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Synthetic Exploration of Oxacalix[2]arene[2]quinazolines

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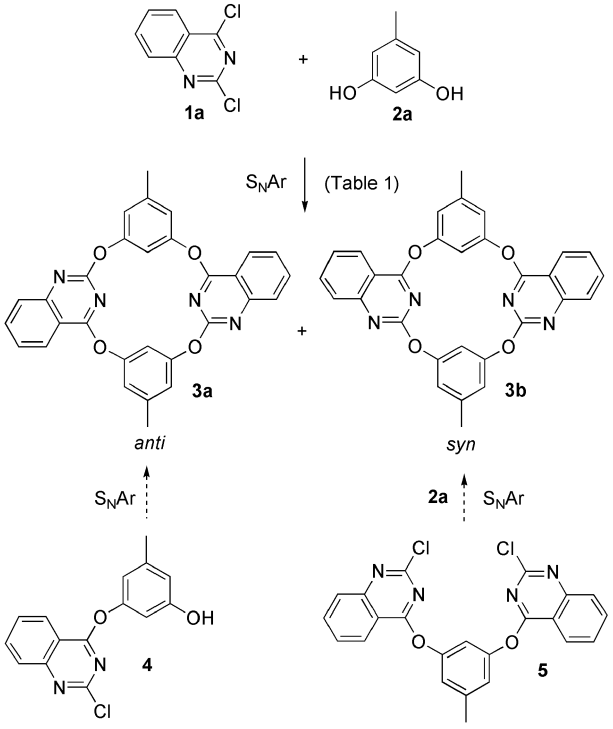
Oxacalix[2]arene[2]quinazoline macrocycles were prepared in good yields, as mixtures of *syn* and *anti* isomers, through nucleophilic aromatic substitution cyclocondensation reactions of 2,4-dichloroquinazolines and *m*-dihydroxybenzenes. The macrocyclization conditions were optimized and the isomeric ratio was investigated by means of one-step and fragment-coupling approaches. The oxacalixarene substitution pattern could easily be varied by altering the dichloroquinazolinyl biselectrophilic and dihydroxyaryl bisnucleophilic building blocks. The solid-state (1,3-alternate) conformational behavior and the oxacalix[4]arene cavity size were explored by X-ray diffraction studies.

Introduction

Heteracalix[*n*]arenes, in which the arene units are linked by heteroatoms rather than methylene units, form a new generation of less explored, yet promising calixarene macrocycles.[1–3] Among these heteracalixarenes, thiacalixarenes have been studied most intensively,[4] mainly due to their straightforward synthesis, whereas aza- and oxacalixarenes, though (at least) equally attractive, have only been emerging more recently.[5–9] To date, most reports on oxacalixarenes describe the synthesis of oxacalix[4]arenes through facile nucleophilic aromatic substitution (S_NAr) strategies employing variously substituted *m*-dihydroxybenzenes and activated arenes, either 1,5-difluoro-2,4-dinitrobenzene or electrophilic *m*-dihalogenated heteroaromatic analogues (e.g., 1,3,5-triazines or pyridines).[7,8] Previous work within our group has focused on the synthesis of oxacalix[*m*]arene[*m*]pyrimidines (*m* = 2–6) through S_NAr reactions of resorcinol derivatives and 4,6-dihalopyrimidines.[8f,8p,8w] It has been demonstrated that oxacalix[*m*]arene[*m*]pyrimidines, due to their high-yielding synthesis, tunable macrocycle size, and ease of elaboration of the substitution pattern, are versatile oxacalixarene platforms for the exploration of various supramolecular applications.[7,10]

In the presented work, we have expanded the scope of our heteracalixarene research through application of another heteroaromatic building block, 2,4-dichloroquinazoline. Because the reactivity of this (5,6-)annulated pyrimidine analogue towards S_NAr is enhanced compared to that of the previously studied 4,6-dichloropyrimidines, it can be envisaged that the macrocyclization reaction could provide the thermodynamically favored oxacalix[4]arene predominantly (over linear oligomers and larger cyclooligomers)



Scheme 1. Single-step and fragment-coupling approaches towards oxacalix[2]arene[2]quinazolines **3a**,**b**.

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under less forcing conditions, for example, at a lower temperature. Moreover, 2,4-dichloroquinazoline is an unsymmetrical reaction partner, in contrast to most electrophilic moieties used so far which contain two initially equally reactive positions.[11] As a result, two oxacalix[4]arene configurational (regio)isomers, with the heteroaromatic components incorporated in either a *syn* or an *anti* arrangement, can be expected on reaction with a resorcinol derivative (Scheme 1).[12] Depending on the applied cyclocondensation conditions, the nature of the reaction (kinetic or thermodynamic control) and the applied synthetic route (direct or fragment-coupling S_NAr approach), one of the oxacalix[2]arene[2]quinazoline isomers may be formed predominantly.

Results and Discussion

Oxacalixarene Synthesis and Exploration of the *antilsyn* Ratio

The quinazolin(on)e framework, to which diverse pharmacological activities have been attributed,[13] is traditionally prepared through cyclization of appropriately substituted benzenes.[13–16] Many functional quinazolines found in the literature are derived from substituted 2,4-dichloroquinazoline precursors, structurally elaborated by S_NAr reactions.[15] Because the 4-position is more reactive, sequential functionalization at both electrophilic positions can easily be performed.

In a first attempt to prepare tetraoxacalix[2]arene[2]quinazolines, 2,4-dichloroquinazoline (**1a**) and orcinol (5-methylbenzene-1,3-diol, **2a**) were mixed in equimolar amounts with an excess amount of K_2CO_3 in dry DMF at 70 °C for 48 h, with the addition of 18-crown-6 (Scheme 1, Table 1, Entry 1). These conditions were chosen as they previously afforded the best results (most thermodynamic control) for analogous 4,6-dichloropyrimidine biselectrophiles.[8f] 2,4-Dichloroquinazoline was easily prepared by dehydroxychlorination ($POCl_3$) of 1*H*,3*H*-quinazoline-2,4-dione.[15b,16] Analysis of the crude cyclooligomerization mixture revealed the presence of two major products, which, after flash chromatographic purification, were identified as oxacalix[4]arene isomers. *anti*- and *syn*-Oxacalix[2]arene[2]quinazoline **3a** and **3b** (Scheme 1) could easily be differentiated on the basis of symmetry through ^{1}H NMR spectroscopy (see Supporting Information), and the *anti* and *syn* regioisomers were obtained as white solids in 42 and 32% yield, respectively (74% overall oxacalix[4]arene yield).

After this initial success, a systematic variation of the different S_NAr reaction parameters (solvent, base, reaction time, and temperature) was performed to study their influence on the oxacalix[4]arene selectivity and the regioisomeric ratio (Table 1). In particular, conditions that were proven to be effective for oxacalix[4]arene formation by other research groups, for example, the Katz and Konishi teams, have been tested.[8b,8e,8h,8k,8o] Solvent dryness was shown to be essential to obtain high yields of the oxacalix[2]arene[2]quinazoline isomers.[17] The reaction temperature has a profound effect on the reaction outcome. When the cyclocondensation reaction was conducted at 100 °C, the total oxacalix[4]arene amount decreased drastically (to ≈12%). On the other hand, the same reaction at room temperature for 24 h afforded only trace quantities of macrocycles (≈1% **3a** + **3b**), whereas acyclic [1+1] adduct **4** was obtained as the major product in 75% yield, together with [2+1] adduct **5** in 7% yield (see structures in Scheme 1). Care has to be taken while performing reactions at room temperature, as vacuum evaporation of DMF at an elevated temperature (≈70 °C) to facilitate further workup initiates cyclooligomerization and inconsistent results may be obtained. At shorter reaction times, increasing quantities of noncyclic precursors **4** and **5** were identified in the crude mixture. On changing the base to Cs_2CO_3 (Table 1, Entry 2) slightly diminished yields were obtained (53% **3a** + **3b**), whereas on applying anhydrous CsF (Table 1, Entry 3) mainly linear oligomers were produced (≈67% **4** and 23% **5**). For the reaction using CsF (2 equiv.) base, a shorter reaction time (1 h) resulted in a similar mixture of linear oligomers (53% **4**, 20% **5**; Table 1, Entry 4).[8h] The combination of Cs_2CO_3 or CsF base and DMSO as the solvent also caused a decrease in the oxacalix[4]arene yield (to 7 and 54%, respectively; Table 1, Entries 5 and 6).[8o] For the reaction employing Cs_2CO_3 base, mainly linear oligomers were observed, whereas for the reaction with CsF larger oxacalix[*n*]arenes ($n > 4$) were formed. The mixture consisting of oxacalix[6]- up to oxacalix[12]arenes, as evidenced by electrospray mass spectrometry (ESI-MS), was found to be inseparable by standard chromatography techniques. On applying triethylamine (2.2 equiv.) as an organic base in

Table 1. Optimization of the one-pot S_NAr conditions towards oxacalix[2]arene[2]quinazolines **3a**,**b**.

Entry	Solvent	Base	*t* (h)	*T* (°C)	% *anti*	% *syn*	% Calix[4][a]
1	DMF	K_2CO_3[b]	48	70	42	32	74
2	DMF	Cs_2CO_3	48	70	33	20	53
3	DMF	CsF	24	70	–[c]	–[c]	–[c,d]
4	DMF	CsF	1	100	1	–[c]	1[e]
5	DMSO	Cs_2CO_3	18	100	5	2	7
6	DMSO	CsF	24	100	33	21	54[f]
7	CH_3CN	Et_3N	18	reflux	–[c]	–[c]	–[c,g]
8	dioxane	K_2CO_3[b]	24	reflux[h]	35	54	89

[a] Isolated yield. [b] Addition of 18-crown-6. [c] Unidentifiable amount. [d] **4** (67%), **5** (23%). [e] **4** (53%), **5** (20%). [f] Larger oxacalix[*n*]arenes were formed as well. [g] **4** (30%), **5** (63%), unreacted **2a**. [h] Preceded by 24 h at room temp.

acetonitrile at reflux (Table 1, Entry 7),[8h] no macrocyclic species were formed and only linear oligomers were observed, that is, mainly **4** (30%) and **5** (63%).

As previously observed,[7] the oxacalix[4]arene seems to be the thermodynamically favored (cyclo)oligomer and high-dilution conditions are not required. Under most of the conditions screened, the concurrent formation of analogous enlarged O-bridged calix[*n*]arenes ($n > 4$) was not observed (apart from trace signals in the ESI-MS). Only for the DMSO/CsF system (Table 1, Entry 6) there seems to be less thermodynamic control, as oxacalix[6]- up to oxacalix[12]arenes were produced as well.

On the basis of previous work by Ponticelli and coworkers, in which DFT calculations were used to confirm that the orientation of an isoxazolopyridine building block has only a minor effect on the stability of bicyclooxacalix[4]arene regioisomers,[8r] it may be presumed that both oxacalix[2]arene[2]quinazoline isomers will have almost the same energy. From the performed reactions so far (Table 1, Entries 1–7), it can be seen that the *anti*-cyclotetramer is generally obtained in slight excess and the isomeric ratio is undergoing rather small fluctuations. To gain more insight on the (relative) thermodynamic stability of the oxacalix[4]arene isomers and their possible interconversion, a basic equilibration study was performed.[8e,8h,8k,8m,8s] Upon treatment of either *anti* or *syn* isomer **3a/b** with a small amount of orcinol (0.1 equiv.) under the currently optimal S_NAr conditions (K_2CO_3, DMF, 70 °C, 24 h), only a very small amount of macrocycle breakup and equilibration of the isomeric mixture was detected (<5% as judged by ^1H NMR spectroscopy and TLC). Both oxacalix[4]arene isomers appear to be reasonably stable under the applied conditions (very slow thermodynamic equilibration process).

For comparison, a similar single-step cyclocondensation reaction was performed with 2,4-dichloropyrimidine (**1b**) as the electrophilic building block. Using the conditions optimized so far (DMF, K_2CO_3, 18-crown-6, 70 °C, 24 h), oxacalix[2]arene[2]pyrimidine isomers **6a**,**b** were obtained in 85% overall yield and a similar isomeric ratio (47% *anti*, 38% *syn*; Figure 1, Table 2), whereas the same reaction employing 4,6-dichloropyrimidine as the biselectrophile afforded 55% of the respective oxacalix[4]arene.[8f]

Both reaction partners could be varied further to obtain diversely functionalized heteracalixhetarene macrocycles. When resorcinol (**2b**) was applied as the bisnucleophile, *anti*- and *syn*-oxacalix[2]benzene[2]quinazolines **7a**,**b** were obtained in 47 and 27% yield, respectively (Figure 1, Table 2). Functionalized quinazoline moieties can also be

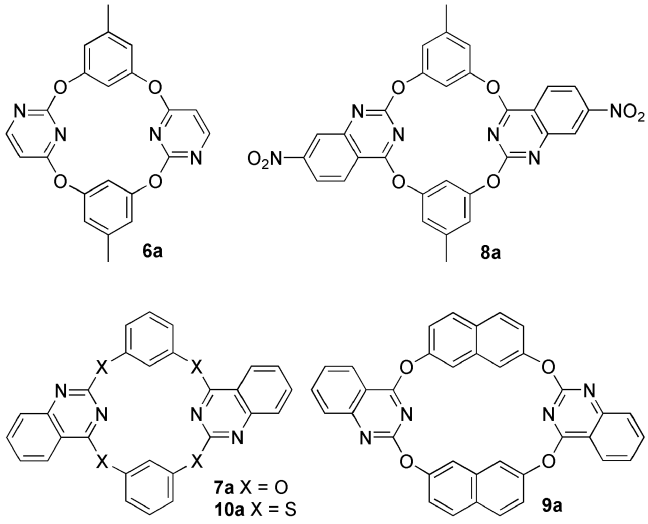

Figure 1. *anti*-Heteracalix[4]arene isomers **6a**–**10a**.

applied. 2,4-Dichloro-7-nitroquinazoline (**1c**) was synthesized in two steps from 4-nitroanthranilic acid through fusion with urea and subsequent chlorination with $POCl_3$.[18] Reaction of **1c** and orcinol at 70 °C afforded only trace amounts of the oxacalix[4]arene isomers. When the reaction was, however, repeated at room temperature, desired oxacalix[4]arenes **8a**,**b** were obtained both in a moderate 18% yield (Figure 1, Table 2). To modulate the size of the oxacalix[4]arene cavity and to modify its host–guest recognition abilities (e.g., through π–π interactions), 2,7-dihydroxynaphthalene (**2c**) was also used as a nucleophilic reaction partner.[8d,8o,8u,10] Although the reduced solubility of oxacalix[2]naphthalene[2]quinazoline isomers **9a**,**b** in common organic solvents somewhat hampered the ease of purification, both isomers could still be obtained in good yields (36% *anti*/*syn*, Figure 1, Table 2).

Thiacalixarenes can be synthesized by similar S_NAr protocols when *m*-benzenedithiols are used as the nucleophilic components. Thiacalix[2]arene[2]quinazoline isomers **10a**,**b** were prepared through reaction of 1,3-benzenedithiol (**2d**) and 2,4-dichloroquinazoline (**1a**) by using the optimal S_NAr conditions,[8f] and although the solubility of the thiacalixarene isomers is limited, they were isolated in 71 and 15% yield, respectively, with a noteworthy preference for the *anti* isomer (Figure 1, Table 2). From the above results it can be concluded that the isomeric ratio is rather nucleophile dependent. The strong bias towards *anti*-thiacalix[4]arene **10a** seems to point to preferential diaryl coupling during the one-pot protocol towards **10a**,**b** (see further).

Table 2. Newly synthesized heteracalix[4]hetarenes **6a**,**b**–**10a**,**b**.[a]

Electrophilic component	Nucleophilic component	% *anti*	% *syn*	% Calix[4][b]
2,4-Dichloropyrimidine (**1b**)	orcinol (**2a**)	**6a** (47)	**6b** (38)	85
2,4-Dichloroquinazoline (**1a**)	resorcinol (**2b**)	**7a** (47)	**7b** (27)	74
2,4-Dichloro-7-nitroquinazoline (**1c**)[c]	orcinol (**2a**)	**8a** (18)	**8b** (18)	36
2,4-Dichloroquinazoline (**1a**)	2,7-dihydroxynaphthalene (**2c**)	**9a** (36)	**9b** (36)	72
2,4-Dichloroquinazoline (**1a**)	1,3-benzenedithiol (**2d**)	**10a** (71)	**10b** (15)	86

[a] General conditions: DMF, K_2CO_3, 18-crown-6, 70 °C, 24 h. [b] Isolated yield. [c] Reaction at room temp.

In a next step, additional fragment-coupling experiments were conducted to achieve more knowledge on the regioselectivity of the oxacalix[4]arene formation (Scheme 1).[7,8a,8i,8k,8v,8w,9] Such stepwise procedures could also be advantageous for the selective synthesis of larger oxacyclophanes or asymmetric (e.g., ABAC) derivatives. Upon autocyclization of [1+1] adduct **4**, only *anti* isomer **3a** would be expected if no ether bond scission and subsequent fragment recombination were involved (dynamic covalent chemistry), whereas treatment of [2+1] fragment **5** with orcinol (1 equiv.) should in principle only provide *syn*-oxacalix[4]arene **3b** and possibly larger (cyclo)oligomers under kinetic conditions (Scheme 1). Diaryl precursor **4** could be obtained in good yield (75%) from the one-pot reaction in DMF (K_2CO_3 base) at room temperature, whereas linear triaryl building block **5**, composed of one orcinol unit that has reacted on the 4-position of two quinazoline molecules, was obtained under similar conditions (0 °C to room temp.) in 91% yield through reaction of precursors **1a** and **2a** in stoichiometric 2:1 quantities. Alternatively, [2+1] adduct **5** was synthesized in a nearly quantitative yield on employing 2.2 equiv. of dichloroquinazoline **1a** in acetone (**2a**, K_2CO_3, 18-crown-6, 48 h at room temp.).[8i,8w]

In a first macrocyclization trial, diaryl precursor **4** was subjected to the so far optimal S_NAr conditions (DMF, K_2CO_3, 18-crown-6, 70 °C, 24 h; Scheme 1). The reaction outcome, *anti*- and *syn*-oxacalix[4]arenes were obtained in 48 and 29% yield, respectively, is clearly pointing to a thermodynamically controlled process with reversible bond formation rather than a kinetically controlled process. The *anti*/*syn* ratio is only slightly higher than that observed for the direct synthesis (compare with Entry 1 in Table 1) and the total oxacalix[4]arene yield is comparable. A shorter reaction time and lower temperature were found ineffective to improve the regioisomeric ratio, as major amounts of unreacted [1+1] adduct **4** remained. Upon cyclization of [2+1] fragment **5** with orcinol under identical conditions, **3a** and **3b** were obtained in 25 and 15% yield, respectively (10% unreacted **5**). It is noteworthy that a higher amount of *anti* isomer **3a** was observed. This unexpected event was attributed to the instability of [2+1] precursor **5**, as formation of diaryl fragment **4** (isolated in 21%) by transetherification was observed to be a major factor.[15a] From the same reaction at room temperature over 60% of **4** was isolated. Apparently the 4-position of the quinazoline heterocycle is the most reactive locus, even when substituted with a phenoxy moiety, causing quinazoline C–O bond cleavage. The two-step convergent [3+1] approach under these conditions is hence not applicable for more selective preparation of the *syn* isomer, and suitable kinetic S_NAr conditions limiting breaking and reordering of the diaryl ether bonds have not been found.

Because previous experiments with dichloropyrimidine-based tri- and pentaaryl fragments have afforded good selectivity for enlarged oxacalix[*m*]arene[*m*]pyrimidines (*m* = 3, 4),[8w] the macrocyclization conditions showing the most kinetic control (1,4-dioxane, K_2CO_3, 18-crown-6, reflux, simultaneous addition of the precursors) and only limited conversion to the thermodynamic oxacalix[4]arene sink were also tested for dichloroquinazolines. Notably, the one-pot synthesis approach under these conditions resulted in an inversion of the regioisomeric ratio. Condensation of orcinol (**2a**) and 2,4-dichloroquinazoline (**1a**) in the presence of K_2CO_3 base and 18-crown-6 in dioxane for 24 h at room temperature and subsequently 24 h at reflux temperature afforded *anti*- and *syn*-oxacalix[4]arene **3a** and **3b** in 35 and 54% yield, respectively (Table 1, Entry 8). Both an excellent overall yield (89%) and a larger *syn* content were observed, although the selectivity is still rather poor. Similar results (37% **3a**, 46% **3b**) were obtained when first aiming at preparing [2+1] adduct **5** at room temperature in dioxane (2:1 ratio **1a**/**2a**, 5 h) and subsequently proceeding to cyclization by orcinol (**2a**) addition (1 equiv.) and reflux (24 h). A reaction temperature of 70 °C was shown to be insufficient for complete precursor conversion.

X-ray Diffraction Studies

The solid-state conformational behavior of some of the novel oxacalix[2]arene[2]quinazoline isomers, that is, *anti* isomer **3a** and *syn* isomer **9b**, has been explored by X-ray crystallography (Figure 2). Single crystals were obtained by vapor diffusion of pentane into a $CHCl_3$ solution of the respective oxacalixarene. As for most oxacalix[4]arene structures reported to date,[7,8] a 1,3-alternate conformation was observed. The cavity structure, symmetry, and dimensions vary of course depending on the respective isomer and the nucleophilic component. The electrophilic character of the quinazoline aromatic rings is clearly visible around the bridging oxygen atoms. The C–O bond is noticeably (on average 0.053 Å for **3a** and 0.058 Å for **9b**) shorter towards the electrophilic quinazoline subunits (Figures S2 and S5, Supporting Information). For *anti* isomer **3a**, the planes formed by the two benzene rings on opposite sides of the oxacalix[4]arene cavity make an angle of 3.4°, which makes

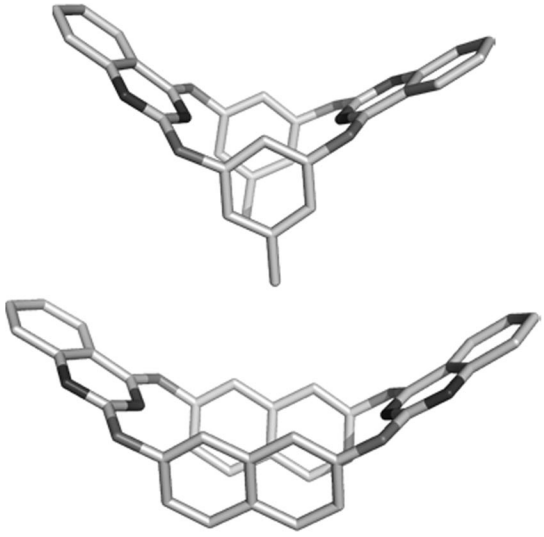

Figure 2. Single-crystal X-ray structures for **3a** (upper structure) and **9b** (lower structure).

them almost parallel, and the angle between the planes formed by the two quinazoline heterocycles is 110.0°. The cavity enclosed by the calixarene skeleton is about 4.53 × 7.01 Å (distances taken between the centroids of the benzene and pyrimidine rings, respectively; Figure S3, Supporting Information). For *syn* isomer **9b**, the planes formed by the nucleophilic naphthalene rings on opposite sides of the oxacalixarene cavity make an angle of 19.1°, and the angle between the planes formed by the quinazoline moieties is 114.0°. The expanded cavity is about 4.16 × 9.50 Å (distances taken between the centroids of the naphthalene and pyrimidine rings, respectively; Figure S6, Supporting Information).

Conclusions

In conclusion, novel oxacalix[2]arene[2]quinazolines have been synthesized by straightforward and efficient S_NAr macrocyclization strategies. Due to the asymmetry of the applied quinazoline electrophilic precursors, two regioisomers were obtained and the relative content of both isomers could be varied (to a certain extent) by changing the reaction conditions and the synthetic protocol. Some elements controlling the isomeric distribution have been clarified, although not everything is fully understood at this stage. Oxacalix[2]arene[2]quinazolines not merely expand the oxacalixarene structural diversity, but contribute to the continuous richness and complexity of the field. The induced asymmetry in these novel oxacalix[4]arenes can be used as a springboard towards increasingly complex macrocycles, for example, inherently chiral macromolecules, with a wide potential in general supramolecular chemistry. Additional benefits of the quinazoline building block are the ease by which the functionalization pattern can be elaborated and likely extension to analogous, more sophisticated azaheterocyclic ring systems, for example, pyrido[3,2-*d*]pyrimidines, pyrazolo[3,4-*d*]pyrimidines, or purines. Furthermore, as the oxacalix[*m*]arene[*m*]quinazoline scaffold orients Lewis basic nitrogen atoms inside the calixarene cavity, selective (metal) ion complexation and supramolecular host–guest recognition (by hydrogen bonding) can be envisaged.[19]

Experimental Section

General: NMR spectra were acquired with commercial instruments (300/400/600 MHz) and chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (TMS) or residual NMR spectroscopic solvent signals. In the ^{1}H NMR spectra, some signals are broadened due to unresolved ^4J couplings. Detailed ^{13}C NMR peak assignments were obtained by analysis of DEPT, HSQC, and HMBC spectra. Mass spectra were obtained with spectrometers with a CI/EI (70 eV ionization energy) or APCI/ESI ion source. Exact mass measurements were acquired in EI mode with resolution 10000. For column chromatography 70–230 mesh silica 60 was used as the stationary phase. Chemicals received from commercial sources were used without further purification. K_2CO_3 (anhydrous, granulated) was ground very well (with mortar and pestle) prior to use. Extra-dry DMSO (over molecular sieves, $H_2O \leq 0.005\%$) was purchased from Fluka. Extra-dry DMF (over molecular sieves, $H_2O < 50$ ppm) was purchased from Acros. CH_3CN was freshly distilled from $CaCl_2$ (and stored over 3 Å molecular sieves) prior to use. 1,4-Dioxane (99.5%, for analysis) was purchased from Acros (and kept over 4 Å molecular sieves).

General Procedure for the Single-Step Synthesis of Oxacalix[2]arene[2]quinazoline Isomers 3a,b: 2,4-Dichloroquinazoline (200 mg, 1.0 mmol, 1 equiv.), orcinol (125 mg, 1.0 mmol, 1 equiv.), K_2CO_3 (415 mg, 3.0 mmol, 3 equiv.), and 18-crown-6 (30 mg, 0.11 mmol) were combined in dry DMF (10 mL), and the mixture was vigorously stirred at 70 °C for 48 h under an argon atmosphere. DMF was removed under vacuum, and the mixture was redissolved in ethyl acetate and washed with distilled water. The organic fraction was dried with Na_2SO_4, filtered, and concentrated under vacuum. The respective oxacalix[4]arene isomers **3a** (*anti*) and **3b** (*syn*) were separated and purified by column chromatography (silica; CH_2Cl_2/ethyl acetate, 95:5), and obtained as pure-white solids. Whenever linear oligomers remained in the reaction mixture (see Table 1), the observed chromatographic elution order (silica; CH_2Cl_2/ethyl acetate, 95:5) was **5**–**3a**–**4**–**3b**. Data for *anti*-oxacalix[2]toluene[2]quinazoline (**3a**): Yield 42% (105 mg). M.p. 305–307 °C. MS (APCI): *m*/*z* = 501.5 [M + H]$^+$. HRMS (EI): calcd. for $C_{30}H_{20}N_4O_4$ 500.1485; found 500.1484. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.26 (s, 6 H, CH_3), 6.58 (s, 2 H, 2-orc), 6.68 (s, 2 H, 4/6-orc), 6.76 (s, 2 H, 4/6-orc), 7.42–7.49 (m, 2 H, 6-quin), 7.79–7.86 (m, 4 H, 7,8-quin), 8.21 (d, $J_{H,H}$ = 8.1 Hz, 2 H, 5-quin) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.2 (CH_3, orc), 113.1, 113.6 (CH, 2-orc), 119.3 (CH, 4/6-orc), 120.3 (CH, 4/6-orc), 124.0 (CH, 5-quin), 125.5 (CH, 6-quin), 126.6 (CH, 8-quin), 135.0 (CH, 7-quin), 140.6 (C, Ci-CH_3-Ph), 152.6 (C, 1/3-orc), 153.66, 153.73 (C, 1/3-orc), 161.3 (C, 2-quin), 169.6 (C, 4-quin) ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 316 (8250) nm. Data for *syn*-oxacalix[2]-toluene[2]quinazoline (**3b**): Yield 32% (80 mg). M.p. 292–293 °C. MS (APCI): *m*/*z* = 501.3 [M + H]$^+$. HRMS (EI): calcd. for $C_{30}H_{20}N_4O_4$ 500.1485; found 500.1486. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.26 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 6.54 (t, $J_{H,H}$ = 1.8 Hz, 2 H, 2-orc), 6.63 (t, $J_{H,H}$ = 1.8 Hz, 2 H, 2-orc), 6.68 (d, $J_{H,H}$ = 1.5 Hz, 2 H, 4/6-orc), 6.78 (d, $J_{H,H}$ = 1.5 Hz, 2 H, 4/6-orc), 7.44–7.50 (m, 2 H, 6-quin), 7.81–7.88 (m, 4 H, 7,8-quin), 8.22 (d, $J_{H,H}$ = 8.0 Hz, 2 H, 5-quin) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.3 (CH_3, orc), 113.0, 114.0 (CH, 2-orc), 119.8 (CH, 4/6-orc), 120.2 (CH, 4/6-orc), 123.9 (CH, 5-quin), 125.4 (CH, 6-quin), 126.9 (CH, 8-quin), 135.0 (CH, 7-quin), 140.2 (C, Ci-CH_3-Ph), 140.9 (C, Ci-CH_3-Ph), 152.9 (C, 1/3-orc), 153.6, 154.0 (C, 1/3-orc), 161.6 (C, 2-quin), 169.5 (C, 4-quin) ppm.

2-Chloro-4-(3-hydroxy-5-methylphenoxy)quinazoline (4): Upon performing the same reaction at room temperature for 24 h, [1+1] adduct **4** was obtained in 75% yield (216 mg). M.p. 176–177 °C. MS (CI): *m*/*z* (%) = 287.1/289.1 (100) [M + H]$^+$, 251.1 (44) [M – Cl]. HRMS (EI): calcd. for $C_{15}H_{11}ClN_2O_2$ 286.0509; found 286.0516. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.35 (s, 3 H, CH_3), 5.37 (br. s, 1 H, OH), 6.59 (s, 1 H, 2-orc), 6.61 (s, 1 H, 4/6-orc), 6.65 (s, 1 H, 4/6-orc), 7.61–7.67 (m, 1 H, 6-quin), 7.88–7.95 (m, 2 H, 7,8-quin), 8.30 (d, $J_{H,H}$ = 8.3 Hz, 1 H, 5-quin) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.6 (CH_3, orc), 106.5 (CH, 2-orc), 114.5 (CH, 4/6-orc), 114.6 (CH, 4/6-orc), 115.1 (quin), 119.3 (CH, 4/6-orc), 120.3 (CH, 4/6-orc), 124.1 (CH, 5-quin), 127.3 (CH, 8-quin), 127.9 (CH, 6-quin), 135.3 (CH, 7-quin), 141.2 (C, Ci-CH_3-Ph), 152.9 (C, 1/3-orc), 153.0 (C, 1/3-orc), 156.1, 156.6, 167.9 (C, 4-quin) ppm.

Single-Step Synthesis of Oxacalix[2]arene[2]quinazoline Isomers 3a,b (Procedure for Optimal *syn*-Oxacalix[4]arene Content): 2,4-Dichloroquinazoline (50 mg, 0.25 mmol, 1 equiv.), orcinol (32 mg, 0.25 mmol, 1 equiv.), K_2CO_3 (87 mg, 1.25 mmol, 5 equiv.), and 18-crown-6 (5 mg, 0.02 mmol) were combined in dry 1,4-dioxane (3 mL). The mixture was vigorously stirred at room temperature for 24 h under an argon atmosphere and subsequently brought to reflux temperature and stirred for another 24 h. Dioxane was removed under vacuum, and the mixture was redissolved in CH_2Cl_2 and washed with distilled water. The organic fraction was dried with $MgSO_4$, filtered, and concentrated under vacuum. The respective oxacalix[4]arene isomers **3a** (22 mg, 35%) and **3b** (34 mg, 54%) were separated by column chromatography (silica; CH_2Cl_2/ethyl acetate, 95:5) and obtained as pure-white solids.

3,5-Bis(2-chloroquinazolin-4-yloxy)toluene (5): A mixture of 2,4-dichloroquinazoline (353 mg, 1.77 mmol, 2.2 equiv.), orcinol (100 mg, 0.81 mmol, 1 equiv.), K_2CO_3 (278 mg, 2.12 mmol), and 18-crown-6 (8 mg, 0.03 mmol) in acetone (10 mL) was stirred under an argon atmosphere at room temperature for 48 h. Acetone was removed under vacuum, CH_2Cl_2 and water were added, the aqueous phase was discarded, and the organic solution was washed with distilled water. The organic fraction was dried with $MgSO_4$, filtered, and concentrated under vacuum. The [2+1] adduct was purified by flash chromatography (silica; CH_2Cl_2/ethyl acetate, 95:5) and obtained as a pure-white solid in a nearly quantitative yield (351 mg, 97%). M.p. 186–187 °C. MS (APCI): *m*/*z* = 449.7 $[M + H]^+$. HRMS (EI): calcd. for $C_{23}H_{14}Cl_2N_4O_2$ 448.0494; found 448.0491. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.48 (s, 3 H, CH_3), 7.08–7.11 (m, 3 H, 2,4,6-orc), 7.62–7.69 (m, 2 H, 6-quin), 7.91–7.94 (m, 4 H, 7,8-quin), 8.33 (d, $J_{H,H}$ = 8.0 Hz, 2 H, 5-quin) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.8 (CH_3, orc), 112.9 (CH, 2-orc), 114.8, 120.3 (CH, 4,6-orc), 124.0 (CH, 5-quin), 127.3 (CH, 8-quin), 128.0 (CH, 6-quin), 135.3 (CH, 7-quin), 141.3 (C, Ci-CH_3-Ph), 152.4 (C, 1,3-orc), 153.0, 155.9 (C, 2-quin), 167.6 (C, 4-quin) ppm.

Oxacalix[2]arene[2]pyrimidine Isomers 6a,b: According to the general procedure, 2,4-dichloropyrimidine (200 mg, 1.34 mmol, 1 equiv.), orcinol (166 mg, 1.34 mmol, 1 equiv.), K_2CO_3 (556 mg, 4.02 mmol, 3 equiv.), 18-crown-6 (30 mg, 0.11 mmol), DMF (10 mL), 70 °C, 48 h. Eluent: CH_2Cl_2/ethyl acetate, 95:5. Data for *anti*-oxacalix[2]toluene[2]pyrimidine (**6a**): Yield: 47% (124 mg). M.p. 249–250 °C. MS (APCI): *m*/*z* = 401.3 $[M + H]^+$. HRMS (EI): calcd. for $C_{22}H_{16}N_4O_4$ 400.1172; found 400.1178. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.19 (s, 6 H, CH_3), 6.42 (s, 2 H, 2-orc), 6.54 (s, 2 H, 4/6-orc), 6.59–6.64 (m, 4 H, 4/6-orc and 5-pyrim), 8.38 (d, $J_{H,H}$ = 5.5 Hz, 2 H, 6-pyrim) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.1 (CH_3, orc), 102.6 (CH, 5-pyrim), 113.6 (CH, 2-orc), 119.5 (CH, 4/6-orc), 120.0 (CH, 4/6-orc), 140.4 (C, Ci-CH_3-Ph), 152.4 (C, 1/3-orc), 153.0 (C, 1/3-orc), 160.9 (CH, 6-pyrim), 165.3 (C, 2-pyrim), 171.1 (C, 4-pyrim) ppm. Data for *syn*-oxacalix[2]toluene[2]pyrimidine (**6b**): Yield: 38% (101 mg). M.p. 96–98 °C. MS (APCI): *m*/*z* = 401.4 $[M + H]^+$. HRMS (EI): calcd. for $C_{22}H_{16}N_4O_4$ 400.1172; found 400.1174. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.23 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 6.42 (s, 1 H, 2-orc), 6.48 (s, 1 H, 2-orc), 6.59–6.66 (m, 6 H, 4,6-orc and 5-pyrim), 8.42 (d, $J_{H,H}$ = 5.6 Hz, 2 H, 6-pyrim) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.18 (CH_3, orc), 21.20 (CH_3, orc), 102.5 (CH, 5-pyrim), 113.76 (CH, 2-orc), 113.81 (CH, 2-orc), 119.8 (CH, 4/6-orc), 120.0 (CH, 4/6-orc), 140.4 (C, Ci-CH_3-Ph), 140.6 (C, Ci-CH_3-Ph), 152.5 (C, 1/3-orc), 153.1 (C, 1/3-orc), 161.0 (CH, 6-pyrim), 165.5 (C, 2-pyrim), 171.1 (C, 4-pyrim) ppm.

Oxacalix[2]arene[2]quinazoline Isomers 7a,b: According to the general procedure, 2,4-dichloroquinazoline (200 mg, 1.0 mmol, 1 equiv.), resorcinol (110 mg, 1.0 mmol, 1 equiv.), K_2CO_3 (415 mg, 3.0 mmol, 3 equiv.), 18-crown-6 (30 mg, 0.11 mmol), dry DMF (10 mL), 70 °C, 24 h. Eluent: CH_2Cl_2/ethyl acetate, 92:8. Data for *anti*-oxacalix[2]benzene[2]quinazoline (**7a**): Yield: 47% (111 mg). M.p. >350 °C. MS (APCI): *m*/*z* = 473.4 $[M + H]^+$. HRMS (EI): calcd. for $C_{28}H_{16}N_4O_4$ 472.1172; found 472.1160. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.76 (t, $J_{H,H}$ = 2.1 Hz, 2 H, 2-resorc), 6.85 (dd, $J_{H,H}$ = 8.0, 1.3 Hz, 2 H, 4/6-resorc), 6.94 (dd, $J_{H,H}$ = 8.0, 1.2 Hz, 2 H, 4/6-resorc), 7.27 (t, $J_{H,H}$ = 8.1 Hz, 2 H, 5-resorc), 7.47–7.53 (m, 2 H, 6-quin), 7.83–7.88 (m, 4 H, 7,8-quin), 8.25 (d, $J_{H,H}$ = 8.3 Hz, 2 H, 5-quin) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 113.2, 117.0 (CH, 2-resorc), 118.9 (CH, 4/6-resorc), 119.9 (CH, 4/6-resorc), 124.1 (CH, 5-quin), 125.6 (CH, 6-quin), 126.8 (CH, 8-quin), 130.1 (CH, 5-resorc), 135.2 (CH, 7-quin), 153.0 (C, 1/3-resorc), 153.9, 154.0 (C, 1/3-resorc), 161.4 (C, 2-quin), 169.7 (C, 4-quin) ppm. Data for *syn*-oxacalix[2]benzene[2]-quinazoline (**7b**): Yield: 27% (64 mg). M.p. 267–268 °C. MS (APCI): *m*/*z* = 473.5 $[M + H]^+$. HRMS (EI): calcd. for $C_{28}H_{16}N_4O_4$ 472.1172; found 472.1162. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.74 (t, $J_{H,H}$ = 2.1 Hz, 1 H, 2-resorc), 6.80–6.86 (m, 3 H, 2,4/6-resorc), 6.94 (dd, $J_{H,H}$ = 8.1, 2.1 Hz, 2 H, 4/6-resorc), 7.20 (t, $J_{H,H}$ = 8.0 Hz, 1 H, 5-resorc), 7.34 (t, $J_{H,H}$ = 8.0 Hz, 1 H, 5-resorc), 7.47–7.53 (m, 2 H, 6-quin), 7.83–7.89 (m, 4 H, 7,8-quin), 8.24 (d, $J_{H,H}$ = 8.0 Hz, 2 H, 5-quin) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 113.0, 117.20 (CH, 2-resorc), 117.27 (CH, 2-resorc), 119.2 (CH, 4/6-resorc), 119.7 (CH, 4/6-resorc), 123.9 (CH, 5-quin), 125.5 (CH, 6-quin), 126.9 (CH, 8-quin), 129.8 (CH, 5-resorc), 130.3 (CH, 5-resorc), 135.2 (CH, 7-quin), 153.1 (C, 1/3-resorc), 153.8 (C, 1/3-resorc), 161.6 (C, 2-quin), 169.5 (C, 4-quin) ppm.

Oxacalix[2]arene[2]quinazoline Isomers 8a,b: According to the general procedure, 2,4-dichloro-7-nitroquinazoline (100 mg, 0.41 mmol, 1 equiv.), orcinol (50 mg, 0.41 mmol, 1 equiv.), K_2CO_3 (170 mg, 1.23 mmol, 3 equiv.), 18-crown-6 (15 mg, 0.06 mmol), dry DMF (7 mL), room temp., 24 h. Eluent: CH_2Cl_2. Data for *anti*-oxacalix[2]toluene[2]quinazoline (**8a**): Yield 18% (22 mg). M.p. >350 °C. MS (ESI+): *m*/*z* = 591.4 $[M + H]^+$. HRMS (EI): calcd. for $C_{30}H_{18}N_6O_8$ 590.1186; found 590.1199. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.32 (s, 6 H, CH_3), 6.58 (s, 2 H, 2-orc), 6.73 (s, 2 H, 4/6-orc), 6.81 (s, 2 H, 4/6-orc), 8.24 (dd, $J_{H,H}$ = 8.8, 1.5 Hz, 2 H, 6-quin), 8.41 (d, $J_{H,H}$ = 9.0 Hz, 2 H, 5-quin), 8.69 (d, $J_{H,H}$ = 1.5 Hz, 2 H, 8-quin) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.3 (CH_3, orc), 113.5 (CH, 2-orc), 116.3, 119.1 (CH, 4/6-orc), 119.6 (CH, 4/6-orc), 120.8 (CH, quin), 122.5 (CH, quin), 126.2 (CH, quin), 141.2 (C, Ci-CH_3-Ph), 152.2, 152.3, 153.4, 154.0, 162.8 (C, 2-quin), 169.7 (C, 4-quin) ppm. Data for *syn*-oxacalix[2]toluene[2]quinazoline (**8b**): Yield: 18% (22 mg). M.p. >350 °C. MS (ESI+): *m*/*z* = 591.2 $[M + H]^+$. HRMS (EI): calcd. for $C_{30}H_{18}N_6O_8$ 590.1186; found 590.1173. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.28 (s, 3 H, CH_3), 2.36 (s, 3 H, CH_3), 6.56 (s, 1 H, 2-orc), 6.65 (s, 1 H, 2-orc), 6.71 (s, 2 H, 4/6-orc), 6.83 (s, 2 H, 4/6-orc), 8.24 (d, $J_{H,H}$ = 9.0 Hz, 2 H, 6-quin), 8.40 (d, $J_{H,H}$ = 9.0 Hz, 2 H, 5-quin), 8.70 (s, 2 H, 8-quin) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.27 (CH_3, orc), 21.32 (CH_3, orc), 113.6 (CH, 2-orc), 113.7 (CH, 2-orc), 116.1, 119.0 (CH, 4/6-orc), 120.1 (CH, 4/6-orc), 120.5 (CH, quin), 122.6 (CH, quin), 126.0 (CH, quin), 140.8 (C, Ci-CH_3-Ph), 141.6 (C, Ci-CH_3-Ph), 152.2, 152.5, 153.2, 154.1, 162.9 (C, 2-quin), 169.5 (C, 4-quin) ppm.

Oxacalix[2]naphthalene[2]quinazoline Isomers 9a,b: According to the general procedure, 2,4-dichloroquinazoline (200 mg, 1.0 mmol, 1 equiv.), 2,7-dihydroxynaphthalene (161 mg, 1.0 mmol, 1 equiv.),

K_2CO_3 (415 mg, 3.0 mmol, 3 equiv.), 18-crown-6 (30 mg, 0.11 mmol), dry DMF (10 mL), 70 °C, 24 h. Extraction solvent $CHCl_3$. Eluent: $CHCl_3$/ethyl acetate, 90:10. Data for *anti*-oxacalix[2]naphthalene[2]quinazoline (**9a**): Yield: 36% (120 mg). M.p. >350 °C. MS (APCI): *m*/*z* = 573.3 [M + H]$^+$. HRMS (EI): calcd. for $C_{36}H_{20}N_4O_4$ 572.1485; found 572.1487. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.96 (dd, $J_{H,H}$ = 8.8, 2.0 Hz, 2 H, 3/6-naphth), 7.02 (dd, $J_{H,H}$ = 8.8, 2.0 Hz, 2 H, 3/6-naphth), 7.18–7.21 (m, 4 H, 1,8-naphth), 7.51–7.61 (m, 6 H, 6-quin/4,5-naphth), 7.86–7.94 (m, 4 H, 7,8-quin), 8.31 (d, $J_{H,H}$ = 8.3 Hz, 2 H, 5-quin) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 113.2, 118.2 (CH, 1/8-naphth), 118.4 (CH, 1/8-naphth), 120.8 (CH, 3/6-naphth), 121.9 (CH, 3/6-naphth), 124.1 (CH, 5-quin), 125.5 (CH, 6-quin), 126.9 (CH, 8-quin), 129.0 (CH, 4/5-naphth), 129.1, 129.2 (CH, 4/5-naphth), 134.1, 135.1 (CH, 7-quin), 150.5 (C, 2/7-naphth), 151.4 (C, 2/7-naphth), 154.1, 161.8 (C, 2-quin), 169.9 (C, 4-quin) ppm. Data for *syn*-oxacalix[2]naphthalene[2]quinazoline (**9b**): Yield: 36% (120 mg). M.p. >350 °C. MS (APCI): *m*/*z* = 573.3 [M + H]$^+$. HRMS (EI): calcd. for $C_{36}H_{20}N_4O_4$ 572.1485; found 572.1474. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.95 (dd, $J_{H,H}$ = 8.8, 2.3 Hz, 2 H, 3/6-naphth), 7.01 (dd, $J_{H,H}$ = 8.8, 2.3 Hz, 2 H, 3/6-naphth), 7.17 (d, $J_{H,H}$ = 2.2 Hz, 2 H, 1/8-naphth), 7.22 (d, $J_{H,H}$ = 2.2 Hz, 2 H, 1/8-naphth), 7.49–7.55 (m, 4 H, 6-quin/4,5-naphth), 7.63 (d, $J_{H,H}$ = 8.8 Hz, 2 H, 4,5-naphth), 7.86–7.94 (m, 4 H, 7,8-quin), 8.30 (d, $J_{H,H}$ = 8.0 Hz, 2 H, 5-quin) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 113.1, 118.2 (CH, 1/8-naphth), 118.6 (CH, 1/8-naphth), 121.3 (CH, 3/6-naphth), 121.5 (CH, 3/6-naphth), 124.0 (CH, 5-quin), 125.4 (CH, 6-quin), 127.0 (CH, 8-quin), 128.8, 128.9 (CH, 4/5-naphth), 129.3 (CH, 4/5-naphth), 129.4, 133.9, 135.1 (CH, 7-quin), 150.7 (C, 2/7-naphth), 151.2 (C, 2/7-naphth), 154.2, 161.9 (C, 2-quin), 169.7 (C, 4-quin) ppm.

Thiacalix[2]arene[2]quinazoline Isomers 10a,b: According to the general procedure, 2,4-dichloroquinazoline (200 mg, 1.0 mmol, 1 equiv.), 1,3-benzenedithiol (150 mg, 1.0 mmol, 1 equiv.), K_2CO_3 (415 mg, 3.0 mmol, 3 equiv.), 18-crown-6 (30 mg, 0.11 mmol), dry DMF (10 mL), 70 °C, 24 h. Extraction solvent $CHCl_3$ (large volumes). Eluent: $CHCl_3$/ethyl acetate, 96:4. Data for *anti*-thiacalix[2]-benzene[2]quinazoline (**10a**): Yield: 71% (192 mg). M.p. >350 °C. MS (APCI): *m*/*z* = 537.2 [M + H]$^+$. HRMS (EI): calcd. for $C_{28}H_{16}N_4S_4$ 536.0258; found 536.0271. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.32 (t, $J_{H,H}$ = 7.8 Hz, 2 H, 5-benz), 7.39 (d, $J_{H,H}$ = 7.8 Hz, 2 H, 4/6-benz), 7.46–7.55 (m, 6 H, 6-quin and 2,4/6-benz), 7.81–7.85 (m, 4 H, 7,8-quin), 8.07 (d, $J_{H,H}$ = 8.3 Hz, 2 H, 5-quin) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 120.8, 124.0 (CH, 5-quin), 126.6 (CH, 6-quin), 126.9, 127.7 (CH, 8-quin), 130.3 (CH, 5-benz), 130.7, 134.7 (CH, 7-quin), 137.5 (CH, 4/6-benz), 137.9 (CH, 4/6-benz), 141.5 (CH, 2-benz), 149.1, 166.7 (2-quin), 172.2 (4-quin) ppm. Data for *syn*-thiacalix[2]benzene[2]-quinazoline (**10b**): Yield: 15% (40 mg). M.p. >350 °C. MS (APCI): *m*/*z* = 537.4 [M + H]$^+$. HRMS (EI): calcd. for $C_{28}H_{16}N_4S_4$ 536.0258; found 536.0258. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.29 (t, $J_{H,H}$ = 7.7 Hz, 2 H, 5-benz), 7.35 (t, $J_{H,H}$ = 7.7 Hz, 2 H, 5-benz), 7.42–7.45 (m, 4 H, 4,6-benz), 7.48–7.52 (m, 3 H, 6-quin and 2-benz), 7.57 (t, $J_{H,H}$ = 1.6 Hz, 1 H, 2-benz), 7.81–7.86 (m, 4 H, 7,8-quin), 8.06 (d, $J_{H,H}$ = 8.2 Hz, 2 H, 5-quin) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 120.7, 123.9 (CH, 5-quin), 126.5 (CH, 6-quin), 127.4, 127.7 (CH, 8-quin), 130.2 (CH, 5-benz), 130.5 (CH, 5-benz), 134.7 (CH, 7-quin), 137.1 (CH, 4/6-benz), 138.3 (CH, 4/6-benz), 141.3 (CH, 2-benz), 141.7 (CH, 2-benz), 149.2, 167.0 (2-quin), 171.7 (4-quin) ppm.

X-ray Structure Determinations: For the structures of oxacalix[4]-arenes **3a** and **9b** intensity data were collected with a SMART 6000 diffractometer equipped with a CCD detector by using Cu-K_α radiation (λ = 1.54178 Å). The images were interpreted and integrated with the program SAINT from Bruker.[20] Both structures were solved by direct methods and refined by full-matrix least-squares on F^2 by using the SHELXTL program package.[21] Non-hydrogen atoms were refined anisotropically, with hydrogen atoms placed in the riding mode with isotropic temperature factors fixed at 1.2 times $U_{(eq)}$ of the parent atoms (1.5 times for methyl groups). CCDC-688453 (for **3a**) and -688454 (for **9b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Single-Crystal Structure of 3a: $C_{30}H_{20}N_4O_4{\cdot}CHCl_3$, crystal size 0.3 × 0.3 × 0.1 mm, M = 619.87, monoclinic, $C2/c$, a = 38.262(8) Å, b = 9.0671(18) Å, c = 18.639(4) Å, β = 118.35(3)°, V = 5691(3) Å^3, T = 100(2) K, Z = 8, $\rho_{calcd.}$ = 1.447 g cm^{-3}, μ(Cu-K_α) = 3.293 mm^{-1}, F(000) = 2544, R_1 = 5.21%, ωR_2 = 12.85 for 4370 reflections with $I_o > 2\sigma(I)$ and *GOOF* = 1.051. The crystal structure was determined by using two datasets with insufficient completeness from two different crystals, 96.6 and 95.9% complete up to 135.4° (2θ). R_{int} for dataset one after absorption correction (SADABS) was 8.45% for 17136 reflections (5578 unique). R_{int} for dataset two after absorption correction (SADABS) was 8.28% for 16413 reflections (5502 unique). The R_{merge} between the two datasets is 7.74 (R_{sigma} 0.0456) for a total of 33549 reflections (5821 unique). Both crystals were similar in size and shape.

Single-Crystal Structure of 9b: $C_{36}H_{20}N_4O_4$, crystal size 0.2 × 0.2 × 0.1 mm, M = 572.56, monoclinic, $C2_1/n$, a = 9.9834(6) Å, b = 18.7663(11) Å, c = 14.7223(9) Å, β = 105.087(4)°, V = 2663.2(3) Å^3, T = 100(2) K, Z = 4, $\rho_{calcd.}$ = 1.428 g cm^{-3}, μ-(Cu-K_α) = 0.775 mm^{-1}, F(000) = 1184, R_1 = 6.09%, ωR_2 = 15.02 for 4370 reflections with $I_o > 2\sigma(I)$ and *GOOF* = 1.053.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for all novel heteracalix[4]arenes and precursors and additional X-ray figures for **3a** and **9b**.

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[1] a) Z. Asfari, V. Böhmer, J. Harrowfield, J. Vicens (Eds.), *Calixarenes 2001*, Kluwer Academic Publishers, Dordrecht, **2001**; b) J. Vicens, J. Harrowfield (Eds.), *Calixarenes in the Nanoworld*, Springer, Dordrecht, **2006**; c) C. D. Gutsche, *Calixarenes: An Introduction* (Ed.: J. F. Stoddart), Royal Society of Chemistry, Cambridge, **2008**.

[2] We prefer the term heteracalixarenes to distinguish the class of heteroatom-bridged metacyclophanes from heterocalixarenes, the heterocyclic analogues of classical C-bridged calixarenes, for example, calixpyrroles (calixhetarenes).

[3] B. König, M. H. Fonseca, *Eur. J. Inorg. Chem.* **2000**, 2303–2310.

[4] Thiacalixarene reviews: a) P. Lhoták, *Eur. J. Org. Chem.* **2004**, 1675–1692; b) N. Morohashi, F. Narumi, N. Iki, T. Hattori, S. Miyano, *Chem. Rev.* **2006**, *106*, 5291–5316.

[5] Azacalixarene review: H. Tsue, K. Ishibashi, R. Tamura in *Heterocyclic Supramolecules I* (Ed.: K. Matsumoto), Topics in Heterocyclic Chemistry, Springer, Berlin, **2008**, vol. 17, pp. 73–96.

[6] Recent additions to the azacalixarene field: a) M. Vale, M. Pink, S. Rajca, A. Rajca, *J. Org. Chem.* **2008**, *73*, 27–35; b) M.

Touil, M. Lachkar, O. Siri, *Tetrahedron Lett.* **2008**, *49*, 7250–7252; c) H. Tsue, K. Ishibashi, S. Tokita, H. Takahashi, K. Matsui, R. Tamura, *Chem. Eur. J.* **2008**, *14*, 6125–6134; d) K. V. Lawson, A. C. Barton, J. D. Spence, *Org. Lett.* **2009**, *11*, 895–898; e) M. Xue, C.-F. Chen, *Org. Lett.* **2009**, *11*, 5294–5297; f) B. Yao, D.-X. Wang, Z.-T. Huang, M.-X. Wang, *Chem. Commun.* **2009**, 2899–2901; g) B. Yao, D.-X. Wang, H.-Y. Gong, Z.-T. Huang, M.-X. Wang, *J. Org. Chem.* **2009**, *74*, 5361–5368; h) J. Clayden, S. J. M. Rowbottom, W. J. Ebenezer, M. G. Hutchings, *Org. Biomol. Chem.* **2009**, *7*, 4871–4880; i) E.-X. Zhang, D.-X. Wang, Z.-T. Huang, M.-X. Wang, *J. Org. Chem.* **2009**, *74*, 8595–8603; j) L.-X. Wang, D.-X. Wang, Z.-T. Huang, M.-X. Wang, *J. Org. Chem.* **2010**, *75*, 741–747.

[7] Oxacalixarene reviews: a) W. Maes, W. Dehaen, *Chem. Soc. Rev.* **2008**, *37*, 2393–2402; b) M.-X. Wang, *Chem. Commun.* **2008**, 4541–4551 (also covering azacalixarenes from the same group).

[8] Recent additions to the oxacalixarene field: a) R. D. Chambers, P. R. Hoskin, A. R. Kenwright, A. Khalil, P. Richmond, G. Sandford, D. S. Yufit, J. A. K. Howard, *Org. Biomol. Chem.* **2003**, *1*, 2137–2147; b) J. L. Katz, M. B. Feldman, R. R. Conry, *Org. Lett.* **2005**, *7*, 91–94; c) J. L. Katz, K. J. Selby, R. R. Conry, *Org. Lett.* **2005**, *7*, 3505–3507; d) F. Yang, L. Yan, K. Ma, L. Yang, J. Li, L. Chen, J. You, *Eur. J. Org. Chem.* **2006**, 1109–1112; e) J. L. Katz, B. J. Geller, R. R. Conry, *Org. Lett.* **2006**, *8*, 2755–2758; f) W. Maes, W. Van Rossom, K. Van Hecke, L. Van Meervelt, W. Dehaen, *Org. Lett.* **2006**, *8*, 4161–4164; g) V. Csokai, B. Kulik, I. Bitter, *Supramol. Chem.* **2006**, *18*, 111–115; h) H. Konishi, K. Tanaka, Y. Teshima, T. Mita, O. Morikawa, K. Kobayashi, *Tetrahedron Lett.* **2006**, *47*, 4041–4044; i) L. Jiao, E. Hao, F. R. Fronczek, K. M. Smith, M. G. H. Vicente, *Tetrahedron* **2007**, *63*, 4011–4017; j) C. Zhang, C.-F. Chen, *J. Org. Chem.* **2007**, *72*, 3880–3888; k) H. Konishi, T. Mita, O. Morikawa, K. Kobayashi, *Tetrahedron Lett.* **2007**, *48*, 3029–3032; l) H.-B. Yang, D.-X. Wang, Q.-Q. Wang, M.-X. Wang, *J. Org. Chem.* **2007**, *72*, 3757–3763; m) Q.-Q. Wang, D.-X. Wang, Q.-Y. Zheng, M.-X. Wang, *Org. Lett.* **2007**, *9*, 2847–2850; n) B.-Y. Hou, Q.-Y. Zheng, D.-X. Wang, M.-X. Wang, *Tetrahedron* **2007**, *63*, 10801–10808; o) J. L. Katz, B. J. Geller, P. D. Foster, *Chem. Commun.* **2007**, 1026–1028; p) W. Van Rossom, W. Maes, L. Kishore, M. Ovaere, L. Van Meervelt, W. Dehaen, *Org. Lett.* **2008**, *10*, 585–588; q) D.-X. Wang, Q.-Y. Zheng, Q.-Q. Wang, M.-X. Wang, *Angew. Chem.* **2008**, *120*, 7595–7598; *Angew. Chem. Int. Ed.* **2008**, *47*, 7485–7488; r) S. Ferrini, S. Fusi, G. Giorgi, F. Ponticelli, *Eur. J. Org. Chem.* **2008**, 5407–5413; s) H. Konishi, T. Mita, Y. Yasukawa, O. Morikawa, K. Kobayashi, *Tetrahedron Lett.* **2008**, *49*, 6831–6834; t) B.-Y. Hou, Q.-Y. Zheng, D.-X. Wang, Z.-T. Huang, M.-X. Wang, *Chem. Commun.* **2008**, 4541–4551; u) C. Capici, D. Garozzo, G. Gattuso, A. Messina, A. Notti, M. F. Parisi, I. Pisagatti, S. Pappalardo, *ARKIVOC* **2009**, *viii*, 199–211; v) M. Li, M.-L. Ma, X.-Y. Li, K. Wen, *Tetrahedron* **2009**, *65*, 4639–4643; w) W. Van Rossom, M. Ovaere, L. Van Meervelt, W. Dehaen, W. Maes, *Org. Lett.* **2009**, *11*, 1681–1684; x) L. Wu, L. Jiao, Q. Lu, E. Hao, Y. Zhou, *Spectrochim. Acta Part A* **2009**, *73*, 353–357; y) M.-L. Ma, X.-Y. Li, K. Wen, *J. Am. Chem. Soc.* **2009**, *131*, 8338–8339; z) J. W. Wackerly, J. M. Meyer, W. C. Crannell, S. B. King, J. L. Katz, *Macromolecules* **2009**, *42*, 8181–8186.

[9] N,O-Bridged calix(hetero)aromatics: a) M.-X. Wang, H.-B. Yang, *J. Am. Chem. Soc.* **2004**, *126*, 15412–15422; b) J.-C. Wu, D.-X. Wang, Z.-T. Huang, M.-X. Wang, *Tetrahedron Lett.* **2009**, *50*, 7209–7211.

[10] W. Van Rossom, O. Kundrát, T. H. Ngo, P. Lhoták, W. Dehaen, W. Maes, *Tetrahedron Lett.* **2010**, *51*, 2423–2426.

[11] Katz et al. reported the formation of a statistical mixture of bicyclooxacalix[4]arene regioisomers starting from an unsymmetrical 2,6-dichloro-3-nitropyrimidine building block (ref.[8c]). Ponticelli et al. performed a similar study based on an isoxazolopyridine precursor (ref.[8r]), whereas Zhang and Chen prepared (diastereo)isomeric oxacalix[4]arenes by virtue of a rigid triptycene structure (ref.[8j]).

[12] Gilbert reported the formation of two isomeric oxacalix[4]arenes in approximately equal amounts starting from 4-substituted resorcinols: E. E. Gilbert, *J. Heterocycl. Chem.* **1974**, *11*, 899–904.

[13] Some examples: a) E. De Clercq, *Curr. Med. Chem.* **2001**, *8*, 1543–1572; b) Y. Xia, Z.-Y. Yang, M.-J. Hour, S.-C. Kuo, P. Xia, K. F. Bastow, Y. Nakanishi, Y. Nampoothiri, T. Hackl, C. Hamelc, K.-H. Lee, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1193–1196; c) P. A. Zunszain, C. Federico, M. Sechi, S. Al-Damluji, C. R. Ganellin, *Bioorg. Med. Chem.* **2005**, *13*, 3681–3689.

[14] A. Witt, J. Bergman, *Curr. Org. Chem.* **2003**, *7*, 659–677.

[15] a) B. Serafin, M. Modzelewski, A. Kurnatowska, R. Kadlubowski, *Eur. J. Med. Chem.* **1977**, *12*, 325–331; b) V. J. Ram, Farhanullah, B. K. Tripathi, A. Srivastava, *Bioorg. Med. Chem.* **2003**, *11*, 2439–2444; c) C. Wéber, A. Bielik, A. Demeter, I. Borza, G. I. Szendrei, G. M. Keserű, I. Greiner, *Tetrahedron* **2005**, *61*, 9375–9380; d) V. Deore, M. V. Lohar, N. Yewalkar, R. Mundada, S. Ranaware, S. Kumar, *J. Heterocycl. Chem.* **2007**, *44*, 495–498.

[16] a) N. A. Lange, W. E. Roush, H. J. Asbeck, *J. Am. Chem. Soc.* **1930**, *52*, 3696–3702; b) K. Kanuma, K. Omodera, M. Nishiguchi, T. Funakoshi, S. Chaki, G. Semple, T.-A. Tran, B. Kramer, D. Hsu, M. Casper, B. Thomsen, Y. Sekiguchi, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3853–3856.

[17] On using regular DMF (not extra dry or carefully dried prior to use), yields dropped dramatically and noncyclic oligomers (sometimes partially hydrolyzed, as in ref.[8k]) were identified in the reaction mixture.

[18] F. H. S. Curd, J. K. Landquist, F. L. Rose, *J. Chem. Soc.* **1948**, 1759–1766.

[19] Some of the reported oxacalix[2]arene[2]quinazolines (**3a/b**, **9a/b**) have very recently been investigated as potential hosts for spherical fullerenes C_{60} and C_{70} (within the framework of a study on oxacalix[2]arene[2]pyrimidine-bisporphyrinoid tweezers as selective receptors towards fullerene C_{70}, see ref.[10]). Unfortunately, no binding was observed for these macrocycles, as evidenced by ^{1}H NMR titration experiments.

[20] *SAINT*, Manual Version 5/6.0, Bruker Analytical X-ray System Inc., Madison, Wisconsin, **1997**.

[21] *SHELXTL-NT*, Manual Version 5.1, Bruker Analytical X-ray System Inc., Madison, Wisconsin, **1997**.

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