Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 2799–2811

The reaction of tetralones with nitriles: a simple approach to the synthesis of new substituted benzo[*h*]quinazolines, benzo[*f*]quinazolines and dibenzo[*a*,*i*]phenanthridines

Antonio Herrera,[a] Roberto Martínez-Alvarez,[a,*] Mourad Chioua,[a] Rachid Chatt,[a] Rachid Chioua,[b] Angel Sánchez[c] and John Almy[d]

[a]*Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense, E-28040 Madrid, Spain*
[b]*Département de Chimie, Faculté des Sciences, Université Abdelmalek Essaâdi, Tétouan, BP 2121, Morocco*
[c]*CAI de Resonancia Magnética Nuclear, Facultad de Ciencias Químicas, UCM, E-28040 Madrid, Spain*
[d]*Department of Chemistry, California State University, Stanislaus, Turlock, CA 95382, USA*

Received 15 December 2005; accepted 5 January 2006

Available online 26 January 2006

Abstract—The one-pot reaction of 1-tetralone with nitriles in the presence of triflic anhydride affords in good yields 2,4-disubstituted 5,6-dihydrobenzo[*h*]quinazolines, which oxidation with DDQ leads to the corresponding benzo[*h*]quinazolines. 2-Tetralone undergoes identical process forming 1,3-disubstituted 5,6-dihydrobenzo[*f*]quinazolines. However, when the reaction of 2-tetralone is carried out with methylthiocyanate as nitrile, 5-methylthiotetrahydrodibenzo[*a*,*i*]phenanthridines are isolated in good yields. Easy transformations of the methylthio group offer possible access to a variety of substituted dibenzo[*a*,*i*]phenanthridines.

1. Introduction

Among the pyrimidine derivatives, one of the prominent compounds are the benzoquinazolines. They constitute the core of naturally ocurring products such as the cytotoxic alkaloid samoquasine A.[1] The benzoquinazoline skeleton is commonly found in substances exhibiting a wide range of biological properties. 1,3-Diaminobenzoquinazolines were evaluted many years ago as antifolate and antimalarial agents.[2] Other benzoquinazoline derivatives are used as substitutes for thymine in nucleic acid complexes,[3] while anilinoquinazolines are potent and selective inhibitors of erbB2 receptor tyrosine kinase.[4] Quinazolinones present inhibitory activity of thymidate synthase.[5–8] Recently, 4-(dimethylamino)quinazolines are described as antagonist for the melanin-concentrating hormone receptor 1[9] and pyrazoloquinazolines are reported as novel Gly/NMDA receptor antagonist.[10]

Phenanthro fused heterocycles are also of interest in many aspects. Natural products such as tylophorine, antofine and cryptoleurine posess the phenanthro fused heterocycle skeleton.[11] Phenanthridine derivatives exhibit interesting pharmacological properties related to the planarity of the system. Consequently, these compounds present a DNA-chain intercalating ability[12] and benzophenanthridines are reported as compounds with topoisomerase I-targeting activity and cytotoxicity.[13] Moreover, this heterocyclic system posesses important photoconducting, opto-electrical switching and photovoltaic properties[14] with many applications in the field of dye-lasers and electroluminiscence.[15]

The construction of the quinazoline moiety involves cyclization of appropriate substituted benzenes whose preparations are not always easy. Other approaches are based on the reaction of 1,3-dicarbonyl compounds with a suitable N–C–N fragment.[16,17] Modern methods employ either catalyst- and solvent free conditions [18] or supercritical carbon dioxide[19] to prepare quinazoline derivatives. The preparation of the phenanthridine ring also requires the selection of suitable precursors that are not easy to synthesize. Some methods make use of appropriately substituted isoquinolines.[20] Other methods employing simple starting compounds are limited by numerous steps and poor yields. The four-step preparation of benzo[*c*]phenanthridine from formaldehyde and 2-methylbenzonitrile has a 6% yield overall.[21] Many methods to prepare quinazolines and phenanthridines are reported in the

Keywords: Pyrimidines; Benzoquinazolines; Benzophenanthridines.
* Corresponding author. Tel.: +34 913944325; fax: +34 913944103; e-mail: rma@quim.ucm.es

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.01.010

literature. In spite of their importance, only very few of them involve less than a few steps.[22]

Herein, we wish to report that the one-pot reaction of 1- and 2-tetralone with nitriles in the presence of triflic anhydride (Tf_2O) affords substituted dihydrobenzo[*h*]quinazolines (**1**), dihydrobenzo[*f*]quinazolines (**2**) and tetrahydro[*a*,*i*]dibenzophenanthridines (**3**) (Fig. 1) in good yields, which can be easily oxidized to their aromatic counterparts.

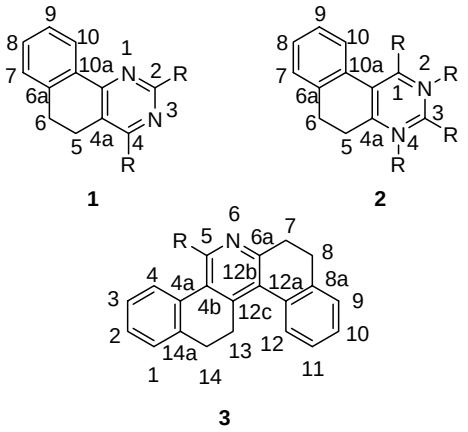
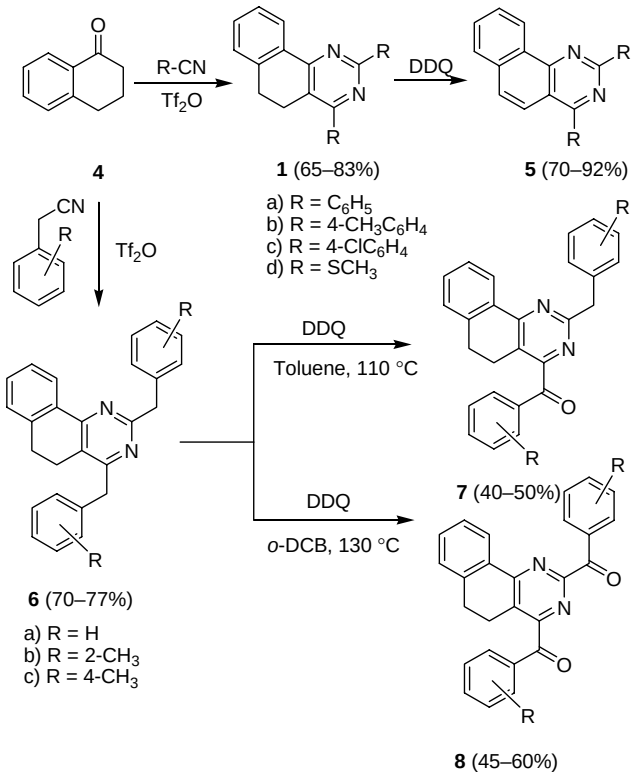


Figure 1. General structure of prepared compounds.

2. Results and discussion

In previous papers we have reported the synthesis of a variety of heterocyclic systems based on the reaction of carbonyl compounds with nitriles in the presence of triflic anhydride.[23–27] The reaction of 1-tetralone (**4**) with various nitriles and Tf_2O under mild conditions (see Section 3) affords 2,4-disubstituted 5,6-dihydrobenzo[*h*]benzoquinazolines (**1**) in good yield (Scheme 1). The well-known mechanism involves the formation of a trifliloxycarbenium ion, which is trapped by the nitrile forming a nitrilium ion. A second molecule of nitrile reacts with the intermediate to give the corresponding quinazoline after elimination of TfOH and loss of a proton.[23] Minor amounts of the vinyl triflate from 1-tetralone (3,4-dihydronaphthalen-1-yl triflate) were detected as side product of the reaction (see Section 3). Its formation is a consequence of a competitive reaction involving the trifliloxycarbenium ion intermediate, which eliminates a proton before it undergoes nucleophilic attack by the nitrile. The oxidation of compounds **1** by means of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in *o*-DCB at 130 °C affords benzoquinazolines **5**. Employing toluene as solvent and hence a lower reaction temperature produces an undesirable mixture of compounds that reduces the yield of this reaction. The use of benzyl nitriles in the reaction with 1-tetralone allows the preparation of 2,4-dibenzyl substituted dihydrobenzoquinazolines **6**. The oxidation of these benzyl derivatives with DDQ can be controlled by the temperature and hence by the choice of the reaction solvent. Thus, when the reaction is carried out in boiling toluene only the methylene group attached at the C4 position reacts to form monocarbonyl compounds **7**. If the reaction is carried out in *o*-DCB at 130 °C both methylene groups are oxidized affording the dicarbonyl compounds **8**.

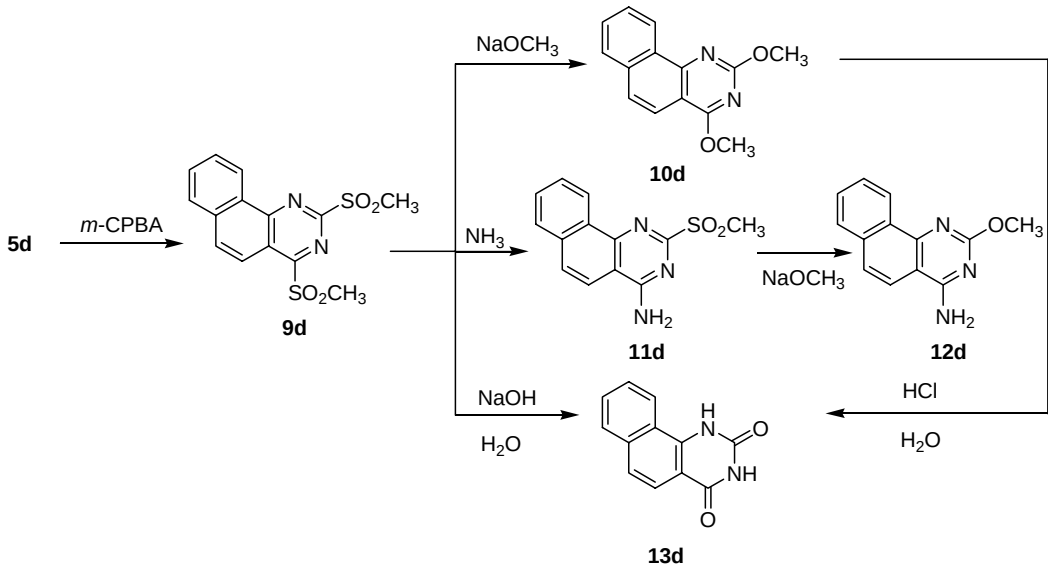
The reaction can be checked using ^{13}C NMR. Compound **6a** exhibits two methylene carbon signals at 41.36 and 45.84 ppm corresponding to both benzyl groups. Using 1D and 2D techniques, the signal at 45.84 ppm was unequivocally assigned to the CH_2 group attached at the C2 position. The reaction of **6a** in boiling toluene affords **7a** whose ^{13}C NMR spectra reveals a new signal at 193.64 ppm representing a new carbonyl group and only one methylene group at 45.79 ppm representing the unreacted benzyl group at the C2 position. In contrast, when the reaction is carried out in *o*-DCB at 130 °C two new carbonyl signals appear at 191.03 and 192.95 ppm, respectively, and both signals of the CH_2 dissapear.



Scheme 1.

The reaction of 1-tetralone (**4**) with methylthiocyanate affords the 2,4-bis(thiomethyl)-5,6-dihydrobenzo[*h*]quinazoline **1d**, which reacts with DDQ to form **5d**.

The easy conversion of the thiomethyl group via nucleophilic displacements into other interesting groups opens a new synthetic route to other quinazoline derivatives otherwise not easy to prepare. Thus, the reaction of **5d** with *m*-CPBA produces the corresponding 2,4-bis(methylsulfonyl) derivative **9d** (Scheme 2). The nucleophilic substitution of the methylsulfonyl group using sodium methoxide affords the dimethoxy derivative **10d**. The reaction of **9d** with ammonia at room temperature permits only the substitution of the methylsulfonyl group at C4 (**11d**) and the subsequent reaction with sodium methoxide leads to the formation of the aminomethoxy derivative **12d**. The hydrolysis of **9d** carried out with boiling aqueous sodium hydroxide forms the uracil **13d**. This compound is also available from the acid hydrolysis of **10d**.



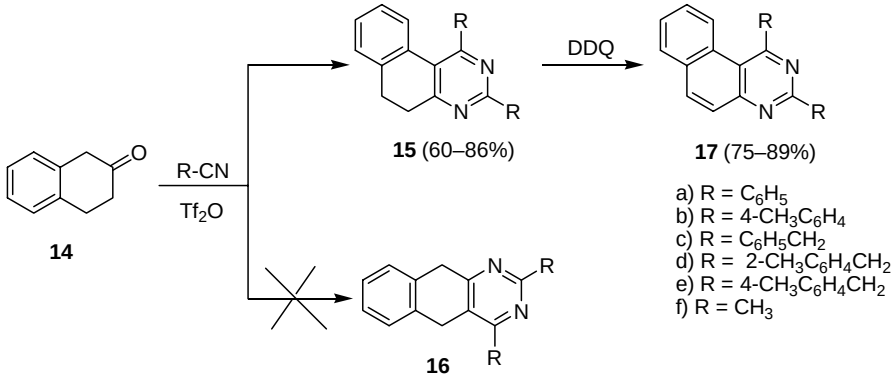
Scheme 2.

The reaction of 2-tetralone (**14**) with nitriles in the presence of triflic anhydride leads to the formation of 1,3-disubstituted 5,6-dihydrobenzo[*f*]quinazolines (**15**), which can be oxidized using DDQ to form the corresponding benzo[*f*]quinazolines (**17**) (Scheme 3).

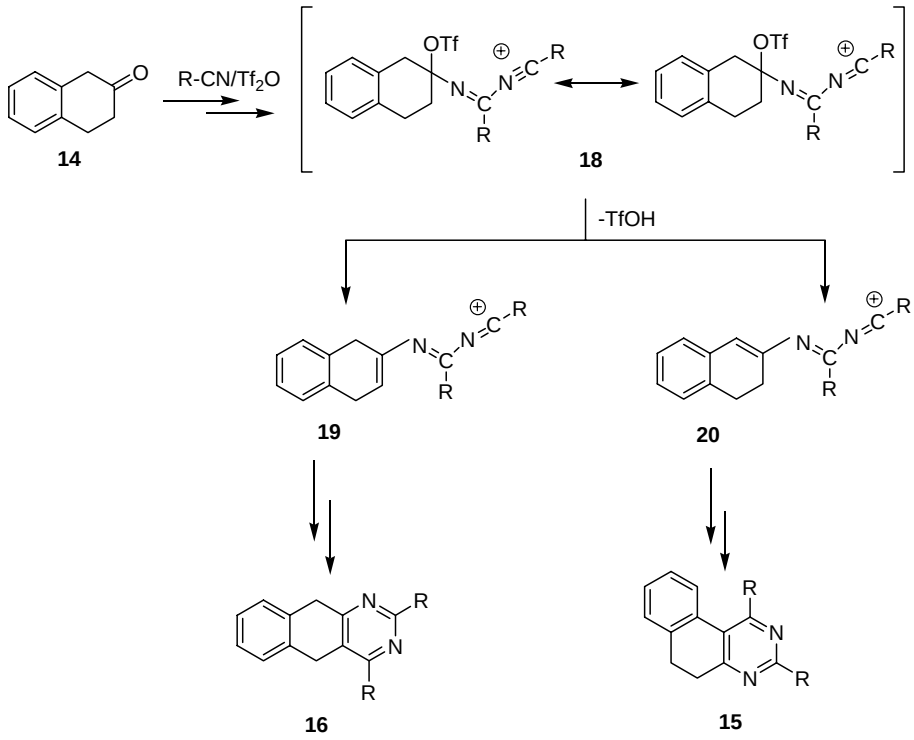
With two different positions alpha to the carbonyl group on 2-tetralone (**14**), one can envisage the formation of two possible products, the isomeric dihydrobenzo[*f*]quinazolines (**15**) and dihydrobenzo[*g*]quinazolines (**16**). In fact, the exclusive formation of quinazolines **15** raises the question of the regioselective advantage of the hydrogen atoms alpha both to the carbonyl and phenyl group. The reaction of linear aliphatic ketones with nitriles was investigated by us[28] demonstrated that the regioselectivity of this process is controlled by the relative stabilities of the cationic intermediates. The general proposed mechanism[24] involves the formation of an imonium intermediate (**18**), which easily eliminates triflic acid (Scheme 4). Trace amounts of 3,4-dihydronaphthalen-2-yl triflate are also formed (see Section 3).

The TfOH elimination leads to the formation of olefins **19** and **20**. Theoretical calculations by means of molecular mechanics (PM3 and AM1) within Hyperchem v6.03 program show that intermediate **20** is more stable than **19**. For example, intermediate **20** is 11.38 kJ mol^{-1} (PM3) more stable than the corresponding isomer **19** when R = C_6H_5. This energy difference explains the formation of quinazolines **15**. To confirm the proposed structure of the dihydrobenzo[*f*]quinazoline we used NOE experiments, which were carried out on compound **15f**. The irradiation of the signal at 2.70 corresponding to the CH_3 on C1 causes a signal enhancement of the aromatic proton H10 (7.60 ppm). In contrast, a hypothetical dihydrobenzo[*g*]quinazoline **16a** should exhibit, under the same irradiation, only a NOE effect in the aliphatic region (Scheme 5).

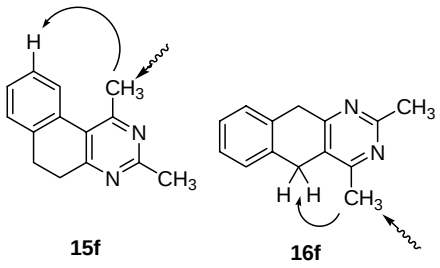
When 2-tetralone (**14**) reacts with benzyl nitriles, 1,3-disubstituted dihydrobenzo[*f*]quinazolines **15c–e** are obtained (Scheme 3). However, if the benzyl nitrile bears electron withdrawing groups, significant amounts of pyrimidines **22** was also obtained in addition to the expected quinazolines **21** (Scheme 6). The amounts of pyrimidines **22** increases at higher temperatures. Surprisingly, benzonitrile also affords a pyrimidine type product **23** when the reaction is carried out at 120 °C. Thus, the reaction of 2-tetralone and benzonitrile was investigated under various temperature conditions. The results show that when this reaction is carried out at room temperature exclusively the quinazoline



Scheme 3.



Scheme 4.



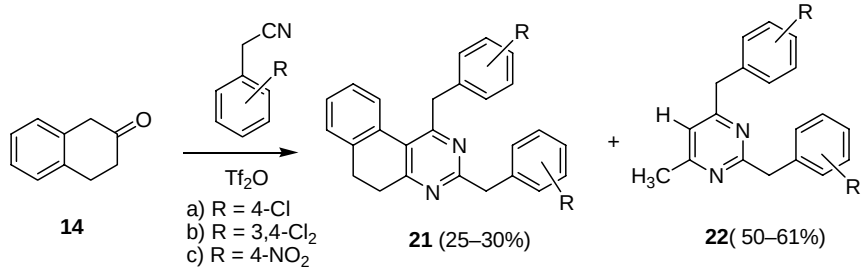
Scheme 5.

15a is exclusively formed while pyrimidine **23** is the main reaction product when the temperature is raised to 120 °C (Scheme 7).

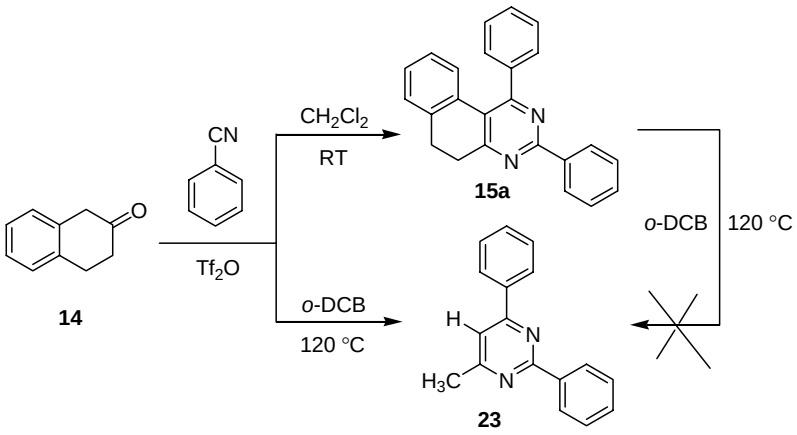
The formation of pyrimidine **23** could not be explained by a fragmentation process promoted by temperature. Heating **15a** in *o*-DCB at 120 °C for several hours, even in the presence of Tf_2O and/or TfOH, does not afford pyrimidine **23**. NOE experiments with compound **22c** were performed to confirm the pyrimidine structure and to achieve the complete assignments of the ^1H NMR signals. Irradiations and signals enhancement are summarized in Scheme 8. The observed results confirm the proposed structure (Scheme 8). Experiments are in progress to determine the exact mechanism of the pyrimidine formation.

The reaction of 2-tetralone (**14**) with methylthiocyanate (Scheme 9) leads to a mixture of the expected dihydrobenzoquinazoline **24** and a new compound, which was identified as tetrahydrodibenzo[*a*,*i*]phenanthridine **25**. The pentacyclic structure of **25** cannot be explained by the general mechanism for the reaction between ketones and nitriles.[23] Moreover, the presence of only one nitrogen atom in the structure of **25** indicates that the cyclodimerisation process of the nitrile does not take place. In contrast to the general mechanism, only one molecule of the nitrile and two molecules of the starting ketone participate in the reaction.

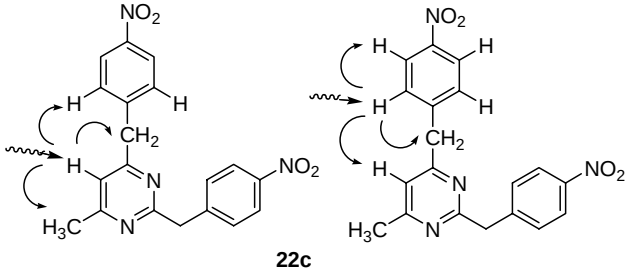
We have proposed a mechanism to explain these results. The first step involves the aldol condensation of the tetralone **14** induced by traces of triflic acid to form the



Scheme 6.



Scheme 7.



Scheme 8.

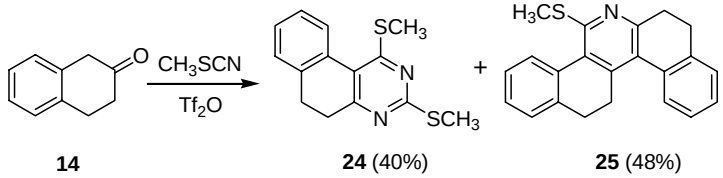
hydroxyketone **26**. The last step of this condensation involves the elimination of a water molecule and affords the two isomeric binaphthalenones **27** and **28** (Scheme 10). The reaction of the enone **27** with methylthiocyanate followed by loss of TfOH and cyclization affords the tetrahydrodibenzo[*a*,*i*]phenanthridine **24**. In contrast, if the enone **28** undergoes the same process, the isomeric tetrahydrodibenzo[*a*,*j*]phenanthridine **30** should be formed. A similar mechanism has been reported that involves an aldol condensation of cyclobutanone and subsequent reaction with only one nitrile molecule has been reported.[29]

In order to distinguish between phenanthridines **25** and **30**, we used NOE experiments. Because the chemical shift of the thiomethyl group (2.69 ppm) is close to the signals of the methylene protons, it is very difficult to irradiate the CH_3S signal without perturbation of other nuclei. To avoid this problem, we prepared several derivatives of **25** based on the reactions shown in Scheme 3. The oxidation of **25** with *m*-CPBA in dichloromethane affords the sulfone **32**, which reacts with a methanolic solution of sodium methoxide leading to the methoxyphenanthridine **33** (Scheme 11).

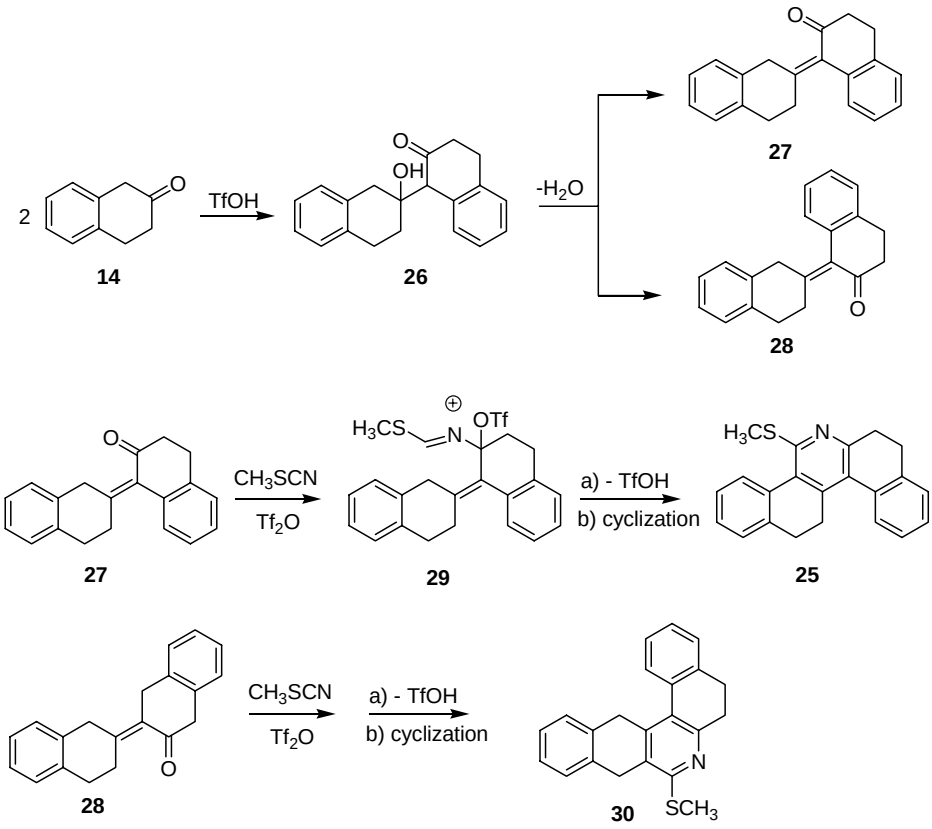
The ^{1}H NMR spectra of **33** shows a singlet at 4.09 ppm corresponding to the CH_3O group, which does not overlap with the signals of H13 and H14. Moreover, H7 and H8 appear as a singlet at 2.29 ppm. Irradiation of the CH_3O signal produces a significant enhancement of the signal at 8.28 ppm corresponding to H4. Another small signal enhancement is observed at 2.29 ppm, which corresponds to H7 and H8 (Scheme 12 and Fig. 2). The structure of the isomeric phenanthridine **34** could be discarded because an irradiation on the methoxy signal could not produce a signal enhancement in the aromatic region.

The reaction of **25** with DDQ affords the totally aromatic phenanthridine **31**. Unfortunately, this compound is unreactive towards nucleophiles and the thiomethyl group cannot be replaced in this polyaromatic system.

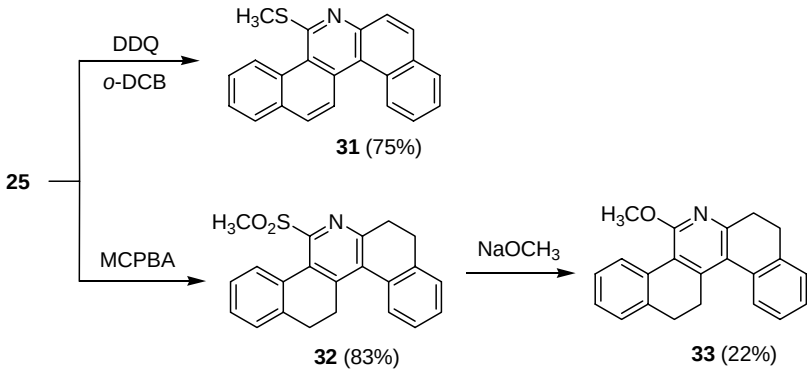
In summary, we report that the one-pot reaction of 1- and 2-tetralone with nitriles affords 2,4-disubstituted dihydrobenzo[*h*]quinazolines and 1,3-disubstituted dihydrobenzo[*f*]quinazolines, respectively. These compounds can be easily converted into their corresponding benzoquinazolines via DDQ oxidation. The reaction of 2-tetralone with nitriles is a regiospecific process and is proposed a mechanism to explain the results. Benzoquinazolines bearing thiomethyl groups can be used as starting materials for the synthesis of several variously substituted quinazolines. On the other hand, the reaction of 2-tetralone with methylthiocyanate is a one-step procedure to obtain substituted dibenzophenanthridines. A mechanism for this reaction is postulated.



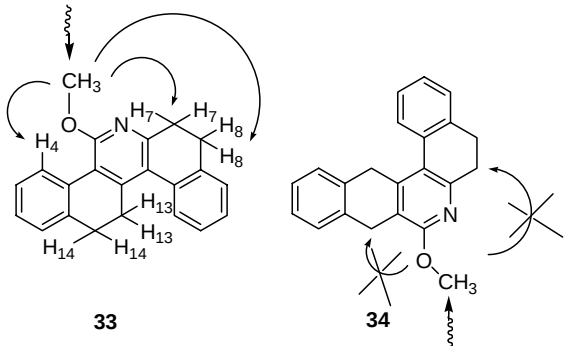
Scheme 9.



Scheme 10.



Scheme 11.



Scheme 12.

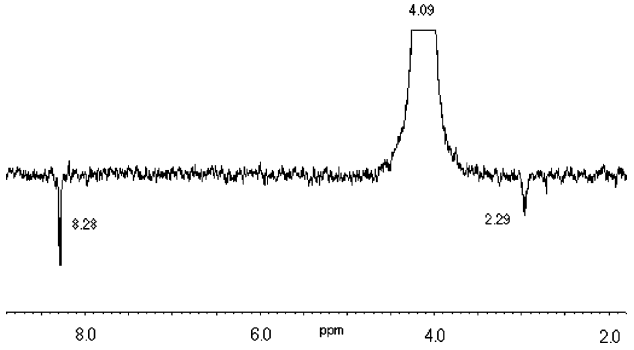


Figure 2.

3. Experimental

3.1. General

All reagents were commercial grade and were used as received unless otherwise indicated. Triflic anhydride was prepared from TfOH and redistilled twice prior to use.[30,31] Solvents were distilled from an appropriate drying agent before use. Reactions were monitored by thin-layer chromatography (TLC) using silica gel plates having $60F_{250}$. Column chromatography was performed using silica gel 60 (70–230 mesh). Melting points were determined on a Gallenkamp apparatus in open capillary tubes and are uncorrected. The IR spectra were measured with a Shimadzu FTIR 8300 instrument and samples pellets were produced with potassium bromide spectroscopic grade. NMR spectra were recorded on a Bruker DPX 300 and Bruker Avance AV 500 at 300 MHz for ^{1}H and 75.47 MHz for ^{13}C and 500 MHz for ^{1}H and 125.72 MHz for ^{13}C, respectively. Chemical shifts are given in δ units (ppm) to residuals $CHCl_3$ (7.26 and 77.0, respectively) and DMSO (2.50 and 39.5, respectively). J values are in Hz. Mass spectra were carried out on a HP 5989A quadrupole instrument at 70 eV with a source temperature of 200 °C. Elemental analysis was carried out with a Perkin-Elmer 2400 CHN apparatus.

3.2. Preparation of 2,4-disubstituted dehydrogenize[*h*]-quinazolines 1a–d: general procedure

A mixture of 1-tetralone (**4**) (0.5 g, 4.3 mmol) and 9 mmol of the corresponding nitrile dissolved in 30 mL of CH_2Cl_2 was cooled at 0 °C. Triflic anhydride (1.3 g, 4.5 mmol) in 15 mL of CH_2Cl_2 was added dropwise. The reaction mixture was allowed to stand to room temperature and stirred at this temperature for 24 h. The reaction can be monitored by TLC. The reaction mixture was hydrolyzed by careful addition of saturated aqueous solution of sodium hydrogen carbonate until was basic. The organic layer was separated, washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue purified by flash chromatography using hexane/ethyl acetate 9:1 as eluent. The crude product was distilled or recrystallized.

3.2.1. 2,4-Diphenyl-5,6-dihydrobenzo[*h*]quinazoline 1a. Purification of crude product by column chromatography afforded 0.93 g (65%), mp 170–171 °C (EtOH); ν (KBr) 1610, 1540, 1400, 770, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.91 (m, 2H, CH_2), 3.10 (m, 2H, CH_2), 7.45 (m, 2H), 7.28 (m, 2H), 7.46 (m, 6H), 7.70 (m, 2H), 8.58 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ: 24.78 (CH_2), 27.82 (CH_2), 123.44, 126.04, 127.26, 127.72, 128.15, 128.29, 128.36, 129.21, 130.80, 133.38, 138.22, 139.00, 160.10, 162.14, 164.28 (arom.) ppm; *m*/*z* (EI, 70 eV): 334 ($M^{+\cdot}$, 63), 333 (100), 127 (20), 77 ($C_6H_5^+$, 59). Anal. Calcd for $C_{24}H_{18}N_2$: C 86.20, H 5.43, N 8.38%, found C 86.04, H 5.39, N 8.29.

3.2.2. 2,4-Bis(4-methylphenyl)-5,6-dihydrobenzo[*h*]-quinazoline 1b. Purification of crude product by column chromatography afforded 1.08 g (70%), mp 169–170 °C ($CHCl_3$/MeOH); ν (KBr) 1615, 1540, 1400, 810, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.44 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.90 (m, 2H, CH_2), 3.10 (m, 2H, CH_2), 7.30 (m, 1H), 7.40 (m, 1H), 7.50 (m, 2H), 7.70 (m, 2H), 8.60 (m, 1H), 8.66 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ: 21.43 (CH_3), 21.53 (CH_3), 24.78 (CH_2), 27.82 (CH_2), 123.44, 126.04, 127.26, 127.72, 128.15, 128.29, 128.36, 129.21, 130.80, 133.38, 138.22, 139.00, 160.10, 162.14, 164.28 (arom.) ppm; *m*/*z* (EI, 70 eV): 362 ($M^{+\cdot}$, 85), 361 (100), 127 (20), 91 ($C_7H_7^+$, 59). Anal. Calcd for $C_{26}H_{22}N_2$: C 86.15, H 6.12, N 7.73%, found C 87.97, H 6.08, N 7.66.

3.2.3. 2,4-Bis(4-chlorophenyl)-5,6-dihydrobenzo[*h*]quinazoline 1c. Purification of crude product by column chromatography gave 1.42 g (83%), mp 118–119 °C ($CHCl_3$/MeOH); ν (KBr) 1600, 1540, 1400, 850, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.92 (m, 2H, CH_2), 3.06 (m, 2H, CH_2), 7.30 (m, 1H), 7.49 (m, 6H), 7.64 (m, 2H), 8.60 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ: 24.77 (CH_2), 27.69 (CH_2), 123.58, 126.04, 127.35, 127.80, 128.60, 129.47, 130.59, 131.07, 133.04, 135.51, 136.48, 1136.53, 136.55, 139.07, 160.41, 161.24, 163.14 (arom.) ppm; *m*/*z* (EI, 70 eV): 402 ($M^{+\cdot}$, 63), 401 (100). Anal. Calcd for $C_{24}H_{16}Cl_2N_2$: C 71.47, H 4.00, Cl 17.58, N 6.95%, found C 71.39, H 3.69, Cl 17.44, N 6.79.

3.2.4. 2,4-Bis(methylthio)-5,6-dihydrobenzo[*h*]quinazoline 1d. Purification of crude product by column chromatography afforded 0.82 g (70%), mp 110–111 °C (EtOH); ν (KBr) 1530, 1440, 1360 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.61 (s, 3H, SCH_3), 2.65 (s, 3H, SCH_3), 2.80 (t, 2H, J=7.2 Hz, CH_2), 2.96 (t, 2H, J=7.2 Hz, CH_2) 7.23 (m, 1H), 7.35 (m, 2H), 8.33 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 12.73 (CH_3S), 14.31 (CH_3S), 22.92 (CH_2), 27.11 (CH_2), 125.94, 127.10, 127.85, 130.66, 132.19, 138.76, 155.78, 167.85, 168.88 (arom.) ppm; *m*/*z* (EI, 70 eV): 274 ($M^{+\cdot}$, 100), 259 (M−CH_3, 27), 241 (M−SH, 65). Anal. Calcd for $C_{14}H_{14}N_2S_2$: C 72.70, H 4.07, N 7.06, S 16.17%, found C 72.72, H 3.90, N 6.90, S 16.05.

3.2.5. 2,4-Dibenzyl-5,6-dihydrobenzo[*h*]quinazoline 6a. Purification of crude product by column chromatography gave 1.08 g (70%), mp 71–72 °C (EtOH); ν (KBr) 1555, 1491, 1390, 740, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.84 (m, 4H, CH_2), 4.21 (s, 2H, CH_2), 4.36 (s, 2H, CH_2), 7.28 (m, 11H), 7.50 (m, 2H), 8.37 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 22.91 (CH_2), 27.31 (CH_2), 41.36 (CH_2), 45.84 (CH_2), 123.68, 125.89, 126.20, 126.42, 127.17, 127.67, 128.25, 128.52, 129.29, 130.64, 132.90, 137.87, 138.80, 139.13, 159.32, 165.68, 167.17 (arom.) ppm; *m*/*z* (EI, 70 eV): 362 ($M^{+\cdot}$, 65), 361 (100). Anal. Calcd for $C_{26}H_{22}N_2$: C 86.15, H 6.12, N 7.73%, found C 87.99, H 6.05, N 7.60.

3.2.6. 2,4-Bis(2-methylbenzyl)-5,6-dihydrobenzo[*h*]quinazoline 6b. Purification of crude product by column chromatography afforded 1.25 g (75%), mp 103–104 °C (EtOH); ν (KBr) 1554, 1384, 742 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.33 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.84 (m, 4H, AA′BB′ system CH_2), 4.15 (s, 2H, CH_2), 4.34 (s, 2H, CH_2), 6.88 (d, 1H, J=7 Hz), 7.15 (m, 7H), 7.38 (m, 3H), 8.35 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 19.98 (CH_3), 20.09 (CH_3), 22.92 (CH_2), 27.40 (CH_2), 38.88 (CH_2), 43.34 (CH_2), 123.84, 125.78, 125.89, 125.98, 126.39, 126.50, 127.22, 127.72, 128.42, 130.09, 130.23, 130.64, 133.01, 136.62, 137.06, 137.72, 138.84, 159.07, 165.73, 167.35 (arom.) ppm; *m*/*z* (EI, 70 eV): 390 ($M^{+\cdot}$, 87), 389 (100),

375 ($M-CH_3$, 10). Anal. Calcd for $C_{28}H_{26}N_2$: C 86.12, H 6.71, N 7.17%, found C 86.00, H 6.66, N 7.09.

3.2.7. 2,4-Bis(4-methylbenzyl)-5,6-dihydrobenzo[*h*]-quinazoline 6c. Purification of crude product by column chromatography afforded 1.30 g (77%), mp 108–109 °C (EtOH); ν (KBr) 1556, 1388, 808, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.30 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.81 (m, 4H, AA′BB′ system CH_2), 4.16 (s, 2H, CH_2), 4.30 (s, 2H, CH_2), 7.12 (m, 7H), 7.39 (m, 4H), 8.35 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 20.99 (CH_3), 21.06 (CH_3), 22.88 (CH_2), 27.30 (CH_2), 40.95 (CH_2), 45.36 (CH_2), 123.65, 125.89, 127.14, 127.64, 128.51, 128.96, 128.13, 129.20, 130.60, 132.91, 134.72, 135.65, 136.03, 138.81, 159.31, 165.82, 167.28 (arom.) ppm; *m/z* (EI, 70 eV): 390 ($M^{+\cdot}$, 100), 389 (100). Anal. Calcd for $C_{28}H_{26}N_2$: C 86.12, H 6.71, N 7.17%, found C 85.99, H 6.61, N 7.15.

3.2.8. 3,4-Dihydronaphthalen-1-yl triflate. This product was isolated from the reaction mixtures in 3–6% yield, bp=50 °C (0.5 Torr, kugelrohr); IR (film)=1420, 1247, 1142 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.52 (m, 2H, CH_2), 2.88 (m, 2H, CH_2), 6.03 (t, 1H, J=5.0 Hz, =CH), 7.29 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ: 22.30 (C3), 26.82 (C4), 117.69 (C=), 118.64 (q, CF_3, J=318 Hz), 121.22, 126.91, 127.73, 128.67, 129.16, 136.23 (arom.), 146.38 (=C) ppm; *m/z* (EI, 70 eV): 278 ($M^{+\cdot}$, 20), 145 (M−Tf, 100), 129 (M−OTf, 21).

3.3. Preparation of benzo[*h*]quinazolines 5: general procedure

A mixture of 0.9 mmol of the corresponding dihydrobenzoquinazoline **1** and DDQ (0.4 g, 1.8 mmol) in 10 mL of *o*-DCB was heated at 120 °C during 3 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using hexane/ethyl acetate 9:1 as eluent.

3.3.1. 1,3-Diphenylbenzo[*h*]quinazoline 5a. Purification of crude product by column chromatography afforded 0.24 g (80%), mp 152–153 °C (EtOH); ν (KBr) 1566, 1490, 804, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.72 (m, 13H), 8.86 (m, 2H), 9.55 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 119.26, 122.82, 125.34, 127.32, 127.82, 128.51, 128.70, 129.65, 130.04, 130.31, 130.48, 135.09, 138.07, 138.47, 151.92, 162.13, 166.76 (arom.) ppm; *m/z* (EI, 70 eV): 332 ($M^{+\cdot}$, 63), 331 (100), 253 (11). Anal. Calcd for $C_{24}H_{16}N_2$: C 86.72, H 4.85, N 8.43%, found C 86.59, H 4.88, N 8.38.

3.3.2. 2,4-Bis(4-methlphenyl)benzo[*h*]quinazoline 5b. Purification of crude product by column chromatography afforded 0.25 g (86%), mp 151–152 °C (EtOH); ν (KBr) 1560, 1439, 1095, 761 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.47 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 7.35 (m, 4H), 7.85 (m, 7H), 8.75 (d, 2H, J=8 Hz) 9.54 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 21.47 (CH_3), 21.56 (CH_3), 119.09, 122.99, 125.34, 127.16, 127.37, 127.68, 128.66, 129.25, 129.88, 130.30 130.82, 135.07, 135.34, 135.88, 139.75, 140.59, 151.85, 160.23, 166.66 (arom.) ppm; *m/z* (EI, 70 eV): 360 ($M^{+\cdot}$, 85), 359 (100), 345 ($M-CH_3$, 20). Anal. Calcd for $C_{26}H_{20}N_2$: C 86.64, H 5.59, N 7.77, found C 86.50, H 5.44, N 7.69.

3.3.3. 2,4-Bis(methylthio)benzo[*h*]quinazoline 5d. Purification of crude product by column chromatography gave 0.23 g (93%), mp 103–104 °C (EtOH); ν (KBr) 1560, 1490, 800, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.71 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 7.77 (m, 5H), 9.16 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 12.74 (CH_3), 14.44 (CH_3), 118.18, 120.06, 125.28, 126.29, 127.08, 127.75, 129.55, 129.64, 135.41, 148.15, 167.26, 169.81 (arom.) ppm; *m/z* (EI, 70 eV): 272 ($M^{+\cdot}$, 100), 257 ($M-CH_3$, 38), 239 (M−SH, 51), 225 ($M-SCH_3$, 13). Anal. Calcd for $C_{14}H_{12}N_2S_2$: C 61.73, H 4.44, N 10.28, S 23.54%, found C 61.66, H 4.40, N 10.11, S 23.44.

3.4. Preparation of monobenzoyldihydrobenzo[*h*]quinazolines 7: general procedure

A mixture of 0.55 mmol of the corresponding dihydroquinazoline **6** and DDQ (0.25 g, 1.1 mmol) in 20 mL of toluene was heated at 100 °C during 3 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using hexane/ethyl acetate 9:1 as eluent.

3.4.1. 4-Benzoyl-2-benzyl-5,6-dihydrobenzo[*h*]quinazoline 7a. Purification of crude product by column chromatography afforded 0.1 g (50%) of an undistillable oil; ν (film) 1676 (C=O), 1569, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.9 (m, 4H, CH_2), 4.35 (s, 2H, CH_2), 7.35 (m, 11H), 7.90 (m, 2H), 8.42 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 22.85 (CH_2), 27.16 (CH_2), 45.79 (CH_2), 123.42, 125.99, 126.41, 127.36, 128.01, 128.36, 128.58, 129.32, 130.62, 131.41, 132.33, 134.06, 135.25, 138.63, 139.37, 160.83, 161.16. 167.21 (arom.), 193.64 (CO) ppm; *m/z* (EI, 70 eV): 376 ($M^{+\cdot}$, 100), 375 (38), 271 ($M-C_6H_5CO$, 25). Anal. Calcd for $C_{26}H_{20}N_2O$: C 82.95, H 5.35, N 7.44%, found C 82.92, H 5.29, N 7.32.

3.4.2. 4-(4-Methylbenzoyl)-2-(4-methylbenzyl)-5,6-dihydrobenzo[*h*]quinazoline 7c. Purification of crude product by column chromatography afforded 0.09 g (40%), mp 113–114 °C (hexane); ν (KBr) 1672 (C=O), 1604, 1555, 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.32 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.87 (m, 4H, CH_2), 4.30 (s, 2H, CH_2), 7.11 (m, 2H), 7.24 (m, 4H), 7.38 (m, 3H), 7.80 (m, 2H), 8.40 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 21.05 (CH_3), 21.85 (CH_3), 22.87 (CH_2), 27.19 (CH_2), 45.38 (CH_2), 123.14, 125.98, 127.31, 129.96, 129.04, 129.16, 129.33, 130.72, 131.31, 132.42, 132.82, 135.63, 135.85, 139.35, 145.21, 161.01, 161.18, 167.41 (arom.), 193.37 (CO) ppm; *m/z* (EI, 70 eV): 404 ($M^{+\cdot}$, 100), 403 (54). Anal. Calcd for $C_{28}H_{24}N_2O$: C 83.14, H 5.98, N 6.93%, found C 83.01, H 5.87, N 6.82.

3.5. Preparation of dibenzoyldihydrobenzo[*h*]quinazolines 8: general procedure

A mixture of 0.70 mmol of the corresponding dihydroquinazoline **6** and DDQ (0.31 g, 1.65 mmol) in 20 mL of *o*-DCB was heated at 150 °C during 3 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using hexane/ethyl acetate 9:1 as eluent.

3.5.1. 2,4-Bis(benzoyl)-5,6-dihydrobenzo[*h*]quinazoline 8a. Purification of crude product by column

chromatography afforded 0.12 g (45%), mp 157–158 °C (EtOH); ν (KBr) 1679 (C═O), 1593, 1452, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.02 (m, 4H, CH_2), 7.47 (m, 9H), 8.02 (m, 4H), 8.42 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 23.38 (CH_2), 26.85 (CH_2), 126.50, 127.35, 128.15, 128.32, 128.78, 130.55, 131.00, 131.57, 132.17, 133.58, 134.42, 134.94, 135.23, 160.44, 161.01, 161.47 (arom.), 191.03, 192.95 (CO) ppm; *m/z* (EI, 70 eV): 390 ($M^{+\cdot}$, 158), 389 (15), 284 (M−C_6H_5CO, 43), 77 ($C_6H_5^+$, 100). Anal. Calcd for $C_{26}H_{18}N_2O_2$: C 79.98, H 4.65, N 7.17%, found C 79.87, H 4.61, N 7.00.

3.5.2. 2,4-Bis(4-methylbenzoyl)-5,6-dihydrobenzoquinazoline 8c. Purification of crude product by column chromatography afforded 0.18 g (60%), mp 143–144 °C (hexane); ν (KBr) 1678 (C═O), 1668 (CO), 1604, 1550, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.42 (s, 6H, CH_3), 2.94 (s, 2H, CH_2), 7.33 (m, 7H), 7.94 (m, 2H), 8.42 (m, 2H), 9.32 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 21.80 (CH_3), 21.86 (CH_3), 23.36 (CH_2), 26.87 (CH_2), 126.48, 126.99, 127.58, 128.12, 129.08, 129.52, 130.66, 131.16, 131.66, 132.05, 132.52, 132.70, 139.37, 144.61, 145.66, 160.75, 161.28, 161.33 (arom.), 190.77, 192.67 (CO) ppm; *m/z* (EI, 70 eV): 418 ($M^{+\cdot}$, 100), 417 (20), 298 (90). Anal. Calcd for $C_{28}H_{22}N_2O_2$: C 80.36, H 5.30, N 6.69%, found C 80.25, H 5.28, N 6.59.

3.5.3. 2,4-Bis(methylsulfonyl)benzo[*h*]quinazoline 9d. To a stirred solution of 2,4-bis(methylthio)benzo[*h*]quinazoline **5d** containing 0.5 g (1.83 mmol) in 20 mL of anhydrous dichloromethane was added slowly a solution of 1.27 g (7.32 mmol) of *m*-CPBA in 20 mL of dichloromethane. The mixture was stirred at room temperature for 4 h. An aqueous solution of $Na_2S_2O_3$ (5%) was then added and the layers shaked and separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers washed with $NaHCO_3$ aqueous solution, brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by recrystallization to give 0.52 g (85%) of **9d**, mp 191–192 °C (EtOH); ν (KBr): 1388, 1303 (SO_2), 1143, 947, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.54 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 7.99 (m, 5H), 9.20 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 39.67 (CH_3), 42.39 (CH_3), 115.17, 118.09, 125.38, 128.53, 128.87, 129.06, 131.91, 132.65, 135.98 (arom.) ppm; *m/z* (EI, 70 eV): 336 ($M^{+\cdot}$, 20), 272 (M−SO_2, 100), 195 (67). Anal. Calcd for $C_{14}H_{12}N_2O_4S_2$: C 49.99, H 3.60, N 8.33, S 19.06%, found C 49.87, H 3.55, N 8.21, S 18.98.

3.5.4. 2,4-Dimethoxybenzo[*h*]quinazoline 10d. A solution containing 0.2 g (0.59 mmol) of **9d** and sodium methoxide (0.15 g, 2.36 mmol) in 20 mL of dry methanol was refluxed for 2 h. After addition of water and extraction with dichloromethane, the organic layers were washed with brine. Elimination of solvent affords a residue, which was purified by recrystallization giving 0.13 g (90%) of **10d**, mp 101–102 °C (EtOH); ν (KBr): 1267, 1195, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.18 (s, 3H, CH_3), 4.21 (s, 3H, CH_3), 7.67 (m, 5H), 7.90 (m, 5H), 9.06 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 54.49 (CH_3), 54.78 (CH_3), 109.38, 119.53, 124.52, 124.93, 126.53, 127.75, 129.30, 135.74, 152.09, 162.37, 169.06 (arom.) ppm; *m/z* (EI, 70 eV): 240 ($M^{+\cdot}$, 47), 239 (100), 225 (M−CH_3, 8). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C 69.99, H 5.03, N 11.66%, found C 69.85, H 4.91, N 11.59.

3.5.5. 4-Amino-2-(methylsulfonyl)benzo[*h*]quinazoline 11d. A continuous stream of ammonia gas was bubbled through a solution of 0.2 g (0.59 mmol) of **9d** in 20 mL of dichloromethane at room temperature. After 2 h, the solvent was eliminated, the residue washed gently with water and purified by recrystallization giving 0.12 g (74%) of **11d**, mp 275 °C (EtOH, decomp.); ν (KBr): 3490, 3298 (NH_2), 1637, 1488, 1313 (SO_2), 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.44 (s, 3H, CH_3), 7.77 (m, 2H), 8.05 (m, 3H), 8.53 (br s, 2H, NH_2), 8.93 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 38.39 (CH_3), 110.66, 119.32, 124.25, 127.56, 127.95, 128.08, 128.95, 129.88, 134.81, 147.74, 162.04, 162.60 (arom.) ppm; *m/z* (EI, 70 eV): 273 ($M^{+\cdot}$, 45), 258 (M−CH_3, 15), 194 (M−CH_3SO_2, 100). Anal. Calcd for $C_{13}H_{11}N_3O_2S$: C 57.13, H 4.06, N 15.37, S 11.73%, found C 57.03, H 3.96, N 15.25, S 11.69.

3.5.6. 4-Amino-2-(methoxy)benzo[*h*]quinazoline 12d. A solution containing 0.2 g (0.59 mmol) of **11d** and sodium methoxide (0.15 g, 2.36 mmol) in 20 mL of dry methanol was refluxed for 2 h. After addition of water and extraction with dichloromethane, the organic layers were washed with brine. Elimination of solvent affords a residue, which was purified by recrystallization giving 0.14 g (85%) of **12d**, mp 274–275 °C (EtOH); ν (KBr): 3450, 3233 (NH_2), 1355, 1078, 796 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.08 (s, 3H, CH_3), 7.59 (m, 4H), 7.78 (m, 1H), 8.80 (br s, 2H, NH_2) 8.98 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 54.25 (CH_3), 106.96, 118.49, 123.85, 124.90, 126.51, 127.54, 129.13, 129.63, 135.48, 151.21, 162.42, 163.33 (arom.) ppm; *m/z* (EI, 70 eV): 225 ($M^{+\cdot}$, 100), 224 (57), 195 (48). Anal. Calcd for $C_{13}H_{11}N_3O$: C 69.32, H 4.92, N 18.66%, found C 69.20, H 4.80, N 18.55.

3.5.7. Benzo[*h*]quinazoline-2,4-(1*H*,3*H*)-dione 13d. Compound **11d** (0.2 g, 0.59 mmol) was suspended in 20 mL of aqueous NaOH 10% and refluxed 2 h. The reaction mixture was acidified with HCl 10% until pH 2 and the solid was collected by filtration and washed gently with cold water. Recrystallization in hot water gave 0.1 g (80%) of **13d**. If the hydrolysis was carried out by reluxing **11d** in aqueous hydrochloric acid 1:1, compound **13** was obtained in 53% yield, mp decomposition; ν (KBr): 3278 (NH), 1664, 1598 (CO), 790, 756 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.10 (d, 1H, J=9.6 Hz), 7.40 (t, 1H, J=9.6 Hz), 7.50 (t, 1H, J=9.6 Hz), 8.78 (d, 1H, J=9.6 Hz) 10.05 (br s, 2H, NH_2) ppm; ^{13}C NMR (DMSO-d_6) δ:109.70, 116.44, 123.25, 124.52, 125.76, 127.37, 128.02, 129.04, 136.54, 153.75 (arom.), 158.64, 165.93 (CO) ppm; *m/z* (EI, 70 eV): 212 ($M^{+\cdot}$, 10), 78 (100). Anal. Calcd for $C_{12}H_8N_2O_2$: C 67.92, H 3.80, N 13.20%, found C 67.79, H 3.71, N 13.13.

3.6. Preparation of 1,3-disubstituted 5,6-dihydrobenzo[*f*]-quinazolines 15a–f: general procedure

A mixture of 2-tetralone (**14**) (0.5 g, 4.3 mmol) and 9 mmol of the corresponding nitrile dissolved in 30 mL of CH_2Cl_2 was cooled at 0 °C. Triflic anhydride (1.3 g, 4.5 mmol) in 15 mL of CH_2Cl_2 was added dropwise. The reaction mixture was allowed to stand to room temperature and stirred at this

temperature for 24 h. The reaction can be monitored by TLC. The reaction mixture was hydrolyzed by careful addition of saturated aqueous solution of sodium hydrogen carbonate until was basic. The organic layer was separated, washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue purified by flash chromatography using hexane/ethylacetate 9:1 as eluent. The crude product was distilled or recrystallized.

3.6.1. 1,3-Diphenyl-5,6-dihydrobenzo[*f*]quinazoline 15a. Purification of crude product by column chromatography afforded 1.01 g (86%), mp 121–122 °C (hexane); ν (KBr) 1603, 1537, 1421, 762, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.09 (m, 4H, CH_2), 6.95 (m, 2H), 7.17 (m, 1H), 7.28 (m, 1H), 7.46 (m, 6H), 7.70 (m, 2H), 8.60 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ: 28.45 (CH_2), 32.14 (CH_2), 123.99, 126.01, 127.83, 127.88, 128.23, 128.46, 128.50, 128.84, 129.40, 129.65, 130.43, 131.14, 137.64, 138.17, 139.54, 161.54, 161.98, 168.96 (arom.) ppm; *m/z* (EI, 70 eV): 334 ($M^{+\cdot}$, 63), 333 (100). Anal. Calcd for $C_{24}H_{18}N_2$: C 86.20, H 5.43, N 8.38%, found C 86.09, H 5.33, N 8.26.

3.6.2. 1,3-Bis(4-methylphenyl)-5,6-dihydrobenzo[*f*]quinazoline 15b. Purification of crude product by column chromatography afforded 0.99 g (80%), mp 180–181 °C (EtOH); ν (KBr) 1539, 1423, 802 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.43 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.07 (m, 4H, CH_2), 6.94 (m, 8H), 7.61, 8.48 ($AA'XX'$system, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ: 21.47 (CH_3), 21.54 (CH_3), 28.50 (CH_2), 32.17 (CH_2), 123.54, 125.97, 127.68, 127.77, 128.20, 128.74, 129.19, 129.21, 129.62, 131.45, 135.02, 136.74, 138.09, 139.44, 140.55, 161.56, 161.91, 168.76 (arom.) ppm; *m/z* (EI, 70 eV): 362 ($M^{+\cdot}$, 77), 361 (100). Anal. Calcd for $C_{26}H_{22}N_2$: C 86.15, H 6.12, N 7.73%, found C 85.98, H 6.09, N 7.65.

3.6.3. 1,3-Dibenzyl-5,6-dihydrobenzo[*f*]quinazoline 15c. Purification of crude product by column chromatography afforded 0.93 g (60%), mp 80–81 °C (EtOH); ν (KBr) 1541, 1494, 1398 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.92 (m, 4H, CH_2), 4.28 (s, 2H, CH_2), 4.37 (s, 2H, CH_2), 7.33 (m, 14H) ppm; ^{13}C NMR ($CDCl_3$) δ: 28.31 (CH_2), 32.18 (CH_2), 41.73 (CH_2), 45.55 (CH_2), 125.47, 126.35, 126.63, 127.65, 127.91, 128.18, 128.32, 128.54, 128.90, 129.27, 130.97, 138.58, 162.67, 166.30, 168.46 (arom.) ppm; *m/z* (EI, 70 eV): 362 ($M^{+\cdot}$, 52), 361 (100). Anal. Calcd for $C_{26}H_{22}N_2$: C 86.15, H 6.12, N 7.73%, found C 85.98, H 5.98, N 7.69.

3.6.4. 1,3-Bis(2-methylbenzyl)-5,6-dihydrobenzo[*f*]quinazoline 15d. Purification of crude product by column chromatography afforded 0.84 g (50%), mp 110–111 °C (EtOH); ν (KBr) 1541, 1394, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.22 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.97 (m, 4H, CH_2), 4.29 (s, 2H, CH_2), 4.31 (s, 2H, CH_2), 6.98 (m, 1H), 7.26 (m, 11H) ppm; ^{13}C NMR ($CDCl_3$) δ: 19.77 (CH_3), 20.01 (CH_3), 28.39 (CH_2), 32.23 (CH_2), 39.76 (CH_2), 43.08 (CH_2), 125.38, 125.79, 126.00, 126.46, 126.77, 127.36, 127.97, 128.16, 128.87, 130.01, 130.14, 130.16, 131.08, 136.60, 137.15, 137.23, 137.52, 138.65, 162.85, 166.54, 168.23 (arom.) ppm; *m/z* (EI, 70 eV): 390 ($M^{+\cdot}$, 100), 389 (26), 375 ($M-CH_3$, 62). Anal. Calcd for $C_{28}H_{26}N_2$: C 86.12, H 6.71, N 7.17%, found C 85.99, H 6.60, N 7.09.

3.6.5. 1,3-Bis(4-methylbenzyl)-5,6-dihydrobenzo[*f*]quinazoline 15e. Purification of crude product by column chromatography afforded 1.25 g (75%), mp 101–102 °C (EtOH); ν (KBr) 1550, 1394, 792 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.34 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.91 (m, 4H, CH_2), 4.23 (s, 2H, CH_2), 4.32 (s, 2H, CH_2), 7.17 (m, 11H), 7.46 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 21.06 (CH_3), 28.31 (CH_3), 32.20 (CH_2), 41.34 (CH_2), 45.17 (CH_2), 125.35, 126.60, 127.68, 127.85, 128.08, 128.73, 129.01, 129.12, 129.21, 131.06, 136.65, 135.79, 138.55, 162.86, 166.49, 168.38 (arom.) ppm; *m/z* (EI, 70 eV): 390 ($M^{+\cdot}$, 57), 389 (100). Anal. Calcd for $C_{28}H_{26}N_2$: C 86.12, H 6.71, N 7.17%, found C 85.89, H 6.61, N 7.08.

3.6.6. 1,3-Dimethyl-5,6-dihydrobenzo[*f*]quinazoline 15f. Purification of crude product by column chromatography afforded 0.54 g (60%), mp 87–88 °C (EtOH); ν (KBr) 1552, 1375, 788 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.62 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.82 (m, 4H, CH_2), 7.23 (m, 3H), 7.50 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 24.65 (CH_3), 25.53 (CH_3), 28.23 (CH_2), 31.86 (CH_2), 124.33, 126.43, 127.51, 127.86, 131.17, 138.41, 161.38, 164.36, 167.24 (arom.) ppm; *m/z* (EI, 70 eV): 210 ($M^{+\cdot}$, 100), 209 (40). Anal. Calcd for $C_{14}H_{14}N_2$: C 79.97, H 6.71, N 13.32%, found C 79.86, H 6.66, N 13.29.

3.7. Synthesis of dibenzyldihydroquinazolines 21 and dibenzylpyrimidines 22

According to the general procedure in Section 3.6, the reaction of 2-tetralone and 4-chlorobenzylnitrile afforded a reaction mixture, which was chromatographied giving 0.56 (30%) of **21a** and 0.90 g (61%) of **22a**.

3.7.1. 1,3-Bis(4-chlorobenzyl)-5,6-dihydrobenzo[*f*]quinazoline 21a. Mp 97–98 °C; ν (KBr) 1541, 1394, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.91 (m, 4H, CH_2), 4.19 (s, 2H, CH_2), 4.31 (s, 2H, CH_2), 7.21 (m, 11H), 7.41 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 28.23 (CH_2), 32.12 (CH_2), 41.05 (CH_2), 44.76 (CH_2), 125.48, 126.68, 127.51, 128.05, 128.39, 128.59, 130.32, 130.60, 132.28, 136.93, 137.16, 138.63, 162.26, 165.87, 168.63 (arom.) ppm; *m/z* (EI, 70 eV): 430 ($M^{+\cdot}$, 59), 429 (100). Anal. Calcd for $C_{26}H_{20}Cl_2N_2$: C 72.39, H 4.67, Cl 16.44, N 6.49%, found C 72.25, H 4.59, Cl 16.38, N 6.36.

3.7.2. 2,4-Bis(4-chlorobenzyl)-6-methylpyrimidine 22a. Undistillable oil; ν (film) 1587, 1545, 1373 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.40 (s, 3H, CH_3), 3.97 (s, 2H, CH_2), 4.18 (s, 2H, CH_2), 6.71 (s, 1H), 7.21 (m, 8H) ppm ^{13}C NMR ($CDCl_3$) δ: 24.13 (CH_3), 43.23 (CH_2), 41.12 (CH_2), 117.08, 128.39, 128.78, 130.50, 130.59, 132.22, 132.71, 136.17, 167.60, 168.68, 168.70 ppm (arom.); *m/z* (EI, 70 eV): 342 ($M^{+\cdot}$, 94), 321 (100). Anal. Calcd for $C_{19}H_{16}Cl_2N_2$: C 66.48, H 4.70, Cl 20.66, N 8.16%, found C 66.31, H 4.65, Cl 20.58, N 8.11.

Using the general procedure in Section 3.6, the reaction of 2-tetralone and 3,4-dichlorobenzylnitrile afforded a reaction mixture, which was chromatographied giving 0.53 (25%) of **21b** and 0.88 g (50%) of **22b**.

3.7.3. 1,3-Bis(3,4-dichlorobenzyl)-5,6-dihydrobenzo[*f*]-quinazoline 21b. Undistillable oil; ν (film) 1541, 1471, 1394 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.92 (m, 4H, CH_2), 4.16 (s, 2H, CH_2), 4.29 (s, 2H, CH_2), 7.04 (m, 1H), 7.30 (m, 9H) ppm ^{13}C NMR ($CDCl_3$) δ: 28.17 (CH_2), 32.06 (CH_2), 40.72 (CH_2), 44.42 (CH_2), 125.67, 126.76, 127.44, 128.16, 128.48, 128.58, 128.71, 130.23, 130.43, 130.55, 130.63, 130.94, 131.12, 132.20, 132.48, 138.45, 138.70, 161.66, 165.31, 168.86 (arom.) ppm; *m/z* (EI, 70 eV): 498 ($M^{+\cdot}$, 48), 497 (100). Anal. Calcd for $C_{26}H_{18}Cl_4N_2$: C 62.42, H 3.63, Cl 28.35, H 5.60%, found C 62.29, H 3.59, Cl 28.22. N 5.55.

3.7.4. 2,4-Bis(3,4-dichlorobenzyl)-6-methylpyrimidine 22b. Mp 83–84 °C (EtOH); ν (film) 1583, 1472, 1363 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.43 (s, 3H, CH_3), 3.95 (s, 2H, CH_2), 4.15 (s, 2H, CH_2), 6.77 (s, 1H), 7.06 (m, 1H), 7.18 (m, 1H), 7.38 (m, 4H) ppm ^{13}C NMR ($CDCl_3$) δ: 24.12 (CH_3), 42.87 (CH_2), 44.78 (CH_2), 117.29, 128.60, 128.65, 130.17, 130.55, 131.09, 132.16, 132.60, 137.79, 138.55, 167.94, 168.26 (arom.) ppm; *m/z* (EI, 70 eV): 410 ($M^{+\cdot}$, 100), 409 (92). Anal. Calcd for $C_{19}H_{14}Cl_4N_2$: C 55.37, H 3.42, Cl 34.41, N 6.80%, found C 55.27, H 3.39, Cl 34.43, N 6.70.

Using the general procedure in Section 3.6, the reaction of 2-tetralone and 4-nitrobenzylnitrile afforded a reaction mixture, which was chromatographied giving 0.58 (30%) of **21c** and 0.78 g (50%) of **22c**.

3.7.5. 1,3-Bis(4-nitrobenzyl)-5,6-dihydrobenzo[*f*]quinazoline 21c. Mp 144–145 °C (MeOH); ν (film) 1543, 1346 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.93 (m, 4H), 4.30 (s, 2H, CH_2), 4.46 (s, 2H, CH_2), 7.36 (m, 8H), 8.14 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ: 28.15 (CH_2), 32.09 (CH_2), 41.62 (CH_2), 45.13 (CH_2), 123.51, 123.63, 125.88, 126.80, 127.30, 128.30, 128.76, 129.89, 130.10, 130.25, 138.75, 145.83, 146.17, 146.78, 161.34, 164.98, 169.14 (arom.) ppm; *m/z* (EI, 70 eV): 452 ($M^{+\cdot}$, 51), 451 (100), 422 (M−NO, 23). Anal. Calcd for $C_{26}H_{20}N_4O_4$: C 69.02, H 4.46, N 12.38%, found C 68.88, H 4.39, N 12.29.

3.7.6. 5-Methyl-2,4-bis(2-nitrobenzyl)pyrimidine 22c. Mp 142–143 (EtOH); ν (film) 1546, 1342 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.93 (s, 3H, CH_3), 4.04 (s, 2H, CH_2), 4.23 (s, 2H, CH_2), 6.75 (s, 1H), 7.38 (m, 4H), 8.08 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ: 24.55 (CH_3), 43.94 (CH_2), 45.91 (CH_2), 117.99, 123.94, 124.27, 130.45, 130.48, 145.52, 146.32, 167.91, 168.39, 168.61 (arom.) ppm; *m/z* (EI, 70 eV): 364 ($M^{+\cdot}$, 100), 363 (97), 334 (M−NO, 23), 317 (M−NO_2H, 20). Anal. Calcd for $C_{19}H_{16}N_4O_4$: C 62.63, H 4.43, N 15.38% found C 62.55, H 4.30, N 15.22.

3.7.7. 3,4-Dihydronaphthalen-2-yl triflate. This product was isolated from the reaction mixtures in 4–7% yield, bp= 50 °C (0.5 Torr, kugelrohr); IR (film)=1420, 1247, 1142 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.72 (t, 2H, J=8.3 Hz, CH_2), 3.08 (t, 2H, J=8.3 Hz, CH_2), 6.51 (s, 1H, =CH), 7.15 (m, 4H) ppm; *m/z* (EI, 70 eV): 278 ($M^{+\cdot}$, 30), 145 (M−Tf, 22), 129 (M−OTf, 100).

3.8. Preparation of benzo[*f*]quinazolines 17: general procedure

A mixture of 0.9 mmol of the corresponding dihydrobenzoquinazoline **15** and DDQ (0.4 g, 1.8 mmol) in 10 mL of *o*-DCB was heated at 120 °C during 3 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using hexane/ethyl acetate 9:1 as eluent.

3.8.1. 1,3-Diphenylbenzo[*f*]quinazoline 17a. Purification of crude product afforded 0.23 g (80%), mp 149–150 °C (EtOH); ν (KBr) 1603, 1531, 1429, 775, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.25 (m, 1H), 7.53 (m, 7H), 7.80 (m, 4H), 8.05 (2H, AB system, J=9.1 Hz), 8.71 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ: 119.34, 126.42, 127.08, 127.33, 127.75, 128.54, 128.63, 128.75, 129.04, 129.14, 130.55, 132.77, 135.59, 137.73, 141.91, 154.35, 159.79, 166.22 (arom.) ppm; *m/z* (EI, 70 eV): 332 ($M^{+\cdot}$, 70), 331 (100). Anal. Calcd for $C_{24}H_{16}N_2$: C 86.72, H 4.85, N 8.43%, found C 86.66, H 4.73, N 8.31.

3.8.2. 1,3-Bis(4-methylphenyl)benzo[*f*]quinazoline 17b. Purification of crude product afforded 0.28 g (86%), mp 174–175 °C (EtOH); ν (KBr) 1604, 1471, 831, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.45 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.29 (m, 5H), 7.50 (m, 1H), 7.63 (d, 2H, J=9.0 Hz), 7.88 (m, 2H), 8.05 (2H, AB system, J=9.56 Hz), 8.59 (d, 2H, J=9.0 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ: 21.53 (CH_3), 21.55 (CH_3), 119.16, 126.28, 128.67, 127.34, 127.71, 128.57, 128.66, 129.15, 129.26, 129.68, 132.65, 135.07, 135.50, 139.12, 139.61, 140.68, 154.34, 159.84, 166.14 (arom.) ppm; *m/z* (EI, 70 eV): 360 ($M^{+\cdot}$, 73), 359 (100). Anal. Calcd for $C_{26}H_{20}N_2$: C 86.64, H 5.59, N 7.77%, found C 86.54, H 5.44, N 7.71.

3.8.3. Reaction of 2-tetralone (14) with benzonitrile in *o*-DCB as solvent. The reaction was carried out following the general procedure in Section 3.6 heating at 120 °C for 24 h. Purification of crude product afforded 0.63 g (60%) of 4-methyl-2,6-diphenylpyrimidine **23**. (Lit.[32]), mp 101–102 °C (EtOH); ν (KBr) 1600, 1570, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.65 (s, 3H, CH_3), 7.47 (s, 1H), 7.53 (m, 6H), 8.22 (m, 2H), 8.60 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ: 24.61 (CH_3), 113.96, 127.20, 128.37, 128.44, 128.85, 130.47, 130.66, 137.29, 163.69, 164.33, 167.76 (arom.) ppm; *m/z* (EI, 70 eV): 246 ($M^{+\cdot}$, 100), 143 (M−C_6H_5CN, 26). Anal. Calcd for $C_{17}H_{14}N_2$: C 82.90, H 5.73, N 11.37%, found C 82.82, H 5.62, N 11.31.

3.9. The reaction of 2-tetralone with methylthiocyanate: general procedure

A mixture of 2-tetralone (**14**) (0.3 g, 2.05 mmol) and 0.62 g (8.56 mmol) of methylthiocyanate dissolved in 10 mL of *o*-DCB was cooled at 0 °C. Triflic anhydride (0.70 g, 2.46 mmol) in 15 mL of *o*-DCB was added dropwise. The reaction mixture was allowed to stand to room temperature and stirred at this temperature for 24 h and then at 120 °C for 3 h. The reaction can be monitored by TLC. The reaction mixture was hydrolyzed by careful addition of saturated aqueous solution of sodium hydrogen carbonate until was basic. The organic layer was separated, washed with brine

and dried over $MgSO_4$. The solvent was removed in vacuo and the residue purified by flash chromatography using hexane/ethylacetate 9:1 as eluent. The crude product afforded 0.22 g (40%) of **24** and 0.31 g (48%) of **25**.

3.9.1. 1,3-Bis(methylthio)-5,6-dihydrobenzoquinazoline 24. Mp 89–90 °C (hexane); ν (KBr) 1523, 1421, 1344 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.61 (s, 3H, SCH_3), 2.63 (s, 3H, SCH_3), 2.85 (m, 4H, CH_2), 7.29 (m, 3H), 8.11 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 13.90 (CH_3S), 14.15 (CH_3S), 28.10 (CH_2), 31.72 (CH_2), 121.86, 126.24, 126.59, 127.85, 127.96, 130.47, 137.89, 165.31, 165.53, 168.02, (arom.) ppm; *m/z* (EI, 70 eV): 274 ($M^{+\cdot}$, 100), 273 (80), 259 (M−CH_3, 18), 241 (M−SH, 19). Anal. Calcd for $C_{14}H_{14}N_2S_2$: C 61.28, H 5.14, N 10.21, S 32.37%, found C 61.17, H 5.09, N 10.11, S 32.22.

3.9.2. 5-(Methylthio)-7,8,13,14-tetrahydrodibenzo[*a*,*i*]-phenanthridine 25. Mp 149–150 °C (EtOH); ν (KBr) 1544, 1427, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.66 (m, 2H, CH_2), 2.69 (s, 3H, SCH_3), 3.03 (m, 6H, CH_2), 7.36 (m, 7H), 8.23 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 14.60 (CH_3S), 28.88 (CH_2), 29.48 (CH_2), 32.95 (CH_2), 124.76, 125.91, 126.12, 127.03, 127.26, 127.68, 127.70, 127.84, 128.56, 129.08, 132.40, 133.18, 138.97, 139.05, 144.70, 153.34, 157.39 (arom.) ppm; *m/z* (EI, 70 eV): 329 ($M^{+\cdot}$, 94), 328 (100), 314 (M−CH_3, 19), 296 (M−SH, 22). Anal. Calcd for $C_{22}H_{19}NS$: C 80.20, H 5.81, N 4.25, S 9.73%, found C 80.10, H 5.77, N 4.11, S 9.65.

3.9.3. 5-(Methylsulfonyl)-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine 32. To a stirred solution of 5-(methylthio)-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine **25** containing 0.5 g (1.52 mmol) in 20 mL of anhydrous dichloromethane was added slowly a solution of 1.1 g (6.54 mmol) of *m*-CPBA in 20 mL of dichloromethane. The mixture was stirred at room temperature for 4 h. An aqueous solution of $Na_2S_2O_3$ (5%) was then added and the layers shaked and separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers washed with $NaHCO_3$ aqueous solution, brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by recrystallization to give 0.45 g (83%) of **28**, mp 234–235 °C (EtOH); ν (KBr): 1402, 1261 (SO_2), 1124, 764 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.71 (t, 2H, J=8.5 Hz, CH_2), 3.01 (m, 4H, 2H), 3.14 (d, 2H, J=8.5 Hz, CH_2), 3.44 (s, 3H, CH_3), 7.35 (m, 6H), 7.50 (m, 1H), 8.27 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 29.15 (CH_2), 29.43 (CH_2), 32.60 (CH_2), 41.78 (CH_3), 126.38, 126.44, 126.62, 128.18, 128.92, 128.95, 129.63, 130.19, 130.96, 131.79, 138.04, 139.67, 148.12, 151.91, 156.62 (arom.) ppm; *m/z* (EI, 70 eV): 361 ($M^{+\cdot}$, 100), 360 (60), 296 (M−SO_2H, 17), 282 (M−CH_3SO_2, 72). Anal. Calcd for $C_{22}H_{19}NO_2S$: C 73.10, H 5.30, N 3.88, S 8.87%, found C 72.95, H 5.25, N 3.76, S 8.77.

3.9.4. 5-Methoxy-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine 33. A solution containing 0.3 g (0.59 mmol) of **32** and sodium methoxide (0.15 g, 2.36 mmol) in 20 mL of dry methanol was refluxed for 2 h. After addition of water and extraction with dichloromethane, the organic layers were washed with brine. Elimination of solvent affords a residue, which was purified by recrystallization giving 0.04 g (22%) of **33**, mp 141–142 °C (EtOH); ν (KBr): 1296, 1066, 796 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.69 (m, 2H, CH_2), 2.93 (s, 4H, CH_2), 3.11 (m, 2H, CH_2), 4.09 (s, 3H, CH_3), 7.27 (m, 7H), 8.27 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 28.45 (CH_2), 29.38 (CH_2), 29.40 (CH_2), 32.68 (CH_2), 53.37 (CH_3), 116.58, 122.79, 125.97, 126.26, 126.60, 126.87, 126.91, 127.65, 128.02, 128.20, 131.57, 133.41, 137.98, 138.64, 146.59, 155.95, 158.82 (arom.) ppm; *m/z* (EI, 70 eV): 313 ($M^{+\cdot}$, 100), 312 (89), 296 (M−CH_3, 10). Anal. Calcd for $C_{22}H_{19}NO$: C 84.31, H 6.11, N 4.47%, found C 84.23, H 6.05, N 4.38.

3.9.5. 5-(Methylthio)dibenzo[*a*,*i*]phenanthridine 31. A mixture of 0.9 mmol of **25** and DDQ (0.83 g, 3.6 mmol) in 10 mL of *o*-DCB was heated at 120 °C during 3 h. The solvent was removed under reduced pressure and the residue is purified by flash chromatography using hexane/ethyl acetate 9:1 as eluent. The crude product afforded 0.22 g (75%) of **31**, mp 133–134 °C (EtOH); ν (KBr) 1261, 1020, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.93 (s, 3H, CH_3), 7.72 (m, 4H), 8.07 (m, 5H), 8.93 (m, 2H), 9.55 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 29.68 (CH_3), 124.26, 125.22, 125.98, 126.53, 126.75, 126.88, 127.54, 127.79, 128.22, 128.83, 129.49, 130.34, 130.69, 132.48, 132.77, 134.83, 172.28 (arom.) ppm; *m/z* (EI, 70 eV): 325 ($M^{+\cdot}$, 61), 324 (100), 310 (M−CH_3, 19), 278 (M−SCH_3, 24). Anal. Calcd for $C_{22}H_{15}NS$: C 81.20, H 4.65, N 4.30, S 9.85%, found C 81.11, H 4.50, N 4.26, S 9.77.

Acknowledgements

We gratefully acknowledge the DGESIC (Spain, grant BQU2002-00406) and the AECI (Spain, grant PR120/00-8980) for financial support. We also thank the CAIs of the UCM for recording MS and NMR spectra and determining the CHN analyses.

References and notes

1. Morita, H.; Sato, Y.; Chang, K.-L.; Choo, C. Y.; Itokawa, H.; Takeya, K.; Kobayashi, J. *J. Nat. Prod.* **2000**, *63*, 1707–1708.
2. Rosowsky, A.; Huang, P. C.; Papathanasopoulos, N.; Modest, E. J. *J. Med. Chem.* **1974**, *17*, 1217–1222.
3. Godde, F.; Toulme, J. J.; Moreau, S. *Biochemistry* **1998**, *37*, 13765–13775.
4. Ballard, P.; Bradbury, R. H.; Hennequin, L. F. A.; Hickinson, M.; Johnson, P. D.; Kettle, J. G.; Klinowska, T.; Morgentin, R.; Ogilvie, D. J.; Olivier, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4226–4229.
5. Pendergast, W.; Dickerson, S. H.; Johnson, J. V.; Dev, I. K.; Ferone, R.; Duch, D. S.; Smith, G. K. *J. Med. Chem.* **1993**, *36*, 3464–3471.
6. Pendergast, W.; Dickerson, S. H.; Johnson, J. V.; Dev, I. K.; Ferone, R.; Duch, D. S.; Hall, W. R.; Humphereys, J.; Kelly, J. M.; Wilson, D. C. *J. Med. Chem.* **1993**, *36*, 2279–2291.
7. Hanlon, M. H.; Ferone, R. *Cancer Res.* **1996**, *56*, 3301–3306.
8. Bavetsias, V.; Jackmann, A. L. *Curr. Med. Chem.* **1998**, *5*, 265–288.

9. Kanuma, K.; Omodera, K.; Nishiguchi, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3853–3856.
10. Varano, F.; Catarzi, D.; Colotta, V.; Calabri, F. R.; Lenzi, O.; Filacchioni, G.; Galli, A.; Costagli, C.; Delflorian, F.; Moro, S. *Bioorg. Med. Chem.* **2005**, *13*, 5536–5549.
11. Li, Z.; Jin, Z.; Huang, R. *Synthesis* **2001**, 2365–2378.
12. Hudson, B. P.; Barton, J. K. *J. Am. Chem. Soc.* **1998**, *120*, 6877–6888.
13. Li, D. J.; Zhao, B.; Sim, S. P.; Li, T.-K.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 3795–3805.
14. Görner, H.; Döpp, D.; Dittmann, A. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1723–1733.
15. Kumar, S.; Manikckam, M. *J. Liq. Crystallogr.* **1999**, *26*, 1097–1099.
16. Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; Blackwell Science: Oxford, 2000.
17. Chakrabarty, M.; Sarkar, S.; Harigaya, Y. *Synthesis* **2003**, 2292–2294.
18. Kumar, V.; Mohan, C.; Gupta, M.; Mahajan, M. P. *Tetrahedron* **2005**, *61*, 3533–3538.
19. Mizuno, T.; Iwai, T.; Ishino, Y. *Tetrahedron Lett.* **2004**, *45*, 7073–7075.
20. Churruca, F.; SanMartín, R.; Carril, M.; Urtiaga, M. K.; Solans, X.; Tellitu, I.; Dominguez, E. *J. Org. Chem.* **2005**, *70*, 3178–3187.
21. Kock, I.; Clement, B. *Synthesis* **2005**, 1052–1054.
22. Sengupta, S. K.; Chateerjee, S.; Protopapa, H. K.; Modest, E. J. *J. Org. Chem.* **1972**, *37*, 1323–1328.
23. Alkyl- and arylpyrimidines: García Martínez, A.; Herrera Fernández, A.; Moreno Jímenez, F.; García Fraile, A.; Hanack, M.; Subramanian, L. R. *J. Org. Chem.* **1992**, *57*, 1627–1630.
24. Alkoxypyrimidines: García Martínez, A.; Herrera Fernández, A.; Martínez-Alvarez, R.; Molero Vilchez, D.; Laorden Gutierrez, M. L.; Subramanian, L. R. *Tetrahedron* **1999**, *55*, 4825–4830.
25. Alkylthio and arylthiopyrimidines: Herrera Fernández, A.; Martínez-Alvarez, R.; Ramiro Pérez, P. *Tetrahedron* **2003**, *59*, 7331–7336.
26. Benzocycloheptapyrimidines: Herrera Fernández, A.; Martínez-Alvarez, R.; Chioua, R.; Chioua, M. *Tetrahedron Lett.* **2003**, 2149–2151.
27. Dialkylamino substituted benzocycloheptapyrimidines: Herrera Fernández, A.; Martínez-Alvarez, R.; Chioua, R.; Benabdelouahab, F.; Chioua, M. *Tetrahedron* **2004**, *60*, 5475–5479.
28. Herrera, A.; Martínez-Alvarez, R.; Chioua, M.; Chiuoa, R.; Sánchez, A. *Tetrahedron* **2002**, *58*, 10053–10058.
29. González, B.; Herrera, A.; Illescas, B.; Martín, N.; Martínez, R.; Moreno, F.; Sánchez, L.; Sánchez, A. *J. Org. Chem.* **1998**, *63*, 6807–6813.
30. Stang, P. J.; Dueber, T. E. *Org. Synth.* **1974**, *54*, 79–84.
31. Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85–126.
32. Nishio, T.; Tokumaga, T.; Omote, Y. *J. Heterocycl. Chem.* **1985**, *22*, 405–407.