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A novel one-pot pseudo-four-component isocyanide-based reaction: an unexpected approach for the synthesis of tetrahydrodiisoindoloquinoxalines and tetrahydrobenzodiisoindoloquinoxalines

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ABSTRACT

A novel isocyanide based one-pot pseudo-four-component strategy for the synthesis of tetrahydrodiisoindoloquinoxaline and tetrahydrobenzodiisoindoloquinoxaline derivatives *via* the reaction of 1,2-diamines, 2-formylbenzoic acid, and an isocyanide at room temperature in good yields without using any catalyst and activation, is described.

1. Introduction

Quinoxalines are an excellent scaffold for drug development, mainly due to their structural similarity to benzodiazepines. They exhibit a wide variety of biological and medicinal activities including: antidiabetic,[1] anticancer, antibacterial,[2] cytotoxic, and antiviral effects, especially, against retroviruses, such as HIV.[3] Some of the compounds containing these heterocyclic cores have demonstrated antidepressant **I**,[4] excitatory amino acid antagonistic **II**,[5] and antiglaucoma activities **III** (Fig. 1).[6] Quinoxalines with an indole ring gave 5-substituted-2-bromoindolo[2,3-*b*]quinoxalines that represent a broad spectrum of antitumor activity with two biochemical mechanism-based screens (cdc2 kinase and cdc25 phosphatase) with IC_{50} of 70 and 25 μM.[7] Also isoindoloquinoxalines are antihypertensive,[8,9] and some of them, such as isoindolo[2,1-*a*]quinoxaline derivatives **IV** showed antiproliferative activity.[10]

Multicomponent reactions (MCRs) are powerful tools for the synthesis of complex biologically relevant molecules. The atom economy of MCRs, their convergent character, operational simplicity, and the structural diversity and complexity of the resulting molecules make this chemistry exceptionally useful for discovery and optimization processes in the pharmaceutical industry. MCRs

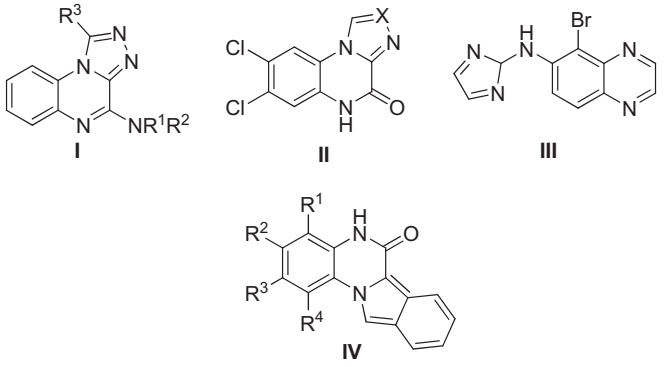

Fig. 1. Examples of medicinal quinoxalines.

especially isocyanide-based MCRs (IMCRs) are fast and selective methods for the synthesis of large libraries of organic molecules by simply varying each component through a chain of consecutive elementary transformations.[11]

Due to the biological and medicinal importance of the products obtained from diamines, and in view of our current studies on isocyanide-based multicomponent reactions (IMCRs) of diamines[12] herein, we report a novel IMCR, which afford 5,12,16b,16c-tetrahydrodiisoindolo[2,1-*a*:1′,2′-*c*]quinoxaline-16b-carboxamides **4a**–**j**

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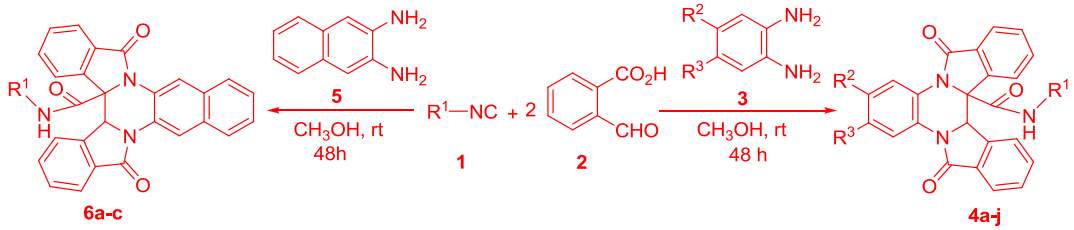
via an unexpected reaction between an isocyanide **1**, formylbenzoic acid[13] **2**, and an aromatic 1,2-diamine **3**. Alternatively, using naphthalene-2,3-diamine **5** instead of aromatic 1,2-diamines produces 5,14,18b,18c-tetrahydrobenzo[*g*]diisoindolo[2,1-*a*:1′,2′-*c*]quinoxaline-18b-carboxamides **6a–c** in good yields at room temperature (Scheme 1).

It is worth mentioning that in the present reaction three amides, two C–C bonds, and two C–N bonds are newly formed. As indicated in Fig. 2, the reaction is straightforward, and treatment of various alkyl, aryl, and alicyclic isocyanides and various *o*-phenylenediamines with formylbenzoic acid in methanol at room temperature and under similar circumstances led to the formation of the



Scheme 1.

2. Results and discussion

In a pilot experiment, 3,4-diaminobenzophenone, formylbenzoic acid, and cyclohexyl isocyanide in methanol were stirred at room temperature. The progress of the reaction was monitored by TLC. After 48 h, the reaction was completed and 9-benzoyl-*N*-cyclohexyl-5,12-dioxo-5,12,16b,16c-tetrahydrodiisoindolo[2,1-*a*:1′,2′-*c*]quinoxaline-16b-carboxamide **4a** was obtained in 90% yield (Scheme 1).

5,12,16b,16c-tetrahydrodiisoindolo[2,1-*a*:1′,2′-*c*]quinoxaline-16b-carboxamide derivatives **4a–j** in good yields. The results are summarized in Table 1. The structure of compounds **4a–j** was deduced from their IR, mass, ^{1}H NMR, and ^{13}C NMR spectral data. For example, the ^{1}H NMR spectrum of **4a** exhibited a multiplet for the cyclohexyl ring at δ=0.77–1.35, a broad singlet at δ=3.15 for C*H*–NH of cyclohexyl, a singlet identified as CH proton at δ=5.21, a multiplet at δ=7.61–8.77 for H-aromatic and –NH of amide. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 30 distinct

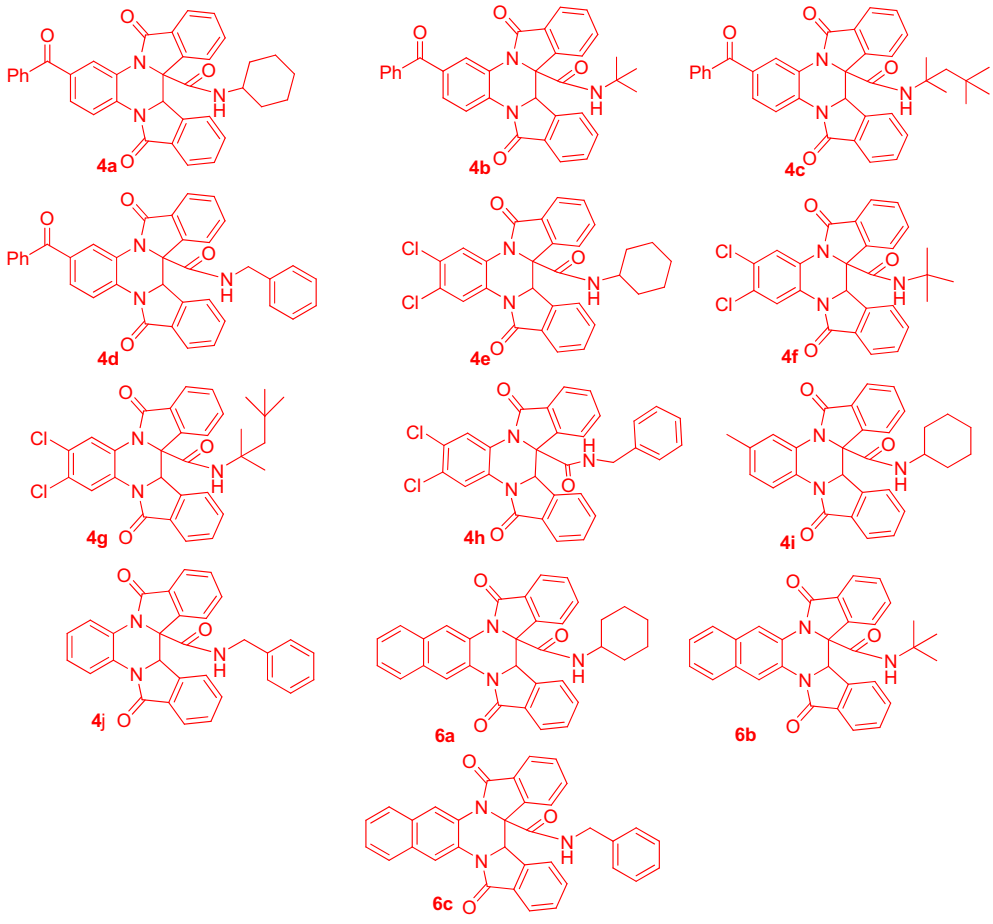


Fig. 2. The structure of compounds **4a–j** and **6a–c**.

Table 1
Synthesis of tetrahydrodiisoindoloquinoxalines **4a–j** and tetrahydrobenzodiisoindoloquinoxalines **6a–c**

Product	R^1	R^2	R^3	Yield (%)
4a	Cyclohexyl	COPh	H	90
4b	*tert*-Butyl	COPh	H	88
4c	1,1,3,3-Tetramethylbutyl	COPh	H	90
4d	Benzyl	COPh	H	82
4e	Cyclohexyl	Cl	Cl	78
4f	*tert*-Butyl	Cl	Cl	88
4g	1,1,3,3-Tetramethylbutyl	Cl	Cl	86
4h	Benzyl	Cl	Cl	75
4i	Cyclohexyl	Me	H	75
4j	Benzyl	H	H	74
6a	Cyclohexyl	Benzo		87
6b	*tert*-Butyl	Benzo		75
6c	Benzyl	Benzo		70

resonances in agreement with the proposed structure. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values.

It is important to note that compound **4a** has two stereogenic centers (C_8 and C_9) and therefore, two pairs of diastereoisomers expected. The ^{1}H NMR and ^{13}C NMR spectra of the crude products showed only one of two possible diastereomers (*RR* or *SS*) were present in the reaction mixture. These structures were confirmed by single-crystal X-ray analysis (Fig. 3).

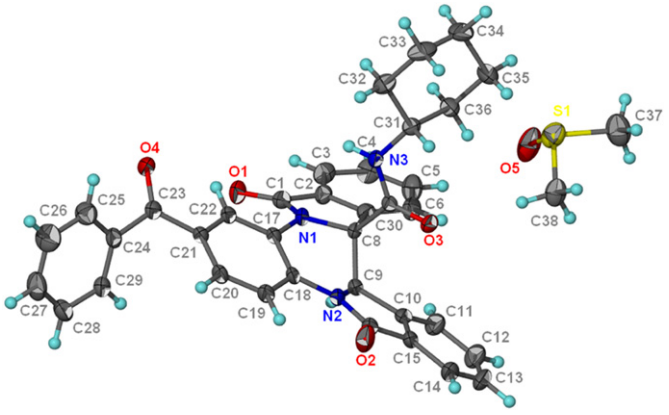


Fig. 3. ORTEP diagram for **4a**.

In view of the success of the above mentioned reaction, we explored the scope of this promising reaction with naphthalene-2,3-diamine, formylbenzoic acid and isocyanides. As indicated in Table 1, the reactions proceed efficiently and led to tetrahydrobenzodiisoindoloquinoxaline derivatives **6a–c** in good yields.

The suggested mechanism for the formation of products **4a–j** and **6a–c** is illustrated in Scheme 2. It is conceivable that, the initial event is the formation of diimine **7** from condensation reaction of **3** or **5** and aldehyde moiety of formylbenzoic acid **2**.[13h] Then cycloadduct **9** was formed by a 4n+2 electrocyclic reaction of **7** and a [1,5]-H shift of **8**. On the basis of the well established chemistry of isocyanides with imines,[11] intermediate **10** was produced by nucleophilic attack of isocyanide **1** to activated iminium **9** and a closure of the five-membered indole ring followed by nucleophilic attack of an H_2O molecule on the nitrilium moiety and production of compound **11**. Finally, tautomerization of intermediate **11** produces compounds **4a–j** or **6a–c**.

For clarifying the proposed mechanism, we have also investigated this reaction using various aliphatic diamines **12** under the same reaction conditions. As can be seen from Scheme 3, the expected product **14** was not obtained, but the reaction progressed *via* a pseudo-four-component condensation reaction and afforded a new class of bis(oxoisoindoline) derivatives **13a–c** compounds (Fig. 4).[13f,g] This result shows, the successful isolation of the products **4a–j** and **6a–c** can be explained to the formation of cycloadduct **8** *via* an electrocyclic reaction. Apparently, aliphatic diamines do not have conjugated systems, which are necessary for a pericyclic reaction.

So, we studied the reaction of 2,3-diaminomaleonitrile **15** with cyclohexyl isocyanide **1** and formylbenzoic acid **2** (Scheme 4). However, due to high stability of the generated imine **16** from reaction of 2,3-diaminomaleonitrile and formylbenzoic acid, formation of cycloadduct **9**, [1,5]-H shift reaction and nucleophilic attack by isocyanide did not occur.[12a]

In summary, we have discovered a novel and efficient one-pot pseudo-four-component condensation reaction leading to tetrahydrodiisoindoloquinoxaline and tetrahydrobenzodiisoindoloquinoxaline derivatives starting from simple and readily available precursors. This novel protocol can be regarded as a new approach for the preparation of synthetically and pharmaceutically relevant isoindoloquinoxaline systems in good to excellent yields at room temperature without using a catalyst. We hope that this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry.

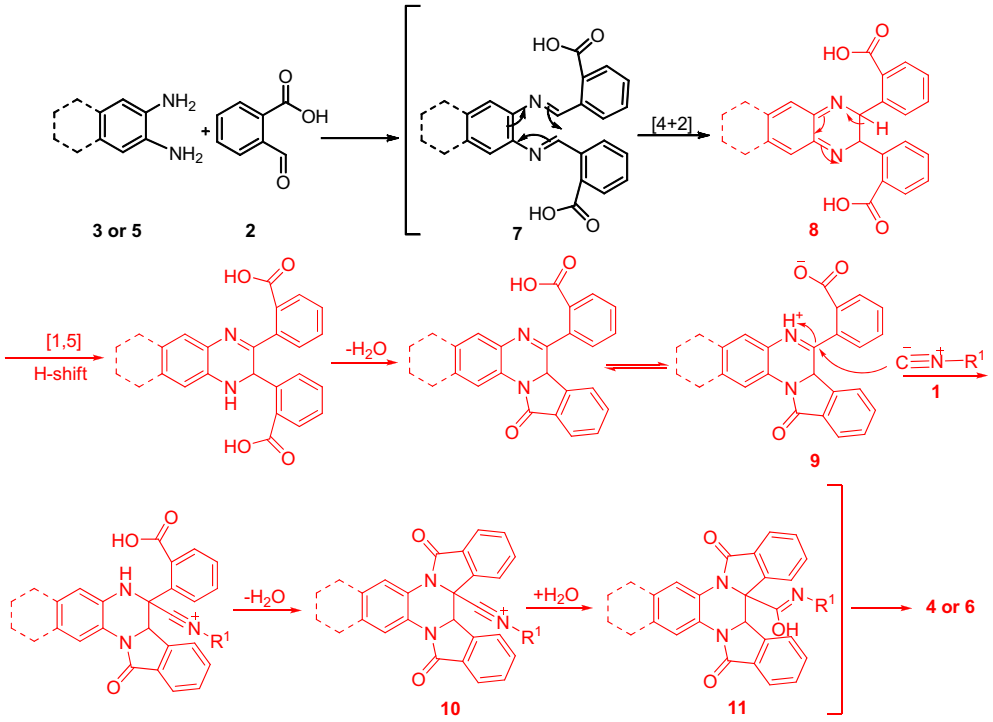
3. Experimental

3.1. General

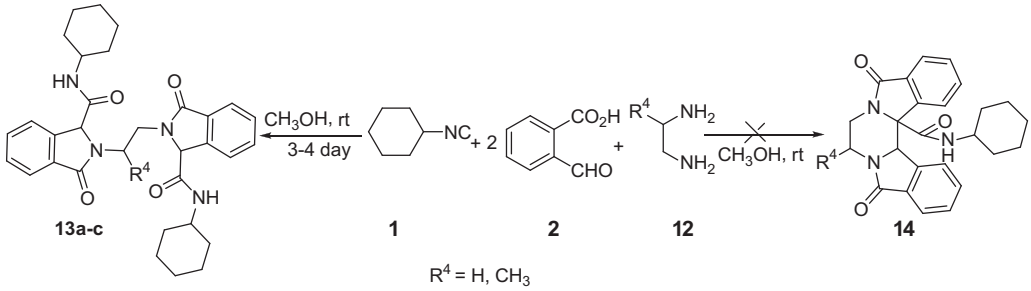
Melting points were measured on an Electrothermal 9200 apparatus. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H NMR Spectra were recorded on a Bruker DRX-300 Avance spectrometer 300.13 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR Spectra are reported in order: number of protons, multiplicity, and approximate coupling constant (*J* value) in hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), br s (broad signal), and Ar (aryl). The ^{13}C NMR spectra were recorded at 75.47 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). The elemental analyses were performed with an Elementar Analysensysteme GmbH VarioEL. All the products are new compounds, which were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra, and Mass spectral data.

3.2. Typical procedure for preparation of 9-benzoyl-*N*-cyclohexyl-5,12-dioxo-5,12,16b,16c-tetrahydrodiisoindolo[2,1-*a*:1′,2′-*c*]quinoxaline-16b-carboxamide (4a)

A solution of 3,4-diaminobenzophenone (0.21 g, 1 mmol), 2-formylbenzoic acid (0.30 g, 2 mmol), and cyclohexyl isocyanide (0.22 g, 2 mmol) in methanol (3 mL) was stirred for 48 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 3/1), the precipitate was filtered off and washed with methanol and the residue was crystallized from acetone to give **4a** as colorless needles crystals (0.51 g, yield 90%); mp 232–235 °C; R_f (33% *n*-hexane/AcOEt) 0.73. IR (KBr) cm^{-1}: 3300, 3065, 2924, 2845, 1710, 1591, 1518, 1440, 1352, 1283, 1152. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 0.77–1.35 (10H, m, 5CH_2 of cyclohexyl), 3.15 (1H, s, C*H*–NH), 5.21 (1H, s, CH), 7.61–8.77 (17H, m, H–Ar and N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.6, 25.4, 31.4, 31.7, 48.3, 63.5, 69.0, 118.6, 123.6, 124.1, 124.6, 124.8, 125.0, 125.2, 126.9, 129.0, 130.2, 131.0, 131.2, 131.8, 132.0, 133.0, 133.7, 137.7, 140.4, 142.2, 164.2, 166.5, 167.1, 194.9. MS *m/z*: 441 (M^+–126, 13), 413 (10), 337 (68),



Scheme 2. Possible mechanism.



Scheme 3. Clarification of the mechanism.

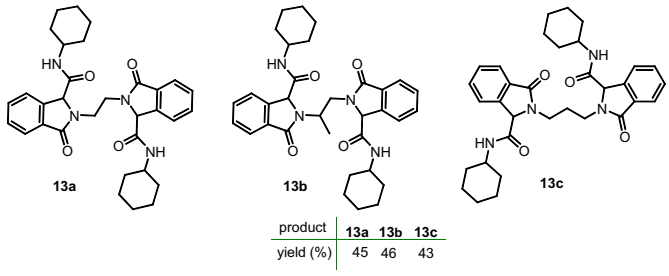
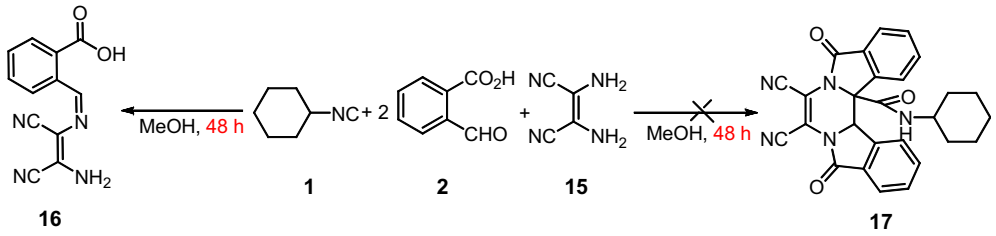


Fig. 4. The structure of bis(oxoisoindoline) derivatives.

309 (20), 280 (30), 279 (56), 251 (12), 177 (15), 151 (25), 105 (100), 77 (62), 55 (55). Anal. Calcd for $C_{36}H_{29}N_3O_4$: C, 76.17; H, 5.15; N, 7.40; found C, 76.33; H, 5.01; N, 7.29. ORTEP diagram for **4a**; summary of data: The Cambridge Crystallographic Data Centre (CCDC) no.: 808,449; unit cell parameters: *a* 8.5028(8) *b* 14.0031(13) *c* 14.2793(13) *α* 78.0530(10) *β* 90.0790(10) *γ* 73.7420(10); space group *P*−1. (Fax: +441 223 336 033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

*3.2.1. 9-Benzoyl-N-tert-butyl-5,12-dioxo-5,12,16b,16c-tetrahydrodiisoindolo[2,1-a:1′,2′-c]quinoxaline-16b-carboxamide (**4b**).* Light yellow powder (0.48 g, yield 88%); mp 252–255 °C; R_f (33% *n*-hexane/AcOEt) 0.71. IR (KBr) cm^{-1}: 3432, 3097, 3084, 3040, 2958, 2920, 2863, 1728, 1714, 1686, 1657, 1601, 1568, 1506, 1363, 1329, 1297, 1256, 1159, 1093. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 0.83 (9H, s, $3CH_3$), 5.18 (1H, s, CH), 7.13–8.75 (17H, m, H–Ar and N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 28.1, 51.3, 64.0, 69.2, 118.6, 123.7, 124.1, 124.9, 126.9, 129.1, 130.2, 131.0, 131.4, 131.9, 133.1, 133.6, 137.7, 140.2, 142.2, 164.1, 166.4, 167.0, 194.9. MS *m/z*: 542 (M^++1, 21), 442 (M^+−100, 80), 413 (19), 337 (40), 279 (15), 105 (100), 77 (40), 57 (25). Anal. Calcd for $C_{34}H_{27}N_3O_4$: C, 75.40; H, 5.02; N, 7.76; found C, 75.62; H, 4.88; N, 7.54.

*3.2.2. 9-Benzoyl-5,12-dioxo-N-(2,4,4-trimethylpentan-2-yl)-5,12,16b,16c-tetrahydrodiisoindolo[2,1-a:1′,2′-c]quinoxaline-16b-carboxamide (**4c**).* Light yellow powder (0.54 g, yield 90%); mp 220–223 °C; R_f (33% *n*-hexane/AcOEt) 0.68. IR (KBr) cm^{-1}: 3347, 3065, 2960, 2877, 1721, 1665, 1591, 1509, 1442, 1353, 1271, 1212, 1150, 1085. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 0.48 (9H, s, $3CH_3$), 0.82 (6H, s, $2CH_3$), 2.04 (2H, CH_2), 5.12 (1H, s, CH), 7.00–8.70 (17H, m, H–Ar and N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 28.6, 29.3,



Scheme 4. Reaction of 2,3-diaminomaleonitrile with cyclohexyl isocyanide and formylbenzoic acid.

31.0, 31.4, 50.0, 55.2, 63.8, 69.3, 118.7, 123.6, 124.1, 124.7, 124.9, 125.2, 126.9, 129.0, 130.1, 130.9, 131.4, 131.8, 133.0, 133.4, 137.7, 140.1, 142.3, 164.0, 166.6, 167.0, 194.9. MS *m/z*: 441 (M^+−156, 24), 337 (60), 280 (27), 279 (65), 177 (15), 151 (31), 105 (85), 77 (73), 57 (100), 41 (47). Anal. Calcd for $C_{38}H_{35}N_3O_4$: C, 76.36; H, 5.90; N, 7.03; found C, 76.54; H, 5.69; N, 7.19.

*3.2.3. 9-Benzoyl-N-benzyl-5,12-dioxo-5,12,16b,16c-tetrahydrodiisoindolo[2,1-a:1′,2′-c]quinoxaline-16b-carboxamide (**4d**).* Light orange powder (0.47 g, yield 82%); mp 233–237 °C; R_f (33% *n*-hexane/AcOEt) 0.66. IR (KBr) cm^{-1}: 3326, 3060, 2918, 2845, 1688, 1591, 1513, 1435, 1351, 1271, 1168, 1090. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 3.75 (1H, br m, C*H*–NH), 4.04 (1H, br m, C*H*–NH), 5.30 (1H, s, CH), 6.79–8.80 (22H, m, H–Ar and N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 42.0, 63.1, 69.1, 118.7, 123.7, 124.1, 125.1, 125.3, 126.3, 126.9, 127.1, 128.4, 129.0, 130.1, 131.2, 131.8, 132.0, 133.0, 133.2, 137.6, 138.9, 140.3, 142.0, 165.5, 166.4, 167.1, 194.8. MS *m/z*: 441 (M^+−134, 52), 337 (50), 279 (16), 247 (15), 231 (17), 177 (17), 151 (19), 133 (22), 91 (100). Anal. Calcd for $C_{37}H_{25}N_3O_4$: C, 77.20; H, 4.38; N, 7.30; found C, 77.44; H, 4.20; N, 7.51.

*3.2.4. 8,9-Dichloro-N-cyclohexyl-5,12-dioxo-5,12,16b,16c-tetrahydrodiisoindolo[2,1-a:1′,2′-c]quinoxaline-16b-carboxamide (**4e**).* Colorless needles crystals (0.41 g, yield 78%); mp >270 °C; R_f (33% *n*-hexane/AcOEt) 0.70. IR (KBr) cm^{-1}: 3294, 2934, 2850, 1721, 1676, 1592, 1528, 1491, 1464, 1399, 1366, 1330, 1291, 1236. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 0.82–1.40 (10H, m, 5CH_2 of cyclohexyl), 3.11 (1H, s, C*H*–NH), 5.16 (1H, s, CH), 7.59–8.70 (11H, m, H–Ar and N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.2, 24.7, 25.3, 31.5, 31.8, 48.5, 63.1, 69.1, 119.6, 123.6, 123.8, 124.1, 124.9, 125.1, 125.3, 126.9, 127.4, 129.0, 131.1, 131.3, 131.8, 133.1, 134.0, 140.3, 142.0, 163.9, 166.4, 166.8. MS *m/z*: 407 (M^+−126, ^{37}Cl, 40), 405 (M^+−126, ^{35}Cl, 45), 377 (25), 349 (24), 314 (27), 277 (23), 176 (37), 151 (25), 130 (15), 102 (28), 83 (27), 55 (100). Anal. Calcd for $C_{29}H_{23}Cl_2N_3O_3$: C, 65.42; H, 4.35; N, 7.89; found C, 65.21; H, 4.56; N, 7.68.

*3.2.5. N-tert-Butyl-8,9-dichloro-5,12-dioxo-5,12,16b,16c-tetrahydrodiisoindolo[2,1-a:1′,2′-c]quinoxaline-16b-carboxamide (**4f**).* Dark blue powder (0.45 g, yield 88%); mp >270 °C; R_f (33% *n*-hexane/AcOEt) 0.73. IR (KBr) cm^{-1}: 3432, 3109, 3072, 3046, 2964, 2933, 2863, 1718, 1692, 1600, 1470, 1404, 1369, 1329. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 0.83 (9H, s, 3CH_3), 5.19 (1H, s, CH), 7.15–8.76 (11H, m, H–Ar and N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 28.2, 51.4, 63.5, 69.3, 119.6, 123.5, 124.1, 124.7, 124.9, 125.3, 127.5, 129.1, 130.0, 130.3, 130.5, 130.9, 131.6, 133.2, 133.4, 133.9, 142.0, 154.6, 163.9, 166.7, 168.8. MS *m/z*: 507 (M^+, ^{37}Cl, 20), 505 (M^+, ^{35}Cl, 22), 405 (M^+−100, 63), 377 (23), 349 (15), 307 (31), 288 (11), 262 (50), 225 (13), 102 (10), 76 (16), 57 (35). Anal. Calcd for $C_{27}H_{21}Cl_2N_3O_3$: C, 64.04; H, 4.18; N, 8.30; found C, 63.81; H, 4.34; N, 8.16.

*3.2.6. 8,9-Dichloro-5,12-dioxo-N-(2,4,4-trimethylpentan-2-yl)-5,12,16b,16c-tetrahydrodiisoindolo[2,1-a:1′,2′-c]quinoxaline-16b-carboxamide (**4g**).* Dark blue powder (0.48 g, yield 86%); mp 223–227 °C; R_f (33% *n*-hexane/AcOEt) 0.75. IR (KBr) cm^{-1}: 3410, 3101, 2939, 2887, 1704, 1586, 1484, 1367, 1226, 1126. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 0.51 (9H, s, 3CH_3), 0.84 (3H, s, CH_3), 0.88 (3H, s, CH_3), 1.32 (2H, AB_q, J=14.4 Hz, CH_2), 5.11 (1H, s, CH), 6.98–8.70 (11H, m, H–Ar and N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 28.5, 29.3, 30.9, 31.4, 50.0, 55.4, 63.4, 69.4, 119.6, 123.6, 123.9, 124.1, 125.0, 125.2, 125.4, 126.9, 127.6, 129.0, 131.0, 131.4, 131.7, 133.1, 133.7, 140.0, 142.2, 163.8, 166.5, 166.7. MS *m/z*: 407 (M^+−156, ^{37}Cl, 100), 405 (M^+−156, ^{35}Cl, 100), 377 (32), 349 (32), 314 (28), 57 (100), 41 (55). Anal. Calcd for $C_{31}H_{29}Cl_2N_3O_3$: C, 66.19; H, 5.20; N, 7.47; found C, 66.40; H, 5.02; N, 7.29.

*3.2.7. N-Benzyl-8,9-dichloro-5,12-dioxo-5,12,16b,16c-tetrahydrodiisoindolo[2,1-a:1′,2′-c]quinoxaline-16b-carboxamide (**4h**).* Light orange needles crystals (0.40 g, yield 75%); mp 210–214 °C; R_f (33% *n*-hexane/AcOEt) 0.67. IR (KBr) cm^{-1}: 3404, 3180, 3065, 2924, 2835, 1683, 1602, 1550, 1482, 1419, 1355, 1309, 1205, 1152, 1095. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 3.80 (1H, m, C*H*–NH), 4.07 (1H, m, C*H*–NH), 5.30 (1H, s, CH), 7.03–8.80 (16H, m, H–Ar and N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 42.0, 62.8, 69.1, 119.7, 123.7, 124.0, 124.2, 125.1, 125.5, 126.3, 127.0, 128.3, 129.2, 131.3, 134.1, 138.8, 165.2, 166.2, 166.9. MS *m/z*: 407 (M^+−134, ^{37}Cl, 100), 405 (M^+−134, ^{35}Cl, 100), 376 (24), 326 (10), 299 (100), 273 (23), 239 (15), 202 (24), 177 (22), 158 (65), 130 (43), 91 (100), 65 (44), 39 (24). Anal. Calcd for $C_{30}H_{19}Cl_2N_3O_3$: C, 66.68; H, 3.54; N, 7.78; found C, 66.47; H, 3.36; N, 7.69.

*3.2.8. N-Cyclohexyl-9-methyl-5,12-dioxo-5,12,16b,16c-tetrahydrodiisoindolo[2,1-a:1′,2′-c]quinoxaline-16b-carboxamide (**4i**).* White powder (0.36 g, yield 75%); mp 254–258 °C; R_f (33% *n*-hexane/AcOEt) 0.69. IR (KBr) cm^{-1}: 3425, 2928, 2844, 1711, 1678, 1510, 1467, 1372, 1082. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 0.79–1.35 (10H, m, 5CH_2 of cyclohexyl), 2.36 (3H, s, CH_3), 3.10 (1H, s, C*H*–NH), 5.02 (1H, s, CH), 7.08–8.41 (12H, m, H–Ar and N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.6, 24.6, 25.4, 31.5, 31.7, 48.3, 63.7, 69.1, 118.6, 119.0, 122.5, 122.7, 123.5, 123.7, 124.6, 124.8, 125.0, 125.2, 128.8, 130.8, 132.2, 132.4, 132.8, 133.3, 140.6, 142.1, 164.4, 166.3, 166.6. MS *m/z*: 351 (M^+−126, 85), 323 (24), 293 (21), 280 (20), 190 (23), 165 (25), 147 (16), 102 (18), 83 (32), 55 (100). Anal. Calcd for $C_{30}H_{27}N_3O_3$: C, 75.45; H, 5.70; N, 8.80; found C, 75.67; H, 5.59; N, 8.62.

*3.2.9. N-Benzyl-5,12-dioxo-5,12,16b,16c-tetrahydrodiisoindolo[2,1-a:1′,2′-c]quinoxaline-16b-carboxamide (**4j**).* Yellow needles crystals (0.35 g, yield 74%); mp 228–230 °C; R_f (33% *n*-hexane/AcOEt) 0.64. IR (KBr) cm^{-1}: 3378, 3070, 3033, 2918, 1720, 1698, 1673, 1612, 1550, 1518, 1500, 1455, 1377, 1356, 1326, 1304. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 4.02 (2H, br s, CH_2), 5.23 (1H, s, CH), 7.00–8.90 (18H, m, H–Ar and N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 42.0, 63.2, 69.3, 125.0, 126.1, 126.8, 128.2, 128.4, 128.8, 129.3, 132.0, 132.1, 132.7, 138.9, 140.8, 141.9, 161.7, 165.4, 166.3. MS *m/z*: 337 (M^+−134, 52), 233 (27), 91 (100), 65 (23). Anal. Calcd for $C_{30}H_{21}N_3O_3$: C, 76.42; H, 4.49; N, 8.91; found C, 76.21; H, 4.67; N, 8.73.

*3.2.10. N-Cyclohexyl-5,14-dioxo-5,14,18b,18c-tetrahydrobenzo[g]diisoindolo[2,1-a:1′,2′-c]quinoxaline-18b-carboxamide (**6a**).* Brown

needles crystals (0.45 g, yield 87%); mp >270 °C; R_f (33% *n*-hexane/AcOEt) 0.79. IR (KBr) cm^{-1}: 3436, 3028, 2929, 2851, 1708, 1683, 1602, 1506, 1469, 1361, 1327, 1294, 1210. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 0.65–1.30 (10H, m, $5CH_2$ of cyclohexyl), 3.09 (1H, s, C*H*–NH), 5.20 (1H, s, CH), 7.35–9.01 (15H, m, H–Ar and N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.6, 25.2, 31.2, 31.7, 36.2, 48.5, 63.7, 69.5, 116.0, 120.3, 123.6, 123.9, 124.7, 124.9, 126.1, 126.4, 126.9, 127.9, 128.9, 129.7, 130.6, 131.0, 132.0, 132.6, 133.5, 140.4, 142.0, 162.8, 164.3, 166.8. MS *m/z*: 513 (M^+, 75), 387 (M^+-126, 82), 359 (31), 331 (30), 126 (20), 83 (61), 55 (100). Anal. Calcd for $C_{33}H_{27}N_3O_3$: C, 77.17; H, 5.30; N, 8.18; found C, 77.40; H, 5.13; N, 8.37.

*3.2.11. N-tert-Butyl-5,14-dioxo-5,14,18b,18c-tetrahydrobenzo[g]diisoindolo[2,1-a:1′,2′-c]quinoxaline-18b-carboxamide (**6b**).* Light brown powder (0.37 g, yield 75%); mp >270 °C; R_f (33% *n*-hexane/AcOEt) 0.75. IR (KBr) cm^{-1}: 3420, 3054, 2966, 2939, 2898, 2861, 1772, 1757, 1724, 1684, 1602, 1508, 1474, 1374, 1322, 1309, 1284, 1211. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 0.74 (9H, s, $3CH_3$), 5.22 (1H, s, CH), 7.25–9.03 (15H, m, H–Ar and N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 28.1, 51.2, 69.7, 87.3, 116.0, 119.9, 123.9, 124.3, 124.7, 124.9, 126.8, 127.7, 129.1, 129.7, 130.6, 130.8, 132.1, 132.5, 132.9, 133.5, 139.9, 141.9, 164.2, 165.4, 168.6. MS *m/z*: 387 (M^+-100, 100), 359 (62), 330 (72), 301 (10), 270 (49), 133 (35), 105 (100), 77 (46), 57 (27). Anal. Calcd for $C_{31}H_{25}N_3O_3$: C, 76.37; H, 5.17; N, 8.62; found C, 76.14; H, 5.32; N, 8.43.

*3.2.12. N-Benzyl-5,14-dioxo-5,14,18b,18c-tetrahydrobenzo[g]diisoindolo[2,1-a:1′,2′-c]quinoxaline-18b-carboxamide (**6c**).* Orange powder (0.36 g, yield 70%); mp 250–252 °C; R_f (33% *n*-hexane/AcOEt) 0.76. IR (KBr) cm^{-1}: 3399, 3060, 3033, 2960, 2924, 2851, 1707, 1680, 1602, 1560, 1507, 1466, 1374, 1330, 1246. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 4.01 (2H, AB_q, J=7 Hz, CH_2), 5.34 (1H, s, CH), 6.39–9.14 (20H, m, H–Ar and N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 41.9, 63.2, 69.6, 116.1, 120.6, 123.7, 124.8, 125.0, 126.0, 126.7, 127.0, 127.8, 128.1, 129.0, 129.7, 131.2, 132.5, 132.7, 133.6, 140.2, 165.6, 166.2, 166.8. MS *m/z*: 521 (M^+, 25), 387 (M^+-134, 40), 359 (16), 331 (15), 91 (100), 65 (18). Anal. Calcd for $C_{34}H_{23}N_3O_3$: C, 78.30; H, 4.44; N, 8.06; found C, 78.52; H, 4.26; N, 8.34.

3.3. Typical procedure for preparation of 2,2′-(ethane-1,2-diyl)bis(*N*-cyclohexyl-3-oxoisoindoline-1-carboxamide) (13a)

A solution of ethylenediamine (0.06 g, 1 mmol), 2-formylbenzoic acid (0.30 g, 2 mmol), and cyclohexyl isocyanide (0.22 g, 2 mmol) in methanol (3 mL) was stirred for 72 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 6/1), the precipitate was filtered off and washed with methanol and the product **13a** was obtained as white powders (0.24 g, yield 45%); mp >270 °C; R_f (17% *n*-hexane/AcOEt) 0.63. IR (KBr) cm^{-1}: 3343, 3264, 3084, 2934, 2854, 1706, 1683, 1651, 1555, 1518, 1467, 1404. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.16–1.65 (20H, m, $10CH_2$ of cyclohexyl), 3.44 (2H, s, 2C*H*–NH), 4.02 (4H, m, $2CH_2$), 5.23 (2H, s, 2CH), 7.50–7.70 (8H, m, H–Ar), 8.50 (2H, br s, N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.9, 25.6, 32.4, 32.6, 48.6, 63.7, 122.8, 123.4, 129.0, 131.7, 132.3, 142.6, 165.9, 168.9. MS *m/z*: 543 (M^++1, 29), 416 (M^+-126, 10), 290 (32), 159 (100), 104 (21), 83 (27), 55 (10). Anal. Calcd for $C_{32}H_{38}N_4O_4$: C, 70.82; H, 7.06; N, 10.32; found C, 70.61; H, 7.29; N, 10.15.

*3.3.1. 2,2′-(Propane-1,2-diyl)bis(N-cyclohexyl-3-oxoisoindoline-1-carboxamide) (**13b**).* White powder (0.26 g, yield 46%); mp >270 °C; R_f (17% *n*-hexane/AcOEt) 0.66. IR (KBr) cm^{-1}: 3261, 3046, 2939, 2850, 1698, 1656, 1541, 1467, 1379, 1316, 1221. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.22–1.70 (23H, m, $10CH_2$ of cyclohexyl and CH_3), 3.00 (1H, br m, CH), 3.52 (2H, s, 2C*H*–NH), 4.07 (1H, br m, CH), 4.62 (1H, br m, CH), 5.35 (1H, s, CH), 5.41 (1H, s, CH), 7.33–7.51 (8H, m, H–Ar), 8.75 (2H, s, 2 N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 15.8, 24.7, 24.9, 25.6, 32.3, 32.5, 32.7, 44.6, 46.3, 48.4, 48.5, 61.3, 63.5, 122.1, 122.7, 123.0, 123.1, 128.5, 128.6, 128.7, 131.4, 131.8, 132.1, 142.5, 143.4, 166.2, 167.8, 168.4, 169.3. MS *m/z*: 557 (M^++1, 25), 430 (M^+-126, 7), 285 (24), 160 (100), 132 (40), 104 (12), 83 (25), 55 (48). Anal. Calcd for $C_{33}H_{40}N_4O_4$: C, 71.20; H, 7.24; N, 10.06; found C, 71.41; H, 6.98; N, 10.31.

*3.3.2. 2,2′-(Propane-1,3-diyl)bis(N-cyclohexyl-3-oxoisoindoline-1-carboxamide) (**13c**).* White powder (0.24 g, yield 43%); mp 265–269 °C; R_f (17% *n*-hexane/AcOEt) 0.61. IR (KBr) cm^{-1}: 3488, 3274, 3072, 2930, 2850, 1695, 1650, 1549, 1467, 1448, 1410. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.15–1.65 (20H, m, $10CH_2$ of cyclohexyl), 2.00 (2H, m, CH_2), 3.00 (2H, m, CH_2), 3.50 (2H, s, 2C*H*–NH), 3.76 (2H, m, CH_2), 5.22 (2H, s, 2CH), 7.53–7.70 (8H, m, H–Ar), 8.56 (2H, d, J=6.50 Hz, 2N*H*–CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.8, 25.6, 26.9, 32.6, 48.5, 63.5, 122.4, 122.7, 123.2, 129.1, 132.2, 142.3, 166.0, 168.5. MS *m/z*: 556 (M^+, 33), 431 (M^+-125, 100), 306 (100), 243 (30), 215 (20), 172 (48), 146 (100). Anal. Calcd for $C_{33}H_{40}N_4O_4$: C, 71.20; H, 7.24; N, 10.06; found C, 71.42; H, 7.11; N, 10.34.

3.4. Typical procedure for preparation of 2-((*E*)-((*Z*)-2-amino-1,2-dicyanovinylimino)methyl)benzoic acid (16)

A solution of 2,3-diaminomaleonitrile (0.10 g, 1 mmol), 2-formylbenzoic acid (0.30 g, 2 mmol), and cyclohexyl isocyanide (0.22 g, 2 mmol) in methanol (3 mL) was stirred for 48 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 6/1), the precipitate was filtered off and washed with methanol and the product **16** was obtained as orange powder; mp 194–199 °C; R_f (17% *n*-hexane/AcOEt) 0.69. IR (KBr) cm^{-1}: 3476, 3444, 3313, 2233, 2205, 1683, 1619, 1556, 1384, 1300, 1265, 1077. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 7.50–8.45 (6H, m, H–Ar and NH_2), 9.05 (1H, s, CH), 13.50 (1H, m, OH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 103.3, 114.3, 114.8, 127.9, 128.7, 130.7, 131.3, 132.1, 132.3, 135.6, 154.5, 168.5. MS *m/z*: 241 (M^++1, 23), 133 (100). Anal. Calcd for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.32; found C, 59.90; H, 3.54; N, 23.14.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.061.

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