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Novel 6-substituted benzothiazol-2-yl indolo[1,2-*c*]quinazolines and benzimidazo[1,2-*c*]quinazolines

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Abstract—The synthetic route to and a preliminary biological evaluation of novel indolo[1,2-*c*]quinazolines (**8**) and benzimidazo[1,2-*c*]quinazolines (**9**) are described. The products were obtained by condensation of the appropriate diamines (e.g. 2-(2-aminophenyl)indole or 2-(2-aminophenyl)benzimidazole) with 2-cyanobenzothiazoles. This work further demonstrates the general applicability of microwaves for a facile and rapid access to original heterocycles with potential pharmaceutical value.

1. Introduction

The thiazole ring is present in various marine or terrestrial natural compounds and a number of structure-activity studies have been made to determine the essential structural requirements associated with its biological activity.[1] In connection with recent works on thiazoloacridines,[2] thiazoloquinolines[3] and substituted benzothiazoles,[4] we previously described the synthesis of new thiazole derivatives[5–9] derived from natural alkaloids extracted from marine organisms (e.g. dercitine and kuanoniamines[1,2]) or plants (e.g. ellipticine).[10] In these studies, our strategy consisted to combine the thiazole ring with various heterocyclic structures and some molecules showed interesting cytotoxicity profiles.[5–9]

Fusion of the thiazole ring onto the heterocyclic skeletons suggested the use of imino-1,2,3-dithiazoles[11,12] which have proved to be highly versatile intermediates in heterocyclic synthesis, undergoing a variety of reactions initiated by nucleophilic attack at different sites on the dithiazole ring (the driving force being the regeneration of the latent cyano group in the dithiazole ring).

In order to increase the biological activity of the molecules, extensive modifications of the carbonitrile function in position 2 of the thiazole ring were performed in our group.[6] It was decided to associate the benzothiazole ring with various polyheterocyclic structures such as indolo[1,2-*c*]quinazoline (I) and benzimidazo[1,2-*c*]quinazoline (II) skeletons which often represent potent cytotoxic agents[13] (Fig. 1).

In this paper we describe the synthetic route and a preliminary biological evaluation to these novel substituted polyheterocyclic compounds which are structurally related to terrestrial or marine alkaloids (e.g. hinckdentine A[14] for the indolo[1,2-*c*]quinazoline ring, see Figure 1). In the course of our work on the application of microwaves in the preparation of bioactive molecules, we have transposed many of the reactions described in this paper to a focused microwave oven specifically designed for organic synthesis,[15] with the aim of achieving striking reduction in reaction times, better yields and cleaner reactions compared to the purely thermal processes.

2. Results and discussion

2.1. Synthesis of benzothiazoles 3 and benzoxazole 4

Using a standard method applied for the preparation of various *N*-arylimino-1,2,3-dithiazoles, the starting anilines were condensed with 4,5-dichloro-1,2,3-dithiazolium chloride **1** (Appel salt)[11] in dichloromethane at room temperature to give the desired imines **2** in good yields.

In the course of a study on the chemistry of Appel salt **1** and its derivatives, we previously showed that 5-(*N*-arylimino)-4-chloro-5*H*-1,2,3-dithiazoles **2**, which are stable crystalline solids, cyclised by vigorous heating to give sulphur, hydrogen chloride and 2-cyanobenzothiazoles.[12] The thermolysis procedure consisted of heating the starting material in the presence of *N*-methylpyrrolidin-2-one

Keywords: microwave irradiation; indolo[1,2-*c*]quinazoline; benzimidazo[1,2-*c*]quinazoline; benzothiazoles.

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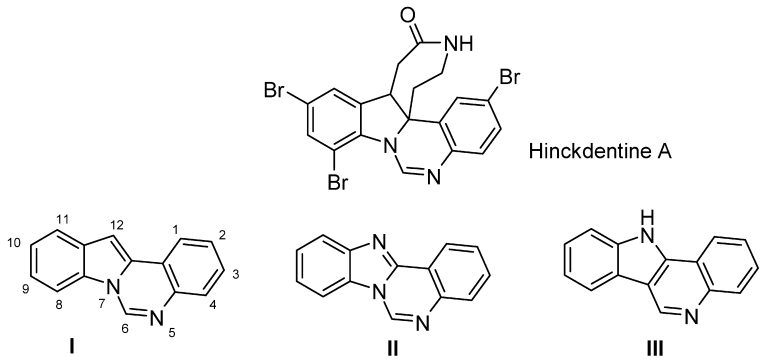


Figure 1.

Table 1. Microwave synthesis of benzothiazoles **3** and benzoxazole **4**

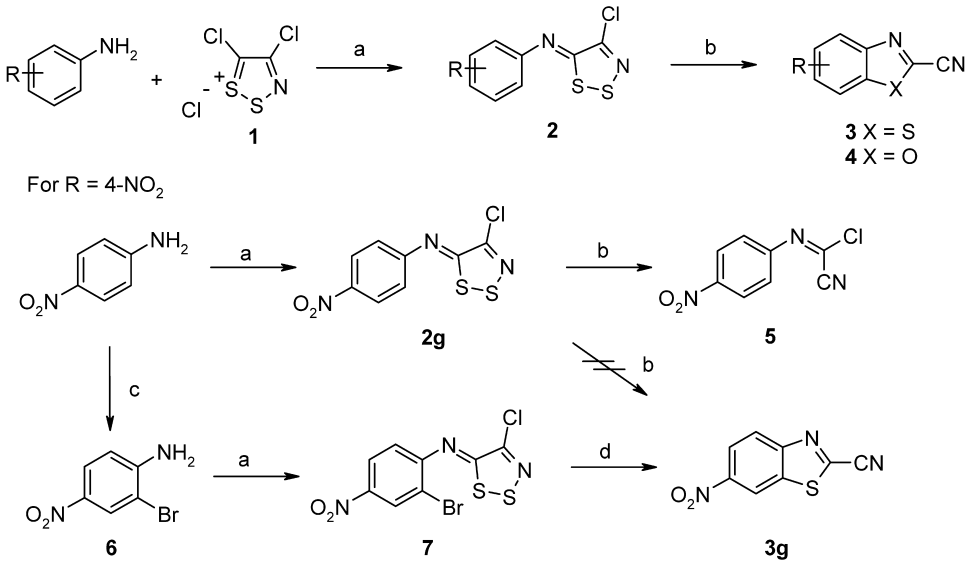
Starting imine **2** (R)	Reaction time (min)	Product (R)	Yields of product (%)
a (H)	1	**3a** (H)	49
b (4-F)	1	**3b** (6-F)	29
c (4-CH_3)	2	**3c** (6-CH_3)	55
d (4-OCH_3)	1	**3d** (6-OCH_3)	48
e (2,5-diCH_3)	1	**3e** (4,7-diCH_3)	58
f (2,5-diOCH_3)	3	**3f** (4,7-diOCH_3)	64
g (2-Br, 4-NO_2)	0.5	**3g** (6-NO_2)	75[a]
h (2-OH)	0.5	**4** (–)	69

[a] Yield of the cyclisation of the intermediate *o*-bromoimine in the presence of CuI with pyridine as solvent (Scheme 1).

(NMP), a polar solvent well adapted for microwave heating. Among the various combinations tested (fixed temperature or/and irradiation power), the best results were obtained by heating the mixture with an irradiation programmed at 90 W and a fixed temperature (150°C) (Table 1). Here again, the comparative study of this methodology performed under classical heating (using oil or metal bath) or microwave irradiation showed that reaction time was considerably reduced, from hours to a few minutes, with the latter technique.

In the previously described thermolysis procedure[12] (which consisted of heating the neat imines **2** under argon at 200–250°C with a metal bath for 1 or 2 min), the amount of starting material was limited to 0.2 g and the products were usually accompanied by complicated mixtures of carbonaceous compounds and impurities which are difficult to eliminate. The alternative microwave method allows a significant scale-up of the quantity of starting material (1 or 5 g instead of 0.2 g in the conventional method) in safe, useful and convenient conditions.

Following the same strategy, a benzoxazole analogue (**4**) was also obtained from 2-aminophenol by an intramolecular attack of the *o*-hydroxy group in the C_5 of the intermediate imine. Cyclisation of the 4-nitroaniline derivative was more difficult and, as we previously described,[12] the presence of a strong electron withdrawing group on the aromatic moiety of the imine **2** reduced dramatically the yield of **3**, to favour the cyanoimidoyl chloride **5** as the major reaction product. A mild procedure, which consists to heat an *ortho* bromoimine in the presence of cuprous iodide in pyridine at reflux, afforded **3** in good yield (Table 1, Scheme 1).



Scheme 1. *Reagents and conditions* (for time and yield see Table 1): (a) Appel salt **1**, CH_2Cl_2, room temperature, 2 h, **2g** (12 h, 70%), **7** (70%); (b) *N*-methylpyrrolidin-2-one, μw (150°C, 90 W) 1–3 min, **3g** (μw 150°C, 150 W, 0.5 min, 47%); (c) Br_2, acetic acid, room temperature, 9 h, 88%; (d) CuI, pyridine reflux, μw (110°C, 90 W), 15 min, 75%.

Table 2. Synthesis of indolo[1,2-*c*]quinazoline and benzimidazo[1,2-*c*]quinazoline derivatives from **3** and **4**

Starting material (R)	Product	Time (min)[a]	Yield (%)	Product	Time (min)[a]	Yield (%)
3a (H)	**8a**	135	64	**9a**	90	70
3b (6-F)	**8b**	240	53	**9b**	150	56
3c (6-CH_3)	**8c**	150	60	**9c**	60	71
3d (6-OCH_3)	**8d**	30	68	**9d**	10	73
3e (4,7-diCH_3)	**8e**	90	61	**9e**	65	65
3f (4,7-diOCH_3)	**8f**	115	54	**9f**	80	58
3g (6-NO_2)	**8g**	24 h	12[b]	**9g**	10 h	18[b]
4 (–)	**8h**	70	69	**9h**	45	77

[a] Time of the microwave irradiation.
[b] P_2S_5, 1,2-dichlorobenzene reflux, μw heating (130°C, 90 W).

2.2. Synthesis of indolo[1,2-*c*]quinazoline and benzimidazo[1,2-*c*]quinazoline derivatives

In contrast to its well studied indolo[3,2-*c*]quinoline counterpart (III) (Fig. 1), the indolo[1,2-*c*]quinazoline ring system (I) is little known and its synthesis has been achieved in only a limited number of ways. Preparation of these two skeletons may involve the use of 2-(2-aminophenyl)indole as a starting material.[2]

It is known that the cyano group in position 2 of the benzothiazole ring is very reactive and that its transformation into acid, amide, amidine and imidate may be easily realised. According to this strategy, the condensation of 2-cyanobenzothiazoles with the commercially available 2-(2-aminophenyl)indole in various solvents (e.g. ethanol, dimethylformamide or NMP) was studied. Unfortunately, the usual conditions did not allow an access to the expected rings. Transposition of this process (same conditions of solvents, quantities and temperatures) in a microwave reactor was also unsuccessful. An alternative procedure, which consists to heat the benzothiazoles and the 2-(2-aminophenyl) indole neat at 220°C (metal bath), required lengthy and tedious conditions. The yields were very low and various impurities were detected in the final mixture. In connection with our recent work on heterocyclic reactions with carbon graphite as support,[16] we discovered that microwave irradiation (150 W) of the two starting compounds at 220°C in the presence of graphite (10% by weight) afforded the indolo[1,2-*c*]quinazoline derivatives (**8a–f** and **8h**) in good yields (Table 2). Under similar experimental conditions (with same quantity of starting material, graphite and same reaction time), a conventional heating allowed a small amount of the products (yields <35%). Whichever method was applied, none of the alternative ring closed product, indolo[3,2-*c*]quinoline (III), was detected.

Following the conditions described above, the parent benzimidazo[1,2-*c*]quinazolines **9a–f** and **9h** were obtained in good yield by condensation of 2-cyanobenzothiazoles **3a–f**, or the benzoxazole **4**, with 2-(2-aminophenyl)benzimidazole (Table 2). As observed above for the formation of the benzothiazoles, reactions with the nitro compound were more difficult than for the other molecules. Then, condensation of the 2-cyano-6-nitrobenzothiazole **6g** with the heterocyclic diamines yielded to complex mixtures devoid of the desired product. Activation of the carbonitrile group was expected by using adapted methods using sulphur derivatives (e.g. S, CS_2 and P_2S_5).[17] The synthesis of compounds **8g** and **9g** was then attempted by nucleophilic addition of the appropriate diamine to the aromatic nitrile **8g** in 1,2-dichlorobenzene in the presence of a catalytic amount of P_2S_5 (Scheme 2). The yields were relatively low but sufficient material was obtained for a complete chemical characterisation of the new products and their preliminary biological evaluation.[18]

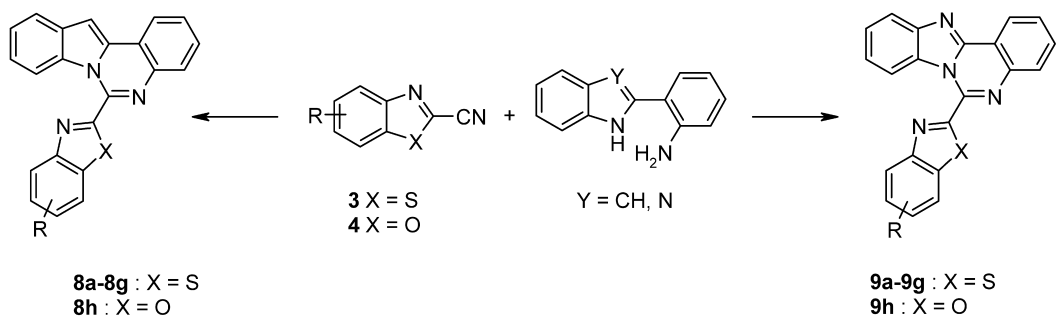
3. Conclusion

In conclusion, a successful strategy is presented for the synthesis of novel indolo[1,2-*c*]quinazolines (**8a–h**) and benzimidazo[1,2-*c*]quinazolines (**9a–h**) obtained by condensation of the appropriate diamines (e.g. 2-(2-aminophenyl)indole or 2-(2-aminophenyl)benzimidazole) with 2-cyanobenzothiazoles. The compounds presented in this paper can be considered as synthetic analogues of the natural alkaloid hinckdentine A and present a close structural analogy with other cytotoxic agents containing a synthetic benzimidazo[1,2-*c*]quinazoline core. In connection with recent published results on the utility of microwaves in multistep organic synthesis, this work confirms that reaction mixtures exposed to microwaves allow an easy and rapid access to original heterocycles with potential pharmaceutical value.

4. Experimental

4.1. General

Commercial reagents were used as received without



Scheme 2. *Reagents and conditions* for compounds **8a–f,h**, **9a–f,h**, (for time and yield see Table 2): graphite (10% by weight), μw (150°C, 150 W); for compounds **8g** and **9g**: P_2S_5 cat., 1,2-dichlorobenzene reflux, μw (130°C, 90 W).

additional purification. Melting points were determinate on a Köfler melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin–Elmer Paragon 1000 PC FT-IR. ^{1}H and ^{13}C NMR were recorded on a JEOL JNM LA 400 (400 MHz) spectrometer (Centre Commun d'Analyses, Université de La Rochelle). The mass spectra (HRMS) were recorded on a Varian MAT 311 in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Université de Rennes). Analytical thin layer chromatography (tlc) was performed on Merck 60F-254 silica gel plates. Column chromatography was performed by using Merck silica gel (70–230 mesh). Focused microwave irradiations were carried out with a Synthewave™ S402 microwave reactor (monomode system, 2450 MHz, 300 W) which has variable speed rotation, visual control, irradiation monitored by PC computer, infrared measurement and continuous feedback temperature control (by PC).

4.2. Synthesis of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene) derivatives 2: general procedures

Appel salt **1** (1.1 equiv.) was added to a solution of aniline derivative (1 g) in dichloromethane (20 mL). The mixture was stirred at room temperature for 2 h (10 h for **2g**) and then washed twice with water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography with light petroleum-dichloromethane (7:3) as the eluent afforded the title compounds **2a**–**d**, **2f** and **g** as yellow solids.

Spectral data for *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene) derivatives **2a**–**d**, **2f** and **g** were consistent with the assigned structures.[12c,19]

4.2.1. 2,5-Dimethyl-*N*-(4-chloro-5*H*-dithiazol-5-ylidene)-aniline (2e). Yellow needles (89%), mp 110°C. IR (KBr): 2928, 1610, 1152, 872 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.17 (d, J=8.0 Hz, 1H), 6.95 (d, J=8.0 Hz, 1H), 6.87 (s, 1H), 2.33 (s, 3H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 158.2, 150.3, 147.7, 137.0, 131.1, 127.1, 126.6, 116.3, 21.1, 17.1. HRMS (EI) calcd for $C_9H_9N_2S_2Cl$ ($M-H^+$) 255.9896. Found: 255.9909.

4.3. Synthesis of 2-cyanobenzothiazoles 3 and 2-cyanobenzoxazoles 4: general procedures

N-arylimino-1,2,3-dithiazole **2** (1 g) was irradiated with *N*-methylpyrrolidin-2-one (10 mL) as the solvent. The irradiation was programmed to maintain a constant temperature (150°C) with a maximal power output of 90 W. After cooling, dichloromethane was added, the organic layer washed with water, dried over $MgSO_4$, and the crude product was purified by column chromatography (silica gel) with light petroleum–dichloromethane as the eluent.

Spectral data for benzothiazoles derivatives **3a**–**d**, **3f** and **g** were consistent with the assigned structures.[12c,19]

4.3.1. 4,7-Dimethylbenzothiazole-2-carbonitrile (3e). Orange needles (58%), mp 90°C. IR (KBr): 3018–2928, 2236, 1904, 1476, 1146, 836 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J=8.0 Hz, 1H), 7.30 (d, J=8.0 Hz, 1H), 2.75 (s, 3H), 2.56 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 151.6, 136.1, 134.7, 132.9, 129.15, 128.64, 128.4, 21.1, 17.9. HRMS (EI) calcd for $C_9H_8N_2S$ ($M-H^+$) 188.0408. Found: 188.0414.

4.3.2. 6-Nitrobenzothiazolyl-2-carbonitrile (3g). 2-Bromo-4-nitro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidenyl)-aniline **7** (1 g, 3.1 mmol), was irradiated in presence of 1.1 equiv. of copper iodure (0.58 g, 3.4 mmol) in pyridine (10 mL) as the solvent. The irradiation was programmed to obtain reflux with a maximal power output of 90 W. After cooling, the mixture was concentrated in vacuo, and washed with water and EtOAc. The organic layer was dried over $MgSO_4$ and removed in vacuo. Purification by column chromatography with light petroleum–dichloromethane (7:3) as the eluent afforded compound **3g** as a pale yellow solid (0.47 g, 75%), mp 163°C. IR(KBr): 3097, 2236, 1613, 1567, 1334 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.96 (d, J=2.4 Hz, 1H), 8.53 (dd, J=8.8, 2,4 Hz, 1H), 8,39 (d, J=8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 112.0, 118.5, 123.1, 126.0, 135.5, 141.7, 147.2, 155.3. HRMS (EI) calcd for $C_8H_3N_3O_2S$ (M^+) 204.9946. Found: 204.9947.

4.3.3. 2-Bromo-4-nitroaniline (6). To a solution of 4-nitroaniline (1 g, 2.24 mmol) in acetic acid (30 mL) was added dropwise 1.1 equiv. of bromine (0.409 mL, 2.46 mmol). The reaction mixture was stirred at room temperature for 2 h, quenched with H_2O and $Na_2S_2O_3$ (30 mL), then extracted with EtOAc (30 mL). The organic layer was washed with a saturated solution of $NaHCO_3$; dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography with light petroleum–dichloromethane (4:6) as the eluent afforded the title compound as a yellow solid (1.38 g, 88%), mp 106°C. IR(KBr): 3488, 3376, 3234, 3206, 3100, 1616, 1482, 1326 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.36 (d, J=2.4 Hz, 1H), 8.02 (dd, J=9.6, 2.4 Hz, 1H), 6.76 (d, J=9.6 Hz, 1H), 4.91 (bs, 2H). ^{13}C NMR ($CDCl_3$) δ 150.0, 138.8, 129.2, 124.9, 113.5, 106.9. HRMS (EI) calcd for $C_6H_3BrN_2O_2$ (M^+) 215.9534. Found: 215.9531.

4.3.4. 2-Bromo-4-nitro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidenyl)aniline (7). A solution of 2-bromo-4-aniline **6** (1 g, 4,63 mmol) in tetrahydrofuran (20 mL) was added to 1.1 equiv. of Appel salt **1** (1.07 g, 5.14 mmol). After 9 h at room temperature, the mixture is concentrated in vacuo and purification by column chromatography with light petroleum–dichloromethane (7:3) as the eluent afforded a pale orange solid (1.15 g, 71 %), mp 124°C. IR(KBr): 3481, 3373, 3098, 1590, 1509, 1349, 860 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.58 (d, J=2.4 Hz, 1H), 8.27 (dd, J=8.8, 2.4 Hz, 1H), 7.24 (d, J=8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 162.5, 155.5, 147.3, 145.2, 129.5, 124.6, 118.6, 115.3. HRMS (EI) calcd for $C_8H_3N_3O_2BrS_2Cl$ (M^+) 350.8539. Found: 350.8540.

4.4. Synthesis of indolo[1,2-*c*]quinazolines (8a–f,h) and benzimidazo[1,2-*c*]quinazolines (9a–f,h): general procedures

Benzothiazoles or benzoxazoles (0,15 g) and commercial diamine (2-(2-aminophenyl) benzimidazole or 2-(2-aminophenyl)indole, 1 equiv. were irradiated in the presence of graphite (10 wt% to the reactants). The irradiation was programmed to obtain a constant temperature (220°C) with

a maximal power output of 150 W. After cooling, the mixture was dissolved in dichloromethane and purified by column chromatography (silica gel) with light petroleum–ethyl acetate (8:2) as the eluent.

4.4.1. 6-Benzothiazol-2-yl-indolo[1,2-*c*]quinazoline (8a). Orange needles (64%), mp 170°C (toluene). IR (KBr): 3105, 3064, 3045, 1381, 758 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.22–8.25 (m, 1H), 8.10–8.16 (m, 2H), 7.81–7.88 (m, 2H), 7.56–7.68 (m, 4H), 7.35–7.39 (m, 2H), 7.18 (dd, J=8.5, 1.0 Hz, 1H), 7.11 (ddd, J=8.8, 6.9, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 161.4, 152.8, 142.2, 138.4, 136.0, 135.0, 131.3, 130.4, 129.1, 128.6, 128.3, 126.9, 126.9, 124.7, 123.9, 122.8, 122.0, 121.9, 121.3, 120.7, 115.1, 96.7. HRMS (EI) calcd for $C_{22}H_{13}N_3S$ ($M-H^+$) 351.0830. Found: 351.0822.

4.4.2. 6-(6-Fluorobenzothiazol-2-yl)-indolo[1,2-*c*]quinazoline (8b). Orange needles (53%), mp 186°C (DMF). IR (KBr): 3122, 3072, 1610, 1544, 1446, 738 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.13–8.20 (m, 2H), 7.81–7.88 (m, 2H,), 7.77 (dd, J=7.6, 2.4 Hz, 1H), 7.55 (m, 2H), 7.36–7.39 (m, 3H), 7.28 (d, J=8.8 Hz, 1H), 7.13 (td, J=6.8, 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 162.8, 161.3, 161.3, 160.3, 149.4, 141.9, 138.3, 137.3, 137.2, 135.0, 131.2, 130.4, 129.2, 128.6, 128.2, 125.8, 125.7, 124.0, 122.8, 122.0, 121.2, 120.7, 166.1, 115.8, 115.2, 108.2, 107.9, 96.8. HRMS (EI) calcd for $C_{22}H_{12}FN_3S$ (M^+) 369.0736. Found: 369.0734.

4.4.3. 6-(6-Methylbenzothiazol-2-yl)-indolo[1,2-*c*]quinazoline (8c). Orange needles (60%), mp 201°C (toluene). IR (KBr): 3064, 2924, 1599, 1539, 1463, 1381, 735 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.08–8.13 (m, 2H), 7.83–7.87 (m, 2H), 7.79 (d, J=8.0 Hz, 1H), 7.52 (m, 2H), 7.44 (dd, J=8.0, 1.2 Hz, 1H), 7.35 (td, J=8.4, 1.2 Hz, 1H), 7.33 (s, 1H), 7.16 (d, J=8.0 Hz, 1H), 7.09 (td, J=8.4, 1.2 Hz, 1H), 2.58 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 160.1, 150.9, 142.3, 138.4, 137.3, 136.2, 135.0, 131.3, 130.4, 129.1, 128.6, 128.5, 128.2, 124.1, 123.9, 122.8, 121.9, 121.6, 121.0, 120.6, 115.1, 96.6, 21.8. HRMS (EI) calcd for $C_{23}H_{15}N_3S$ (M^+) 365.0987. Found: 365.0979.

4.4.4. 6-(6-Methoxybenzothiazol-2-yl)-indolo[1,2-*c*]quinazoline (8d). Orange needles (68%), mp 174°C (toluene). IR (KBr): 3099, 3064, 3013, 2944, 1610, 1510, 1269 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.09–8.14 (m, 2H), 7.80–7.86 (m, 2H), 7.54–7.59 (m, 2H), 7.52 (d, J=2.5 Hz, 1H), 7.35–7.39 (m, 2H), 7.25–7.28 (m, 1H) 7.24 (dd, J=9.0, 2.5 Hz, 1H), 7.12 (td, J=8.6, 1.3 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 159.1, 158.6, 147.4, 142.3, 138.4, 137.7, 135.1, 131.4, 130.4, 129.1, 128.4, 128.2, 125.2, 123.9, 122.8, 121.9, 121.2, 120.6, 116.8, 115.3, 103.8, 96.6, 55.9. HRMS (EI) calcd for $C_{23}H_{15}N_3OS$ (M^+) 381.0936. Found: 381.0935.

4.4.5. 6-(4,7-Dimethylbenzothiazol-2-yl)-indolo[1,2-*c*]quinazoline (8e). Orange needles (61%), mp 204°C (DMF). IR (KBr): 3380, 3048, 2924, 2850, 1598, 1466, 1374, 720 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.12–8.15 (m, 1H), 7.85–7.88 (m, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.53–7.58 (m, 2H), 7.32–7.38 (m, 4H), 7.27 (d, J=8.0 Hz, 1H), 7.08–7.13 (m, 1H), 2.74 (s, 3H), 2.66 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 159.8, 152.0, 142.6, 138.4, 136.6, 135.1, 132.0, 131.5, 130.4, 129.3, 129.1, 128.4, 128.2, 127.5, 126.9, 123.8, 122.8, 121.7, 121.2, 120.5, 155.6, 96.6, 21.3, 18.1. HRMS (EI) calcd for $C_{24}H_{17}N_3S$ (M^+) 379.1143. Found: 379.1146.

4.4.6. 6-(4,7-Dimethoxybenzothiazol-2-yl)-indolo[1,2-*c*]quinazoline (8f). Orange needles (54%), mp 221°C (DMF). IR (KBr): 3128, 3068, 3018, 2950, 2848, 1782, 1530, 776 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.05–8.12 (m, 1H), 7.72–7.85 (m, 2H), 7.49–7.56 (m, 2H), 7.25–7.34 (m, 2H), 7.04–7.10 (m, 2H), 6.86–6.96 (m, 2H), 4.00 (s, 3H), 3.99 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 160.3, 149.0, 148.2, 144.1, 142.1, 138.3, 134.7, 131.3, 130.2, 129.0, 128.3, 128.2, 126.8, 123.7, 122.7, 121.9, 121.1, 120.4, 115.0, 107.8, 106.8, 96.5, 56.5, 56.2. HRMS (EI) calcd for $C_{24}H_{17}N_3O_2S$ (M^+) 411.1041. Found: 411.1042.

4.4.7. 6-(Benzoxazol-2-yl)-indolo[1,2-*c*]quinazoline (8h). Orange solid (70%), mp 162°C (toluene). IR (KBr): 3098, 3058, 2966, 2942, 1606, 1534, 1390, 744 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.10–8.14 (m, 1H), 7.98–8.02 (m, 1H), 7.89–7.93 (m, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.23 (t, J=8.0 Hz, 1H), 7.47–7.59 (m, 4H), 7.37 (t, J=7.6 Hz, 1H), 7.33 (s, 1H), 7.12 (t, J=8.8 Hz, 1H), 6.88 (d, J=8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 150.3, 140.6, 138.1, 134.4, 130.4, 130.1, 129.2, 128.9, 128.6, 127.5, 127.1, 125.7, 124.1, 122.8, 122.3, 121.6, 121.4, 120.8, 113.3, 111.4, 111.4, 96.6. HRMS (EI) calcd for $C_{22}H_{13}N_3O$ (M^+) 335.1059. Found: 335.1043.

4.4.8. 6-Benzothiazol-2-yl-benzo[4,5]imidazo[1,2-*c*]quinazoline (9a). Yellow needles (70%), mp 188°C (toluene). IR (KBr): 3109, 3072, 1320, 754 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.79 (d, J=7.8 Hz, 1H), 8.28 (d, J=8.0 Hz, 1H), 8.16 (d, J=8.8 Hz, 1H), 8.11 (d, J=7.6 Hz, 1H), 8.05 (t, J=7.6 Hz, 1H), 7.83 (t, J=7.2 Hz, 1H) 7.78 (t, J=6.8 Hz, 1H), 7.55–7.68 (m, 3H), 7.33 (t, J=8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 161.4, 153.0, 148.0, 144.4, 141.9, 141.4, 136.3, 132.0, 129.4, 129.4, 128.5, 127.3, 127.0, 126.2, 124.7, 124.5, 122.9, 122.0, 119.9, 119.1, 116.4. HRMS (EI) calcd for $C_{21}H_{12}N_4S$ (M^+) 352.0783. Found: 352.0808.

4.4.9. 6-(6-Fluorobenzothiazol-2-yl)-benzo[4,5]imidazo[1,2-*c*]quinazoline (9b). Yellow needles (56%), mp 223°C (toluene). IR (KBr): 3122, 3050, 3014, 1518, 1194, 851, 746 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.78 (dd, J=8.4, 1.6 Hz, 1H), 8.30 (d, 1H), 8.23 (dd, J=8.8, 5.2 Hz, 1H), 8.04 (d, J=8.4 Hz, 2H), 7.84 (td, J=7.2, 1.6 Hz, 1H), 7.74–7.79 (m, 2H), 7.58 (t, J=6.8 Hz, 1H), 7.34–7.43 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 163.0, 161.5, 161.5, 160.6, 149.7, 148.0, 144.4, 141.6, 141.3, 137.7, 137.5, 131.9, 129.5, 129.4, 128.4, 126.2, 125.9, 125.8, 124.5, 122.9, 120.0, 119.0, 116.5, 116.2, 116.0, 108.2, 107.9. HRMS (EI) calcd for $C_{21}H_{11}N_4FS$ (M^+) 370.0688. Found: 370.0665.

4.4.10. 6-(6-Methylbenzothiazol-2-yl)-benzo[4,5]imidazo[1,2-*c*]quinazoline (9c). Yellow needles (71%), mp 212°C (toluene). IR (KBr): 3100, 3077, 3030, 1623, 1586, 1524, 762 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.76 (dd, J=7.6, 1.2 Hz, 1H), 8.13–8.17 (m, 2H), 8.13–8.06 (m, 2H), 7.88 (s, J=1.2 Hz, 1H), 7.82 (td, J=7.2, 1.6 Hz, 1H), 7.75 (td, J=7.6, 0.8 Hz,1H), 7.56 (td, J=6.8, 0.8 Hz, 1H), 7.47 (dd, J=8.4, 1.2 Hz, 1H), 7.32 (td, J=8.4, 0.8 Hz, 1H), 2.60 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 160.1, 151.2, 148.0, 144.5, 142.0,

141.4, 137.8, 136.5, 131.9, 129.4, 129.3, 128.8, 128.4, 126.1, 124.4, 124.1, 122.8, 121.5, 119.9, 119.0, 116.4, 21.8. HRMS (EI) calcd for $C_{22}H_{14}N_4S$ (M^+) 366.0939. Found: 366.0943.

4.4.11. 6-(6-Methoxybenzothiazol-2-yl)-benzo[4,5]imidazo[1,2-*c*]quinazoline (9d). Yellow needles (73%), mp 200°C (toluene). IR (KBr): 3128, 3071, 2966, 2916, 2832, 1602, 1525, 1277, 751 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.75 (dd, J=10.1, 1.3 Hz, 1H), 8.30 (d, J=8.6 Hz, 1H), 8.11 (d, J=9.0 Hz, 1H), 8.00 (t, J=8.1 Hz, 1H), 7.77 (ddd, J=7.6, 7.5, 1.6 Hz, 1H), 7.71 (ddd, J=7.4, 7.1, 1.2 Hz, 1H), 7.54 (ddd, J=8.1, 7.8, 1.0 Hz, 1H), 7.46 (d, J=2.5 Hz, 1H), 7.32 (ddd, J=8.5, 7.2, 1.2 Hz, 1H), 7.21 (dd, J=9.0, 2.5 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 159.3, 158.6, 148.0, 147.5, 144.2, 141.9, 141.3, 138.1, 131.8, 129.4, 129.1, 128.2, 126.1, 125.2, 124.4, 122.7, 119.8, 118.8, 117.0, 116.7, 103.6, 55.9. HRMS (EI) calcd for $C_{22}H_{14}N_4OS$ (M^+) 382.0888. Found: 382.0866.

4.4.12. 6-(4,7-Dimethylbenzothiazol-2-yl)-benzo[4,5]imidazo[1,2-*c*]quinazoline (9e). Yellow needles (65%), mp 228°C (DMF). IR (KBr): 3125, 3075, 2966, 2916, 1583, 1517, 1450, 1326, 736 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.80 (d, J=7.6 Hz, 1H), 8.42 (d, J=8.4 Hz, 1H), 8;06 (t, J=7.2 Hz, 2H), 7.84 (t, J=7.2 Hz, 1H), 7.76 (t, J=7.6 Hz, 1H), 7.58 (t, J=8.4 Hz, 1H), 7.37 (t, J=7.6 Hz, 2H), 7.31 (t, J=7.2 Hz, 1H), 2.82 (s, 3H), 2.68 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 160.0, 152.7, 148.5, 144.84, 142.7, 141.8, 137.3, 132.4, 132.2, 130.0, 129.7, 129.65, 128.0, 127.7, 126.5, 124.8, 122.9, 120.2, 119.4, 117.4, 21.6, 18.5. HRMS (EI) calcd for $C_{23}H_{16}N_4S$ (M^+) 380.1096. Found: 380.1093.

4.4.13. 6-(4,7-Dimethoxybenzothiazol-2-yl)-benzo[4,5]-imidazo[1,2-*c*]quinazoline (9f). Orange needles (58%), mp 223°C (DMF). IR (KBr): 3132, 3075, 3007, 2932, 1772, 1632, 1524, 1276, 770 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.40 (s, 1H), 8.49 (d, J=8.8 Hz, 1H), 8.27 (d, J=8.0 Hz, 1H), 8.15 (d, J=8.4 Hz, 1H), 8.02 (m, 1H), 7.94 (m, 1H), 7.70 (m, 1H), 7.50 (m, 1H), 6.97 (s, 2H), 4.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 150.1, 150.0, 147.3, 142.3, 138.4, 135.1, 131.4, 130.4, 129.1, 128.6, 128.4, 128.2, 123.8, 122.8, 121.9, 121.1, 120.6, 119.8, 115.2, 105.4, 102.1, 96.5, 56.4, 56.2. HRMS (EI) calcd for $C_{23}H_{16}N_4O_2S$ (M^+) 412.0994. Found: 412.1009.

4.4.14. 6-(Benzoxazol-2-yl)-benzo[4,5]imidazo[1,2-*c*]quinazoline (9h). Yellow solid (77%), mp 194°C (toluene). IR (KBr): 3122, 3078, 1588, 1554, 1150, 739 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.80 (dd, J=8.0, 1.6 Hz, 1H), 8.14 (d, J=8.0 Hz, 1H), 8.04 (t, J=8.0 Hz, 2H), 7.86 (td, J=8.4, 2.0 Hz, 1H), 7.80 (t, J=8.4 Hz, 2H), 7.55–7.64 (m, 3H), 7.34 (td, J=7.2, 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 154.8, 150.6, 147.5, 144.3, 141.2, 140.6, 136.6, 132.1, 129.9, 128.9, 128.7, 127.7, 126.3, 125.8, 124.4, 123.3, 121.7, 120.2, 119.4, 114.8, 111.8. HRMS (EI) calcd for $C_{21}H_{12}N_4O$ (M^+) 336.1011. Found: 336.1009.

4.5. Synthesis of 6-(6-nitrobenzoxazol-2-yl)-benzo-[4,5]imidazo[1,2-*c*]quinazoline (8g) and 6-(6-nitrobenzothiazol-2-yl)-indolo[1,2-*c*]quinazoline (9g)

6-Nitrobenzothiazol-2-carbonitrile (0.15 g, 0.73 mmol) and commercial diamine (2-(2-aminophenyl)benzimidazole or 2-(2-aminophenyl)indole, 1 equiv.) were irradiated in the presence of a catalytic amount (10%) of phosphorous pentasulfur with 1,2-dichlorobenzene (10 mL) as the solvent. The irradiation was programmed to reach 110–120°C with a maximal power output of 90 W. After cooling, the mixture was dissolved in dichloromethane and purified by column chromatography (silica gel) with dichloromethane as the eluent.

4.5.1. 6-(6-Nitrobenzothiazol-2-yl)-indolo[1,2-*c*]quinazoline (8g). Red solid (12%), mp 186°C (toluene). IR (KBr): 3131, 3002, 3068, 1526, 1337, 1078, 750 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.98 (d, J=3.5 Hz, 1H), 8.45 (dd, J=14.0, 3.5 Hz, 1H), 8.28 (d, J=16.0 Hz, 1H), 7.78–7.86 (m, 1H), 7.53–7.59 (m, 2H), 7.34–7.42 (m, 3H), 7.14 (td, J=12.0, 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 167.5, 156.2, 146.1, 141.3, 138.0, 136.4, 135.0, 131.1, 130.4, 129.2, 129.1, 128.3, 124.9, 124.1, 122.8, 122.1, 122.0, 121.3, 120.8, 118.5, 115.2, 97.0. HRMS (EI) calcd for $C_{22}H_{12}N_4O_2S$ (M^+) 396.0681. Found: 396.0684.

4.5.2. 6-(6-Nitrobenzoxazol-2-yl)-benzo[4,5]imidazo[1,2-*c*]quinazoline (9g). Orange solid (18%), mp 255°C (toluene). IR (KBr): 3084, 3062, 1572, 1522, 1345, 754 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.04 (d, J=2.4 Hz, 1H), 8.81 (d, J=8.0 Hz, 1H), 8.52 (dd, J=9.2, 2.0 Hz, 1H), 8.42 (t, J=7.2 Hz, 2H), 8.05–8.10 (m, 2H), 7.87 (t, J=8.0 Hz, 1H), 7.81 (t, J=8.0 Hz, 1H), 7.62 (t, J=7.2 Hz, 1H), 7.41 (t, J=7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 167.7, 156.4, 147.9, 146.4, 144.3, 141.0, 136.7, 132.1, 130.1, 129.3, 128.5, 126.4, 125.7, 125.1, 124.5, 123.0, 122.2, 120.1, 119.2, 118.4, 116.6. HRMS (EI) calcd for $C_{21}H_{11}N_5O_2S$ (M^+) 397.0634. Found: 397.0665.

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References

1. (a) Molinski, T. F. *Chem. Rev.* **1993**, *93*, 1825–1838. (b) Gunawardana, G. P.; Kohmoto, S.; Gunasekara, S. P.; McConnel, O. J.; Koehn, F. E. *J. Am. Chem. Soc.* **1988**, *110*, 4856–4858. (c) Gunawardana, G. P.; Kohmoto, S.; Burres, N. S. *Tetrahedron Lett.* **1989**, *30*, 4359–4362.
2. (a) Robin, M.; Faure, R.; Périchaud, A.; Galy, J. P. *Heterocycles* **2000**, *53*, 387–395. (b) Hanoun, J. P.; Faure, R.; Galy, J. P.; Elguero, J. *J. Heterocycl. Chem.* **1996**, *33*, 747–750. (c) Barbe, J.; Boyer, G.; Carignano, I.; Elguero, J.; Galy, J. P.; Morel, S.; Oughedani, R. *Tetrahedron Lett.* **1991**, *32*, 6709–6710.
3. Alvarez-Ibarra, C.; Fernandez-Granda, R.; Quiroga, M. L.;

Carbonell, A.; Cardenas, F.; Giralt, E. *J. Med. Chem.* **1997**, *40*, 668–676.
4. (a) Wells, G.; Bradshaw, T. D.; Diana, P.; Seaton, A.; Shi, D.-F.; Westwell, A. D.; Stevens, M. F. G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 513–515. (b) Bradshaw, T. D.; Wrigley, S.; Shi, D.-F.; Schultz, R. J.; Paull, K. D.; Stevens, M. F. G. *Br. J. Cancer* **1998**, *77*, 745–752.
5. Besson, T.; Guillard, J. *Tetrahedron* **1999**, *55*, 5139–5144.
6. Bénéteau, V.; Besson, T.; Guillard, J.; Léonce, S.; Pfeiffer, B. *Eur. J. Med. Chem.* **1999**, *34*, 1053–1060.
7. Besson, T.; Guillard, J.; Rees, C. W. *Tetrahedron Lett.* **2000**, *41*, 1027–1030.
8. Lamazzi, C.; Chabane, H.; Thiéry, V.; Pierré, A.; Léonce, S.; Pfeiffer, B.; Renard, P.; Guillaumet, G.; Besson, T. *J. Enz. Inh. Med. Chem.* **2002**. in press.
9. Chabane, H.; Lamazzi, C.; Thiéry, V.; Guillaumet, G.; Besson, T. *Tetrahedron Lett.* **2002**, *43*, 2483–2486.
10. (a) Sengupta, S. K.; Cheng, X. C. C. In *Cancer Chemotherapeutic Agents*; Foye, W. O., Ed.; ACS Professional Reference Books: Washington, DC, 1995; pp 246–251. (b) Moody, C. J. *Synlett* **1994**, 681–688. (c) Kansal, V. K.; Potier, P. *Tetrahedron* **1986**, *42*, 2389–2408. (d) Sainsbury, M. *Synthesis* **1977**, 437–448.
11. Appel, R.; Janssen, H.; Siray, M.; Knoch, F. *Chem. Ber.* **1985**, *118*, 1632–1643.
12. (a) Bénéteau, V.; Besson, T.; Rees, C. W. *Synth. Commun.* **1997**, *27*, 2275. (b) Bénéteau, V.; Besson, T.; Guillard, J.; Léonce, S.; Pfeiffer, B. *Eur. J. Med. Chem.* **1999**, *34*, 1053. (c) Besson, T.; Rees, C. W.; Roe, D. G.; Thiéry, V. *J. Chem. Soc., Perkin Trans. 1* **2000**, 555–561.
13. (a) Helissey, P.; Cros, S.; Giorgi-Renault, S. *Anti-Cancer Drug Des.* **1994**, *9*, 51–57. (b) Brana, M. F.; Castellano, J. M.; Keilhauer, G.; Machuca, A.; Martin, Y.; Redondo, C.; Schlick, E.; Walker, N. *Anti-Cancer Drug Des.* **1994**, *9*, 527–538. (c) Riou, J. F.; Helissey, P.; Grondard, L.; Giorgi-Renault, S. *Mol. Pharmacol.* **1991**, *40*, 699–706. (d) Ibrahim, E.; Montgomerie, A. M.; Sneddon, A. H.; Proctor, G. R.; Green, B. *Eur. J. Med. Chem.* **1988**, *23*, 183–188.
14. (a) Billimmoria, A. D.; Cava, M. P. *J. Org. Chem.* **1994**, *59*, 6777–6782. (b) Hinckdentine A (**1**) as been isolated from the bryozoan *Hincksinoflustra denticulata*, collected off the eastern coast of Tasmania: Blackman, A.; Hambley, T. W.; Picker, R.; Taylor, W. C.; Thirasana, N. *Tetrahedron Lett.* **1987**, *28*, 5561–5564.
15. Focused microwave irradiations were carried out at atmospheric pressure with a Synthewave S402 Prolabo microwave reactor (300 W, monomode system) which has quartz reactors, visual control, irradiation monitored by PC computer, infrared measurement and continuous feedback temperature control (by PC). Equipment of the oven can be completed by an external stirring system, a condenser and dropping funnel allowing conditions close to those involved in classical methods; it is also possible to work under dry atmosphere or in vacuo if necessary. Commarmot, R.; Didenot, R.; Gardais, J. F. French Patent 84/03496, 1986; *Chem. Abstr.* **1986**, *105*, 17442. A CEM Discover™ focused microwave reactor (300 W, monomode system) which has in situ magnetic variable speed, may also be used.
16. (a) Frère, S.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* **2001**, *42*, 2791–2794. (b) Soukri, M.; Guillaumet, G.; Besson, T.; Aziane, D.; Aadil, M.; Essassi, El M.; Akssira, M. *Tetrahedron Lett.* **2000**, *41*, 5857–5860.
17. Anastassiadou, M.; Danoun, S.; Crane, L.; Baziard-Mouysset, G.; Payard, M.; Caignard, D.-H.; Rettori, M.-C.; Renard, P. *Bioorg. Med. Chem.* **2001**, *9*, 585–592, and references cited therein.
18. Biological evaluation. No precise target has been yet identified for this type of compounds in the benzothiazol-6-yl indolo- or benzimidazoquinazoline series. By analogy with related molecules bearing a indolo[3,2-*c*]quinoline or benzimidazo[1,2-*c*]quinazoline planar ring system,[13] it was postulated that the newly designed compounds might bind to DNA and interfere with the DNA cleaving activities of topoisomerases. Unfortunately, no inhibition of human topoisomerases I or II was observed but a few compounds appear to bind to DNA. This is the case, for example, with compound **9h** which slightly stabilises duplex DNA against heat denaturation and presents a significant hypochromic effect upon interaction with DNA. Nucleic acids might be considered as possible receptors for these molecules, at least some of them. Detailed studies are in progress to delineate further the strength and mode of binding to DNA by these molecules. A preliminary study has been carried out to investigate the cytotoxic potential of the molecules. They were all found to be only modestly cytotoxic toward CEM human leukaemia cells with IC_{50} values >5 μM. Other cell lines are currently tested and the results of the biological and pharmacological studies will be reported in due course.
19. English, R. F.; Rakitin, O. A.; Rees, C. W.; Vlasova, O. G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 201–205.