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MOLECULAR DESIGN AND SYNTHESIS OF 4,8-DI(HETERO)ARYLQUINAZOLINES WITH POTENTIAL APPLICATIONS IN QUADRATIC NONLINEAR OPTICS. DIAZINES PART 48

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Abstract – In the aim to define a structure NLO properties relationship, theoretical calculations have been used to investigate the role of different parts (substituents and π-system) of disubstituted conjugated systems based on naphthalene, cinnoline and quinazoline moieties. Using metallation and cross-coupling reactions we report here the synthesis of new 4,8-di(hetero)arylquinazolines and their quadratic NLO properties.

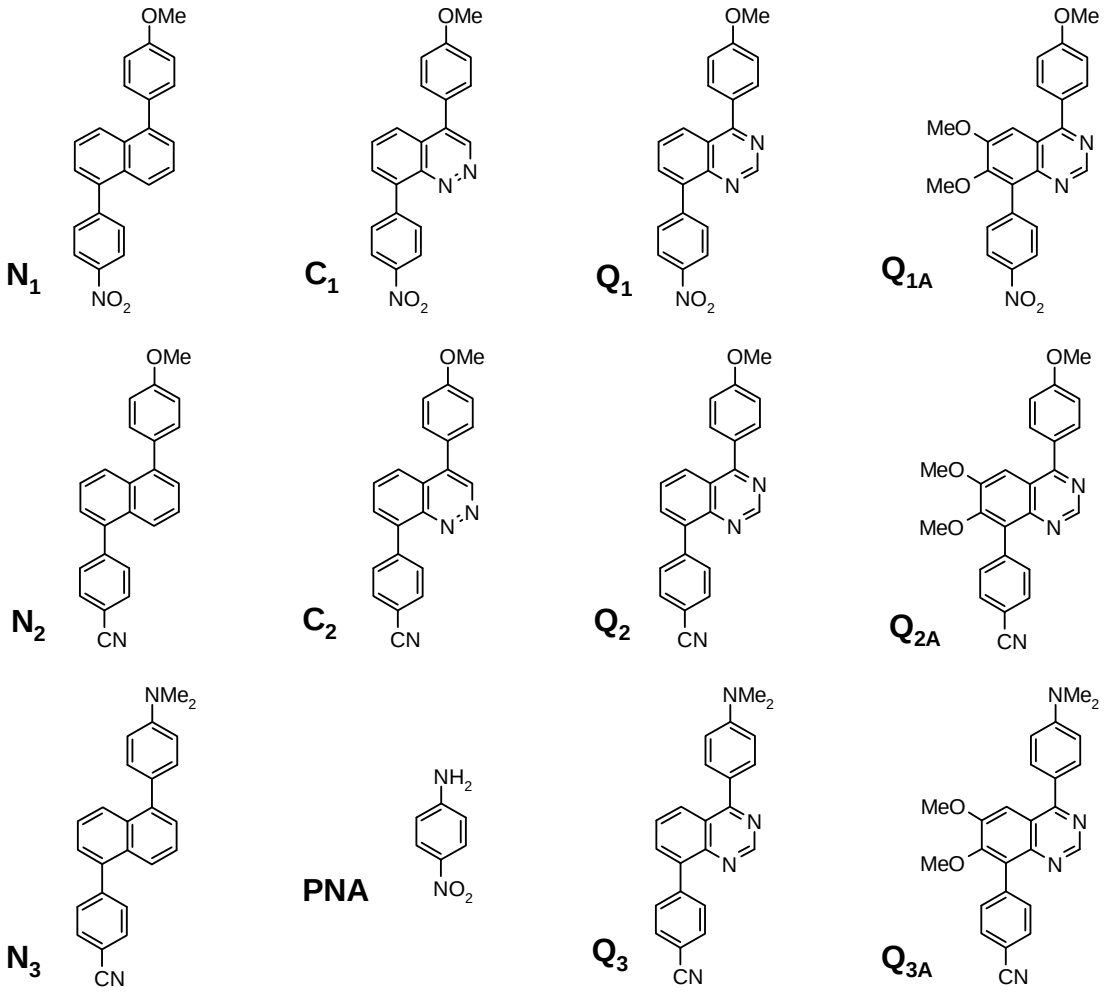
INTRODUCTION

Photonic technologies based on nonlinear optic (NLO) applications, such as light speed optical communications, integrated optics, optical data processing and storage,[1] and more recently biologic membranes imaging[2] require materials with high quadratic hyperpolarisability values of β.

A typical NLO chromophore consists of an electron-withdrawing group (A) and an electron-donating group (D) connected by a π-electronic conjugated system. The delocalization of π electrons in such molecules lead to internal charge transfert (CT) and often to large first-order hyperpolarizabilities (β).

A polarized π-system can be generated by fusing or linearly connecting heteroaromatic systems of different electron densities. Moreover, the introduction of aromatic rings improves the

transparency-nonlinearity trade-off and the thermal stability, both factors being critical for electro-optical applications.[3-5] In this paper, we propose conjugated systems based on naphthalene (**N**), cinnoline (**C**) and quinazoline (**Q**) moieties ; derivatives are disubstituted at 1/5 or 1/8 positions by benzene rings bearing electron-donating or withdrawing groups (Scheme 1).



Scheme 1

RESULTS AND DISCUSSION

The molecular engineering for systems with enhanced values of β is generally based on the classical two-level model illustrated by the relationship (1): [6-8]

$$\beta = \frac{3e^2\hbar^2}{2m}\frac{W}{\left[W^2-(2\hbar\omega)^2\right]\left[W^2-(\hbar\omega)^2\right]}f\Delta\mu \qquad (1)$$

in which f and $\Delta\mu$ represent respectively the oscillator strength of the lowest absorption transition and the dipole moment difference between the ground state and the lowest charge transfer excited state, while W is

the energy of this last state and $\hbar\omega$ the energy of the applied laser.

Theoretical calculations have been used to investigate the role of the different parts (A, D and the π-system) in the molecule and to define a structure-NLO properties relationship. The main goal of this work is to evaluate the quadratic NLO interest of **N**, **C** and **Q** π-systems and not to obtain directly optimized values of β. Standard donor (OMe, NMe_2) and acceptor groups (CN, NO_2) have been used in order to compare properties of these systems (Scheme 1). These properties have been also compared to those of *p*-nitroaniline (PNA), as a reference molecule in the field of quadratic NLO.

Hyperpolarisabilities values are reported in Table 1 with optical data involved in the two-level model relationship (1). Using CNDO/S calculations, we have determinated the calculated transition wavelength (λ_{max}^{th}), the dipole moment difference ($\Delta\mu$) between the ground state and the first charge transfer excited state, and the transition oscillator strength (*f*) (Table 1). For comparison with molecules without resonance effects, the static (at $\hbar\omega = 0$) first-order hyperpolarizability (β_0^{th}) was calculated as detailed in ref. 9. Calculated values, which correspond to the projection of the vectoriel part of the hyperpolarisability onto the direction of the ground state dipole moment μ, are directly comparable to experimental values.

Molecules $\mathbf{Q_1}$ and $\mathbf{Q_2}$ present the weakest static β values of 9 and 7 10^{-30} esu respectively, which are comparable to that PNA molecule (8 10^{-30} esu) with red shifted linear absorption properties (347 and 333 nm respectively) with respect to those of PNA (310 nm).

The effect of the acceptor group is weak; comparing molecules of type 1 and 2 with OMe groups and the same **N**, **C** and **Q** π-system, the slight decrease from NO_2 to CN systems of β values is mainly due to the decrease of $\Delta\mu$, while other parameters of relationship (1) remain nearly constant. The effect of donor group is higher, when comparing molecules of type 3 and 2 with CN acceptor group ; as in the case of the acceptor group, the effect can be mainly ascribed to the decrease $\Delta\mu$ values. These results are in good agreement with the higher strength of NO_2 and NMe_2 groups with respect to that of CN and OMe respectively.

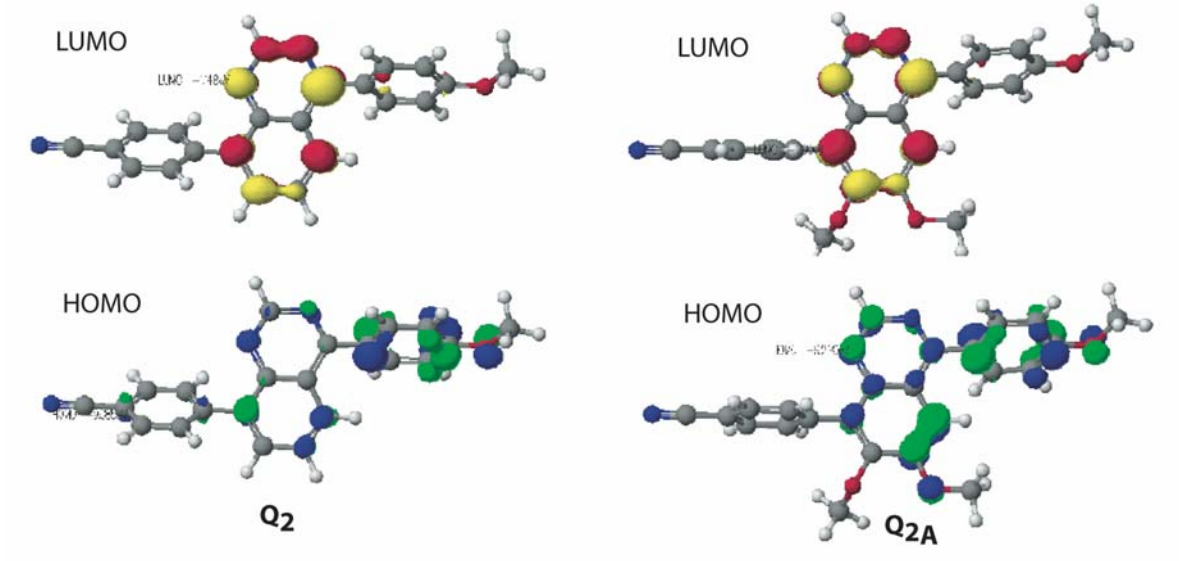
Table 1 Theoretical data for **N**, **C** and **Q** type molecules :

Structure	λ_{max}^{th} (nm)	f	$\Delta\mu$ (D)	β_0^{th} (10^{-30} esu)
PNA	310	0.6	6.8	8
$\mathbf{N_1}$	358	0.7	5.9	12
$\mathbf{C_1}$	349	0.8	6.1	14
$\mathbf{Q_1}$	347	0.7	3.5	9
$\mathbf{Q_{1A}}$	371	0.6	3.3	14

N_2	357	0.8	4.8	10
C_2	348	0.8	5.2	11
Q_2	333	0.8	3.9	7
Q_{2A}	362	0.6	2.7	10
N_3	383	0.7	9.0	16
Q_3	334	0.6	11	11
Q_{3A}	367	0.7	4.2	19

Maximum absorption wavelength ($\lambda_{\max}^{th}$) oscillator strength of the transition (f), dipole moment difference (Δμ) between the ground and the first excited charge transfer states, and first-order hyperpolarizability (β_{th}^{0}).

The weak effect of acceptor groups on NLO properties is illustrated by the vizualization of the HOMO-LUMO transition for molecules **Q_2** and **Q_{2A}** (Scheme 2), which highlights a main transfer transition between the donor and the quinazoline moiety, while the CN acceptor group is weakly involved in the charge transfer .

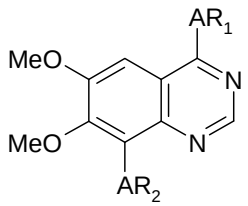


Scheme 2

For same A and D groups, the most efficient family is **Q_A**. An increase of β values is obtained for this family with respect of values calculated for the **Q** serie ; β values of 9 (14), 7 (14) and 11 (19) 10^{-30} esu are obtained for **Q_1** (**Q_{1A}**), **Q_2** (**Q_{2A}**) and **Q_3** (**Q_{3A}**) respectively, with a red shift of the lowest excited state *i.e.* 347 (371), 333 (362), 334 (367) nm for $\lambda_{\max}^{th}$ and a decrease of $\Delta\mu$ values as 3.5 (3.3), 3.9 (2.7) and 11.0 (4.2) D. Both methoxy groups at 6 and 7 positions of the quinazoline part influence significantly the

charge transfer, as presented on Scheme 2 from the comparison between HOMO-LUMO transitions in **Q_2** and **Q_{2A}** molecules, which shows that the HOMO molecular orbital is especially affected by methoxy groups.

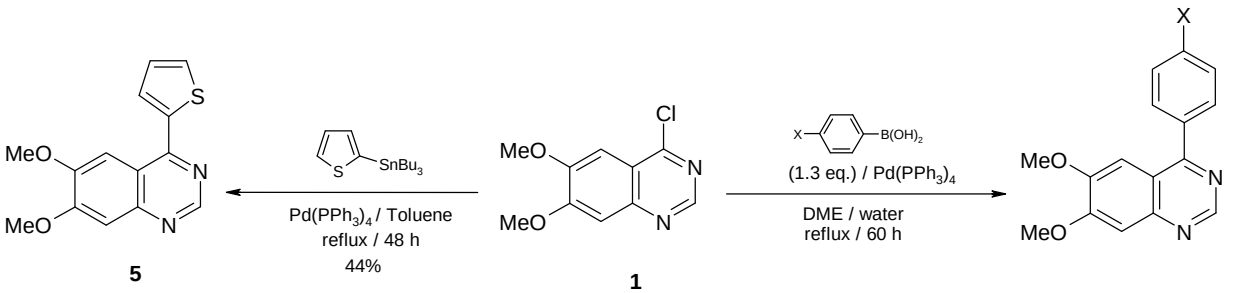
These preliminar theoretical calculations allowed us to establish that structures with naphthalene (**N**) or cinnoline (**C**) core present similar first-order hyperpolarizabilities (β_0), better than for quinazoline (**Q**). More interestingly, the presence of two methoxy groups at 6 and 7 positions improves significantly the first-order hyperpolarizability in quinazoline series. These results urged us to synthesize various 6,7-dimethoxy-4,8-diarylquinazolines (Scheme 3).



Scheme 3

Starting from 4-chloro-6,7-dimethoxyquinazoline **1**,[10] through using a synthetic route previously described by us,[11] we accessed to several new 4,8-di(hetero)arylquinazolines.

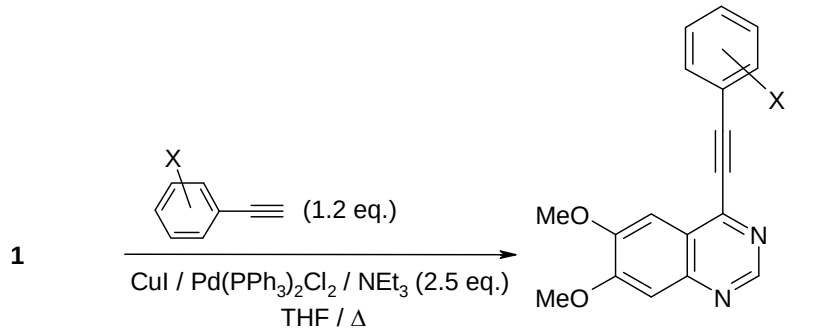
A first cross-coupling reaction of various 4-substituted arylboronic acids carried out in dimethoxyethane as solvent with **1** afforded the expected 4-aryl-6,7-dimethoxyquinazolines **2-4** in good yield. Under the same experimental conditions, this reaction failed with 2-thienylboronic acid. When the cross-coupling was performed under Stille conditions with 2-tributylstannylthiophene in toluene, compound **5** was obtained in moderate yield (Scheme 4)



Scheme 4

With the aim to introduce an ethynylbenzene, we performed a Sonogashira cross-coupling reaction of compound **1** with several substituted arylacetylenes. In order, to determine the best experimental conditions we varied the reaction conditions of **1** with phenylacetylene, the expected compound **6** was obtained in good yield when the coupling reaction was carried out with 3 mol % of $Pd(PPh_3)_2Cl_2$, 3

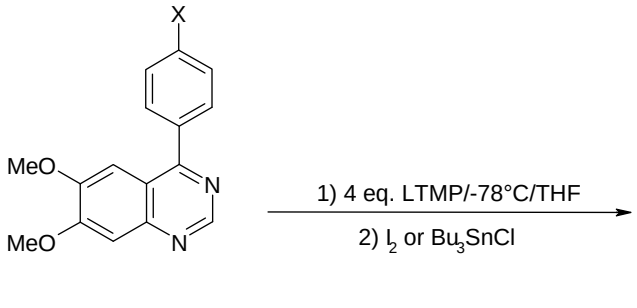
mol % of CuI, and 2.5 equiv. of triethylamine in THF under reflux for 20 h. These conditions were extended to other arylacetylenes to give compounds **7- 9** (Scheme 5).



6 X = H 93%
7 X = *p*-NMe_2 92%
8 X = *p*-OMe 78%
9 X = 2,4 F 21%

Scheme 5

In order to lithiate at the C_8 position the benzene moiety of quinazolines, compounds **2-5** were reacted with lithium tetrametylpiperidide (LTMP), then a further reaction of the lithio derivative with iodine or with tributyltin chloride as the electrophile was performed. Compound **2** gave the 8-substituted derivatives **10-11**, and compound **3** led to **12**, in good yields (Scheme 6).

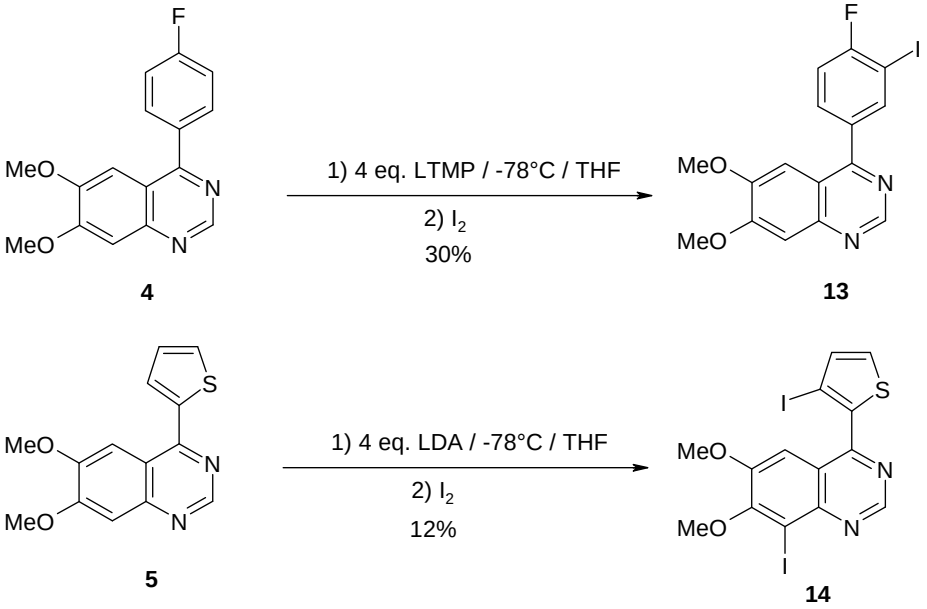


10 X = OMe E = I 80%
11 X = OMe E = $SnBu_3$ 92%
12 X = NMe_2 E = I 75%

Scheme 6

When iodine was used as the electrophile, unexpected results were observed with compounds **4** and **5**. For compound **4** bearing a fluorine atom on the phenyl group**,** iodination occurred exclusively at the *ortho* position of the fluorine atom leading to compound **13** in low yield. It could be assumed that the associated electron-withdrawing effects of the diazine moiety and fluorine makes hydrogen H_3 of the phenyl group sufficiently acidic to be deprotonated by LTMP. With the compound **5**, when LTMP was used as metallating agent, an unseparable mixture of polyiododerivatives, was obtained. With a base such as the lithium diisopropylamide (LDA), less basic than LTMP, we observed a simultaneous iodination at the 8 position of the quinazoline and at the C_3 position of the thiophene moiety leading to compound **14** in very

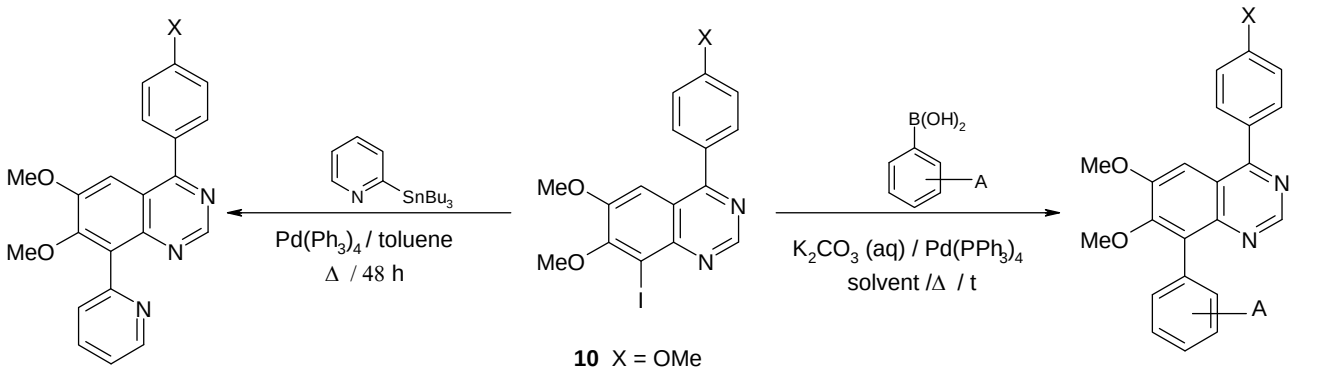
low yield (Scheme 7). As previously, the competitive deprotonation on the benzene and the thiophene ring results from the strong electron-withdrawing effect of the diazine moiety, allowing an unusual lithiation of the thiophene moiety.



Scheme 7

It could be also noticed that all attempts using this method to introduce an iodine atom at the C_8 position of compounds **6**-**9** failed.

To synthesize 4,8-diarylquinazolines, a subsequent Suzuki cross-coupling reaction was carried out with iodo compounds **10** and **12** and several phenylboronic acids bearing an electronwithdrawing group, affording compounds **15**-**20** in moderate to good yields. When the Stille coupling reaction was performed with 2-tributylstannylpyridine, compounds **19** and **20** were obtained (Scheme 8).



Scheme 8

Using metallation and cross-coupling reactions we have reported the synthesis of six new 4,8-di(hetero)arylquinazolines of a high thermal stability particularly for molecules **15-19**, which present melting points at 176-222 °C (Table 2).

Table 2 Melting points (T) for molecules **15-20**

Compound	**15**	**16**	**17**	**18**	**19**	**20**
T (°C)	215	210	199	222	176	137

Theoretical NLO properties could be compared for five compounds (**15**, **16**, **18-20**), as shown in Table 3. Molecules **16** and **18** are the most efficient.

Table 3 Theoretical NLO properties for **15**, **16**, **18-20**

Compound	λ_{max}^{th} (nm)	f	$\Delta\mu$ (D)	β_0^{th} (10^{-30} esu)
PNA	310	0.6	6.8	8
15 (**Q_{2A}**)	362	0.6	2.7	14
16 (**Q_{3A}**)	367	0.7	4.2	19
18	367	0.6	3.8	19
19	358	0.5	3.4	12
20	361	0.6	3.7	13

Maximum absorption wavelength (λ_{max}^{th}), oscillator strength of the transition (f), dipole moment difference ($\Delta\mu$) between the ground and the first excited charge transfer states, and first-order hyperpolarizability (β_{th}^{0}).

Although these calculations have been already validated on polyenic systems by comparison with experimental data,[9,12] the reliability of the procedure was assessed by comparison of the computed wavelength (λ_{max}) and first-order hyperpolarizability (β_0^{th}) of **PNA**, **Q_2** and the molecule **19** with experimental (EFISH) measurements (Table 4). Experimental results are in good agreement with computed data.

Table 4 Theoretical and experimental NLO data for **PNA**, $\mathbf{Q_{2A}}$ and compounds **18-20.**

Compound	λ_{max}^{exp}	λ_{max}^{th}	f	μ	$\mu\beta_{\hbar\omega}^{exp}$ ($\hbar\omega$)	$\mu\beta_0^{exp}$	$\mu\beta_0^{th}$	β_0^{th}
PNA[13]	321	310	0.6	8.2	103 (1.17 eV)	59	66	8
$\mathbf{Q_{2A}}$	329	362	0.6	8.7	125 (0.65 eV)	107	101	10
18	397	367	0.6	11.3	110 (0.65 eV)	87	207	19
19	342	358	0.5	5.0	90 (0.65 eV)	75	34	12
20	375	361	0.6	5.6	50 (0.65 eV)	41	63	13

Theoretical and experimental maximum absorption wavelength (λ_{max}^{th} and λ_{max}^{exp}) in nm, theoretical oscillator strength of the transition (f), theoretical ground state dipole moment μ in D, and theoretical first-order hyperpolarizability β_0^{th} in 10^{-30} esu and experimental (theoretical) scalar product μβ ($\mu\beta_{\hbar\omega}^{exp}$ at the applied energy laser $\hbar\omega$ and the static $\mu\beta_0^{exp}$ ($\mu\beta_0^{th}$)) in 10^{-48} esu.

CONCLUSION

The aim of this work was to predict and understand the first hyperpolarisability value (β) of new conjugated systems based on naphthalene (**N**), cinnoline (**C**) and quinazoline (**Q**) moieties; quadratric NLO properties of these disubstituted systems at 1/5 or 1/8 positions by benzene rings bearing standard electron-donating or withdrawing groups were evaluated theoretically in good agreement with some experimental EFISH data. The higher efficiency of the $\mathbf{Q_A}$ serie was predicted with a weak influence of the acceptor used for calculations, while the nature of donor substituents play a more significant role in the value of the hyperpolarisability value β.

Using metallation and cross-coupling reactions we described the synthesis of six new compounds with the quinazoline $\mathbf{Q_A}$, as a new charge transfer system. The hyperpolarisabilty value β was calculated for all these new compounds and was measured for some of these systems using the EFISH method. The main conclusions of this work can be summarized as follows: (i) although selected molecules for synthesis were not optimized in terms donor and acceptor for high β values, these quinazoline derivatives present quadratic hyperpolarisabilities higher than that of *p*-nitroaniline, in spite of significant torsional angles (~60°) between the π-system and donor or acceptor groups; (ii) these molecules offer some advantages, which could make them good candidates for NLO materials : they present a high thermal stability (melting points at 137-222 °C), and most efficient systems are accessible in fair yields. Futhermore, these molecules can be suitably functionalized at the methoxy place to be used for NLO applications.

EXPERIMENTAL

The geometry of molecules was optimized by using Sybyl, i.e. Tripos force field and PM3 from MOPAC package.[14] For each molecule, different electronic state features, i.e. singlet-state energies and dipoles moments, were obtained by a configuration interaction (CI) procedure based on the CNDO/S method using the QCPE program #382.[15] The energies of the excited states were evaluated by configuration interactions restricted to 50-100 lowest states, until convergence of the hyperpolarisability value was obtained.

For comparison of molecules without resonance effects, the static (at $\hbar\omega = 0$) first-order hyperpolarizability (β_0^{th}) was calculated from equations derived from the Ward perturbation theory.[16] β_{ijk} components of the tensor and the *x*, *y* and *z* components were calculated using the realtionship (2):

$$\beta_i = \beta_{iii} + \sum_{i \neq j} ((\beta_{ijj} + 2\beta_{jii})/3 \quad i = x, y, z \qquad (2)$$

For comparison with EFISH data (described below), the product $\mu\beta_0^{th}$ was calculated from the relation (3).[9]

$$\beta^{th} = \frac{\beta_x\mu_x + \beta_y\mu_y + \beta_z\mu_z}{\|\mu\|} \qquad (3)$$

The experimental quadratic hyperpolarizability was determinated by using the well-known EFISH (Electric Field Induced Second Harmonic) method.[3a] The set-up, which was previously described,[17] consisted in a *Q*-switched Nd:YAG laser pumping a Raman cell to create the operating wavelength at 1.907 μm ($\hbar\omega = 0.65$ eV) ; this method allows to measure the product $\mu\beta$ at the applied laser energy $\hbar\omega$. The static value $\mu\beta_0^{\exp}$ was determinated from the dispersion relation (4) deduced directly from the two-level equation (1):

$$\beta_{\hbar\omega}^{\exp} = \beta_0^{\exp} f(W,\omega) \qquad (4)$$

in which $f(W,\omega)$ is the dispersion factor with $f(W,\omega) = \frac{1}{\left[1-(2\hbar\omega/W)^2\right]\left[1-(\hbar\omega/W)^2\right]}$.

General:

Melting points were determined on a Kofler hot-stage. The ^{1}H, ^{13}C and ^{19}F spectra were recorded on a Bruker AC 300 (300 MHz ^{1}H, 75 MHz ^{13}C, 282 MHz ^{19}F) instrument. Microanalyses were performed on

a Carlo Erba CHNOS 1160 apparatus. The IR spectra were obtained as potassium bromide pellets with a Perkin-Elmer Paragon 500 spectrophotometer.

All reagents were of commercial quality and were purchased from Acros, Aldrich Chemical Co. or Avocado. The Pd(0)-catalyst $Pd(PPh_3)_4$ was prepared according to the literature.[18] 4-Trifluoromethyl-, 4-methoxyphenyl-, 4-*N*,*N*-dimethylaminophenyl- and 4-cyanophenylboronic acids were synthesized by halogen-metal exchange followed by reaction with trimethylborate or triisopropylborate from the commercially available 1-bromo-4-trifluoromethylbenzene, 4-bromoanisole, 4-bromo-*N*,*N*-dimethylaniline or 4-bromobenzonitrile.

Procedure A for direct lithiation by lithium alkylamide.

A solution of *n*-BuLi (1.6 M or 2.5 M in hexane) was added to cold (-50 °C), stirred and anhydrous THF (15 mL) under an atmosphere of dry nitrogen. Then 2,2,6,6-tetramethylpiperidine (TMPH) or diisopropylamine (LDAH) was added. The mixture was warmed to 0 °C. After 20 min, the temperature was lowered to -78 °C and the substrate dissolved in 5 mL of THF was added. After a time t_1 at temperature T_1, the electrophile was introduced and stirring was continued for a time t_2 at T_2. Hydrolysis was then carried out using a mixture of EtOH and water (5/5). When the electrophile was iodine, the solution was decolorized with sodium thiosulfate. After concentration, the residue was extracted with CH_2Cl_2 or EtOAc (3x15 mL). The combined organic extracts were dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

Procedure B for cross-coupling of arylboronic acids with heteroaryl halide under Suzuki conditions.

A mixture of the heteroaryl halide (2 mmol), the arylboronic acid (1.3 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), aqueous 2M K_2CO_3 (2 equiv.) and degassed DME (12 mL) and H_2O (3 mL) or EtOH (1 mL) in degassed toluene (15 mL) was heated under reflux and under nitrogen for 15-48 h. The reaction mixture was cooled, diluted with 15 mL of water and CH_2Cl_2 (1/1) and the organic layers separated. The aqueous layer was extracted with CH_2Cl_2 (3x15 mL), the combined organic extracts were dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

Procedure C for cross-coupling of heteroaryl halides with tributylstannylheteroarene under Stille conditions.

A solution of tributylstannylheteroarene, aryl halide (0.8 equiv.) and $Pd(PPh_3)_4$ (0.05 equiv.) in degassed toluene (15 mL) was heated under reflux under nitrogen atmosphere for a time *t*. After cooling, a mixture of water (10 mL) and CH_2Cl_2 (10 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3x20 mL). The combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

Procedure D for cross-coupling of heteroaryl halides with arylacetylenes.

Triethylamine (0.69 mL, 5 mmol) was added to a mixture of arylacetylene (1.2 equiv.), 4-chloro-6,7-dimethoxyquinazoline **1**,[10] (450 mg, 2 mmol), bis(triphenylphospine)palladium (II) dichloride (42 mg, 0.06 mmol), copper(I) iodide (12 mg, 0.06 mmol) and 30 mL THF in a round-bottom flask under an atmosphere of dry nitrogen at rt. The reaction mixture was stirred at 65 °C for 20 h. After cooling, water (10 mL) and CH_2Cl_2 (10 mL) were added. The aqueous phase was extracted with CH_2Cl_2 (3x20 mL). The combined organic extracts were washed with water (10 mL) then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

6,7-Dimethoxy-4-(4'-methoxyphenyl)quinazoline (2)[11]

Coupling reaction of 4-methoxyphenylboronic acid (1.4 equiv.) with **1**[10] (450 mg, 2 mmol) according to the general procedure **B** (toluene, *t* = 38 h) gave after purification by column chromatography (silica gel, eluent : EtOAc) 580 mg 98%) of **2** as a pale yellow solid, mp 144-145 °C; ^{1}H NMR ($CDCl_3$): δ 9.12 (s, 1H, H_2); 7.72 (d, *J* = 8.4 Hz, 2H, H_{Ph}); 7.33,7.32 (2s, 2H, H_5, H_8); 7.05 (d, *J* = 8.4 Hz, 2H, H_{Ph}); 4.03 (s, 3H, OMe); 3.88, 3.87 (2s, 6H, 2 OMe); ^{13}C NMR ($CDCl_3$) : δ 165.3 (C_4), 155.6 (C_6), 154.0 (C_2), 151.8 ($C_{4'}$), 150.2 (C_7), 149.4 (C_{8a}), 131.3 ($C_{2'}$,$C_{6'}$), 125.4 ($C_{1'}$), 118.8 (C_{4a}), 112.1 ($C_{3'}$,$C_{5'}$), 107.3 (C_8), 105.0 (C_5), 56.7 (OMe), 56.4 (OMe), 40.6 (NMe_2). Anal. Calcd for $C_{17}H_{16}N_2O_3$ (296.33): C, 68.91; N, 9.45; H, 5.44. Found: C, 68.65; N, 9.41; H, 5.31.

6,7-Dimethoxy-4-(4'-*N*,*N*-dimethylaminophenyl)quinazoline (3)

Coupling reaction of 4-*N*,*N*-dimethylaminophenylboronic acid (1.3 equiv.) with **1**[10] (450 mg, 2 mmol) according to the general procedure **B** (toluene, *t* = 40 h) gave after purification by column chromatography (silica gel, eluent : EtOAc) 510 mg (94%) of **3** as an orange solid, mp 181-182 °C; ^{1}H NMR ($CDCl_3$) : δ 9.11 (s, 1H, H_2); 7.75 (d, *J* = 8.7 Hz, 2H, $H_{2'/6'}$); 7.50 (s, 1H, H_5); 7.34 (s, 1H, H_8); 6.84 (d, *J* = 8.7 Hz, 2H, $H_{3'/5'}$); 4,06 (s, 3H, OMe); 3.93 (s, 3H, OMe); 3.06 (s, 6H, NMe_2); ^{13}C NMR ($CDCl_3$) : δ 165.3 (C_4), 155.6 (C_6), 154.0 (C_2), 151.8 ($C_{4'}$), 150.2 (C_7), 149.4 (C_{8a}), 131.3 ($C_{2'}$,$C_{6'}$), 125.4 ($C_{1'}$), 118.8 (C_{4a}), 112.1 ($C_{3'}$,$C_{5'}$), 107.3 (C_8), 105.0 (C_5), 56.7 (OMe), 56.4 (OMe), 40.6 (NMe_2). Anal. Calcd for $C_{18}H_{19}N_3O_2$ (309.37): C, 69.88; N, 13.58; H, 6.19. Found: C, 69.84; N, 13.54; H, 6.26.

6,7-Dimethoxy-4-(4'-fluorophenyl)quinazoline (4)

Coupling reaction of 4-fluorophenylboronic acid (1.3 equiv.) with **1**[10] (450 mg, 2 mmol) according to the general procedure **B** (toluene, *t* = 40 h) gave after purification by column chromatography (silica gel, eluent : EtOAc /petroleum ether (6/4)) 472 mg (83%) of **4** as a yellow solid, mp 201-202 °C; ^{1}H NMR ($CDCl_3$): δ 9.18 (s, 1H, H_2); 7.78 (q, *J* = 8.7 and 5.6 Hz, 2H, $H_{2'/6'}$); 7.39 (s, 1H, H_5); 7.27 (m, 3H, $H_{8/3'/5'}$); 4.08 (s, 3H, OMe); 3.91 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$) δ 165.5 (d, *J* = 427.5 Hz, $C_{4'}$), 162.2 (C_4), 156.0

(C_6), 153.8 (C_2), 150.7 (C_7), 149.4 (C_{8a}), 133.9 ($C_{1'}$), 131.6 (d, J = 31.8 Hz, $C_{2'}$,$C_{6'}$), 118.8 (C_{4a}), 116.1 (d, J = 86.6 Hz, $C_{3'}$,$C_{5'}$), 107.3 (C_8), 103.7 (C_5), 56.7 (OMe), 56.3 (OMe); ^{19}F NMR ($CDCl_3$) δ –111.2. Anal. Calcd for $C_{16}H_{13}FN_2O_2$ (284.29) C, 67.60, N, 9.85, H, 4.61. Found C, 67.32, N, 9.81, H, 4.65.

6,7-Dimethoxy-4-(2'-thienyl)quinazoline (5)

Coupling reaction of 2-tributylstannylthiophene[19] (1.3 equiv.) with **1**[10] (450 mg, 2 mmol) according to the general procedure **C** (toluene, t = 48 h) gave after purification by column chromatography (silica gel, eluent : EtOAc) 479 mg (44%) of **5** as a yellow solid, mp 140-141 °C; ^{1}H NMR ($CDCl_3$): δ 9.10 (s, 1H, H_2); 7.81 (d, J = 3.4 Hz, 1H, $H_{5'}$); 7.74 (s, 1H, H_5); 7.63 (d, J = 5.3 Hz, 1H, $H_{4'}$); 7.36 (s, 1H, H_8); 7.26 (m, 1H, $H_{3'}$); 4.08 (s, 3H, OMe); 4.02 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$) δ 156.8 (C_4), 155.4 (C_6), 153.0 (C_2), 150.5 (C_{ar}), 149.2 (C_{ar}), 141.3 (C_{ar}), 131.9 (CH_{ar}), 129.7 (CH_{ar}), 127.9 (CH_{ar}), 117.1 (C_{4a}), 106.9 (C_8), 103.0 (C_5), 56.1 (OMe), 55.9 (OMe). Anal. Calcd for $C_{14}H_{12}N_2O_2S$ (272.33) C, 61.75, N, 10.29, H, 4.44, S, 11.77. Found C, 61.72, N, 10.25, H, 4.46, S, 11.29.

6,7-Dimethoxy-4-phenylethynylquinazoline (6)

Coupling reaction of phenylacetylene (0.26 mL, 1.2 equiv.) with **1** (450 mg, 2 mmol) according to the general procedure **D** gave after purification by column chromatography (silica gel, eluent : EtOAc / petroleum ether (6/4)) 540 mg (93%) of **6** as an orange solid, mp 146-147 °C; ^{1}H NMR ($CDCl_3$): δ 9.10 (s, 1H, H_2); 7.68 (m, 2H, $H_{2'/6'}$); 7.53 (s, 1H, H_8); 7.42 (m, 3H, $H_{3''/4''/5''}$); 7.30 (s, 1H, H_5); 4.08 (s, 3H, OMe); 4.02 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$) δ 156.6 (C_6 or C_7), 153.8 (C_2), 151.2 (C_6 or C_7), 148.8 (C_4), 148.4 (C_{8a}), 132.5 ($C_{2'}$,$C_{6'}$), 130.2 ($C_{4'}$), 128.8 ($C_{3'}$,$C_{5'}$), 121.7 (C_{4a}), 121.5 ($C_{1'}$), 106.9 (C_5), 103.3 (C_8), 97.9 (C_β), 85.5 (C_α), 56.7 (OMe), 56.3 (OMe). MS (CI) m/z 291 MH^+, 100). Anal. Calcd for $C_{18}H_{14}N_2O_2$ (290.32) C, 74.47, N, 9.65, H, 4.86. Found C, 74.32, N, 9.81, H, 4.85.

6,7-Dimethoxy-4-(4'-*N*,*N*-dimethylaminophenyl)ethynylquinazoline (7)

Coupling reaction of 4-*N*,*N*-dimethylaminophenylphenylacetylene (348 mg, 1.2 equiv.) with **1** (450 mg, 2 mmol) according to the general procedure **D** gave after purification by column chromatography (silica gel, eluent : EtOAc /petroleum ether (6/4)) 613 mg (92%) of **7** as an orange solid, mp 228-229 °C; ^{1}H NMR ($CDCl_3$): δ 9.08 (s, 1H, H_2); 7.60-7.56 (m, 3H, $H_{8/2'/6'}$); 7.30 (s, 1H, H_5); 6.70 (d, J = 8.7 Hz, 2H, $H_{3'/5'}$); 4.11 (s, 3H, OMe); 4.07 (s, 3H, OMe);3.05 (s, 6H, NMe_2); ^{13}C NMR ($CDCl_3$): δ 156.6 (C_6 or C_7), 153.7 (C_2), 151.1 ($C_{4'}$), 150.6 (C_6 or C_7), 149.5 (C_4), 147.8 (C_{8a}), 133.9 ($C_{2'}$,$C_{6'}$), 121.4 (C_{4a}), 111.6 ($C_{3'}$,$C_{5'}$), 107.2 ($C_{1'}$), 106.6 (C_5), 103.6 (C_8), 101.2 (C_β), 84.9 (C_α), 56.4 (OMe), 56.1 (OMe), 40.0 (NMe_2). Anal. Calcd for $C_{20}H_{19}N_3O_2$ (333.39) C, 72.05, N, 12.60, H, 5.74. Found C, 72.43, N, 11.97, H, 5.84.

6,7-Dimethoxy-4-(4'-methoxyphenyl)ethynylquinazoline (8)

Coupling reaction of 4-methoxyphenylphenylacetylene (318 mg, 1.2 equiv.) with **1** (450 mg, 2 mmol) according to the general procedure **D** gave after purification by column chromatography (silica gel, eluent : EtOAc /petroleum ether (6/4)) 500 mg (78%) of **8** as an orange solid, mp 154-155°C; ^{1}H NMR ($CDCl_3$): δ 9.07 (s, 1H, H_2); 7.61 (d, J = 8.7 Hz, 2H, $H_{2'/6'}$); 7.51 (s, 1H, H_8); 7.27 (s, 1H, H_5); 6.91 (d, J = 8.7 Hz, 2H, $H_{3'/5'}$); 4.07 (s, 3H, OMe); 4.04 (s, 3H, OMe); 3.82 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$): δ 161.4 ($C_{4'}$), 156.4 (C_6 or C_7), 153.9 (C_2), 151.1 (C_6 or C_7), 149.2 (C_{8a}), 148.3 (C_4), 134.2 ($C_{2'}$, $C_{6'}$), 121.4 (C_{4a}), 114.5 ($C_{3'}$, $C_{5'}$), 113.4 ($C_{1'}$), 106.9 (C_5), 103.5 (C_8), 98.7 (C_β), 84.9 (C_α), 56.6 (OMe), 56.3 (OMe), 55.5 (OMe). MS (CI) *m/z* 321 (MH^+, 100). Anal. Calcd for $C_{19}H_{16}N_2O_3$ (320.35) C, 71.24, N, 8.74, H, 5.03. Found C, 71.60, N, 8.17, H, 5.47.

6,7-Dimethoxy-4-(2',4'-difluorophenyl)ethynylquinazoline (9)

Coupling reaction of 2,4-difluorophenylphenylacetylene (166 mg, 1.2 equiv.) with **1** (450 mg, 2 mmol) according to the general procedure **D** gave after purification by column chromatography (silica gel, eluent : EtOAc /petroleum ether (6/4)) and recristallization in EtOAc 137 mg (21%) of **9** as a beige solid, mp 228-229 °C; ^{1}H NMR ($CDCl_3$): δ 9.14 (s, 1H, H_2); 7.68 (m, 2H, $H_{6'/8}$); 7.33 (s, 1H, H_5); 7.00-6.93 (m, 2H, $H_{3'/5'}$);4.10 (s, 3H, OMe); 4.08 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$): δ 165.8 (m, $C_{C\text{-}F}$), 162.4 (m, $C_{C\text{-}F}$), 156.7 (C_6 or C_7), 153.9 (C_2), 151.5 (C_6 or C_7), 148.5 (C_4), 148.4 (C_{ar}), 135.1 (d, J = 34.6 Hz, $C_{6'}$), 127.4 (C_{ar}), 121.8 (C_{4a}), 112.5 (dd, J = 86.7 et 14.4 Hz, $C_{5'}$), 106.9 (C_5), 104.8 (t, J = 101.1 Hz, $C_{3'}$), 103.5 (C_8), 90.3 (C_β), 82.4 (C_α), 56.7 (OMe), 56.4 (OMe); ^{19}F NMR ($CDCl_3$): δ –103.5 (d, J = 9.2 Hz, 1F), –105.0 (d, J = 10.3 Hz, 1F). Anal. Calcd for $C_{18}H_{12}F_2N_2O_3$ (326.31) C, 66.26, N, 8.59, H, 3.71. Found C, 66.60, N, 8.44, H, 3.31.

6,7-Dimethoxy-8-iodo-4-(4'-methoxyphenyl)quinazoline (10)

Metallation of **2** (100 mg, 0.34 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.86 mL), TMPH (4.1 equiv., 0.24 mL) in anhydrous THF (15 mL) at T = –78 °C followed by reaction with iodine (2.5 equiv., 215 mg) in solution with anhydrous THF (10 mL), t = 2 h, gave after purification by column chromatography (silicagel, eluent: EtOAc /petroleum ether (6/4)) 119 mg (80%) of **10** as a beige solid, mp 154-155 °C; ^{1}H NMR ($CDCl_3$): δ 9.30 (s, 1H, H_2); 7.74 (d, J = 8.8 Hz, 2H, $H_{2'/6'}$); 7.45 (s, 1H, H_5); 7.08 (d, J = 8.8 Hz, 2H, $H_{3'/5'}$); 4.02 (s, 3H, OMe); 3.91 (s, 6H, 2 OMe); ^{13}C NMR ($CDCl_3$): δ 166.3 (C_4), 161.4 ($C_{4'}$), 156.9 (C_6 or C_7), 154.3 (C_2), 153.2 (C_6 or C_7), 148.1 (C_{8a}), 131.5 ($C_{2'}$,$C_{6'}$), 129.7 ($C_{1'}$), 121.5 (C_{4a}), 114.4 ($C_{3'}$, $C_{5'}$), 106.1 (C_5), 98.0 (C_8), 61.1 (OMe), 56.4 (OMe), 55.7 (OMe). Anal. Calcd for $C_{17}H_{15}INO_2$ (422.22) C, 48.36, N, 6.63, H, 3.58. Found C, 48.36, N, 6.53, H, 3.82.

6,7-Dimethoxy-4-(4'-methoxyphenyl)-8-tributylstannylquinazoline (11)

Metallation of **2** (100 mg, 0.34 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.86

mL), TMPH (4.1 equiv., 0.24 mL) in anhydrous THF (15 mL) at T = –78 °C followed by reaction with tri-*n*-butyltin chloride (2.5 equiv., 0.023 mL) in solution with anhydrous THF (10 mL), *t* = 1 h, gave after purification by column chromatography (silicagel, eluent: EtOAc /petroleum ether (2/8)) 183 mg (92%) of **11** as a pale yellow solid, mp 57-58 °C; ^{1}H NMR ($CDCl_3$): δ 9.12 (s, 1H, H_2); 7.76 (d, *J* = 8.7 Hz, 2H, $H_{2'/6'}$); 7.38 (s, 1H, H_5); 7.08 (d, *J* = 8.7 Hz, 2H, $H_{3'/5'}$); 3.92 (s, 3H, OMe); 3.90 (s, 3H, OMe) 1.55 (m, 6H, 3 CH_2 $_{SnBu3}$); 1.29 (2m, 12H, 6 CH_2 $_{SnBu3}$); 0.87 (t, *J* = 7.1-7.6 Hz, 9H, 3 CH_3 $_{SnBu3}$); ^{13}C NMR ($CDCl_3$): δ 164.6 (C_4), 160.4 ($C_{4'}$), 160.3 (C_7), 153.1 (C_6), 152.3 (C_{8a}), 151.9 (C_2), 135.4 (C_8), 130.7 ($C_{2'}$,$C_{6'}$), 130.2 ($C_{1'}$), 120.7 (C_{4a}), 113.6 ($C_{3'}$,$C_{5'}$), 105.4 (C_5), 60.8 (OMe), 57.1 (OMe), 54.9 (OMe) 28.9 (3 CH_2 $_{SnBu3}$), 27.0 (3 CH_2 $_{SnBu3}$), 13.3 (3 CH_3 $_{SnBu3}$), 11.6 (3 CH_2 $_{SnBu3}$). Anal. Calcd for $C_{29}H_{42}N_2O_3Sn$ (585.36) C, 59.51, N, 4.79, H, 7.23. Found C, 59.36, N, 4.67, H, 7.38.

6,7-Dimethoxy-8-iodo-4-(4'-*N*,*N*-dimethylaminophenyl)quinazoline (12)

Metallation of **3** (100 mg, 0.33 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.86 mL), TMPH (4.1 equiv., 0.24 mL) in anhydrous THF (15 mL) at T = –78 °C followed by reaction with iodine (2.5 equiv., 215 mg) in solution with anhydrous THF (10 mL), *t* = 2 h, gave after purification by column chromatography (silicagel, eluent: EtOAc /petroleum ether (6/4)) 108 mg (75%) of **12** as an orange solid, mp 202-203 °C; ^{1}H NMR ($CDCl_3$): δ 9.22 (s, 1H, H_2); 7.71 (d, *J* = 8.7 Hz, 2H, $H_{2'/6'}$); 7.55 (s, 1H, H_5); 6.80 (d, *J* = 8.7 Hz, 2H, $H_{3'/5'}$); 3.98 (s, 3H, OMe); 3.89 (s, 3H, OMe); 3.04 (s, 6H, NMe_2); ^{13}C NMR ($CDCl_3$): δ 166.8 (C_4), 156.8 (C_6), 154.6 (C_2), 153.1 ($C_{4'}$), 152.0 (C_7), 148.3 (C_{8a}), 131.7 ($C_{2'}$ or $C_{6'}$), 131.4 ($C_{2'}$ or $C_{6'}$), 124.8 ($C_{1'}$), 121.6 (C_{4a}), 112.5 ($C_{3'}$ or $C_{5'}$), 112.2 ($C_{3'}$ or $C_{5'}$), 106.9 (C_5), 98.1 (C_8), 61.2 (OMe), 56.5 (OMe), 40.6 (NMe_2). MS (CI) *m/z* 436 (MH^+, 100%), 422 (5%), 310 (MH^+ - I, 16%), 292 (4%). Anal. Calcd for $C_{18}H_{18}IN_3O_2$ (435.27) C, 49.67, N, 9.65, H, 4.17. Found C, 49.53, N, 9.69, H, 3.97.

6,7-Dimethoxy-4-(4'-fluoro-3'-iodophenyl)quinazoline (13)

Metallation of **4** (200 mg, 0.70 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 1.75 mL), TMPH (4.1 equiv., 0.48 mL) in anhydrous THF (15 mL) at T = –78 °C followed by reaction with iodine (2.5 equiv., 215 mg) in solution with anhydrous THF (10 mL), *t* = 2 h, gave after purification by column chromatography (silicagel, eluent: EtOAc) 86 mg (80%) of **13** as an orange solid, mp 170-171 °C; ^{1}H NMR ($CDCl_3$): δ 9.16 (s, 1H, H_2); 8.20 (dd, *J* = 6.0 et 1.9 Hz, 1H, $H_{2'}$); 7.73 (m, 1H, $H_{6'}$); 7.38 (s, 1H, H_5); 7.24 (m, 1H, $H_{5'}$); 7.21 (s, 1H, H_8); 4.07 (s, 3H, OMe); 3.92 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$): δ 162.8 (d, *J* = 990 Hz, $C_{4'}$), 162.4 (C_4), 156.1 (C_6), 153.2 (C_2), 150.9 (C_7), 149.5 (C_{8a}), 141.0 (d, *J* = 8.9 Hz, $C_{2'}$), 135.8 (d, *J* = 14.4 Hz, $C_{1'}$), 131.5 (d, *J* = 31.8 Hz, $C_{6'}$), 118.9 (C_{4a}), 116.2 (d, *J* = 98.2 Hz, $C_{5'}$), 107.5 (C_5), 103.5 (C_8), 82.2 (d, *J* = 104.0 Hz, $C_{3'}$), 56.9 (OMe), 56.7 (OMe); ^{19}F NMR

($CDCl_3$): δ -92.2.Anal. Calcd for $C_{16}H_{12}FIN_2O_3$ (410.19) C, 46.85, N, 6.83, H, 2.95. Found C, 47.21, N, 6.93, H, 2.87.

6,7-Dimethoxy-8-iodo-4-(2'-(3'-iodothienyl))quinazoline (14)

Metallation of **5** (136 mg, 0.50 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 1.25 mL), DIPAH (4.1 equiv., 0.28 mL) in anhydrous THF (15 mL) at T = –78 °C followed by reaction with iodine (2.5 equiv., 318 mg) in solution with anhydrous THF (10 mL), *t* = 2 h, gave after recrystallization 31 mg (12%) of **13** as an orange solid, mp 226-227°C; ^{1}H NMR ($CDCl_3$): δ 9.14 (s, 1H, H_2); 7.89 (d, *J* = 3.7 Hz, 1H, $H_{5'}$); 7.81 (s, 1H, H_5); 7.60 (d, *J* = 3.7 Hz, 1H, $H_{4'}$); 4.08 (s, 3H, OMe); 3.95 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$): δ 156.7 (C_{ar}), 156.5 (C_4), 153.4 (C_{ar}); 153.0 (C_2), 147.5 (C_{8a}), 146.2 ($C_{2'}$), 138.9 (CH_{ar}), 133.7 (CH_{ar}), 119.0 (C_{4a}), 105.0 (C_5), 98.7 (C_8), 84.7 ($C_{3'}$),56.1 (OMe), 55.9 (OMe). Anal. Calcd for $C_{14}H_{10}I_2N_2O_2S$ (524.12) C, 32.08, N, 5.34, H, 1.92, S, 6.12. Found C, 32.02, N, 5.32, H, 1.86, S, 6.05.

6,7-Dimethoxy-8-(4''-cyanophenyl)-4-(4'-methoxyphenyl)quinazoline (15)

Coupling of 4-cyanophenylboronic acid (1.3 equiv.) with **10** (844 mg, 2 mmol) according to the general procedure B (*t* = 40 h) gave after purification by column chromatography (silica gel, eluent EtOAc) 175 mg (22%) of **30** as a beige solid, mp 215-216 °C; ^{1}H NMR ($CDCl_3$): δ 9.42 (s, 1H, H_2); 7.79 (m, 4H, $H_{2'/6'/2''/6''}$); 7.62 (d, *J* = 8.3 Hz, 2H, $H_{3''/5''}$); 7.55 (s, 1H, H_5); 7.11 (d, *J* = 8.3 Hz, 2H, $H_{3'/5'}$); 3.96 (s, 3H, OMe); 3.92 (s, 3H, OMe); 3.74 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$): δ 165.9 (C_4), 161.5 ($C_{4'}$), 153.7 (C_2), 153.2 (C_6 or C_7), 153.1 (C_6 or C_7), 146.7, 139.4, 132.3, 131.9, 131.5, 130.6, 130.2, 121.2 (CN), 119.4 (C_{4a}), 114.6 ($C_{3'}$, $C_{5'}$), 111.7 ($C_{4''}$), 106.1 (C_5), 61.6 (OMe), 56.3 (OMe), 55.8 (OMe). MS (CI) *m/z* 397 ($MH^{+\cdot}$, 84%), 396 ($MH^{+\cdot}$- 1, 100%). Anal. Calcd for $C_{24}H_{19}N_3O_2$ (397.44) C, 72.53, N, 10.57, H, 4.82. Found C, 72.93, N, 10.22, H, 4.67.

6,7-Dimethoxy-8-(4''-cyanophenyl)-4-(4'-*N*,*N*-dimethylaminophenyl)quinazoline (16).

Coupling of 4-cyanophenylboronic acid (1.3 equiv.) with **12** (255 mg, 0.6 mmol) according to the general procedure B (*t* = 40 h) gave after purification by column chromatography (silica gel, eluent EtOAc) 172 mg (70%) of **16** as an orange solid, mp 210-211 °C; ^{1}H NMR ($CDCl_3$): δ 9.12 (s, 1H, H_2); 7.80 (m, 4H, $H_{2'/6'}$ and $2H_{PhCN}$); 7.67 (s, 1H, H_5); 7.62 (d, *J* = 8.3 Hz, 2H, $2H_{PhCN}$); 6.88 (d, *J* = 8.7 Hz, 2H, $H_{3'/5'}$); 3.98 (s, 3H, OMe); 3.72 (s, 3H, OMe); 3.10 (s, 6H, NMe_2); ^{13}C NMR ($CDCl_3$): δ 166.1 (C_4), 153.7 (C_2), 152.8 (C_6 or C_7), 152.6 (C_6 or C_7), 151.8 ($C_{4'}$), 146.6 (C_{8a}), 139.5 ($C_{1''}$), 132.2 (2 CH_{PhCN}), 131.8 (2 CH_{ar}), 131.3 (2 CH_{ar}), 130.4 (C_8), 124.9 ($C_{1'}$), 120.9 (C_{4a}), 119.3 (CN), 112.0 ($C_{3'}$, $C_{5'}$), 111.5 ($C_{4''}$), 106.5 (C_5), 61.4 (OMe), 56.2 (OMe), 40.4 (NMe_2). HRMS (FAB) calculated for $C_{25}H_{23}N_4O_2$: 411.1821. Found: 411.1808.

6,7-Dimethoxy-4-(4'-*N*,*N*-dimethylaminophenyl)-8-(4''-trifluoromethylphenyl)quinazoli-ne (17)

Coupling of 4-trifluoromethylphenylboronic acid (1.3 equiv.) with **12** (500 mg, 1.1 mmol) according to the general procedure B (*t* = 48 h) gave after purification by column chromatography (silica gel, eluent EtOAc) 229 mg (46%) of **17** as a yellow solid, mp 199-200 °C; ^{1}H NMR ($CDCl_3$): δ 9.11 (s, 1H, H_2); 7.77 (m, 4H, $H_{2'/6'/3''/5''}$); 7.65 (s, 1H, H_5); 7.61 (d, *J* = 8.3 Hz, 2H, $H_{2''/6''}$); 6.86 (d, *J* = 9 Hz, 2H, $H_{3'/5'}$); 3.96 (s, 3H, OMe); 3.69 (s, 3H, OMe); 3.08 (s, 6H, NMe_2); ^{13}C NMR ($CDCl_3$): δ 166.0 (C_4), 153.6 (C_2), 152.8 (C_{ar}), 152.7 (C_{ar}), 151.8 (C_{ar}), 146.8 (C_{8a}), 138.1 (C_{ar}), 131.7 (2 CH_{ar}), 131.3 (2 CH_{ar}), 131.0 (C_{ar}), 129.9 (C_{ar}), 129.5 (C_{ar}), 125.0 ($C_{1'}$, $C_{3''}$, $C_{5''}$), 120.9 (C_{4a}), 117.1 (CF_3), 112.0 ($C_{3'}$, $C_{5'}$), 106.1 (C_5), 61.4 (OMe), 56.2 (OMe), 40.4 (NMe_2); ^{19}F NMR ($CDCl_3$) : δ –62.9. Anal. Calcd for $C_{25}H_{22}F_3N_3O_2$ (453.47) C, 66.22, N, 9.27, H, 4.89. Found C, 66.19, N, 9.33, H, 4.89.

6,7-Dimethoxy-4-(4'-*N*,*N*-dimethylaminophenyl)-8-(3''-nitrophenyl)quinazoline (18)

Coupling of 3-nitromethylphenylboronic acid (1.3 equiv.) with **12** (600 mg, 1.37 mmol) according to the general procedure B (*t* = 48 h) gave after purification by column chromatography (silica gel, eluent EtOAc /petroleum ether (6/4)) 472 mg (80%) of **18** as an orange solid, mp 222-223 °C; ^{1}H NMR ($CDCl_3$): δ 9.12 (s, 1H, H_2); 8.40 (t, *J* = 1.5 Hz, 1H, $H_{2''}$); 8.30 (m, 1H, $H_{4''}$); 7.86 (dt, *J* = 7.9 and 1.5 Hz, 1H, $H_{6''}$); 7.59 (d, *J* = 9 Hz, 2H, $H_{2'/6'}$); 7.70-7.65 (m, 2H, $H_{5/5''}$); 6.88 (d, *J* = 9 Hz, 2H, $H_{3'/5'}$); 3.98 (s, 3H, OMe); 3.76 (s, 3H, OMe); 3.10 (s, 6H, NMe_2); ^{13}C NMR ($CDCl_3$): δ 166.1 (C_4), 153.7 (C_2), 152.8 (C_7), 152.7 (C_6), 151.8 ($C_{4'}$), 148.1 ($C_{3''}$), 146.6 (C_{8a}), 137.7 ($C_{6''}$), 135.9 ($C_{1''}$), 131.4 ($C_{2'}$, $C_{6'}$), 129.7 (C_8), 128.8 ($C_{5''}$), 126.6 ($C_{2''}$), 124.9 ($C_{1'}$), 122.7 ($C_{4''}$), 120.9 (C_{4a}), 112.0 ($C_{3'}$, $C_{5'}$), 106.6 (C_5), 61.5 (OMe), 56.2 (OMe), 40.4 (NMe_2). Anal. Calcd for $C_{24}H_{22}N_4O_4$ (430.47) C, 66.97, N, 13.02, H, 5.15. Found C, 66.72, N, 13.03, H, 5.11.

6,7-Dimethoxy-4-(4'-methoxyphenyl)-8-(2''-pyridyl)quinazoline (19).

Coupling reaction of 2-tributylstannylpyridine (1.2 equiv.) with **10** (844 mg, 2mmol) according to the general procedure **C** (toluene, *t* = 48 h) gave after purification by column chromatography (silica gel, eluent : EtOAc / CH_2Cl_2 (4/6)) 672 mg (90%) of **19** as an orange solid, mp 176-177 °C; ^{1}H NMR ($CDCl_3$): δ 9.15 (s, 1H, H_2); 8.81 (m, 1H, $H_{6''}$); 7.86 (td, *J* = 7.5 and 1.9 Hz, 1H, $H_{4''}$); 7.77 (m, 2H, $H_{2'/6'}$); 7.53 (s, 1H, H_5); 7.48 (dd, *J* = 7.5 and 1.2 Hz, 1H, $H_{3''}$); 7.37 (m, 1H, $H_{5''}$); 7.09 (m, 2H, $H_{3'/5'}$); 3.94 (s, 3H, OMe); 3.92 (s, 3H, OMe); 3.79 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$): δ 165.6 (C_4),161.3 ($C_{4'}$), 154.5 ($C_{2''}$), 153.7 (C_2 ,C_6 or C_7), 153.3 (C_6 or C_7), 149.7 ($C_{6''}$), 147.5 (C_{8a}), 136.3 ($C_{4''}$), 131.7 (C_{4a}), 131.5 ($C_{2'}$, $C_{6'}$), 130.4 (C_1), 126.5 ($C_{3''}$), 122.8 ($C_{5''}$), 121.0 (C_8), 114.4 ($C_{3'}$, $C_{5'}$), 105.9 (C_5), 62.0 (OMe), 56.3 (OMe), 55.7 (OMe). Anal. Calcd for $C_{22}H_{19}N_3O_3$ (373.42) C, 70.76, N, 11.25, H, 5.13. Found C, 71.05, N, 11.08, H, 5.01.

6,7-Dimethoxy-4-(4'-*N*,*N*-dimethylaminophenyl)-8-(2''-pyridyl)quinazoline (20).

Coupling reaction of 2-tributylstannylpyridine (1.2 equiv.) with **12** (262 mg, 0.6mmol) saccording to the general procedure **C** (toluene, t = 48 h) gave after purification by column chromatography (silica gel, eluent : EtOAc) 139 mg (60%) of **20** as an orange solid, mp 137-138 °C; ^{1}H NMR ($CDCl_3$): δ 9.06 (s, 1H, H_2); 8.76 (d, J = 4.1 Hz, 1H, $H_{6''}$); 7.80 (td, J = 7.5 and 1.9 Hz, 1H, $H_{4''}$); 7.73 (m, 2H, $H_{2'/6'}$); 7.61 (s, 1H, H_5); 7.44 (d, J = 7.9 Hz, 1H, $H_{3''}$); 7.31 (m, 1H, $H_{5''}$); 6.80 (m, 2H, $H_{3'/5'}$); 3.91 (s, 3H, OMe); 3.74 (s, 3H, OMe); 3.03 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$): δ 165.9 (C_4), 154.7 ($C_{2''}$), 153.8 (C_2), 153.4 (C_7), 152.9 (C_6), 151.8 ($C_{4'}$), 149.7 ($C_{6''}$), 147.4 (C_{8a}), 136.2 ($C_{4''}$), 131.5 (C_8), 131.4 ($C_{2'/6'}$), 126.5 ($C_{3''}$), 125.3 ($C_{1'}$), 122.7 ($C_{5''}$), 120.9 (C_{4a}), 112.1 ($C_{3'/5'}$), 106.5 (C_5), 61.9 (OMe), 56.3 (OMe), 40.5 (OMe). Anal. Calcd for $C_{23}H_{22}N_4O_2$ (386.46) C, 71.48, N, 14.50, H, 5.74. Found C, 71.85, N, 14.35, H, 5.95.

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