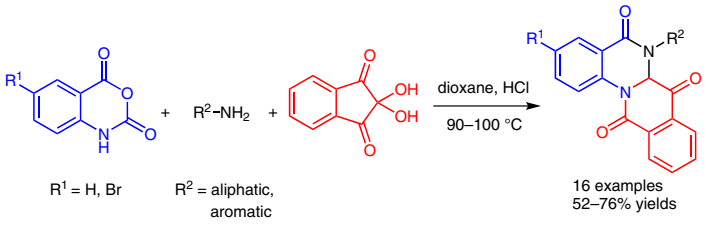
Synlett V. N. Murthy et al. Letter

A Simple Approach for the Synthesis of Fused Quinazoline-Based Tetracyclic Compounds via a Multicomponent Reaction Strategy

V. Narayana Murthy[a]
Satish P Nikumbh[a]
S. Praveen Kumar[a]
Y. Chiranjeevi[a]
L. Vaikunta Rao[b]
Akula Raghunadh*[a]

[a] Technology Development Centre, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd, Hyderabad 500049, India
raghunadha@drreddys.com
[b] Department of Chemistry, GIS, GITAM University, Visakhapatnam 530045, India



Received: 02.04.2016
Accepted after revision: 03.06.2016
Published online: 13.07.2016
DOI: 10.1055/s-0035-1562465; Art ID: st-2016-d0230-l

Abstract A simple method for the synthesis of tetracyclic quinazolinone derivatives via a multicomponent reaction strategy from isatoic anhydride and amine with ninhydrin has been developed.

Key words isatoic anhydride, ninhydrin, tetracyclic quinazolinone, multicomponent reaction

The tetracyclic quinazolinone ring system is an important core unit of many biological active naturally occurring alkaloids and pharmaceuticals.[1] The alkaloids include tryptanthrin (**1**),[2] phaitanthrin C (**2**),[3] ophiuroidine (**3**),[4] (–)-benzomalvin A (**4**),[5] auranthine (**5**),[6] and asperlicin D (**6**)[7] (Figure 1). All the tetracyclic quinazolinone-based natural products[8] possess interesting biological activity and therefore have been extensively investigated for useful pharmaceutical activity. However, a limited number of synthetic strategies have been reported in the literature for the synthesis of fused tetracyclic quinazolinone compounds.[9] In this context, we have reported the synthesis of various quinazolinone-based biologically active natural products and their derivatives.[10]

Recently, we published a short and efficient methodology for the synthesis of 2-amino-3-substituted quinazolinone derivatives.[11] We explored the possibility of a simple, catalyst-free synthesis of 6,6a-dihydro-5*H*-isoquinolino[2,3-*a*]quinazol ine-5,7,12-trione derivatives with isatoic anhydride (**9**),[12] amine **8**, and ninhydrin (**7**)[13] via a multicomponent reaction strategy.

The retrosynthetic strategy employed for the synthesis of 6,6a-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-5,7,12-trione derivatives is depicted in Scheme 1. It was proposed that the 6,6a-dihydro-5*H*-isoquinolino [2,3-a] quinazoline-5,7,12-trione derivatives **10** may be obtained by reaction of isatoic anhydride (**9**) with an amine **8** and ninhydrin (**7**).

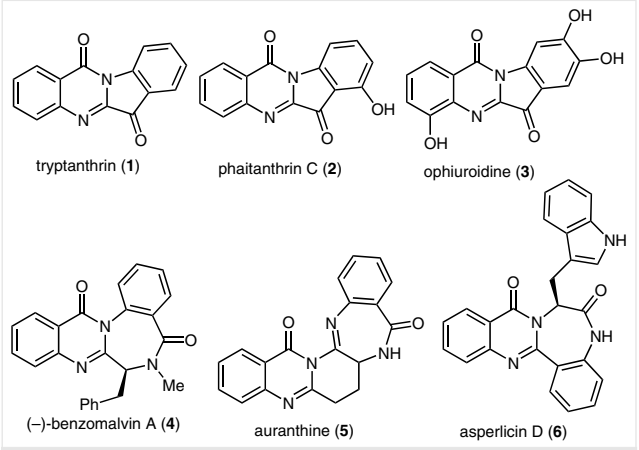
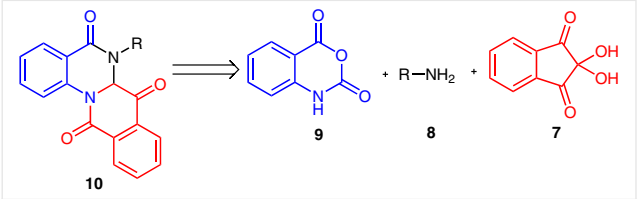


Figure 1 Examples of various natural products that contain tetracyclic quinazolinone skeleton

In a model study, optimized conditions utilized 1.0 equivalent isatoic anhydride (**9**), 1.0 equivalent of *n*-butyl amine, and 1.0 equivalent of ninhydrin (**7**). Various acids, such as aqueous HCl, H_2SO_4, 10% HCl in 1,4-dioxane, Wang resin, Amberlite IR120, acetic acid, trifluoroacetic acid,



Scheme 1 Retrosynthesis of **10**

Table 1 Screening of Various Acids[a]

Entry	Acid reagent	Isolated yield (%)
1	10% aq HCl	42
2	5% aq HCl	36
3	10% HCl in 1,4-dioxane	71
4	10% methanolic HCl	56
5	10% aq H_2SO_4 solution	32
6	Wang resin	45
7	Amberlite IR120	31
8	AcOH	37
9	TFA	30
10	$BF_3{\cdot}OEt_2$	22
11	$FeCl_3$	18
12	$TiCl_4$	15

[a] Reaction conditions: isatoic anhydride (1.0 equiv), *n*-butylamine (1.0 equiv), and ninhydrin (1.0 equiv) at 100 °C in a sealed tube.

$BF_3{\cdot}OEt_2$, $FeCl_3$, and $TiCl_4$ were screened (Table 1, entries 1–12). The best result was obtained when the reaction was performed in the presence of 10% HCl in 1,4-dioxane (Table 1, entry 3).

To explore the generality of this reaction, we employed a variety of substituted aliphatic and aromatic amines, and the results are summarized in Table 2.

Scheme 2 describes a plausible mechanism for the three-component reaction leading to compound **10**. The nucleophilic attack of primary amine on carbonyl group of isatoic anhydride followed by ring opening and subsequent decarboxylation will yield to compound **11**. Nucleophilic attack of amine to the keto group of ninhydrin will yield imine intermediate **12**; which on subsequent cyclization lead to compound **13**. Nucleophilic attack of amine on the keto group yields fused aziridine intermediate **14**, the subsequent rearrangement leads to the formation of **10**.

Table 2 Synthesis of Various Tetracyclic Quinazolinone Derivatives[a]

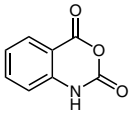
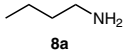
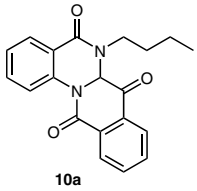
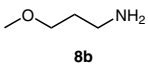
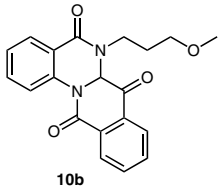
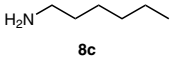
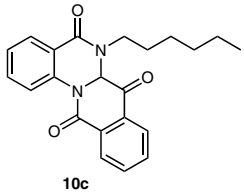
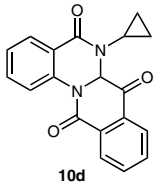
Entry	Isatoic anhydride	Amine	Product	Isolated yield (%)
1	 **9a**	 **8a**	 **10a**	71
2	**9a**	 **8b**	 **10b**	64
3	**9a**	 **8c**	 **10c**	63
4	**9a**	 **8d**	 **10d**	67

Table 2 (continued)

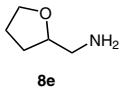
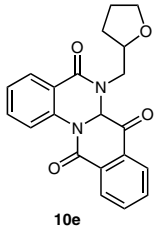
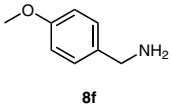
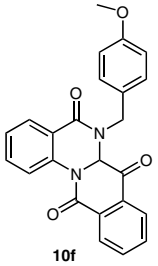
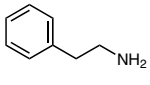
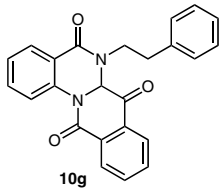
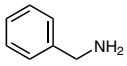
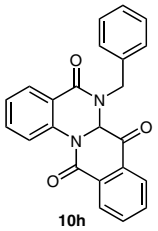
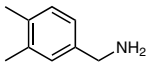
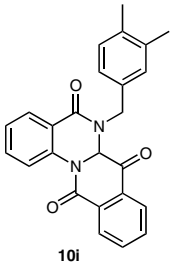
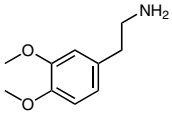
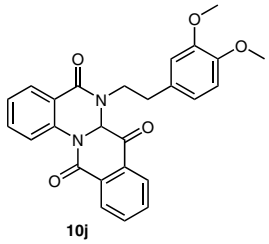
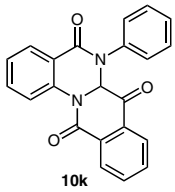
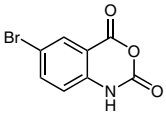
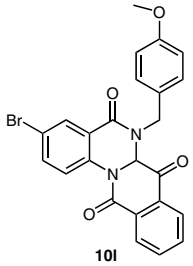
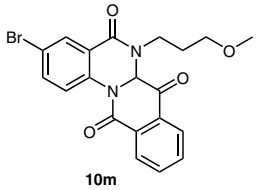
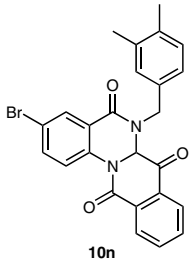
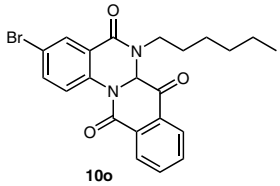
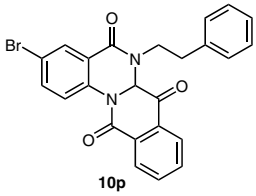
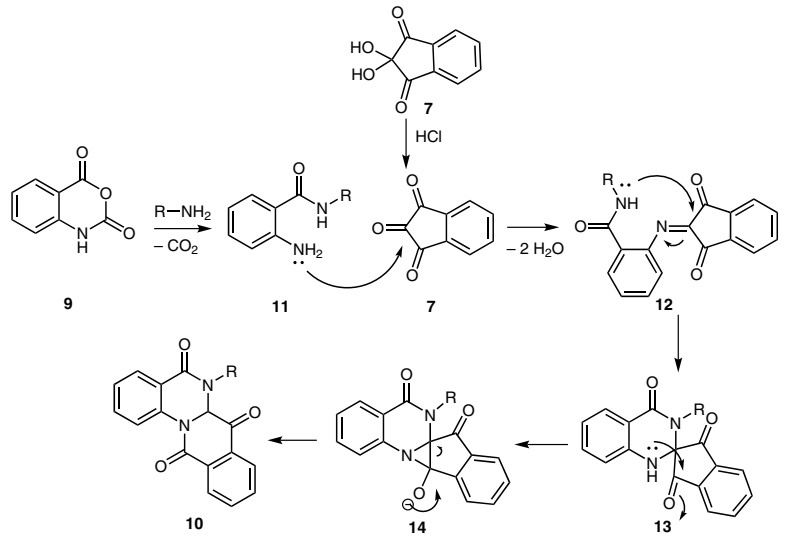
Entry	Isatoic anhydride	Amine	Product	Isolated yield (%)
5	**9a**	 **8e**	 **10e**	68
6	**9a**	 **8f**	 **10f**	75
7	**9a**	 **8g**	 **10g**	73
8	**9a**	 **8h**	 **10h**	71
9	**9a**	 **8i**	 **10i**	73
10	**9a**	 **8j**	 **10j**	74

Table 2 (continued)

Entry	Isatoic anhydride	Amine	Product	Isolated yield (%)
11	**9a**	 **8k**	 **10k**	52
12	 **9b**	**8f**	 **10l**	75
13	**9b**	**8b**	 **10m**	74
14	**9b**	**8i**	 **10n**	72
15	**9b**	**8c**	 **10o**	74
16	**9a**	**8g**	 **10p**	76

[a] All reactions were carried out in 10% HCl in 1,4-dioxane at 100 °C.



Scheme 2 The proposed reaction mechanism for the formation of **10**

In conclusion, we have developed an efficient novel protocol for the synthesis of 6,6a-dihydro-5*H*-isoquinolino[2,3a]quinazoline-5,7,12-trionederivatives in good yields from isatoic anhydride, amine, and ninhydrine in a one-pot process.[14,15]

Acknowledgment

The authors would like to thank Dr. Vilas Dahanukar, Dr. H Rama Mohan, Dr. K. B. Shiva Kumar, and the analytical group of CPS-DRL for spectroscopic data.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562465.

References and Notes

(1) (a) Lee, S. H.; Son, J.-K.; Jeong, B. S.; Jeong, T.-C.; Chang, H. W.; Lee, E.-S.; Jahng, Y. *Molecules* **2008**, *13*, 272. (b) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787.

(2) Friedländer, P.; Roschdestwensky, N. *Ber. Dtsch. Chem. Ges.* **1915**, *48*, 1841.

(3) Jao, C. W.; Lin, W. C.; Wu, Y. T.; Wu, P. L. *J. Nat. Prod.* **2008**, *71*, 1275.

(4) Bourne, G. T.; Utkina, N. K.; Denisenko, V. A. *Tetrahedron Lett.* **2007**, *48*, 4445.

(5) Sugimori, T.; Okawa, T.; Eguchi, S.; Kakehi, A.; Yashima, E.; Okamotot, Y. *Tetrahedron* **1998**, *54*, 7997.

(6) Kshirsagar, U. A.; Puranik, V. G.; Argade, N. P. *J. Org. Chem.* **2010**, *75*, 2702.

(7) (a) Chang, R. S. L.; Lotti, V. J.; Monaghan, R. L.; Birnbaum, J.; Stapley, E. O.; Goetz, M. A.; Albers-Schorberg, G.; Patchett, A. A.; Liesch, J. M.; Hensens, O. D.; Springer, J. P. *Science* **1985**, *230*, 177. (b) Liesch, J. M.; Hensen, O. D.; Goetz, M. A. *J. Antibiot.* **1988**, *41*, 878.

(8) (a) Sum, H. H.; Barrow, C. J.; Sedlock, D. M.; Gillum, A. M.; Cooper, R. *J. Antibiot.* **1994**, *47*, 515. (b) Rahbek, L.; Breinholt, J.; Frisvad, J. C.; Christophersen, C. *J. Org. Chem.* **1994**, *74*, 1789. (c) Rahbek, L.; Breinholt, J. *J. Nat. Prod.* **1999**, *72*, 904.

(9) Madhubabu, M. V.; Shankar, R.; More, S. S.; Basaveswara Rao, M. V.; Syam Kumar, U. K.; Raghunadh, A. *RSC Adv.* **2016**, *6*, 36599.

(10) Raghavendra, R. K.; Ramamohan, M.; Raghunadh, A.; Suresh Babu, M.; Praveen Kumar, S.; Kalita, D.; Laxminarayana, E.; Prasad, B.; Pal, M. *RSC Adv.* **2015**, *5*, 61575.

(11) Murthy, N. V.; Nikumbh, S. P.; Praveen Kumar, S.; Vaikunta Rao, L.; Raghunadh, A. *Tetrahedron Lett.* **2015**, *56*, 5767.

(12) Shvekhgeimer, M. G. A. *Chem. Heterocycl. Compd.* **2001**, *37*, 385.

(13) Ziarani, G. M.; Lashgari, N.; Azimian, F.; Kruger, H. G.; Gholamzadeh, P. *ARKIVOC* **2015**, 1.

(14) **Synthesis of 6-Substituted 6,6a-Dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-5,7,12-trione Derivatives 10a–p: General Procedure**
To a solution of isatoic anhydride (1.0 equiv) in 1,4 dioxane (4.0 mL) amine **8** (1.0 equiv) was added, and the reaction was heated to reflux for 3–4 h. The reaction progress was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, then ninhydrin (1.0 equiv) followed by HCl in dioxane (3 M) solution (2.0 mL) were added, and the mixture was heated in a sealed tube for 8–10 h. After completion of the reaction, the solvent was evaporated under vacuum, and the residue was purified by column chromatography in EtOAc–hexane (3:7).

(15) **Representative Analytical Data**
6-Butyl-6,6a-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-5,7,12-trione (10a)
Orange solid; yield 71%; mp 155–157 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.19–8.14 (m, 3 H, ArH), 7.71 (d, *J* = 6.8 Hz, 1 H, ArH), 7.32 (t, *J* = 6.4 Hz, 1 H), 6.84 (t, *J* = 7.2 Hz, 1 H, ArH,), 6.61 (d, *J* = 8.0 Hz, 1 H), 3.07 (t, *J* = 7.2 Hz, 2 H), 1.34–1.28 (m, 2 H),

1.15–1.05 (m, 4 H), 0.69 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 194.84, 162.90, 144.97, 139.04, 138.10 (3 C), 133.54, 127.25, 124.47 (3 C), 118.38, 114.28, 113.75, 74.32, 43.28, 30.36, 19.42, 13.37. HRMS: *m/z* calcd for $C_{20}H_{19}N_2O_3$ [M + H]: 335.1396; found: 335.1400.

6-Cyclopropyl-6,6a-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-5,7,12-trione (10d)

Brown solid; yield 67%; mp 205–208 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.18–8.14 (m, 4 H, ArH), 7.66 (d, *J* = 7.2 Hz, 2 H), 7.29–7.25 (m, 1 H, ArH), 6.77 (t, *J* = 7.2 Hz, 1 H), 6.57 (d, *J* = 8.0 Hz, 1 H, ArH), 2.29–2.23 (m, 1 H), 0.60–0.55 (m, 2 H), 0.39–0.35 (m, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.21, 163.89, 145.11, 139.14, 137.97 (3 C), 133.62, 127.34, 124.35 (3 C), 118.46, 114.91, 113.81, 74.71, 26.96, 8.27 (2 C). HRMS: *m/z* calcd for $C_{19}H_{15}N_2O_3$ [M + H]: 319.1083; found: 319.1068.

6-[(Tetrahydrofuran-2-yl)methyl]-6,6a-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-5,7,12-trione (10e)

Yellow solid; yield 68%; mp 194–197 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.09–8.00 (m, 4 H, ArH), 7.76 (s, 1 H), 7.72 (d, *J* = 7.8 Hz, 1 H, ArH), 7.28–7.24 (m, 1 H, ArH), 6.80 (t, *J* = 7.2 Hz, 1 H, ArH), 6.59 (d, *J* = 8.0 Hz, 1 H, ArH), 4.01 (dd, J_1 = 8.2 Hz, J_2 = 1.6 Hz,1 H), 3.70–3.68 (m, 1 H), 3.40–3.36 (m, 1 H), 2.87–2.81 (m, 1 H), 2.68–2.62 (m, 1 H), 1.78–1.74 (m, 1 H), 1.56–1.50 (m, 2 H), 1.41–1.36 (m, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 192.88, 163.44, 144.68, 138.95, 138.79, 137.12 (2 C), 136.36, 133.44, 127.53, 124.14, 123.92, 118.76, 115.81, 114.33, 77.33, 73.67, 65.76, 43.98, 27.76, 24.57. HRMS: *m/z* calcd for $C_{21}H_{19}N_2O_4$ [M + H]: 363.1345; found: 363.1352.

6-(3,4-Dimethoxyphenethyl)-6,6a-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-5,7,12-trione (10j)

Orange solid; yield 74%; mp 159–161 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.13–8.12 (m, 4 H, ArH), 7.73 (d, *J* = 8.0 Hz, 1 H, ArH), 7.66 (s, 1 H, ArH), 7.29 (t, *J* = 7.6 Hz, 1 H), 6.80 (t, *J* = 7.2 Hz, 1 H, ArH), 6.69 (d, *J* = 7.6 Hz, 1 H, ArH), 6.59 (d, *J* = 7.6 Hz, 1 H, ArH), 6.47 (s, 1 H), 6.43 (d, *J* = 8.0 Hz, 1 H, ArH), 3.63 (s, 6 H), 3.27 (t, *J* = 7.6 Hz, 2 H), 2.65 (t, *J* = 7.6 Hz, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 194.57, 162.88, 147.18, 145.03, 139.01 (2 C), 137.93 (3 C), 133.65, 130.54, 127.24, 124.39 (3 C), 120.19, 118.49, 114.36, 113.85, 112.01, 113.73, 74.36, 55.30, 55.17, 45.58, 34.01. HRMS: *m/z* calcd for $C_{26}H_{23}N_2O_5$ [M + H]: 443.1607; found: 443.1605.

3-Bromo-6-(3-methoxypropyl)-6,6a-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-5,7,12-trione (10m)

Orange solid; yield 74%; mp 205–207 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.19–8.15 (m, 4 H, ArH), 7.94 (s, 1 H, ArH), 7.74 (d, *J* = 8.0 Hz, 1 H, ArH), 7.45 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1 H, ArH), 6.57 (d, *J* = 8.8 Hz, 1 H, ArH), 3.16 (t, *J* = 8.8 Hz, 2 H), 3.13–3.08 (m, 2 H), 3.02 (s, 3 H), 1.63–1.56 (m, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 194.31, 161.88, 144.15, 139.00, 138.24 (3 C), 136.09, 129.23, 124.60 (3 C), 116.21, 115.82, 109.37, 74.19, 69.10, 57.48, 41.46, 28.18. HRMS: *m/z* calcd for $C_{20}H_{18}N_2O_4Br$ [M + H]: 429.0450; found: 429.0444.

3-Bromo-6-hexyl-6,6a-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-5,7,12-trione (10o)

Orange solid; yield 74%; mp 145–147 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.20–8.15 (m, 4 H, ArH), 7.92 (s, 1 H), 7.74 (d, *J* = 7.6 Hz, 1 H, ArH), 7.44 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1 H, ArH), 6.56 (d, *J* = 8.8 Hz, 1 H), 3.05 (t, *J* = 7.6 Hz, 2 H), 1.32–1.23 (m, 2 H), 1.13–1.05 (m, 6 H), 0.75 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 194.42, 161.71, 144.16, 138.96, 138.26 (3 C), 136.01, 129.27, 124.57 (3 C), 116.20, 115.97, 109.35, 73.98, 43.59, 30.48, 27.93, 26.79, 21.67, 13.71. HRMS: *m/z* calcd for $C_{22}H_{22}N_2O_3Br$ [M + H]: 441.0814; found: 441.0805.

3-Bromo-6-phenethyl-6,6a-dihydro-5*H*-isoquinolino[2,3-*a*]quinazoline-5,7,12-trione (10p)

Yellow solid; yield 76%; mp 211–213 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.22–8.17 (m, 4 H, ArH), 7.98 (s, 1 H), 7.75 (d, *J* = 7.6 Hz, 1 H), 7.47 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1 H, ArH), 7.29–7.27 (m, 2 H, ArH), 7.21–7.10 (m, 1 H, ArH), 6.98 (d, *J* = 6.8 Hz, 2 H), 6.59 (d, *J* = 8.4 Hz, 1 H), 3.24 (t, *J* = 8.0 Hz, 2 H), 2.71 (t, *J* = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 194.16, 161.78, 144.21, 139.09 (2 C), 138.22 (3 C), 136.17, 129.26, 128.38 (3 C), 128.22 (3 C), 126.33, 124.64, 116.31, 115.88, 109.51, 74.29, 45.53, 34.34. HRMS: *m/z* calcd for $C_{24}H_{18}N_2O_3Br$ [M + H]: 461.0501; found: 461.0507.