArH), 7.00 (t, 8.8 Hz, 1 H, ArH), 4.90 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.0, 158.5, 141.2, 133.2, 132.5, 130.3, 123.4, 122.4, 116.9, 115.4, 110.0, 40.3 ppm. MS: *m/z* (%) = 271.2 $[M + H]^+$. Anal. Calcd for $C_{15}H_8F_2N_2O$ (270.06): C, 66.67; H, 2.98; N, 10.37; O, 5.92. Found: C, 66.58; H, 2.87; N, 10.29; O, 5.83.

10-Phenylisoindolo[1,2-*b*]quinazolin-12(10*H*)-one (28)
Yield 72%; mp 210 °C. IR (KBr): 1732, 1646 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 8.10 (d, *J* = 7.5 Hz, 1 H, ArH), 7.88–7.78 (m, 3 H, ArH), 7.49 (d, *J* = 7.0 Hz, 1 H, ArH), 7.35–7.21 (m, 8 H, ArH), 6.47 (s, 1 H, CH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.8, 165.9, 153.2, 143.1, 138.9, 133.9, 133.8, 132.8, 129.7, 128.8, 128.7, 128.1, 127.8, 127.8, 127.3, 126.4, 126.2, 123.2, 122.3, 54.5 ppm. MS: *m/z* (%) = 311.2 $[M + H]^+$. Anal. Calcd for $C_{21}H_{14}N_2O$ (310.11): C, 81.27; H, 4.55; N, 9.03; O, 5.16. Found: C, 81.20; H, 4.50; N, 8.92; O, 5.10.

10-Methylisoindolo[1,2-*b*]quinazolin-12(10*H*)-one (29)
Yield 70%; mp 123 °C. IR (KBr): 2925, 1728, 1648 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.6 Hz, 1 H, ArH), 7.81 (d, *J* = 7.2 Hz, 1 H, ArH), 7.64–7.57 (m, 2 H, ArH), 7.40 (d, *J* = 8.0 Hz, 1 H, ArH), 7.26–7.21 (m, 1 H, ArH), 7.18–7.15 (m, 1 H, ArH), 7.12 (d, *J* = 6.8 Hz, 1 H, ArH), 5.41 (q, *J* = 6.4 Hz, 1 H, CH), 1.51 (d, *J* = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 149.9, 139.8, 134.5, 132.9, 132.0, 130.6, 128.6, 127.8, 127.7, 127.7, 127.5, 123.2, 122.1, 47.9, 23.6 ppm. MS: *m/z* (%) = 249.2 $[M + H]^+$. Anal. Calcd for $C_{16}H_{12}N_2O$ (248.09): C, 77.40; H, 4.87; N, 11.28; O, 6.44. Found: C, 77.32; H, 4.81; N, 11.20; O, 6.36.

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(17) **8-Aminoisoindolo[1,2-*b*]quinazolin-12(10*H*)-one (1)**
Mp 280–282 °C (recrystallized from CH_2Cl_2). IR (KBr): 3474, 1688, 1645 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.95 (d, *J* = 8.0 Hz, 1 H, ArH), 7.86 (d, *J* = 6.8 Hz, 1 H, ArH), 7.78–7.68 (m, 2 H, ArH), 7.13 (d, *J* = 8.4 Hz, 1 H, ArH), 6.52 (dd, *J* = 2.4, 8.2 Hz, 1 H, ArH), 6.46 (s, 1 H, ArH), 5.54 (s, 2 H, NH_2), 4.80 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.9, 148.8, 143.8, 134.2, 132.8, 131.3, 129.7, 129.4, 128.8, 122.8, 122.6, 121.2, 113.2, 111.7, 40.3 ppm. MS: *m/z* (%) = 250.2 $[M + H]^+$. Anal. Calcd for $C_{15}H_{11}N_3O$ (249.09): C, 72.28; H, 4.45; N, 16.86; O, 6.42. Found: C, 72.19; H, 4.38; N, 16.80; O, 6.35.