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NATURAL PRODUCT INSPIRED *meta/para'*-BIARYL ETHER LACTAM MACROCYCLES BY DOUBLE UGI MULTICOMPONENT REACTIONS

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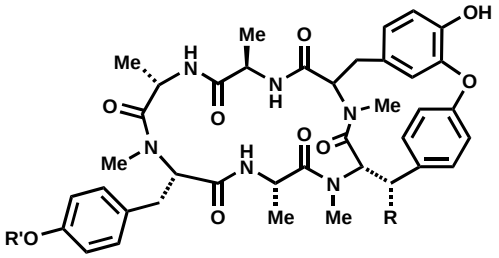
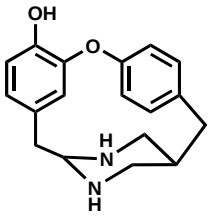
This paper is dedicated to Prof. Ivar Ugi for his achievements in computational chemistry and multicomponent reactions.

Abstract – Isonitrile *meta/para'*-functionalized biaryl ethers can serve as key building blocks for the highly efficient and diverse one step production of natural product inspired peptide/peptoid macrocycles, thereby forming up to 54-membered rings with eight or even sixteen new bonds. Aliphatic diamine and diacid tethers give access to two different classes of biaryl ether cyclopeptoids, either with exo/endo or exclusively endo dipeptidic moieties.

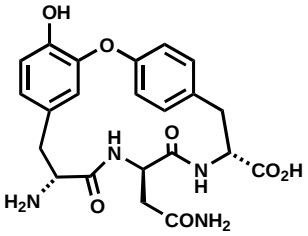
Cycloisodityrosines are prominent cyclic peptides and peptoids that contain the isodityrosine residue. This moiety is characterized by a biaryl ether unit substituted at the *meta, para*' (3, 4') position.[1,2] It is present in several bioactive natural products, e. g. bouvardin (**1**), deoxybouvardin (**2**), RA-VII (**3**), piperazinomycin (**4**), OF-4949 (**5**) and K-13 (**6**). The macrocyclic *meta, para'*-representatives are usually 14- or 17-membered rings.[2]



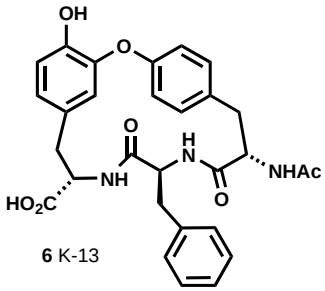
1 bouvardin R = OH, R' = H
2 deoxybouvardin R = H, R' = H
3 RA-VII R = H, R' = Me



4 piperazinonomycin



5 OF-4949

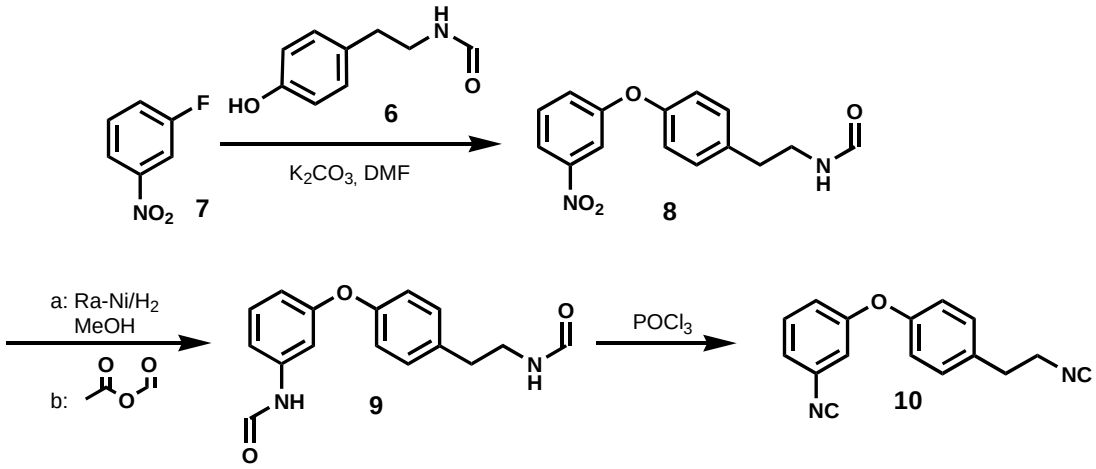


6 K-13

Due to their intriguing structure and their biological profile, they have been targets of several synthetic efforts.[3,4] In the context of our studies on the diversity oriented synthesis of macrocycles, the generation of a variety (library) of natural like congeners of this class of 3,4'-biaryl ether compounds appeared highly desirable.[5] To rapidly achieve a high degree of diversification, a convergent, low-step synthetic sequence is most convenient. Very recently, we reported a new strategy termed *MiB*, in that a *m*ultiple *m*ulticomponent *m*acrocyclization *i*ncluding *b*ifunctional *b*uilding *b*locks (MiB) is utilized, e. g., through an Ugi-reaction to achieve the synthesis of macrocyclic peptide and peptoid scaffold within one step. The principles of this strategy have been outlined elsewhere.[6] With suitable steroid-bisisonitriles and diacids or diamines, macrocycles up to 68-membered ones could be obtained in reasonable to excellent yields.[7]

The general strategies reported so far for the preparation of the cycloisodityrosines range from cycloamidation, $TlNO_3$-mediated oxidative coupling or Ullmann reaction to nucleophilic aromatic substitution.[8] The cycloamidation has been used mainly to synthesize the 17-membered cycloisodityrosines, all attempts to gain access to the 14 membered derivatives failed. In addition, macrolactamization also failed for the synthesis of 16-membered congeners, which show structural resemblance. All these approaches bear in common that the syntheses are rather lengthy, they need excess metal reagents in coupling reactions, and certain macrocyclic sizes are excluded.

Previously, in our group a two-step approach was established to produce phenylen-ansa macrocycles inspired by 14-membered cyclopeptide alkaloids by subsequent Ugi- and nucleophilic displacement reactions, leading to cyclized products.[9] However, this approach is not ideal towards natural biaryl ether macrocyclic congeners due to the difficult cyclization step. In this communication we show that a variety of macrocycles bearing the 3,4'-biaryl ether moiety can be obtained easily by utilizing the Ugi-MiB approach.

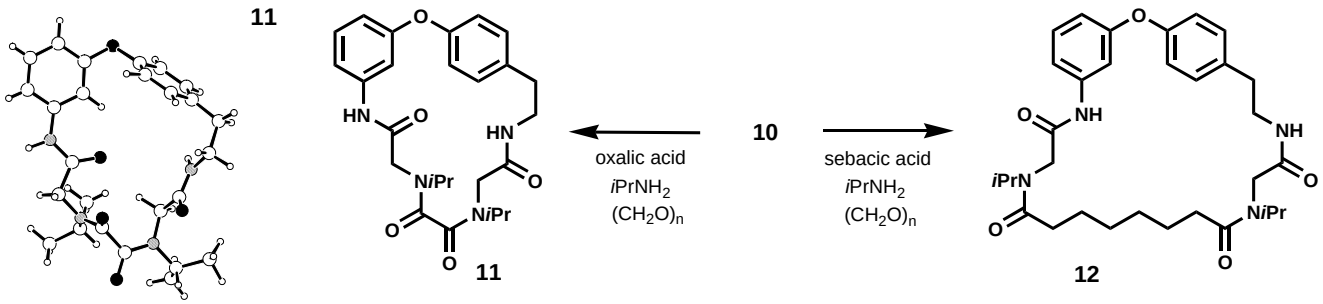


Scheme 1 Synthesis of 3,4'-bisfunctionalized biaryl ether **10** (43% overall yield).

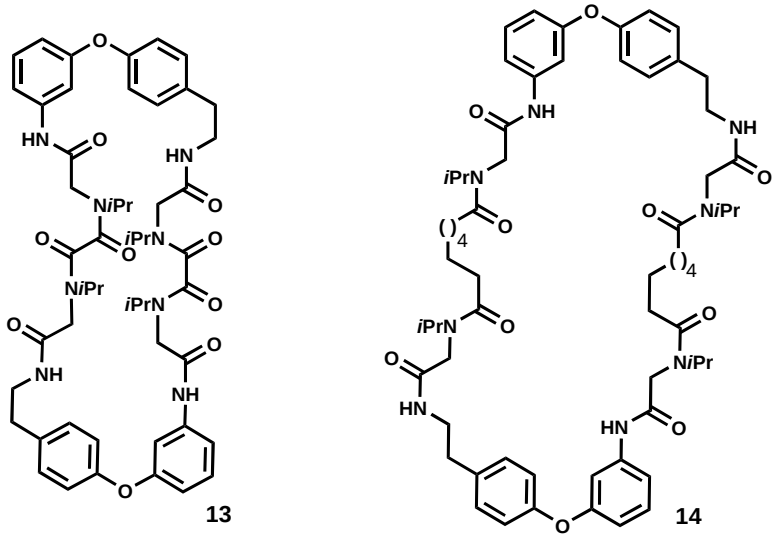
The bisisonitrile **10** with a 3,4'-biaryl ether core unit appeared to be an ideal starting material to initiate an Ugi-MiB synthesis (Scheme 1).[10,11] Starting from commercially available **7**, nucleophilic displacement with the formamide **6** afforded the biaryl ether **8** in 48% yield. Formation of the second formamide moiety was done via reduction of the nitro group and subsequent amidation with the mixed anhydride of formic and acetic acid.[12] Stirring at room temperature for three hours led to complete conversion in almost quantitative yield. For aromatic amines, this procedure appears to be the most effective one; other procedures afforded **9** in lower yields and required prolonged reaction times. The dehydration was, however, done under the classical conditions provided by Ugi in his early work.[13] The overall yield for the synthesis of **10** was 43%.

With this building block, the macrocyclizations were achieved by the envisioned one-pot double Ugi-MiB which were carried out under pseudo-dilution conditions by slow parallel addition of the bisfunctionalized building blocks with a syringe pump.[5a,6,7,14,9] This addition, although slow, is superior to other procedures. In earlier studies we proved that it even suffices to slowly add only one bifunctional building block, if its two ends show differential reactivity.[14] Thus, a solution of the aryl-alkyl bisisonitrile **10** was slowly added to the reaction mixture containing the other three components via a syringe pump. As the second bisfunctionalized starting material, diacids or diamines with varying chain lengths and functionalities have been used. As the third component isopropyl amine or acetic acid, respectively, have been utilized as the monofunctionalized Ugi-starting materials, completed by paraformaldehyde as fourth component. The latter was chosen solely for analytical reasons. Any other aldehyde or ketone can be used equally well or is even better with respect to yield but will give diastereomeric products more difficult to analyze by NMR.

While using bisisonitrile **10** and dicarboxylic acids, macrocyclizations to, e. g. **12**, can be accomplished (Scheme 2). With the short and rigid oxalic acid, the corresponding macrocycle is only formed in very



Scheme 2 MiB-Ugi of bisisonitrile **10** with dicarboxylic acids.

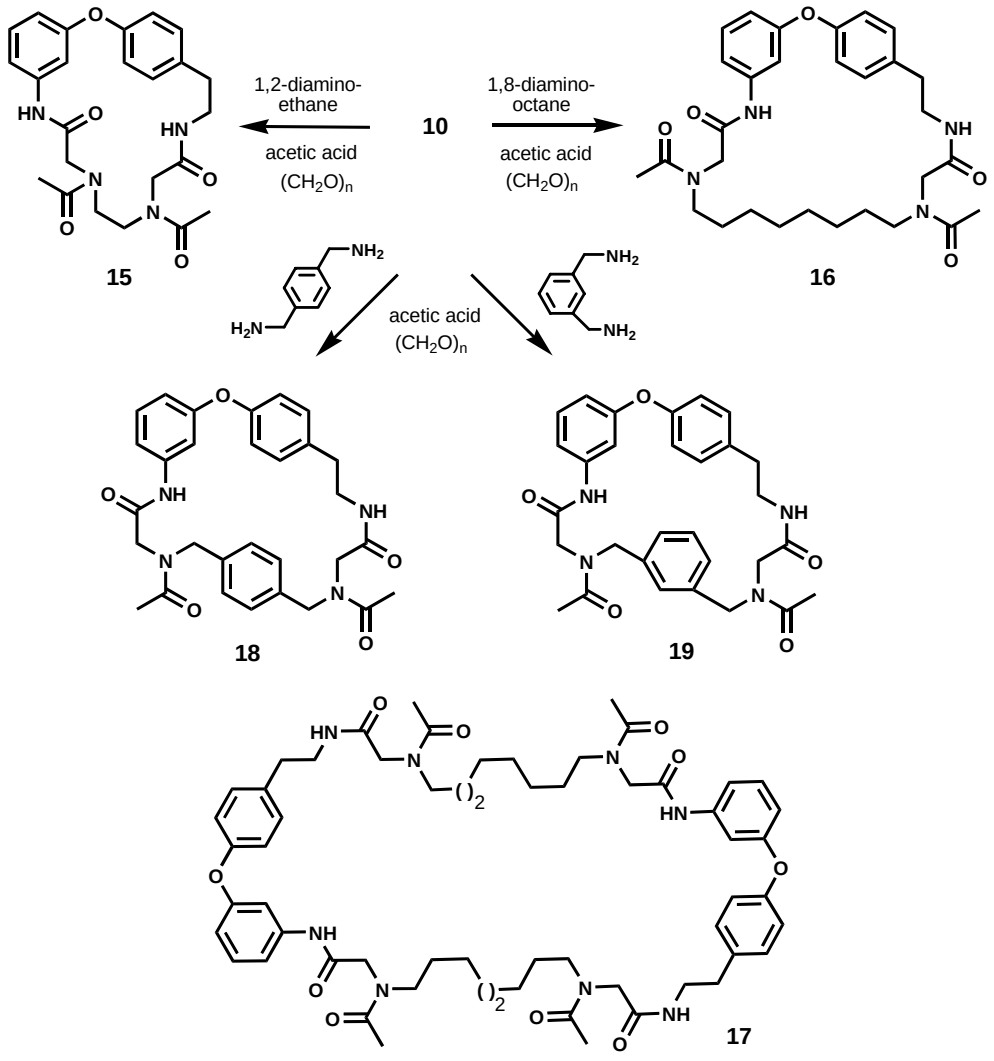


small amounts (2.5 %), whereas sebacic acid forms macrocycle **12** in good yields (46 %). For the discussion of the yields one has to consider, that in a single reaction step eight bonds (3 endocyclic, 1 exocyclic) are formed, referring to over 90% yield for a single bond formation including the macrocyclization. The structural integrity was determined by NMR and MS-methods. In case of **11**, X-ray additionally revealed the formation of the desired macrocycle (see ORTEP-drawing in Scheme 2 left, a cocrystallizing methanol is omitted for clarity). In contrast to the macrocycles with longer spacer units, the oxalic acid derived lactam **11** has sufficient rigidity for X-ray analysis without badly resolved regions due to excessive thermal movement or conformational disorientation of the flexible elements. The two phenyl groups of the biaryl ether are almost perpendicular. One of the two peptoid bonds in the crystal is s-*cis* configured whereas the other amide bonds (one peptoid, two peptide) are s-*trans*. This conformational setup with exactly one s-*cis* amide bond appears to be, based on a small number of x-rays, rather typical for smaller double Ugi-MiB products in crystals.

The differing yields for the formation of **11** and **12** clearly demonstrate that formation of the macrocycle is highly dependent on the strain of the formed products. Compared to earlier experiments with less flexible bisisonitriles,[14] the bisisonitrile **10** is much more flexible and because of one *meta*'-connection allows more curvature, thus leading to products even with the smallest dicarboxylic acid. However, while

using oxalic acid, mass spectrometry showed the presence of a series of side products, which could not be isolated with reasonable effort. The spectra indicated open chain intermediates as well as dimeric and trimeric macrocycles (e. g. dimer **13**). The formation of lactam **12** was also accompanied by the formation of the next higher oligomer as secondary product, the 54-membered macrocycle **14**, which is formed via a double Ugi-MiB in 10 % yield.

The products formed by the use of a bisisonitrile/dicarboxylic acid combination possess solely endocyclic peptide bonds, whereas with diamines endo- and exocyclic peptide bonds (Scheme 3) result. In strong correlation to the results obtained for the dicarboxylic acids, short- and long-chained diamines yielded the appropriate products **15** and **16**. With 1,2-diamino ethane, **15** is formed in 3 % yield, with 1,8-diamino octane, **16** is formed in 33 %, referring to 87 % for a single bond formation. The dimer **17** can be isolated in 6 % yield (referring to 83 % for a single bond formation).



Scheme 3 Ugi-MiB from bisisonitrile **10** and diamines.

Ugi-MiB products can also be formed when using more rigid *m*- and *p*-aminomethyl substituted benzylamines. The yield of macrocycle **18** using *para*-disubstituted aromatic bisamine is 43 %, whereas the *meta*-substituted congener is leading to **19** in 46 % yield. Interestingly, no dimer formation was detected with these more rigid building blocks.

In summary, the Ugi-MiB approach with 3,4'-distubstituted biaryl ethers affords in one step natural product inspired ether-lactam macrocycles. The yield of the macrocycles is dependent on the flexibility of the employed difunctional building blocks. Within the context of diversity oriented synthesis this approach is amenable to produce a variety of structurally diverse products. Further studies to use these in host-guest studies will be on the agenda next.

EXPERIMENTAL

General: Reactions were monitored by TLC on silica gel 60 F_{254} (Merck) with detection either by UV light or charring with 10% H_2SO_4 in EtOH. Solutions were concentrated under reduced pressure at 40 °C. Column chromatography was performed on silica gel 60 (0.063-0.200 mm, Merck). ^{1}H NMR spectra (500,or 300 MHz) and ^{13}C NMR spectra (75.5 or 126 MHz) were recorded with spectrometers Varian Mercury 300 and Bruker Avance 500, respectively, at 300 K if not indicated otherwise. δ_H (ppm) and δ_C (ppm)-values are referred to the solvent signals: $CDCl_3$ (δ_H 7.26, δ_C 77.0), DMSO-d_6 (δ_H 2.50, δ_C 39.7) and MeOD (δ_H 3.30, δ_C 49.0). EI mass spectrometry was performed on an AMD 402 (AMD Intectra GmbH) instrument. The high resolution positive ion ESI mass spectra were obtained from a Bruker Apex 70e Fourier transform ion cyclotron resonance mass spectrometer (Bruker Daltonics, Billerica, USA) equipped with an Infinity™ cell, a 7.0 Tesla superconducting magnet (Bruker, Karlsruhe, Germany), an RF-only hexapole ion guide and an external electrospray ion source (Agilent). IR spectra were measured with a Bruker IFS 28. Elemental analyses were performed on a CHNS automatic elemental analyzer Flash EA (ThermoQuest). All compounds for which elemental analytical data are not available were chromatographically homogeneous, and NMR and mass spectral data were in full agreement with the assigned structures.

X-Ray data are deposited at the Cambridge Crystallographic Data Centre

N-{4-[4-(3-Nitrophenoxy)phenyl]ethyl}formamide (**8**)

A mixture of *N*-[2-(4-hydroxyphenyl)ethyl]formamide (**7**, 5 g, 30 mmol),[10] *m*-fluoronitrobenzene (**6**, 3.5 mL, 33 mmol) and K_2CO_3 (5 g) in *N*,*N*-dimethylformamide (35 mL) was refluxed for 4 d. The mixture was poured in ice-water and extracted with chloroform. The combined organic layers were washed with water, dried (Na_2SO_4), filtered, and concentrated. Recrystallization from EtOH gave **8** as light-brown solid (4.12 g, 48%). TLC (CH_2Cl_2-MeOH, 9:1) R_f 0.49. ^{1}H NMR (300 MHz; $CDCl_3$) δ: 8.17 (s, 1 H,

CHO); 7.92 – 7.95 (m, 1 H, CH); 7.76 (s, 1 H, CH); 7.48 (t, 1 H, J 8.2 Hz, CH); 7.21 – 7.34 (m, 3 H, 3 CH); 6.99 – 7.03 (m, 2 H, 2 CH); 5.76 (br, s, 1 H, NH); 3.60 (t, 2 H, J 8.6 Hz, CH_2); 2.88 (t, 2H, J 6.7 Hz, CH_2). ^{13}C NMR (75 MHz; $CDCl_3$) δ: 161.0 (CHO); 158.3 (C); 154.0 (C); 149.0 (C); 135.0 (C); 130.4 (2 CH); 130.2 (CH); 124.0 (CH); 119.9 (2 CH); 117.5 (CH); 112.5 (CH); 39.3 (CH_2); 34.9 (CH_2); ESI – MS of $C_{15}H_{14}N_2O_4$ ($M+H^+$ = 287.2; $M+Na^+$ = 309.5; $M–H^–$ = 285.3).

N-{4-[3-(4-Formylaminoethyl)phenoxy]phenyl}formamide (**9**).

A suspension of Raney nickel in water (approx. 2 g wet) was washed with water until the washings remain neutral. After washing with MeOH a solution of *N*-{2-[4-(3-nitrophenoxy)phenyl]-ethyl}formamide (**8**, 1.0 g, 3.5 mmol) in MeOH (100 mL) was added and the reaction mixture was stirred for 24 h under hydrogen atmosphere and then filtered through Celite. Concentration of the filtrate gave the amine intermediate as a pale yellow syrup (0.85 g, 95%). Subsequently, the crude reaction mixture was dissolved in THF (100 mL) and NEt_3 (1.1 g, 10.5 mmol) was added and heated to reflux. To this solution 10.6 mL of the mixed anhydride was added dropwise. The mixed anhydride was prepared by heating acetic anhydride (4.8 g, 70 mmol) together with formic acid (7.2 g, 105 mmol) for 3 h at 60°C. After 2 h the starting material was consumed, solvent and acid residues were removed under reduced pressure. Column chromatography on silica ($CHCl_3$:MeOH, 9:1) of the residue gave **9** as a brown solid (0.92 g, 97%). TLC ($CHCl_3$:MeOH, 9:1) R_f 0.25. ^{1}H NMR (300 MHz; $CDCl_3$) δ: 8.33 (s, 1 H, CHO); 8.15 (s, 1 H, CHO); 7.14 – 7.29 (m, 5 H, 5 CH); 6.96 – 7.00 (m, 2 H, 2 CH); 6.77 – 6.80 (m, 1 H, 1 CH); 5.65 (br, s, 1 H, NH); 3.48 – 3.59 (m, 2 H, CH_2); 2.81 – 2.87 (m, 2 H, CH_2). ^{13}C NMR (75 MHz; $CDCl_3$) δ: 162.1 (CHO); 161.2 (CHO);159.0 (C); 155.2 (C); 138.3 (C); 133.6 (C); 133.6 (CH); 130.0 (CH); 129.9 (2 CH); 119.6 (CH); 119.3 (2 CH); 114.6 (CH); 39.3 (CH_2); 34.8 (CH_2). ESI – MS of $C_{16}H_{16}N_2O_3$ ($M+H^+$ = 285.1; $M+Na^+$ = 307.0; $M–H^–$ = 283.5).

4-[3-(4-Isocyanoethyl)phenoxy]phenylisocyanide (**10**).

To a mixture of *N*-{4-[3-(4-formylaminoethyl)phenoxy]phenyl}formamide (**9**, 0.72 g, 2.6 mmol) and NEt_3 (3.5 mL, 25 mmol) in THF (10 mL) was added dropwise a solution of $POCl_3$ (0.6 mL, 6.2 mmol) in THF (10 mL) at -60 °C, within 2 h. Stirring was continued for 5 h at rt, the mixture was poured in ice-water and extracted with diethyl ether. The combined organic layers were washed with water, dried (Na_2SO_4), filtered, and concentrated. **10** was obtained as a dark-brown oil (0.61 g, 94%). TLC ($CHCl_3$:MeOH, 9:1) R_f 0.88; IR: $\nu_{(KBr)}$ 2151cm^{-1} (-NC); 2130 cm^{-1} (-NC); ^{1}H NMR (300 MHz; $CDCl_3$) δ: 7.33 (t, 1H, J 8.1 Hz, CH); 7.75 (d, 2 H, J 8.6 Hz, 2 CH); 6.95 – 7.11 (m, 5 H, 5 CH); 3.63 (t, 2 H, J 7.0 Hz, CH_2); 2.99 (t, 2H, J 6.9 Hz, CH_2). ^{13}C NMR (75 MHz; $CDCl_3$) δ: 164.2 (C); 158.0 (C); 156.6 (NC); 154.7 (C); 132.7 (C); 130.4 (CH); 130.2 (2 CH); 120.7 (CH); 119.8 (2 CH); 119.2 (CH); 115.8 (CH); 43.0

(CH_2); 34.9 (CH_2). ESI – MS of $C_{16}H_{16}N_2O_3$ ($M+H^+$ = 249.2; $M+Na^+$ = 271.3). The diisonitrile is reactive, elemental analysis was not reliable under normal conditions.[10]

Representative procedure for an Ugi-MiB

11,14-Diisopropyl-2-oxa-8,11,14,17-tetraaza-tricyclo[18.2.2.13,7]pentacosa-1(23),3(25),4,6,20(24),21-hexaene-9,12,13,16-tetraone (**11**).

A mixture of paraformaldehyde (120 mg, 4.0 mmol), isopropylamine (0.36 mL, 4.0 mmol) and sodium sulfate (2 g) in MeOH (40 mL) was stirred for 2 h at rt. Then, MeOH (130 mL) and oxalic acid (90 mg, 1.0 mmol) were added and stirring was continued for another 30 min. A solution of 3-[4-(2-isocyanoethyl)phenoxy]phenylisocyanide **10** (248 mg, 10 mmol) in $CHCl_3$ (20 mL) was added slowly to the reaction mixture using a syringe pump (flow rate 0.1 mL/h). The reaction mixture was filtered and concentrated under reduced pressure. Column chromatography on silica ($CHCl_3$:MeOH, 95:5) of the residue gave **11** as an amorphous solid which was crystallized from MeOH (12 mg, 2.5%). TLC ($CHCl_3$:MeOH, 95:5) R_f 0.34. ^{1}H NMR (500 MHz, DMSO/$CDCl_3$ 9:1) δ: 10.00 (s, 1H, NH(17)); 7.51 (t, 1H, $^3J_{7,8}$ 4.8 Hz, H-8); 7.47 („t“, 1H, $^4J_{21,23}$ 2.5 Hz, $^4J_{19,23}$ 2.0 Hz, H-23); 7.33 („d“, 2H, H-4,4’); 7.21 („t“, 1H, $^3J_{19,20} = {}^3J_{20,21}$ 8.2 Hz, H-20); 6.98 („d“, 2H, H-3,3’); 6.79 (ddd, 1H, $^3J_{20,21}$ 8.2 Hz, $^4J_{21,23}$ 2.5 Hz, $^4J_{19,21}$ 1.0 Hz, H-21); 6.54 (ddd, 1H, $^3J_{19,20}$ 8.2 Hz, $^4J_{19,23}$ 2.0 Hz, $^4J_{19,21}$ 1.0 Hz, H-19); 4.21 (septet, 1H, H-25); 4.05 (br, 1H, H-10a); 4.00 (br, 2H, H-15); 3.93 (septet, 1H, $^3J_{24,26}$ 6.6 Hz, H-24); 3.69 (br, 1H, H-10b); 3.38 (br q, 2H, H-7); 2.80 (br, 2H, H-6); 1.13 (d, 3H, ^{3}J 7.3 Hz, H-27); 1.02 (br, 3H, H-26). ^{13}C NMR (126 MHz, DMSO/$CDCl_3$ 9:1) δ: 168.3 (C-9); 166.2 (C-16); 165.5 (C-13); 164.5 (C-12); 160.4 (C-22); 153.0 (C-2); 140.3 (C-18); 136.5 (C-5); 130.7 (C-4,4’); 129.5 (C-20); 122.1 (C-3,3’); 111.2 (C-21); 110.8 (C-19); 105.7 (C-23); 49.2 (C-24); 47.1 (C-15); 46.2 (C-25); 42.3 (C-10); 41.0 (C-7); 33.1 (C-6); 20.2 (br, C-26); 19.2 (C-27). ESI-MS of $C_{26}H_{32}N_4O_5$ (M, 480.2) m/z 481.3 [M+H]+, 503.3 [M+Na]+; HRMS of $C_{26}H_{32}N_4O_5Na$ (M+Na) 503.2255, calcd. 503.2264; X Ray: Formula $C_{26}H_{32}N_4O_5 \times CH_3OH$, Unit cell parameters: a 5.8032(13) b 21.211(6) c 11.093(3) beta 94.88(3), space group P21; deposited at the Cambridge Crystallographic Data Centre allocated under the deposition number CCDC 650966.

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